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THE IMPACT OF MUSIC THERAPY ON ENHANCING COGNITIVE FUNCTION AND THE LEVELS OF BRAINDERIVED NEUROTROPHIC FACTOR IN THE PLASMA OF SCHIZOPHRENIC PATIENTS WITH RISPERIDONE TREATMENT

Mikael Sri Pabilang[1], Andi Jayalangkara Tanra[1*], Kristian Liaury[1], Andi Alfian Zainuddin[2], Erlyn Limoa[1], Irfan Idris[3], Saidah Syamsuddin[1], Sonny T. Lisal[1],

[1]Department of Psychiatry, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia
ORCID iD 0000-0002-9171-9605
[1*]Department of Psychiatry, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia
ORCID iD 0000-0002-3962-4190
[1]Department of Psychiatry, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia
ORCID iD 0000-0003-0085-9715
[2]Department of Public Health and Community Medicine, Hasanuddin University, Makassar, Indonesia, ORCID iD 0000-0001-6293-232X
[1]Department of Psychiatry, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia
ORCID iD 0000-0002-3183-6674
[3]Department of Physiology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia
ORCID iD 0000-0002-7350-8687
[1]Department of Psychiatry, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia
ORCID iD 0000-0002-4331-1680
[1]Department of Psychiatry, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia
ORCID iD 0000-0001-8996-6722

***Corresponding Authors:** Andi Jayalangkara Tanra
*Department of Psychiatry, Faculty of Medicine, Hasanuddin University, Jalan, Perintis Kemerdekaan Km.10, Tamalanrea, Makassar, South Sulawesi, Indonesia, 90245, ORCID iD : 0000-0002-3962-4190**,** Short Title: Prof., MD., PhD, Email: andijtanra.unhas@gmail.com

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Abstract
This study aimed to investigate the effect of music therapy on the cognitive function and plasma BDNF levels of schizophrenia patients undergoing risperidone therapy. The study utilized quasi-

experimental research and divided the 45 subjects into a treatment group and a control group. The treatment group received risperidone therapy and active and receptive music therapy for 4 weeks/12 sessions, while the control group received only risperidone therapy. Cognitive function was measured using the MoCA-Ina scale, and plasma BDNF levels were also measured. The study found that there was a significant increase in the MoCA-Ina score in both the treatment and control groups, but the treatment group had a higher increase. Additionally, the treatment group showed a significant increase in plasma BDNF levels, while the control group showed a decrease. Comparisons between the two groups showed that the addition of music therapy improved cognitive function, especially in the memory and abstraction domains. Furthermore, there was a significant correlation between changes in MoCA-Ina scores and plasma BDNF levels. Overall, combining music therapy with risperidone therapy can enhance the quality of life of schizophrenia patients by improving their cognitive function.

Keywords Schizophrenia, Music Therapy, Risperidone, Cognitive Function, Plasma BDNF

Introduction

Schizophrenia is a severe psychological condition that has significant effects on people, families, and the wider community. It is a long-lasting illness marked by various symptoms, including distorted beliefs, sensory perceptions, disorganized expressions, and diminished mental and emotional functioning. Impaired cognitive function is a core feature that is disturbed in schizophrenic patients which causes sufferers to decline in function in various aspects of life and ultimately have implications for social and economic life (3–5). Non-pharmacological approaches are usually used after the patient has passed the acute phase, namely in the stabilization phase and the maintenance phase (stable) such as psychotherapy and psychosocial interventions (6). Music therapy as a modality of psychosocial intervention has been studied in several countries regarding its effectiveness in improving positive, negative symptoms and social cognition in schizophrenia patients (1,7). Music therapy's effect on physiological responses and neural, endocrine, and cardiovascular activities has been linked to emotional and mental stability, cognitive function, positive conduct, and emotional improvement (8-10). Furthermore, music therapy has been shown to improve emotional relaxation, cognitive processing abilities, and behavioral improvements in individuals with persistent schizophrenia (2, 7).

