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Correlation Between Cognitive Function and Serum Levels of Brain-Derived Neutrophic Factor in Schizophrenia

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Abstract

Background: Schizophrenia is a chronic psychiatric disorder characterized by significant cognitive impairments, including deficits in attention, processing speed, and executive function. Brain-Derived Neurotrophic Factor (BDNF) is known to play a key role in neuroplasticity and cognitive processes; however, its relationship with cognitive function in schizophrenia remains unclear. **Objective**: This research aims to determine the correlation between serum BDNF levels and cognitive function with the Trail Making Test. **Methods**: A cross-sectional study was conducted on 50 schizophrenia patients. The population is schizophrenia patients at Reksodiwiryo Padang Hospital, Padang. The sampling method is a consecutive sampling. The statistical test used is Spearman's correlation. **Results**: A significant proportion of participants demonstrated cognitive impairments (50% in Trail Making Test-A (TMT-A) and 60% in Trail Making Test-B), no statistically significant correlation was found between serum BDNF levels and TMT scores (TMT-A: r = -0.073, p = 0.612; TMT-B: r = -0.263, p = 0.065). **Conclusion**: This research found no statistically significant correlation between BDNF levels and TMT A and B. The findings suggest that serum BDNF may not directly correlate with cognitive impairments in schizophrenia, specifically executive function and attention, as assessed by the TMT.

Keywords: BDNF, Cognitive deficit, Schizophrenia

Original Research Article

INTRODUCTION

Schizophrenia is a severe and chronic mental disorder with a lifetime prevalence of 1%. The symptoms of schizophrenia are diverse and encompass a wide range of cognitive, perceptual, and behavioral disturbances. These include delusion, which is a false belief that is not based on reality and persists despite evidence to the contrary. Hallucinations are sensory perceptions that appear real but are created by the mind, such as hearing voices or seeing things that are not present. The other symptom is disorganized speech, which is characterized by a lack of coherence and logical flow, making it difficult for others to understand. Catatonic behavior, such as unusual postures, movements, or irresponsiveness, can significantly impact the individual's daily functioning. Negative symptoms are reduced emotional expression, diminished motivation, social withdrawal, and lack of enjoyment in daily activities. Diverse symptoms can significantly impair an individual's social, educational, and occupational functioning, contributing to the severe and chronic nature of schizophrenia. The

symptoms can significantly impact the individual's daily functioning and social interaction (Kaplan & Sadock, 2022; Siever & Davis, 2004).

Schizophrenia causes significant suffering in the sufferer and causes disturbances in various aspects of life, such as social, educational, and work. Schizophrenia affects approximately 24 million people worldwide, or about 1 in every 300 individuals. Among them, about 1 in 222 are adults. (WHO, 2022) The incidence of schizophrenia in Asia is between 0.5% and 1.0% of the population. In Indonesia, schizophrenia is included among the top 3 most prevalent mental health conditions that cause the highest levels of disability and impairment among the population. West Sumatra, a province located in the western region of the country, ranks 5th in the nation for the prevalence of households with members suffering from various schizophrenic disorders. (Charlson et al., 2018; Kemenkes RI, 2019)

The underlying cause of schizophrenia is not yet known for sure. Some hypotheses link schizophrenia to impaired brain development and neuropsychological deficits in brain regions and functional circuits of neurons. Schizophrenia progresses through three phases: the prodromal (prepsychotic) phase, the early onset of psychosis, and the chronic disease. The core symptoms of schizophrenia include positive and negative symptoms, and symptoms of cognitive impairment. Cognitive impairment is a hallmark characteristic observed in the prodromal phase of schizophrenia, even before the full manifestation of psychotic symptoms. This early emergence of cognitive decline renders it a valuable indicator for tracking the progression of the disorder over time. (Dietz et al., 2020)

