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SOCIAL COGNITION AND OXIDATIVE STRESS IN SCHIZOPHRENIA PATIENTS AND FIRST-DEGREE RELATIVES OF PATIENTS

Selma Çilem Kızılpınar[1], Makbule Çiğdem Aydemır[2], Özlem Doğan[3], Fatma Bahar Atak-Akkus[4] & Zeynel Baran[5]

1 Department of Psychiatry, Ankara University, Faculty of Medicine, Ankara, Turkey, uygurcilem@gmail.com
Present Adress; Adana City Research and Training Hospital, Adana, Turkey
2 Department of Psychiatry, Ankara University, Faculty of Medicine, Ankara, Turkey, aydemircigdem@gmail.com
3 Department of Biochemistry, Ankara University, Faculty of Medicine, Ankara, Turkey, ozlemdogan@ankara.edu.tr
4 Department of Psychiatry, Ankara University, Faculty of Medicine, Ankara, Turkey, f.baharatak@gmail.com
Present Adress; Kars Harakani State Hospital, Kars, Turkey
5 Department of Psychology, Hacettepe University, Faculty of Letters Ankara, Turkey, znbaran@hacettepe.edu.tr

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Summary

Background: *Endophenotypes are biological and behavioral markers that indicate a genetic predisposition to complex neuropsychiatric disorders such as schizophrenia. We aimed to explore whether some neuropsychiatric and biochemical measurements can be identified as an endophenotype and investigate the possible confounding effects of working memory, and general intellectual skills on social cognition.*

Subject and Methods: *Patients with remitted schizophrenia (PG) (n=26), first-degree relatives of schizophrenic patients (RG) (n=25), and healthy controls (HCG) (n=36) were compared in terms of oxidative stress parameters -serum Superoxide Dismutase, Catalase, Glutathione Peroxidase (GPx), Nitrite, Nitrate, Malondialdehyde, and Total Glutathione levels-, social cognition measured by the Reading the Mind in the Eyes Test and working memory measured by the N-back Task. Groups were compared, assuming that HCG had a genetically lower risk of schizophrenia compared to PG and RG.*

Results: *HCG performed significantly better than PG and RG, who were genetically at high risk, in terms of social cognition (respectively p=0.000, p=0.014), working memory (respectively p=0.001, p=0.003), and had statistically lower Glutathione Peroxidase (GPX) level than the PG and RG (both p:0.000). After controlling for the effect of the general intellectual abilities measured by the Raven Standard Progressive Matrices Test and working memory the differences between groups on the Eyes Test disappeared (p=0.057). However, this value tended to be significant.*

Conclusions: *It was concluded that social cognition and working memory and GPx level may be used as endophenotypes and social cognition, working memory, and general intellectual skills are different but strongly related constructs. Endophenotypes guide treatment targets even after the disease has developed. The results of our study showed that in addition to psychopharmacological treatments, interventions to reduce oxidative stress and approaches to improve cognitive skills will have a positive impact on the disease's progression.*

Keywords; *schizophrenia, social cognition, endophenotype, oxidative stress, neurocognition*

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INTRODUCTION

Schizophrenia is defined as a mental disorder that disrupts patients' various mental functions (Tandon et al. 2013). Endophenotypes have been defined as unobtrusive measurable elements, along the pathway between disease and genotype (Gottesman & Gould 2003). They are indicators of sensitivity to psychopathology and markers of genetic predisposition (Beauchaine & Marsh 2006). Relatives of schizophrenia patients display endophenotypes rather than overt disease presentation (Benes 2007, Greenwood et al. 2019). Endophenotype studies shed light on the etiology of the disease, distinguish healthy individuals from patients, predict high-risk individuals, and contribute to the development of more specific agents in the treatment and prevention of the disease (Lenzenweger 1999). Many endophenotypes have been identified for schizophrenia (Allen et al. 2009, Light et al. 2012, Louchart-de la Chapelle et al. 2005, Swerdlow et al. 2015).

Social cognition, which is referred to as the ability to think about oneself and others, is a function that requires an extensive neural network, including processes from the sensory perception of the stimulus to the genesis of behavior (Adolphs 2001) social cognition impairment is also seen in other psychiatric disorders, but it has been reported to be common in schizophrenia and psychotic disorders and social cognition may also be an endophenotype (Bora et al. 2009, Sprong et al. 2007, Pentaraki

2012). Some authors, however, state that these findings are the result of disregarding the impact of other cognitive functions on social cognition and that a social cognition deficit cannot be considered an endophenotype (Kelemen et al. 2004, Pentaraki et al. 2012).