BDNF, or brain-derived neurotrophic factor, is a neurotropin-secreting growth factor. Its primary role in the central nervous system is to increase neuronal proliferation and survival, synaptic plasticity, and long term potentiation. Because BDNF plays a complicated role in the regulation of cognitive function in people, it has received a lot of attention. It is also linked to the neurodevelopmental theory of schizophrenia since it affects the development and physiology of the CNS. Plasma BDNF levels in schizophrenia patients have been studied, and studies have indicated a positive association between plasma and cerebrospinal fluid (CSF) BDNF levels in people.

There has not been any previous study conducted on the impact of music therapy on cognitive function among individuals with schizophrenia and how it correlates with the levels of BDNF in the blood. The existence of significant findings in this study can provide information about good non-pharmacological management in schizophrenic patients and will ultimately improve the prognosis of the disease. In addition, the application of music therapy as a non-pharmacological therapy modality is quite simple and does not require a lot of money. On this consideration, researchers are interested in conducting this research.

Materials and Methods Research Design

A quasi-experimental research was undertaken in the Dadi Regional Special Hospital in South Sulawesi Province, Indonesia, between February and March 2021. To measure before and post-test findings, the study employed random group selection and a single-blind approach. The ethical

committee of Hasanuddin University's Faculty of Medicine accepted the study with the number 130/UN4.5.4.5.31/PP36/2022.

Subject

The participants of this research were male patients who were diagnosed with schizophrenia according to the DSM-V criteria, with ages ranging from 20 - 50 years, with disease onset of less than five years, and who had passed the acute phase with a PANSS-EC score below fifteen. They were also willing and able to attend music therapy sessions and receive 2-4 mg/day of risperidone treatment. Individuals were not included in the research if they fulfilled one or more of the subsequent conditions: had coexisting organic ailments, had a past of drug usage prior to being hospitalized, took anti-inflammatory medicine and antibiotics, were not consistent in attending all music therapy sessions, were not regular in taking risperidone medication, and if the individual declined to carry on with the investigation. This research enrolled 45 patients who satisfied the eligibility requirements. The participants were separated into two groups: the treatment group, which included 22 patients, and the control group, which had 23 subjects. All research participants provided informed consent.

Procedure

Participants who were assigned to the experimental group were administered with Risperidone with a dosage of 4-6 mg every day, along with engaging in music therapy activities that involved both giving and receiving for a duration of 4 weeks which amounted to a total of 12 sessions. Music therapy was carried out for 60 minutes per session with the division of the first 15 minutes and the last 15 minutes being used for receptive music therapy (listening to Mozart 432 Hz classical music with an intensity of 70-120 dB, expressing the meaning of the selected song and expressing the feelings experienced at each end of the session) and 30 minutes was used for active music therapy (singing and improvising songs selected by the subject and following the beat of the song by hand). The control group consisted of 23 individuals who were administered only 4-6 mg/day of Risperidone while closely monitored. Both the groups' MoCA-Ina scores (which is the Indonesian adaptation of the Montreal Cognitive Assessment) were evaluated at the beginning of the research and at the end of week 4, post 12 sessions. The plasma BDNF levels were also measured at the onset of the study and at the conclusion of week 4 for both groups.

BDNF levels were assessed using ELISA and processed at Hasanuddin University Medical Research Center (HUMRC).

A total of 3cc of blood was extracted from the median cubital vein of the patient, and the resulting sample was subjected to centrifugation. The plasma obtained was then transferred into three different wells - blank, standard, and sample. The blank wells contained no blood sample, but did receive a dose of horseradish peroxidase (HRP). The standard wells received 50 l of normal solution, 40 l of a special solution, and 10l of serum. Finally, 40 l of special solution and 10 l of serum were injected into the sample wells. Except for the blank wells, all wells received 50 l of HRP. The plates were incubated for an hour at 37 °C after being capped and lightly shook.

Statistical Analysis

Data processing was carried out using the SPSS 24.0 computer program. The distribution of data is not normally distributed based on the Saphiro-Wilk test, so to see the significance of the research results, the Wilcoxon, Mann Whitney, Spearman and Kruskal Wallis tests are used.