Schizophrenic patients experience impaired cognitive performance in all cognitive domains, including processing speed, attention and alertness, working memory, verbal learning, visual learning, reasoning/ problem-solving, and social cognition. Schizophrenic patients frequently experience difficulties maintaining attention, becoming easily distracted. This affects their ability to follow conversations or instructions and hampers productivity. (Alkan et al., 2021; Charernboon & Patumanond, 2017; B. Zhang et al., 2017) Verbal memory impairment is quite common and often moderate to severe in schizophrenia. This disorder makes it difficult for schizophrenic patients to handle social and interpersonal situations that require attention. People with schizophrenia have difficulty choosing words (verbal function) that which causes poor interpersonal and community function. (Charernboon & Patumanond, 2017)

Brain-derived neurotrophic factor (BDNF) is a secretory polypeptide distributed in the central nervous system (CNS). BDNF is called neurotropin, which regulates the proliferation, differentiation, survival, and death of nerve and glial cells. BDNF is expressed by glutamatergic neurons and glial cells in the brain. A large number suggests that BDNF affects synaptic plasticity, resulting in critical changes in cognitive, learning, and memory functions. In schizophrenia patients, low levels of BDNF can inhibit cognitive functions such as memory, attention, and executive function. Low levels of BDNF can interfere with this process, resulting in decreased neural adaptability and, consequently, deficits in cognitive function. (Di Carlo et al., 2019)

Cognition refers to the mental processes involved in acquiring knowledge and understanding through thought, experience, and senses. It encompasses various high-level intellectual functions and processes such as attention, memory, knowledge, decision-making, planning, reasoning, judgment, perception, understanding, language, and visuospatial functions. Cognitive processes use existing knowledge and generate new knowledge. (Dhakal & Bobrin, 2024) Cognitive deficit refers to impairments that affect various aspects of cognition. It has been linked to poor functional outcomes and occurs in most patients, impairing their ability to establish social interactions, plan, adapt, or solve problems. Cognitive dysfunction in schizophrenia has been extensively studied and documented, typically involving impairments in memory, attention, executive functions, learning, and, to a lesser extent, social cognition. (Mascio et al., 2021)

The Trail Making Test (TMT) is a neuropsychological test commonly used to evaluate cognitive function, especially as it relates to visual-motor processing, cognitive flexibility, sustained attention, and executive function. The test consists of two parts, namely TMT A and TMT B. TMT A evaluates processing speed, visual search, and attention by requiring participants to connect numbered dots (1 to 25) in sequential order as quickly as possible. TMT B assesses the ability to shift between mental sets, requiring participants to alternate between numbers and letters (e.g., 1, A, 2, B) in sequence.

(Lóra & Atalin, 2024) Significant cognitive impairments are frequently seen in patients with schizophrenia, particularly in executive function, attention, and processing speed. Patients with schizophrenia frequently perform badly on TMT Part A. Patients with schizophrenia typically exhibit markedly longer completion times and more TMT-B errors, indicative of set-shifting and cognitive flexibility deficiencies. (Laere et al., 2018)

BDNF is a critical neurotrophic factor involved in synaptic plasticity, neurogenesis, and neural survival, especially in the prefrontal cortex and hippocampus, which are regions essential for cognitive functioning. Cognitive function includes attention and executive function. (Miranda et al., 2019) Low BDNF levels in schizophrenia are associated with structural and functional deficits in these brain regions, which impact attention and executive function. Lower BDNF levels can disrupt the ability to sustain focus and manage cognitive workload, resulting in poor performance on both TMT-A (basic attention) and TMT-B (complex attention with task switching). (Nurjono et al., 2012; Z. Zhang et al., 2023)

In Indonesia, research on the correlation of cognitive function with BDNF levels is still limited. Therefore, researchers are interested in researching the correlation of cognitive function with BDNF levels using an instrument that can measure verbal and neurocognitive cognitive function, namely the TMT. This research aims to determine the correlation between serum BDNF levels and cognitive using TMT. Hypothesis of the research is there is a significant positive correlation between serum BDNF levels and TMT, in schizophrenia patients. These results can also be considered anti-inflammatory as an additional therapy in addition to antipsychotics to help improve the cognitive function of schizophrenia patients to improve the quality of life of schizophrenic patients.

