Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2022;47(3):1263-1272
DOI: 10.17826/cumj.1135374

ARAŞTIRMA / RESEARCH

Effects of TSH, fT3 and fT4 levels on neurocognitive symptoms in patients with schizophrenia

Şizofreni hastalarında TSH, fT3 ve fT4 düzeylerinin nörobilişsel belirtiler üzerine etkisi

Hatice Kaya[1], Batuhan Ayık[2]

[1]Istanbul Sultanbeyli State Hospital, Sultanbeyli Community Mental Health Center, Department of Psychiatry, Istanbul, Turkey,

[2]Istanbul Erenkoy Education and Research Hospital, Department of Psychiatry, Istanbul, Turkey,

Cukurova Medical Journal 2022;47(3):1263-1272

Abstract

Purpose: The aim of this study is to examine the relationship between thyroid hormone levels and positive, negative, general, and cognitive symptoms in euthyroid patients with psychosis.

Materials and Methods: Thirty-three schizophrenia patients were included in this cross-sectional study. Sociodemographic and clinical data of the participants, positive and negative symptoms assessment scale (PANSS), general assessment of functionality scale (GAF), and clinical global impression scale (CGI) scores were recorded. The relationships between TSH, fT3, and fT4 levels and cognitive performances of patients which is measured via a neurocognitive battery consisting of Trail Making Test (TMT) A, TMT B, verbal fluency test (VFT), digit span (DS), forward and backward, and Wisconsin Card Sorting Test (WCST) were investigated.

Results: Significant correlations were found between fT3 levels and WCST performances. fT3 levels was significantly correlated with the number of categories achieved in WCST (r=.508; p=0.003). A significant correlation was found between fT4 levels and TMT B (r=-.376; p=0.031) and VFT (p=.355; p=0.043) performances. In the linear regression model, it was found that fT3 levels significantly predicted the number of categories achieved in WCST (UB=1.680; p=0.029).

Conclusion: The results of our study suggested that fT3 has more significant effects, primarily on executive functions, compared to T4.

Keywords:. cognitive dysfunction; schizophrenia, thyroid hormones

Öz

Amaç: Bu çalışmamızda ötiroid psikoz hastalarında tiroid hormon düzeyleri ile pozitif, negatif, genel ve bilişsel belirtiler arasındaki ilişkiyi incelemeyi amaçladık.

Gereç ve Yöntem: Çalışmaya 33 şizofreni hastası dahil edildi. Katılımcıların sosyodemografik ve klinik verileri, Pozitif ve Negatif Belirtileri Değerlendirme Ölçeği (PANSS), İşlevselliğin Genel Değerlendirilmesi Ölçeği (IGD), Klinik Global İzlenim Ölçeği (KGI) skorları kaydedildi. İz sürme, Sözel Akıcılık Testi, İleri ve Geri Sayı Menzili ile Wisconsin Kart Sayma Testinden (WKST) oluşan bir nörobilişsel batarya uygulanan hastaların bilişsel performanslarının TSH, sT3 ve sT4 düzeyleri ile ilişkisi araştırıldı.

Bulgular: sT4 düzeyleri ile İz Sürme B (r=-,376; p=0,031) ve Sözel Akıcılık test (p=,355; p=0,043) performansları arasında anlamlı derecede ilişki saptandı. Linear regresyon modelinde sT3 düzeylerinin WKST- tamamlanan kategori sayısını (UB=1.680; p=0.029) anlamlı derecede yordadığı saptandı..

Sonuç: Çalışmamızın sonuçları sT3 ün özellikle yürütücü işlevler üzerinde sT4'e kıyasla daha belirleyici etkileri olduğunu düşündürmüştür. İleride yapılacak daha geniş katılımlı araştırmalar, bilişsel belirtilerin tedavisinde tiroid hormon replasmanının etkinliğini belirlemek açısından önemli görünmektedir.

Anahtar kelimeler: bilişsel disfonksiyon, şizofreni, tiroid hormonları

Yazışma Adresi/Address for Correspondence: Dr. Batuhan Ayık, Istanbul Erenkoy Education and Research Hospital, Department of Psychiatry, Istanbul, Turkey, E- mail: batuayik@hotmail.com
Geliş tarihi/Received: 25.06.2022 Kabul tarihi/Accepted: 25.08.2022

INTRODUCTION

Schizophrenia is a disease with positive, negative, affective, and cognitive symptoms and causes chronic disability. Studies show that cognitive symptoms are present even before the onset of the disease and are one of the essential causes of functional decline[1,2]. Cognitive symptoms are present in approximately 75% of patients, and even when positive symptoms regress, cognitive symptoms usually remain unchanged[2]. On the other hand, the etiopathogenesis of neurocognitive symptoms has not been fully clarified, and studies aimed at understanding neurohormonal mechanisms that may be associated with cognitive symptoms remain up-to-date.