Results

This research involved selecting 45 individuals, and they were split into two batches: a treatment group consisting of 22 individuals and a control group consisting of 23 individuals.
Description of the characteristics and distribution of research subjects, can be seen in Table 1.

Table 1. Sociodemographic Characteristics

Characteristics		Treatment n=22 (%)	Control n=23 (%)	p value
Age	21-30	5 (22.7%)	1 (4.3%)	*0.387
	31-40	9 (40.9%)	11 (47.8%)	
	41-50	8 (36.4%)	11 (47.8%)	
Disease Onset	1 Year	1 (4.5%)	0 (0%)	*0.239
	2 Years	5 (22.7%)	6 (26.1%)	
	3 Years	6 (27.3%)	8 (34.8%)	
	4 Years	6 (27.3%)	7 (30.4%)	
	5 Years	4 (18.2%)	2 (8.7%)	
Education	No School	0 (0%)	2 (8.7%)	*0.868
	Elementary School/ Equivalent	8 (36.4%)	9 (39.1%)	
	Junior High School/ Equivalent	3 (13.6%)	4 (17.4%)	
	High School/ Equivalent	8 (36.4%)	8 (34.8%)	
	Undergraduate	3 (13.6%)	0 (0%)	
Occupation	Farmer	6 (27.3%)	10 (43.5%)	*0.683
	Entrepreneur	3 (13.6%)	7 (30.4%)	
	Employee	8 (36.4%)	0 (0%)	
	Not Working	5 (22.7%)	6 (26.1%)	
Marital Status	Not married	14 (63.6%)	11 (47.8%)	*0.240
	Married	7 (31.8%)	9 (39.1%)	
	Divorced	1 (4.5%)	3 (13%)	

One-way ANOVA : Homogeneity of variance test (*p>0.05)

Table 1 indicates that there is no significant difference (p>0.05) between the variables of the treatment and control groups that were examined in this study, making it possible to proceed with additional statistical analyses. Table 2 displays the results of the analysis of the changes in MoCA-Ina scale scores and plasma BDNF levels following twelve sessions of music therapy.

Table 2. Changes in MoCA-Ina scale scores and plasma BDNF levels Treatment and Control

Group	N	MoCA-Ina			Plasma BDNF Level		
		Median Week 0 (Min-Max)	Median Week 4 (Min-Max)	P value	Median Week 0 (Min-Max)	Median Week 4 (Min-Max)	P value
Treatment	n= 22	19.0 (8-26)	21.0 (10-28)	*0.002	1.1062 (0.6469-10.7758)	1.2190 (0.8634-10.0773)	*0.024
Control	n= 23	14.0 (6-26)	15.0 (9-27)	*0.049	1.6316 (0.1720-10.4600)	1.4595 (0.0325-11.2752)	*0.042

Wilcoxon Test (*p<0.05)

According to Table 2, both groups saw a substantial increase in MoCA-Ina Scale scores; however, the treatment group experienced a greater increase than the control group. Furthermore, whereas the treatment group's plasma BDNF levels increased significantly, the control group's levels decreased significantly.

Table 3. Comparative Analysis of Changes in Plasma BDNF Levels in the Two Groups

	Group (n)	Median (Minimum-Maximum)	P value
Changes in Plasma BDNF Levels (week 0-4)	Treatment (n=22)	0.1354 (-1.6184-4.8237)	*0.005
	Control (n=23)	-0.1107 (-6.3594-1.0546)	

Mann-Whitney test (*p>0.05)

Information presented in table 3 illustrates that there exists a noteworthy distinction in alterations (delta value) in plasma BDNF levels between the cohort who received a total of 12 music therapy sessions and the group in the control group.