MATERIALS AND METHODS

Research has been carried out at the Padang Reksodiwiryo Hospital during September-November 2024. This research has been approved by the Health Research Ethics Committee of the Faculty of Medicine, Baiturrahmah University, with No. 18/ETIK-FK-UNBRAH/03/09/2024. The target population in this study is all patients diagnosed with schizophrenia. The affordable population is schizophrenia patients who are undergoing treatment at Reksodiwiryo Padang Hospital

The inclusion criteria of the study were schizophrenia patients diagnosed with schizophrenia, aged 18-60 years, receiving antipsychotics, and the patient/guardian agreeing to participate in the study after being provided with information about the study and signing a statement of willingness. In this study, schizophrenia was defined according to established diagnostic criteria PPDGJ-III, requiring the presence of characteristic psychotic symptoms such as delusions, hallucinations, disorganized speech or behavior, or negative symptoms, with a minimum duration of one month of active-phase symptoms and overall disturbance lasting at least six months. Diagnosis was established by a psychiatrist based on clinical interview and mental status examination. Exclusion Criteria are patients with intellectual disabilities, in a state of anxiety or uncooperativeness, using anti-inflammatory drugs, having neurological disorders, and a history of substance and alcohol abuse in the past 1 year. This study is a *cross-sectional* study with a sample selection, which is a *consecutive sampling method*, which is 50 schizophrenia patients.

Cognitive function was measured using the Trail Making Test (TMT), a validated neuropsychological instrument frequently used in clinical and research settings to assess short-term memory and executive function. The TMT consists of two parts: TMT-A, which evaluates processing speed, visual-motor coordination, and attention. TMT-B, which assesses cognitive flexibility, task-switching ability, and executive function. This instrument was chosen for its suitability in capturing cognitive deficits associated with schizophrenia, particularly executive dysfunction. The Indonesian version has been validated by the Psychiatry Department of the Faculty of Medicine, Universitas Indonesia (FKUI), ensuring its reliability and cultural appropriateness for the study population. The material needed in this study is a peripheral vein specimen used for BDNF level examination using an ELISA kit. Blood serum was examined using the ELISA method and using a kit at the Biomedical Laboratory of the Medical Faculty of Baiturrahmah University.

Descriptive statistics were calculated for the sample demographics and key variables, such as BDNF levels and TMT performance. Spearman's Correlation was used to analyze the relationship between serum BDNF levels and cognitive function as measured by TMT-A and TMT-B. BDNF levels are continuous but may not follow a normal distribution. TMT scores represent ordinal or skewed data related to task completion time.

RESULTS

Based on Table 1, it was obtained that out of 50 samples, most of the patients were men (66%), with the largest age group in the range of 31-40 years (34%). Patients' education levels vary, with the majority only completing education up to high school (48%). As many as 4% of patients have no formal education, while 14% successfully complete higher education. Based on Socio-Economic Characteristics, as many as 42% of patients do not work, and 62% have no income. Working patients are mostly in the informal sector (42%). Almost half of the patients were unmarried (48%), while the rest were married (28%) or divorced/separated (24%).

Most patients have been sick for more than 5 years (60%), with 32% experiencing a duration of 1-5 years, and only 8% with a duration of less than 1 year. As many as 48% of patients have no history of hospitalization, while 42% have been treated 1-5 times, and 10% have been treated more than 5 times. The combination of first-generation antipsychotics (APG I) and second-generation (APG II) antipsychotics is the most used therapeutic regimen (36%). Some patients also received a combination therapy with mood stabilizers (20%), anticholinergics (12%), or benzodiazepines (14%). As many as 6% of patients only use APG II without a combination.

Table 1. Characteristics of the Research Sample

Variable	n	%
Gender		
man	33	66
Woman	17	34
Education Level		
No School	2	4
Elementary school	8	16
Junior high school	9	18
Senior High School	24	48
College	7	14
Work		
Not Working	21	42
Housewives	8	16
Private	21	42
Income		
None	31	62
<5 million rupiah	19	38
Marital status		
Unmarried	24	48
Marry	14	28
Divorce/Separation	12	24
Age		
20-30 years old	11	22
31-40 years old	17	34
41-50 years old	11	22
51-60 years old	11	22`
Duration of Illness		
<1 year	4	8
1-5 years	16	32
>5 years	30	60
Hospitalization History		
Never	24	48