Thyroxine (T4) and triiodothyronine (T3) are synthesized by the thyroid gland and are responsible for the regulation of many biological actions. The storage and transport form of thyroid hormone is conjugated thyroxine, and the active ingredient is free thyroxine (fT4). Total thyroxine consists of T4 and fT4, and only 0.02% of the circulating hormone is fT4. T4 undergoes extra-thyroidal transformation to T3, which is three to four times more active than T4[3]. Thyroid hormones play an essential role in the differentiation and growth of the brain and, therefore, in cognitive functions. They have genomic effects on the brain and contribute to brain development through their effects on actin polymerization, microfilament organization, and neuronal migration[4]. In addition, thyroid hormones ensure the maintenance of normal energy (glucose) consuming processes, which are necessary for essential brain functions such as neurotransmission and memory[5]. Impairments in cognitive functions such as attention, memory, language, visual perception, and executive functions have been shown in individuals with hypothyroidism. In addition, there are studies showing that patients with mild or subclinical hypothyroidism also have reversible cognitive disorders[6-8]. It has also been shown that people with overt thyrotoxicosis have impaired attention/concentration and executive functions[9]. In addition, high and low TSH levels have also been shown to be associated with poor cognitive function, even in euthyroid individuals[10].

Although neurohormonal disorders play an essential role in the pathophysiology of mental diseases, it is challenging to conduct hormonal studies in which the effect of drug use is excluded, especially in chronic diseases such as schizophrenia, because patients who do not use drugs yet are usually in the early stages of the disease and this makes it difficult to understand the effect of the progressive disease process on the hormonal system. Studies in patients with schizophrenia have reported abnormalities in the thyroid system, such as the decreased activity of the hypothalamo-pituitary-thyroid axis, low T3 levels, and increased thyroid autoantibodies[11]. A recent study showed that fT3 and fT4 levels are lower, and TSH is higher in female patients and in the chronic phase of the disease[12]. Studies have examined the relationship between thyroid hormones and cognitive processes in various disease groups over the critical role of thyroid dysfunction in neurodegenerative and neurodevelopmental processes For example, there are studies suggesting that the direct harmful effect of thyroxine discharge on cholinergic neurons increases the risk of Alzheimer's Disease, and thyroid hormone replacement has been shown to improve emotional and cognitive symptoms in patients[13,14]. Studies on the relationship between neurocognitive symptoms and the thyroid hormone system in patients with schizophrenia are relatively limited. In a study on early psychosis patients, higher fT4 levels (but not TSH or thyroid antibodies) were associated with better cognitive performance in attention/ vigilance and general cognition[15]. In the 1-year follow-up study of the same group, the highest and lowest fT4 values were found to be associated with decreased attention[16]. Another study in 93 patients with schizophrenia showed that fT3 levels were associated with better mini-mental test scores but not with positive, negative, and general psychotic symptoms[17]. To our knowledge, there is no study examining the relationship between thyroid hormones and neurocognitive and clinical symptoms in euthyroid schizophrenic patients, based on this we aimed to test the hypothesis that higher thyroid hormone levels are associated with better neurocognitive performance in patients with schizophrenia, even if they are euthyroid. From this point of view, in our study, we aimed to examine the relationship between fT3, fT4, and TSH and cognitive symptoms and clinical factors such as CGI, GAF, and PANSS scores in patients with schizophrenia.

MATERIALS AND METHODS

Participants

Thirty-three patients who were treated at the Sancaktepe Community Mental Health Center for at

least one year and met the schizophrenia criteria according to DSM-5[18] were included in this cross-sectional study. 10 patients who met the inclusion and exclusion criteria and accepted to participate in the study but could not complete neuropsychological tests, 5 patients who were found to have a history of acute illness in the last 6 months after being included in the study, and 6 patients whose thyroid hormone levels were not within the reference range in blood tests were excluded from the study. After obtaining the consent of the patients, sociodemographic and clinical data were recorded, global assessment of functionality (GAF) and global clinical impression (symptom severity) scales (CGI-SS) and Positive and Negative Syndrome Scale (PANSS) were applied to measure disease severity and functionality, and then a detailed neurocognitive battery was applied, and TSH, fT4 and fT3 levels were measured simultaneously. All data collection and psychiatric and neurocognitive tests of the patients were performed by two senior psychiatrists in two sessions and took at least 2 hours.

Ethics committee approval from SBU Erenköy Mental and Nervous Diseases Training and Research Hospital was received for our study (date/number: 09.05.2022/25) and written informed consent was obtained from all participants. Our study complies with the Declaration of Helsinki[19].

Inclusion criteria ere meeting DSM-5 criteria for schizophrenia, age 18 to 50 years old, Being able to read and write and no hospitalization nor signs of acute illness in the last 6 months. Exclusion criteria were presence of comorbid mental retardation or pervasive developmental disorder to prevent confounding degenerative effect on neurocognitive functionality, evidence of any active substance or alcohol use, Electroconvulsive therapy (ECT) within the last 1 year and severe head trauma within 6 months.