Table 4. Comparative Analysis of Domain Changes in the MoCA-Ina Scale of the Two Groups

MoCA-Ina Component	Groups (n)	Median (MinimumMaximum)	P value
Changes in Visospatial / Executive	Treatment (n=22) Control (n= 23)	0.50 (0-2) 0.00 (-2-2)	0.071
Naming Change	Treatment (n=22) Control (n=23)	0.00 (-1-1) 0.00 (-1-2)	0.740
Memory Change	Treatment (n=22) Control (n=23)	1.00 (-1-3) 0.00 (-1-1)	0.012*
Change of Attention	Treatment (n=22) Control (n=23)	0.00 (-1-3) 0.00 (-2-2)	0.123
Change of	Treatment(n=22) Control (n=23)	0.00 (-1-2) 0.00 (-2-2)	0.114
Change of Abstraction	Treatment (n=22) Control (n=23)	1.00 (-1-2) 0.00 (-1-1)	0.027*
Change of Orientation	Treatment (n=22) Control (n=23)	0.00 (-4-2) 0.00 (-2-1)	0.123

Mann-Whitney Test (*p<0.05)

Table 4 shows that there are significant differences in changes of memory function and abstraction in the treatment group compared to the control group.

Table 5. Correlation analysis of changes in the MoCA-Ina scale score and plasma BDNF levels of the two groups

	Plasma BDNF Level Change	
	Treatment Group	Control Group
Change in MoCA-Ina Score	r = 0.499 p = 0,018* n = 22	r = 0.755 p < 0,001* n = 23

Spearman Correlation Test (*p<0.05)

In both groups, Table 5 demonstrates a substantial positive association (unidirectional), with a moderately high correlation in the treatment group and a strong correlation in the control group, between changes in plasma BDNF levels and changes in the MoCA-Ina scale score.

Discussion

To the best of the author's understanding, this trial is the first to investigate how music therapy affects the levels of Brain Derived Neurotrophic Factor (BDNF) in the blood and enhances cognitive function in individuals with schizophrenia. BDNF is a neurotrophin that plays a crucial role in neuronal development and neuroplasticity, and its imbalance is closely linked to neurotransmitter imbalances

such as glutamate and dopamine, which are characteristic of mental conditions like schizophrenia (11, 14, 15).

The MoCA-Ina scale was employed in this research to monitor the cognitive function of participants. Scientifically, Risperidone, an atypical antipsychotic, has been established to have positive effects on enhancing positive and negative clinical symptoms and halting deterioration of cognitive function among individuals with schizophrenia. This is largely attributed to Risperidone's capacity to obstruct limbic D2 receptors and 5HT2A receptors in cortical glutamate neurons (3,16–18). This theory supports the results of this study where all subjects in the treatment group and control group experienced a significant increase in the MoCA-Ina scale score at week 4 (Table 2) which indicated a significant improvement in cognitive function after being given Risperidone therapy.

The treatment subjects in this study were given music therapy with active and receptive (passive) methods for 12 sessions with a duration of 60 minutes each session. The active method used was singing and improvising the song chosen by the subject himself and following the beat of the song by hand, while the receptive (passive) method was listening to Mozart classical music 432 Hz with an intensity of 70-120 dB, expressing the meaning of the selected song. and express the feelings experienced after each session (10,19,20). The study's findings indicated that the participant's total score in the MoCA-Ina assessment significantly improved in the treatment group compared to the control group (as seen in Table 2). Similarly, the memory function and abstraction domains demonstrated considerable improvement in the MoCA-Ina scale domain (as shown in Table 4). These results support previous studies that reported the benefits of music therapy in enhancing cognitive abilities in schizophrenic patients. One research study discovered that including 13 music therapy sessions had a positive impact on the cognitive abilities of schizophrenic patients (7). In another systematic review, various studies reported improvements in cognitive abilities, specifically in memory and abstraction domains of schizophrenic patients who underwent music therapy (2). A study has revealed that regular exposure to rhythmic auditory stimuli facilitates memory formation, similarly it is said that new neurons increase in the Mozart stimulus group and the generation of new neurons in the dentate gyrus is essential for maintaining normal learning, thinking and memory processes (21).