1-5x	21	42
>5-10x	5	10
Medicatiom		
FGA	0	0
SGA	3	6
Combination of FGA and SGA	18	36
Combination of FGA/SGA and mood stabilizer	10	20
Combination of FGA/SGA and anticholinergics	6	12
Combinations of FGA/SGA, Trihexyphedinidyl and benzodiazepines	6	12
Combination of APG I/II and Benzodiazepines	7	14

Based on Table 2, the average level of BDNF in the population is 566.3 pg/mL, with a standard deviation of 236.6 pg/mL, and a minimum value range of 103.9 pg/mL to a maximum of 1090.5 pg/mL**.** The mean BDNF level (566.3 pg/mL) observed in this study is lower than the levels typically reported in healthy individuals, which are often above 800 pg/mL in previous studies. This finding supports existing evidence that schizophrenia is associated with decreased neurotrophic function and impaired synaptic plasticity.

Table 2. BDNF level

	mean	**SD**	**Min-maks**
BDNF level	566.3	236.6	103.9-1090.5

Table 3. Cognitive function with TMT

	TMT A		**TMT B**	
	n	%	n	%
Deficit	25	50	30	60
Normal	25	50	20	40

In this study, it was found that as many as 50% of the population showed a deficit in TMT A and 60% in deficit in TMT B. The scatter plot presents the relationship between BDNF levels and the TMT-A categories in schizophrenia patients. There is no clear separation or trend between the two TMT-A categories (normal vs. deficit). Both groups display a similar range of BDNF levels, suggesting no strong association between BDNF levels and TMT-A performance

There is no clear distinction in BDNF levels between participants with normal TMT-B performance (1.0) and those with deficits (2.0). Both groups display a wide range of BDNF values, roughly between 200 pg/mL to over 1000 pg/mL. The classification of serum BDNF levels in this study was conducted using a tertile-based approach. Based on this method, serum BDNF concentrations were divided into three categories: low (≤ 451.7 pg/mL), normal (451.7–675.2 pg/mL), and high (≥ 675.2 pg/mL). From the total of 50 subjects, 17 participants (34%) were classified as having low serum BDNF, 16 participants (32%) fell within the normal range, and 17 participants (34%) were categorized as high.

Clinically, lower BDNF levels have been consistently associated with cognitive impairment and more severe psychopathology in schizophrenia (Green et al., 2020; Zhang et al., 2020). Conversely, higher BDNF levels may reflect better neuroplasticity and cognitive reserve. Thus, stratification into tertiles provides a useful framework for analyzing the relationship between BDNF concentrations and cognitive performance in this population. In this study, serum BDNF levels were dichotomized into two categories based on the median concentration. Participants with serum BDNF levels of ≤ 528.88 pg/mL were classified as the normal BDNF group, while those with levels > 528.88 pg/mL were classified as the high BDNF group. The equal distribution of subjects between the normal (n = 25; 50%) and high (n = 25; 50%) BDNF groups ensures adequate statistical power for subsequent comparative analyses of cognitive performance and clinical variables. Elevated BDNF levels in the high group may indicate better neuroplasticity and cognitive resilience, whereas levels closer to the median are commonly

observed in patients with moderate symptom severity or chronic illness stages (Zhang et al., 2020). The findings need to be confirmed in a larger sample, but this result suggests a possible link between lower BDNF levels and worse executive function, including cognitive flexibility and task switching.

Table 4. Correlation BDNF level and the Trail Making Test

	TMT A		TMT B	
	p	r	p	r
BDNF level	0.073	0.612	0.263	0.065

Based on Table 4, the correlation analysis showed that serum BDNF levels were not significantly associated with cognitive performance as measured by TMT A or TMT B. Although there was a tendency toward a moderate positive correlation between BDNF and TMT A (r=0.612), the result was not statistically significant (p = 0.073). Similarly, for TMT B, the correlation was very weak and non-significant (r=0.065; p = 0.263). These findings suggest that, in this study population, serum BDNF levels were not a reliable predictor of executive function and attention as assessed by the Trail Making Test.