Data collection tools

Sociodemographic and clinical data form

It is a data collection form that includes age, gender, education, employment status, comorbid psychiatric or physical diseases, history of suicide attempt or ECT, body mass index, family history of any psychiatric disorder, alcohol, substance, or tobacco use, and also the age of onset of the disease, the duration of untreated psychosis and the number of drugs used

Positive and Negative Symptom Scale (PANSS):

The Positive and Negative Syndrome Scale (PANSS) was used to measure the severity of symptoms in patients with schizophrenia[20]. The reliability and validity of the PANSS in the Turkish population were tested in 1999, and Cronbach's alpha values were 0.71 for the general psychopathology subscale, 0.75 for positive symptoms, and 0.77 for negative symptoms[21]. The scale includes seven items for positive symptoms, seven for negative symptoms, and 16 for general psychopathology. Each item is scored between 1 and 7, and 4 different points are calculated. These are positive, negative, general psychopathology scores, and total PANSS scores.

Global Assessment of Functioning (GAF)

GAF was used to assess the severity and improvement of patients' symptoms[22]. The GAF is a 100-point scale that measures a patient's overall psychological, social, and occupational functioning, with higher scores indicating higher levels of functionality.

Clinical Global Impression-Symptom Severity (CGI-SS)

CGI-SS scale was used to score the severity of the disease[23]. It is a 7-point Likert-type scale (1: normal; 2: borderline mentally ill; 3: mildly ill; 4: moderately ill; 5: markedly ill, 6: severely ill; 7: extremely ill).

Trail Making Tests (TMT A-B)

Trail Making Test-A contains 25 circles numbered from 1 to 25, and participants are asked to draw lines to connect these numbers in ascending order. In the Trail Making Test-B, circles contain both numbers and letters. Participants are asked to connect the circles using numbers and letters in ascending order[24]. Participants are evaluated based on the time it takes to complete the test. These tests measure processing speed and working memory[25]. The Turkish validity and reliability study of the scale was performed by Türkeş et al[26] and Cronbach's alpha values were 0.87 for TMT A- time and 0.77 for TMT B- time.

Verbal Fluency Tests (VFT)

Participants are asked to count the maximum number of animals in 60 seconds in categorical verbal fluency. In phonemic fluency, the words starting with the letters K, A, and S are required to be counted in 60 seconds, except for proper nouns, and in this process, correct words, repetitions, and out-of-category words are recorded in 15-second intervals[27]. The Turkish

validity and reliability study of the scale was performed by Tümaç and Canbeyli[28]. Cronbach's alpha values were calculated and found to be 0.90 for phonemic fluency and 0.64 for semantic fluency tests.

Wisconsin Card Sorting Test (WCST)

The computer version of the WCST was used to assess executive function and working memory. In this test, the cards differ in color, number, and shape. Participants are expected to find the matching rule based on the written feedback given as "true" or "false." During the test, the rules are changed, and participants are expected to discover the new rule. Dependent variables are the number of correct answers and sets completed. Scoring includes total correct answers, percentage of error (%), perseverative responses (%), perseverative errors (%), non-perseverative errors (%), conceptual level responses (%), the total number of answers, categories achieved, the number of attempts for completing first category, failure to maintain the set and learning to learn. Learning to learn is calculated for participants who complete at least 3 categories. Positive learning to learn score indicates that learning ability increases as the categories are completed[29]. The Turkish validity and reliability study of the scale was performed by Karakaş et al[30]. In this study, the reliability of the measurements was determined as 0.84 Cronbach's Alpha coefficient.

Digit Span (DS) Tests

In the DS forward test, patients are asked to repeat a sequence of numbers in the same way after the tester, and the test measures short-term auditory recall. In the DS Backward test, which measures working memory, patients are asked to repeat the numbers in reverse order[31]. The Turkish validity and reliability study of the scale was performed by Karakaş et al[2] The Cronbach's Alpha coefficient for this test was found to be 0.69.

Statistical analysis

SPSS 22.0 was used for statistical analyses. Descriptive statistics were used to report the minimum, maximum, mean, and standard deviation, and the distribution of the variables was evaluated with the Kolmogorov-Smirnov test. Descriptive statistics of the data are given as mean and standard deviation for those with normal distribution and as median (min-max) for those without normal distribution. Independent samples T-test was used to compare normally distributed numerical variables. Mann Whitney U-test was used to compare non-normally distributed numerical variables. Pearson and Spearman Rho Correlation Analyzes were used to determine the linear relationship between the data. The group was divided into two based on the mean fT3 and fT4 values, and the two groups were compared among themselves in terms of cognitive tests with Mann Whitney-U test. To evaluate whether fT3 predicts WCST performances, multiple linear regression model was conducted with fT3 levels and disease duration. A p-value smaller than 0.05 was considered statistically significant.