Oxidative stress which means an imbalance between oxidants and antioxidants may one of the important biological mechanisms underlying the developmental processes of neuropsychiatric diseases (Lante et al. 2007, Reddy & Reddy 2011, Flatow et al. 2013). Toxic levels of oxidants may cause tissue damage, especially in the Central Nervous System, and may play a role in the etiology of various neuropsychiatric diseases has been examined. Superoxide anion radical, hydroxyl radical, singlet oxygen and hydrogen peroxide, and peroxynitrite are some important oxidants, which are called Reactive Oxygen and Reactive Nitrogen Species (ROS and RNS). The effects of ROS and RNS must be neutralized by enzymatic or non-enzymatic antioxidant mechanisms to protect the tissue from oxidative damage. Measurement of the reactive species level is quite difficult and misleading and needs some special technique due to those reactive species are highly 'reactive' molecules and having very short half-lives (Agarwal et al. 2004, Murphy et al. 2022). Oxidative stress levels can be evaluated indirectly by the measurement of antioxidant enzyme levels such as Superoxide Dismutase (SOD), GPx, and Catalase (CAT) and some lipid peroxidation products like Malondialdehyde (MDA) and Thiobarbituric Acid Reactive Substances (TBARS) (Halliwell et al. 1999, Valko et al. 2007, Othmen et al. 2008). There are substantial studies focused on oxidative stress indicators as possible biomarkers in schizophrenia and these studies generally measured the levels of antioxidant enzymes in various tissues, lipid peroxidation end products like MDA, and the levels of non-enzymatic antioxidants such as vitamin E and alpha lipoic acid (Boskovic et. al 2011, Ciobica et al. 2011, Solberg et al. 2019). Moreover, Emiliani et al. (2014) emphasized that the underlying mechanism of oxidative stress in schizophrenia is an old story. Studies conducted in schizophrenic patients indicate that toxic damage increases due to both the increase in prooxidants and the decrease in antioxidants for example reduced SOD levels (Flatow et al. 2013) reduced CAT levels (Raffa et al. 2011) and increased GPx levels (Raffa et al. 2009) in red blood cells, increased plasma SOD levels (Martinez-Cengotitabengoa et al. 2012), increase nitric oxides (NO) and lipid peroxides (Khan et al. 2002) in schizophrenic patients. In a meta-analysis study, in which studies comparing schizophrenia patients with healthy controls in terms of oxidative stress parameters were examined, higher TBARS, NO level, lower SOD activity, and insignificant differences in GPx and CAT activity were reported (Zhang et al. 2010). Changes in oxidative balance in patients with schizophrenia have also been reported in many other studies that we could not mention (Pandya et al. 2013, Goh et. al 2022). But there are limited reports of oxidative stress markers in genetically vulnerable individuals such as first-degree relatives of patients with schizophrenia. In a study aimed at comparing red blood cell GPx, SOD, CAT, and plasma TBARS levels among schizophrenic patients, unaffected siblings of schizophrenic patients, and healthy controls, significantly higher GPX, lower SOD and CAT activities, and higher TBARS levels were reported in schizophrenic patients and unaffected relatives (Othmen et al. 2008). During our research, we did not find any other publications investigating oxidative stress indicators in the relatives of unaffected patients. The question of whether oxidative stress parameters may be used as an endophenotype is not clear still due to not enough publications. (Bray & Taylor 1993, Lanté et al. 2007). It has measured the levels of SOD, GPx, CAT, MDA, and NO, which in previous studies showed significant differences between patients with schizophrenia and healthy controls.

The purpose of this study was whether these neuropsychiatric and biochemical measurements could be used to determine an endophenotype, as well as to examine the relationship between oxidative stress and social cognition in the etiology of schizophrenia. Unlike previous studies on the subject, this one aims to assess general intellectual skills and working memory, which may have a confounding effect on social cognition, as well as to control for such effects.

SUBJECTS AND METHODS

Subjects

For all participants in the study, conditions that could affect neurocognitive testing and the level of oxidative stress in the blood were taken into account. For this reason, participants between 18 and 65, with at least five years of education, no history of substance abuse or use of any drugs that may affect oxidative stress (steroids, oral contraceptives, antioxidant vitamins, xanthine oxidase inhibitors, and non-steroidal anti-inflammatory drugs), no additional psychiatric diagnosis as ascertained by the Clinical Interview Form (SCID-I) or any medical conditions that may affect their cognitive status (neurological disease, severe physical illness, history of brain trauma, or Electroconvulsive Treatment in the previous

6 months), were recruited in the study. The blood was drawn after eight hours of fasting and not smoking.