This research had some study limitations, which include the study's sample size, 50 participants, which limits the power to detect statistically significant correlations. Studies with larger samples and multicenter designs are needed to validate these findings. The consecutive sampling may have excluded patients unable to attend appointments, potentially skewing the results toward more stable cases of schizophrenia. The study's cross-sectional nature prevents establishing causality between BDNF levels and cognitive function. Longitudinal studies would be better suited for understanding the directionality of this relationship.

DISCUSSION

In the study, many schizophrenia patients were men (66%). Recent studies show that men have an earlier onset of schizophrenia than women, usually in their late teens to early 20s. Men also tend to have more severe symptoms, including negative and cognitive symptoms, which can affect the long-term prognosis. Most patients have a maximum level of high school education (48%). Research shows that schizophrenia often interferes with formal education due to the onset of symptoms that often occur at a young age, which affects learning ability and participation in educational settings. (Sommer et al., 2020)

Patients with schizophrenia who have low levels of education often face significant challenges in social functioning, which ultimately limits their job opportunities. The result found that a substantial number of these patients were not working and had a low income, defined as less than 5 million rupiah per month. The difficulty in participating in meaningful work is frequently associated with debilitating negative symptoms, such as apathy and cognitive impairments, which act as major obstacles to achieving success in the workplace. These issues are consistent with research findings that identify schizophrenia as a leading contributor to global disability. So, educational and occupational support for affected individuals is needed. (Philip et al., 2020a)

A significant portion of the patients (48%) were identified as unmarried, underscoring the substantial impact of the illness on their relationships. The presence of negative symptoms, such as anhedonia and social withdrawal, often hampers patients' ability to establish and maintain meaningful connections with others. Besides that, the social stigma associated with this illness plays a critical role in diminishing the chance of patients getting married or having long-term relationships. Together, these factors create challenges that profoundly affect the social lives of individuals dealing with this condition. (Charernboon & Patumanond, 2017)

Most patients have a duration of disease of more than 5 years. This extended duration of illness is closely associated with a progressive decline in both cognitive and social functioning, which becomes increasingly difficult to recover despite ongoing therapy. Schizophrenia is characterized by a deteriorative course for many individuals, particularly in untreated or poorly managed cases. Prolonged illness exacerbates deficits in cognitive domains such as working memory, attention, and executive function, which are needed for daily living and independence. Social skills and relationships

often deteriorate as negative symptoms become more pronounced over time. Research indicates that longer illness duration correlates with more severe impairments in neurocognitive performance. (Millan et al., 2012)

Most patients in the study received a combination of First-Generation Antipsychotics (FGAs/APG I) and Second-Generation Antipsychotics (SGAs/APG II), supplemented with medications such as anticholinergics to manage extrapyramidal side effects and benzodiazepines to address agitation or insomnia. Recent studies suggest that combination therapy is effective for patients with complex symptom profiles by addressing both positive and negative symptoms. However, these regimens should be carefully tailored to minimize adverse effects, such as metabolic syndrome—commonly associated with SGAs—and tardive dyskinesia, a side effect often linked to prolonged use of FGAs. Recent studies suggest that combination therapy could be beneficial for managing complex symptoms of schizophrenia, but it should be carefully considered to minimize side effects such as metabolic syndrome and tardive dyskinesia. (Charernboon & Patumanond, 2017; Farah, 2018; Philip et al., 2020b)

The results showed that BDNF levels in the schizophrenic population were lower than in the healthy population, with significant variability between individuals. The average BDNF levels (566.3 pg/mL) in this population were in a lower range than the healthy population in some studies. These results are in accordance with the meta-analysis in 17 studies with 1,114 schizophrenia patients and 970 controls, which reported a moderate reduction in peripheral BDNF concentrations in those with schizophrenia. (Goren, 2016)

BDNF levels may be elevated in schizophrenic patients who are on antipsychotic treatment or when their clinical condition improves. Antipsychotic treatment, especially atypical antipsychotics, can improve BDNF expression through improved neuroplasticity. The research conducted by Skibinska found that the BDNF levels in schizophrenia patients were significantly higher compared to the control group at the beginning of the study ($p < 0.01$). Schizophrenia patients had an overall serum BDNF level of 31.94 ± 11.43 ng/ml (combined patients using medication and those not using medication). The healthy control group had lower BDNF levels, at 22.69 ± 6.52 ng/ml. (Skibinska et al., 2019a)