RESULTS

A total of 33 psychosis patients, 12 female, and 21 males, were included in our study. While the mean age and education period of the patients were 30.61±8.56 and 9.25±3.29 years, respectively, the mean BMI was found to be 26.51±5.45. From the clinical features of the patients, the mean duration of disease was 10.93±7.68, and the age of onset was 19.69±3.69. While the number of psychotropic drugs used was 2.57±1.39, the CGI, GAF, and PANSS total scores were 4.36±0.78, 54.09±10.49, and 70.42±15.15, respectively. While fT3 and fT4 levels of the patients were 3.19±0.41 and 1.11± 0.23, respectively, mean TSH levels were 1.96± 0.83. Male and female patients were compared, and no significant differences were observed in terms of sociodemographic and clinical data. Sociodemographic and clinical data of the patients are summarized in Table 1.

The TMT-A and B test performances of the tests performed to determine the cognitive test performances of the patients were 42 (27-168) and 108 (63-600) seconds, respectively. Verbal Fluency semantic and phonemic test performances were found to be 16.48±4.41 and 26.84±10.89 words, respectively. While the DS forward was 5.63± 0.92 digits, the DS backward was 3.48± 0.89 digits. Of the WCST subcomponents for the evaluation of executive functions, the total responses were 128 (75-128), the total corrects were 63.87±16.52, and the number of categories achieved was 2.84±2.09. In addition, there was a significant relationship between disease duration and TMT A (r= 0.34, p=0.04), and B (r=0.35, p=0.04), and WCST total correct (r= -0.41, p=0, 01), total error (r=0.44, p=0.01), and the number of categories achieved (r= -0.59, p<0.01). The cognitive test scores of the patients are summarized in Table 2.

Table 1. Sociodemographic and Clinical Data

Sociodemographic and Clinical Data	Descriptive Statistics
Age, Mean (SD)	30.61 (8.56)
Education (years), Mean (SD)	9.25 (3.29)
Gender, n(%)	
Female	12 (36.4)
Male	21 (63.6)
Marital Status, n(%)	
Married	5 (15.2)
Single	25(75.8)
Other	3 (9.1)
Age at the onset of disease, Mean (SD)	19.69 (3.69)
Duration of illness, Mean (SD)	10.93 (7.68)
Number of psychotrops, Mean (SD)	2.57 (1.39)
PANSS total, Mean (SD)	70.42 (15.15)
CGI, Mean (SD)	4.36 (0.78)
GAF, Mean (SD)	54.09 (10.49)
fT4, Mean (SD)	1.11 (0.23)
fT3, Mean (SD)	3.19 (0.41)
TSH, Mean (SD)	1.96 (0.83)
BMI, Mean (SD)	26.51 (5.45)

SD: Standard Deviation, PANSS: Positive and Negative Syndrome Scale, CGI: Clinical Global Impression, GAF: Global Assessment of Functioning, BMI: Body Mass Index

Table 2. Cognitive tests

Cognitive Tests	Descriptive Statistics
TMT-A, median (min-max)	42 (27-168)
TMT-B, median (min-max)	108 (63-600)
VF Categorical	16.48 (4.41)
VF Phonemic	26.84 (10.89)
DS forward, Mean (SD)	5.63 (0.92)
DS backward Mean (SD)	3.48 (0.89)
WCST total reaction, median (min-max)	128 (75-128)
WCST total corrects, Mean (SD)	63.87 (16.52)
WCST.categories achieved, Mean (SD)	2.84 (2.09)
WCST total errors, Mean (SD)	57.78 (23.76)
WCST.perseverative errors, Mean (SD)	36.90 (22.62)

TMT: Trail Making Test VF: Verbal Fluency SD: Standard Deviation, WCST: Wisconsin Card Sorting Test, DS: Digit span

The relationship between thyroid function tests and sociodemographic and clinical data was investigated using correlation analyses. There was a negative correlation between fT4 and age (r= -0.4; p=0.02) and disease duration (r= -.47; p<0.01). A weak negative correlation was found between fT4 levels and WCST- number of perseverative errors (r= -0.34; p=0.04) and TMT-B scores (r= -0.37, p=0.03). In addition, a weak positive correlation was found between fT4 and VF-phonemic fluency (r= 0.35, p=0.04). A negative correlation was found between fT3 and age (r= -0.41; p=0.01) and disease duration (r= -0.48; p<0.01). Between fT3 levels and WCST-category number (r=0.5; p<0.01) and WCST total correct (r=0.41; p=0.01), positive WCST-perseverative error (r= -0.4); p=0.02) and WCST-total error (r= -0.38; p=0.02) was found to be negatively correlated. No significant correlation was found between thyroid function tests and scale scores reflecting disease severity such as CGI, GAF, PANSS, and other cognitive tests. Correlations between thyroid function tests and clinical and cognitive parameters are summarized in Table-3.