The effect of music therapy on BDNF levels is physiologically mediated by the transmission of sound waves from the music being played into brain electrical impulses, which in turn stimulate dopaminergic neurons in various brain areas, including the limbic area and the prefrontal cortex area (22-24). This study observed a statistically significant rise in plasma BDNF levels in the treatment group (table 2) when compared to changes in BDNF in the control group (table 3). A previous comprehensive review indicated that nonpharmacological therapies such cognitive remediation, physical activity, and yoga increased plasma/serum BDNF levels in schizophrenia patients (12,13). This conclusion was corroborated by a rat research that found an increase in BDNF levels in the hypothalamus after 21 days of music exposure (25). The dopaminergic system, which is stimulated by routine music therapy, is believed to increase BDNF expression through intracellular calcium mobilization, thereby accelerating neuronal maturation and differentiation. It is also worth noting that dopamine neuron cells are crucial for the synthesis of BDNF mRNA (14,26). Several studies have demonstrated that dopamine is a major neurotransmitter involved in neuroplasticity, with dopaminergic neurons in the brain's reward network (the VTA and NA) being implicated in reward-related cortical remodeling, learning, and LTP of the hippocampus (24).

In several previous studies, it was suggested that the administration of several types of antipsychotics such as first generation antipsychotics and several second generation antipsychotics such as Risperidone had the potential to reduce BDNF levels in schizophrenic patients (12,26,27). The control group that was only given Risperidone therapy in this study showed a significant decrease in plasma

BDNF levels after 4 weeks of monitoring (Table 2) although the assessment of cognitive function showed a significant increase (Table 2). Longterm blockade of dopamine receptors throughout the dopaminergic pathway as the main mechanism of action of typical antipsychotics as well as some atypical types such as risperidone may underlie this condition (16). In theory, it is said that a decrease in dopaminergic cells will reduce the level of BDNF mRNA expression so that it will have an impact on reducing BDNF synthesis (14,28). From these results, the researcher assumes that clinical improvement of cognitive function is not always the same as biologically assessed improvement in this case plasma BDNF levels and this indicates that BDNF is not the only factor that affects the improvement of cognitive function in schizophrenic patients. It is known that schizophrenic patients experience a gradual deterioration in cognitive function decline, even from the beginning of life, it has shown a decline in several domains of cognitive function such as visuospatial ability and processing speed (29). This cognitive deterioration is said to be strongly associated with genetic susceptibility factors that have been proven by long-term studies (30,31). The process of cognitive decline experienced by patients with schizophrenia may explain the different results in this study.

BDNF has been widely studied as a biomarker 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 (11,12,14,32). This study showed a significant relationship between changes in cognitive function (total MoCA-Ina score) and changes in plasma BDNF levels in subjects receiving music therapy and in subjects receiving only risperidone (table 5).

These findings are consistent with previous studies, which discovered a positive relationship between serum BDNF levels and cognitive capacities such as memory, executive function, processing speed, and attention (33-35). An updated study found that verbal memory, working memory, processing speed, and verbal fluency performance were all significantly associated to BDNF levels (12,36). Through the stimulation of NMDA receptors in the hippocampus and prefrontal region, BDNF also has a significant impact on synaptic plasticity. It was indicated while examining the connection between cognition and BDNF that the loss of one functioning copy of the BDNF gene was associated with decreased cognitive performance (14).

The selection of subjects in this study did not consider more specific types of schizophrenia patients such as in ICD-10 and also the distance of onset of schizophrenic disorders was taken too far even though it was known that each type of schizophrenic disorder had a different level of deterioration. This is a limitation of this study, so it is recommended for further research to select specific schizophrenic subjects with a shorter distance of onset of the disorder. Another limitation of the study was that the measurement of BDNF levels and the cognitive function assessment scale was not carried out in the middle of the session so that the stages of changing of MoCA-Ina score and BDNF levels were less specific. Therefore, it is recommended in future studies to measure BDNF levels and a cognitive function assessment scale in the middle of a music therapy session.

Conclusion

The provision of music therapy as an adjuvant to treatment with therapeutic doses of risperidone is very effective for improving cognitive function, especially in the memory and abstraction domains and is effective for increasing plasma levels of Brain Derived Neurotrophic Factor (BDNF) in schizophrenic patients. There is a positive correlation between BDNF levels and cognitive function in schizophrenic patients.

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