Some of the factors that affect BDNF levels in schizophrenic patients are antipsychotic treatment, symptom severity, metabolic factors, stress, and genetic polymorphism. Antipsychotics, especially atypical ones such as risperidone and olanzapine, are known to increase BDNF levels. More severe symptoms of schizophrenia are often associated with lower BDNF levels, but they can increase with clinical improvement. Metabolic disorders such as elevated triglycerides and dyslipidemia can be associated with higher levels of BDNF. Polymorphisms such as val66met in the BDNF gene also play a role in variations in serum BDNF levels. (Di Carlo et al., 2019; Nieto et al., 2023; Skibinska et al., 2019b)

Second-generation antipsychotics such as clozapine and olanzapine have been shown to upregulate BDNF expression, and it can potentially improve cognitive outcomes. In contrast, first-generation antipsychotics may exert limited or neutral effects on BDNF levels and cognition. Variability in medication regimens—such as type, dosage, and adherence—may contribute to differences in BDNF levels and TMT performance. (Philip et al., 2020b)

In TMT B, a stronger negative association was found between BDNF levels and test results, although this association was not statistically significant. TMT-B evaluates higher-order cognitive processes, such as task-switching, working memory, and cognitive flexibility. These functions involve a network of brain regions, including the prefrontal cortex, hippocampus, and subcortical structures. BDNF alone may not fully account for executive dysfunction. A study by Xiao et al. (2017) found that while BDNF influences cognition, its effects are interdependent with neurotransmitter imbalances and prefrontal dysfunction. (Xiao et al., 2017)

This study has several limitations that need to be acknowledged. The relatively small sample size ($n = 50$) may have reduced statistical power, which could limit the ability to detect significant associations between BDNF levels and cognitive performance. Since the cross-sectional methodology cannot determine whether low BDNF levels cause or result from cognitive problems in schizophrenia, it further restricts the ability to draw conclusions about causality. Finally, confounding factors such as medication use, physical activity, and diet were not controlled for, and using a single cognitive test (TMT) may not fully capture the complexity of cognitive dysfunction. Future studies with larger sample

sizes, longitudinal designs, and broader neuropsychological assessments are needed to confirm and expand upon these findings.

The findings from this study suggest potential implications for clinical practice, particularly in the management of cognitive deficits in schizophrenia. While BDNF levels did not show a statistically significant relationship with cognitive function, trends observed highlight the importance of BDNF as a potential biomarker for cognitive impairment. Clinicians could explore adjunctive strategies to elevate BDNF levels, such as physical exercise, nutritional interventions, and pharmacological treatments targeting neuroplasticity. Integrating cognitive rehabilitation programs with therapies aimed at enhancing BDNF levels may provide synergistic benefits. Additionally, early monitoring of BDNF levels and cognitive function in schizophrenia patients could facilitate early intervention, ultimately improving quality of life and functional recovery.

Future research should prioritize larger-scale, multicenter studies with longitudinal designs to investigate the causal relationship between BDNF levels and cognitive function. Longitudinal studies can clarify whether changes in BDNF precede or result from cognitive impairments in schizophrenia. Interventional studies exploring the effect of nutritional supplementation and pharmacological treatments on BDNF levels and cognitive functions are particularly promising. A deeper understanding of the domains and groups most impacted by BDNF deficits will be possible through thorough cognitive tests and subgroup studies.

CONCLUSION

The mean BDNF level in the study population showed considerable variability (103.9–1090.5 pg/mL). Cognitive deficits were prevalent in the population, with 50% of participants showing deficits in TMT-A (visual-motor processing and attention) and 60% showing deficits in TMT-B (executive function and cognitive flexibility). There was no statistically significant correlation between BDNF levels and TMT-A and TMT-B performance. While no significant relationships were found, the trends suggest that BDNF may still play a role in cognitive processes. The small sample size, variability in BDNF levels, and the cross-sectional nature of the study may influence the lack of statistical significance.

CONFLICT OF INTEREST

There is no conflict of interest in this article.

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