Table 3. Relationship between Thyroid Function Tests and Cognitive Tests and Clinical Data

		WCST.CAb	WCST PE.b	WCST TE b	WCST TC b.	VF phonemicb	TMT-B a
TSH	R	.194	-.049	-.202	.211	-.083	.122
	P	.280	.787	.259	.238	.644	.497
	N	33	33	33	33	33	33
fT4	R	.299	**-.347***	-.139	.268	**.355***	**-.376***
	P	.091	**.048**	.439	.132	**.043**	**.031**
	N	33	33	33	33	33	33
fT3	R	**.508****	**-.403***	**-.381***	**.410***	.048	-.268
	P	**.003**	**.020**	**.029**	**.018**	.793	.131
	N	33	33	33	33	33	33

WCST: Wisconsin Card Sorting Test WCST.CA: WCST-categories achieved, WCST PE: WCST perseverative errors, WCST TE: WCST total errors, WCST TC: WCST total corrects, VF: Verbal Fluency Test, TMT-B: Trail Making Test B
a: Spearman correlation b: Pearson correlation tests performed.
* Weak relationship ** Moderate relationship

Table 4. Comparison of cognitive tests between two groups according to fT3 levels

	fT3	N	M (min-max)	Z	P
WCST. categories achieved	<=3.19	17	1(0-6)	-3.689	**<0.001**
	>3.19	16	4.5(1-6)		
WCST perseverative errors	<=3.19	17	45(7-86)	-1.965	**.049**
	>3.19	16	21(6-75)		
WCST total corrects	<=3.19	17	55(35-81)	-3.063	**.002**
	>3.19	16	74(41-97)		
WCST. total errors	<=3.19	17	73(13-93)	-2.936	**.002**
	>3.19	16	38(11-87)		

WCST: Wisconsin Card Sorting Test, Mann-Whitney-U test

In addition, the mean value of fT3 levels was determined as 3.19 ng/l, and the patients were divided into two groups based on the median fT3 value and compared in terms of WCST performance. Patients with higher fT3 levels had WCST total correct ($Z= -3.06$, $p<0.01$), number of categories achieved ($Z= -3.68$, $p<0.001$), perseverative error ($Z= -1.96$, $p=0.04$) and total error ($Z= -2.93$, $p<0.01$) categories were found to perform significantly better. The comparison of WCST performances between the two groups according to fT3 levels is summarized in Table 4. When the same procedure was repeated according to the fT4 Mean value, no significant difference was found between the two groups in terms of cognitive parameters.

A linear regression model was formed assuming fT3 level as an independent variable and disease duration and the number of WCST-categories achieved ($R2=0.415$; $p<0.001$) as the dependent variables. In our study, the fact that fT3 levels were associated with WCST performances measuring executive functions, and literature data on the negative effects of disease duration on executive functions in psychosis patients were effective in the selection of dependent variables. WCST-categories achieved which is one of the most frequently used parameters in studies evaluating the executive functions of psychosis patients, was chosen as the independent variable. Both disease duration ($p=0.003$) and fT3 levels ($p=0.029$) had a significant effect on WCST-category number. This model is summarized in Table 5.

Table-5. Multiple regression analysis with WCST-categories achieved and independent variables

	UB	SE	SB	T	LB	UB	p
(Constant)	-1.102	2.549		-0.432	-6.307	4.103	0.669
Duration of Disease	-.129	.040	-.473	-3.252	-.210	-.048	0.003
fT3	1.680	.734	.333	2.290	.182	3.179	0.029

UB: Unstandardized Beta; SE: Standard Error; SB: Standardized Beta Coefficient; CI: Confidence Interval, LB: Lower Bound; UB: Upper Bound

DISCUSSION

This study investigated the relationship between thyroid function tests and clinical parameters such as disease duration, severity, functionality, and neurocognitive test scores in patients with schizophrenia. While no significant correlation was found between thyroid function tests and scale scores reflecting disease severity such as CGI, GAF, and PANSS, some significant correlations were found between TFT and neurocognitive test scores. Thyroid hormones play an important role in neurodevelopmental stages such as synaptogenesis and, cell migration, neuronal and glial cell differentiation processes. It has been shown that maternal and fetal hypothyroidism causes irregularity in cell migration in the neocortex and disruptions in interhemispheric connections. It is known that pyramidal cells in the neocortex and hippocampus are significantly affected in hypothyroidism[33]. Therefore, it is accepted that there is a loss of function in many cognitive areas in schizophrenia, which is accepted as a neurodevelopmental disease[34]. In addition, our study conducted with euthyroid chronic psychosis patients revealed a linear relationship between thyroid hormone levels and specific cognitive functions.

Particularly attention, memory, and executive functions are the main cognitive areas that are thought to be affected in schizophrenia[34]. It is accepted that these areas are affected by the interaction of the frontal and limbic regions of the brain, thus reflecting a frontotemporal loss of function Apart from chronic schizophrenia patients, many studies report specific cognitive impairments in first-episode patients who did not use medication and even in their unaffected relatives[35]. It has been demonstrated by imaging, behavioral, and psychophysiological studies performed so far that mainly executive functions are significantly affected in schizophrenia[36,37]. Executive functions include some skills such as planning and sequencing behaviors, problem-solving, abstraction ability, and cognitive flexibility. Although executive functions are related mainly to the frontal cortex, the connections of the frontal region with the temporal and limbic regions play a role in the regulation of these functions. The prefrontal cortex plays a vital role in processing and integrating internal and external information, abstracting and problem-solving, and planning, executing, and evaluating behavior[38]. Frontal dysfunctions can lead to disruptions in planning and execution and persistent and rigid behavior. The Wisconsin Card Sorting Test (WCST) can measure many of these deficiencies. It has been demonstrated in many studies that schizophrenia patients whose executive functions were evaluated with WCST performed poorly, especially in the number of categories achieved and perseverative error areas[39,40]. Since our study was conducted only with a patient group, it was not possible to compare the cognitive test performances of the patients with healthy controls. However, the correlation of disease duration with WCST total corrects, total errors, number of categories achieved, and TMT A and B are consistent with the results of previous studies showing loss of function in cognitive domains such as attention, memory, and executive functions in patients with schizophrenia.

In our study, a moderate correlation was found between the number of categories achieved and fT3 levels, and it was found that patients with high fT3 levels achieved more categories. It is known that patients with schizophrenia have significant deficits in executive functions such as abstract thinking and cognitive flexibility, and the number of categories achieved is an essential parameter in revealing these deficits[39]. This result suggested that low thyroid

hormone levels are associated with more impaired executive functions in patients with schizophrenia. It is known that thyroid hormones within the normal range have critical importance in terms of cognitive skills such as attention and memory[41]. Studies investigating the relationship between thyroid hormone levels and cognitive skills in psychotic patients are relatively limited. In a study conducted with psychosis patients, fT4 changes within the normal range were found to have significant effects, primarily on attention[15]. The authors stated that not evaluating fT3 levels is one of the limitations of this study. In another study conducted with patients with chronic schizophrenia, higher fT3 levels were found to be associated with higher MMSE scores[17]. In the same study, it was emphasized that T3 replacement therapy could improve cognitive performance and that new studies should be conducted on this subject. In our study, when the patients were divided into two groups according to their mean fT3 levels, WCST performances were found to be significantly higher in the patient group with high fT3 levels, but no difference was found between the cognitive performances of the patients who were divided into two groups according to their mean fT4 levels. These results suggest that fT3 levels are more closely related to cognitive symptoms than fT4. In another study conducted with euthyroid female patients, similar to our study, it was found that higher fT3 levels in the normal range are associated with higher performance in processing speed and executive functions reflecting precortical functions[42]. The fact that T3 in target cells functions as an active hormone and thyroid hormones show their functions through central T3 receptors may explain the fact that fT3 is more closely associated with cognitive symptoms.

As a result of the linear regression analysis, we found that fT3 levels and disease duration significantly predicted the number of WCST categories achieved. However, it has been reported that THs play critical roles in the formation processes of astrocytes. In addition, it is known that as the duration of the disease increases in the course of schizophrenia, loss of astrocyte functions occurs[43]. This result obtained in our study suggested that the regulating effects of disease duration and THs on astrocytes may be determinative of cognitive symptoms.

In a recent study, fT4 changes in the normal range in patients with psychosis were found to closely affect attention performance[16]. Another study emphasized that increased fT4 levels in patients with psychosis were associated with better attention performance, but no such relationship was found in the healthy control group[15]. Our study found a linear relationship between fT4 levels and the TMT B scores, which evaluates attention functions. This result is consistent with the results of the above studies and suggests that fT4 levels play a more important role in attention in schizophrenia patients compared to fT3 and that new studies with larger samples are needed on this subject.

Our study found no relationship between positive and negative symptoms, disease severity or functionality, or thyroid hormone levels. Similarly, Ichioka et al. found no association between thyroid hormone levels and positive, negative, and general symptoms in schizophrenia patients[17]. This finding is important in terms of demonstrating that thyroid hormones have an effect on cognitive symptoms rather than disease severity or positive and negative symptoms.

There are some strengths and limitations of our study. There are relatively limited studies examining the relationship between thyroid function tests and neurocognitive and clinical symptoms in patients with schizophrenia. Despite the application of a very comprehensive neurocognitive battery in our study, the limited number of participants may have negatively affected the statistical analysis. Due to the cross-sectional design of our study, it was not possible to establish a cause-effect relationship. Since it was conducted only with the patient group, the results obtained could not be compared with another clinical or healthy group. However, the effect of psychiatric and other medical drugs that may have an effect on cognitive performance could not be evaluated. Finally, the number of participants was relatively small, and the statistical power might be affected negatively.

In conclusion, this study found that fT3 and fT4 levels were associated with cognitive impairment in schizophrenia patients, while parameters related to disease severity and positive or negative symptoms were independent of thyroid levels. Information on the etiopathogenesis of cognitive symptoms, which is one of the most important causes of disability in schizophrenia, is limited, and drugs used in the treatment of schizophrenia are primarily aimed at reducing positive and negative symptoms. The results of our study are important in terms of showing that thyroid hormone levels are closely related to cognitive performance in patients with psychosis, even if they are euthyroid. We believe that it would

be an appropriate approach for clinicians to closely monitor thyroid hormone levels in the follow-up and treatment of cognitive symptoms in psychosis patients. Future studies with higher number of participants will be useful for better understanding the relationship between thyroid dysfunctions and cognitive symptoms and for bringing thyroid replacement therapies to the agenda for the treatment of cognitive symptoms.

Yazar Katkıları: Çalışma konsepti/Tasarımı: HK, BA; Veri toplama: HK, BA; Veri analizi ve yorumlama: BA; Yazı taslağı: HK, BA; İçeriğin eleştirel incelenmesi: BA; Son onay ve sorumluluk: HK, BA; Teknik ve malzeme desteği: HK, BA-; Süpervizyon: HK; Fon sağlama (mevcut ise): yok.
Etik Onay: Bu çalışma için Erenköy Ruh ve Sinir Hastalıkları Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kuruldan 09.05.2022 tarih ve 25 sayılı kararı ile etik onay alınmıştır.
Hakem Değerlendirmesi: Dış bağımsız.
Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.
Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.
Author Contributions: Concept/Design : HK, BA; Data acquisition: HK, BA; Data analysis and interpretation: BA; Drafting manuscript: HK, BA; Critical revision of manuscript: BA; Final approval and accountability: HK, BA; Technical or material support: HK, BA; Supervision: HK; Securing funding (if available): n/a.
Ethical Approval: For this study, ethical approval was obtained from the Clinical Research Ethics Committee of Erenköy Mental and Nervous Diseases Training and Research Hospital with the decision dated 09.05.2022 and numbered 25.
Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
Financial Disclosure: Authors declared no financial support

REFERENCES

1. Reichenberg A, Weiser M, Rapp MA, Rabinowitz J, Caspi A, Schmeidler J et al. Elaboration on premorbid intellectual performance in schizophrenia: Premorbid intellectual decline and risk for schizophrenia. Arch Gen Psychiatry. 2005;62:1297-304.
2. Santesteban-Echarri O, Paino M, Rice S, González-Blanch C, McGorry P, Gleeson J et al. Predictors of functional recovery in first-episode psychosis: A systematic review and meta-analysis of longitudinal studies. Clin Psychol Rev. 2017;58:59-75.
3. Ortiga-Carvalho TM, Chiamolera MI, Pazos-Moura CC, Wondisford FE. Hypothalamus-pituitary-thyroid axis. Compr Physiol. 2016;6:1387-428.
4. Leonard JL. Non-genomic actions of thyroid hormone in brain development. Steroids. 2008;73:1008-12.
5. Bégin ME, Langlois MF, Lorrain D, Cunnane SC. Thyroid function and cognition during aging. Curr Gerontol Geriatr Res. 2008;2008:474868.
6. Osterweil D, Syndulko K, Cohen SN, Pettier-Jennings PD, Hershman JM, Cummings JL et al. Cognitive function in non-demented older adults with hypothyroidism. J Am Geriatr Soc. 1992;40:325-35.
7. Monzanil F, Del Guerra P, Caracciol N, Pruneti CA, Puccil E, Luisit M et al. Subclinical hypothyroidism: neurobehavioral features and beneficial effect of l-thyroxine treatment. Clin Investig. 1993;71:367-71.
8. Zhu DF, Wang ZX, Zhang DR, Pan ZL, He S, Hu XP et al. fMRI revealed neural substrate for reversible working memory dysfunction in subclinical hypothyroidism. Brain. 2006;129:2923-30.
9. Samuels MH. Thyroid disease and cognition. Endocrinol Metab Clin North Am. 2014;43:529-43.
10. Wahlin Å, Bunce D, Wahlin TBR. Longitudinal evidence of the impact of normal thyroid stimulating hormone variations on cognitive functioning in very old age. Psychoneuroendocrinology. 2005;30:625-37.
11. Othman SS, Kadir KA, Hassan J, Hong GK, Singh BB, Raman N. High prevalence of thyroid function test abnormalities in chronic schizophrenia. Aust N Z J Psychiatry. 1994; 28:620-4.
12. Zhu Y, Ji H, Tao L, Cai Q, Wang F, Ji W et al. Functional status of hypothalamic–pituitary–thyroid and hypothalamic–pituitary–adrenal axes in hospitalized schizophrenics in Shanghai. Front Psychiatry. 2020;11:65.
13. Zhang N, Du H, Wang J, Cheng Y. A pilot study on the relationship between thyroid status and neuropsychiatric symptoms in patients with Alzheimer disease. Chin Med J (Engl). 2012;125:3211-6.
14. Bunevicius R. Thyroid disorders in mental patients. Curr Opin Psychiatry. 2009;22:391-5.
15. Barbero JD, Gutiérrez-Zotes A, Montalvo I, Creus M, Cabezas Á, Solé M et al. Free thyroxine levels are associated with cognitive abilities in subjects with early psychosis. Schizophr Res. 2014;166:37-42.
16. Labad J, Barbero JD, Gutiérrez-Zotes A, Montalvo I, Creus M, Cabezas et al. Free thyroxine levels are associated with cognitive changes in individuals with a first episode of psychosis: A prospective 1-year follow-up study. Schizophr Res. 2016;171:182-6.
17. Ichioka S, Terao T, Hoaki N, Matsushita T, Hoaki T. Triiodothyronine may be possibly associated with better cognitive function and less extrapyramidal symptoms in chronic schizophrenia. Prog Neuro-Psychopharmacology Biol Psychiatry. 2012;39:170-4.
18. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders Fifth Edition. Arlington, American Psychiatric Association, 2013.
19. World Medical Association. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. Bull World Health Organ. 2001;79:373-4.
20. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13:261-76.
21. Kostakoglu E, Batur S, Tiryaki A, Gogus A. Reliability and validity of the Turkish version of the Positive and Negative Syndrome Scale (PANSS). Turk Psikoloji Dergisi. 1999;14:23-34.

22. Aas IH. Guidelines for Rating Global Assessment of Functioning (GAF). Ann Gen Psychiatry. 2011;10:1-11.
23. Guy W. ECDEU Assessment Manual For Psychopharmacology. Rockville, MD, US Department of Health, 1976.
24. Tischler L, Petermann F. Trail Making Test (TMT). Z Klin Psychol Psychiatr Psychother. 2010;58:79-81.
25. Reitan RM. The relation of the trail making test to organic brain damage. J Consult Psychol. 1955;19:393.
26. Türkeş N, Can H, Kurt M, Elmastaş Dikeç B. İz Sürme Testi'nin 20-49 yaş aralığında Türkiye için norm belirleme çalışması. Turk Psikiyatri Derg. 2015;26:189-196.
27. Lezak MD, Howieson DB, Loring DW, Hannay JH , Fischer JS. Neuropsychological Assessment. New York, Oxford University Press, 2004.
28. Tümaç A. Normal deneklerde frontal hasarlara duyarli bazi testlerde performansa yaş ve eğitimin etkisi (Yüksek lisans tezi). İstanbul, İstanbul Üniversitesi, 1997.
29. Heaton RKK, Chelune GJ, Talley JL, Kay GG, Curtiss G, Oreg S et al. Wisconsin Card Sorting Test Manual: Revised and Expanded. Odessa, FL, Psychological Assessment Resources, 1993.
30. Karakaş S, Irak MEO. Wisconsin Kart Eşleme Testi (WCST) ve Stroop Testi TBAG formu puanlarının test içi ve testler-arası ilişkileri. Ulusal Psikoloji Kongresi özet kitabı. 1998;44.
31. Wechsler, D. Wechsler Memory Scale - Third Edition Administration and Scoring Manual. San Antonio, TX Psychol. Corp. 1997.
32. Karakaş S. Bilnot Bataryası El Kitabı: Nöropsikolojik Testler için Araştırma ve Geliştirme Çalışmaları. Ankara, Dizayn Ofset, 2004.
33. Santisteban P, Bernal J. Thyroid development and effect on the nervous system. Rev Endocr Metab Disord. 2005;6:217-28.
34. Üçok A, Direk N, Koyuncu A, Keskin-Ergen Y, Yüksel Ç, Güler J et al. Cognitive deficits in clinical and familial high risk groups for psychosis are common as in first episode schizophrenia. Schizophr Res. 2013;151:265-9.
35. Kelleher I, Murtagh A, Clarke MC, Murphy J, Rawdon C, Cannon M. Neurocognitive performance of a community-based sample of young people at putative ultra high risk for psychosis: Support for the processing speed hypothesis. Cogn Neuropsychiatry. 2013;18:9-25.
36. Chan RCK, Chen EYH, Law CW. Specific executive dysfunction in patients with first-episode medication-naïve schizophrenia. Schizophr Res. 2006.
37. Holmes AJ, MacDonald A, Carter CS, Barch DM, Stenger VA, Cohen JD. Prefrontal functioning during context processing in schizophrenia and major depression: An event-related fMRI study. Schizophr Res. 2005;76:199-206.
38. Wobrock T, Ecker UKH, Scherk H, Schneider-Axmann T, Falkai P, Gruber O. Cognitive impairment of executive function as a core symptom of schizophrenia. World J Biol Psychiatry. 2009;10:442-51.
39. Everett J, Lavoie K, Gagnon JF, Gosselin N. Performance of patients with schizophrenia on the Wisconsin Card Sorting Test (WCST). J Psychiatry Neurosci. 2001;26:123-30.
40. Fatouros-Bergman H, Cervenka S, Flyckt L, Edman G, Farde L. Meta-analysis of cognitive performance in drug-naïve patients with schizophrenia. Schizophr Res. 2014; 158:156-62.
41. Boelaert K, Franklyn JA. Thyroid hormone in health and disease. J Endocrinol. 2005;187:1-15.
42. Grigorova M, Sherwin BB. Thyroid hormones and cognitive functioning in healthy, euthyroid women: A correlational study. Horm Behav. 2012;61:617-22.
43. Kolomeets NS, Uranova N. Ultrastructural abnormalities of astrocytes in the hippocampus in schizophrenia and duration of illness: A postmortem morphometric study. World J Biol Psychiatry. 2010;11:282-92.