The schizophrenia patient group consists of people who have been followed up with the diagnosis of schizophrenia for at least 1 year in the outpatient clinic of our hospital, who is currently in remission, and whose drug use has been stable for at least 3 months. For subjects in this group, schizophrenia was re-diagnosed with the SCID-1 interview (Ozkurkcugil et al. 1999), and both symptom severity and remission were evaluated with the Positive and Negative Syndrome Scale (Kay & Lindenmayer 1987). Information on demographic variables and data on various clinical characteristics such as age at onset of disease, total disease duration, medications, cigarette consumption (packs/year), alcohol, and substance use were obtained from all participants. Height and weight measurements were taken for all participants. Body Mass Index (BMI) was calculated by dividing the person's body weight in kilograms by the square meter of the height (BMI= (kg)/(m2)).

Permissions were obtained from Ankara University Clinical Research Ethics Committee (Date: 25.03.2019, with decision number 06-479-19) following the principle of the Declaration of Helsinki and Good Clinical Practice. It was obtained consent from all participants, or their legally authorized representatives.

METHODS

Neurocognitive Assessments

Reading the Mind in the Eyes Test (Eyes Test):

The Eyes Test is a first-level Theory of Mind (ToM) test and helps to provide information about emotion recognition, empathy, and social perception as sub-domains of social cognition (Harkness et al. 2005). The original version of the test consists of 36 pictures showing only the eye area of a person (Baron-Cohen et al. 2001). In the Turkish validity and reliability study, it was reported that 32 items scale is reliable for clinical and healthy groups. One person's eye area is only shown in each picture. Emotional expressions describing the mental states of the person in the picture were added to the picture corners. There is 1 correct answer and 3 distracting answers for each picture (Yildirim et al. 2011). Pictures were presented in a booklet, and the participants were asked to choose the best option that describes the emotion shown in the picture and were given a response chart to record their correct answers. There was no time limit during the procedure. The total number of correct answers about the emotion exhibited in the pictures were accepted as the Eyes Test Score.

N-back Task:

The working memory performance is assessed with the n-back task. During this test, the participant is expected to respond if the stimulus shown on the screen coincides with the stimulus shown "n" times before. This test was developed using the 'E-prime Professional 2.0' software. Considering the difficulty level, only the 2-back task was used in our study. Various letters were chosen as stimuli (Owen et al. 2005). The task was explained to all participants at the beginning, and then a practice test was given. After at least 3 correct responses, the main test was started. In the test's evaluation, measurements were calculated by the recommendations of Stanislav and Todorov (Stanislaw & Todorov 1999). Since the d-prime value provided a valid evaluation in many studies, only the d-prime value was used in the statistics in our study (Gillespie et al. 2015).

Raven Standard Progressive Matrices (RSPM) Test:

The general intellectual skills of the participants were evaluated with the RSPM test developed by J. C. Raven (Raven 2008, Tunali & Emir 2017). Although it is not valid and reliable for schizophrenia patients, it has been used in many schizophrenia studies (Caspi et al. 2003, Morrison et al. 2006, Parnas et al. 2001, Pentaraki et al. 2008). This test generally involves discovering the relationship between items. It has been reported that this test gives comparable results with the WAIS-R (Weschler Intelligence Scale for Adults-Revised Form) and WISC-R (Weschler Intelligence Scale for Children-Revised Form) (Morrison et al. 2006, Pentaraki et al. 2012, Raven 2000). The test's being short, non-verbal, and less affected by socioeconomic status, cultural characteristics, and sensory and motor abilities are its strong characteristics (Raven 2000). RSPM total score was used in this study.

Biochemical Analysis

After 8 hours of fasting and non-smoking, 10 cc peripheral blood samples were drawn from all participants. After that, the samples were centrifuged and the serum part was separated. Serum Superoxide Dismutase (SOD), CAT, Glutathione Peroxidase (GPx), Nitrite, Nitrate, Malondialdehyde (MDA), and Total Glutathione levels were measured using the enzyme-linked immunosorbent test method (ELISA). For Nitric Oxide (NO) measurement, nitrite and nitrate values were calculated separately and NO levels were determined by adding these two parameters. Test kits were provided by Cayman Chemical Company, USA, and by Elabscience, USA. The procedure for the test method was performed by the distributor's instructions. In our study, optical density was

measured spectrophotometrically at a wavelength of 450 nm ± 2 nm.

Statistical analysis

Initially, the data were examined in terms of missing, incorrect, and extreme values and in terms of the assumptions of the statistical tests to be applied. Parametric tests are used if the assumptions are provided, and non-parametric tests are used if they are not provided. ANCOVA analysis was performed in order to control the variables that may have a confounding effect on the parameters that we found to differ between the groups. Pearson Chi-Square Test was used for comparisons between categorical variables. Pearson Correlation Test was used to reveal the direction and strength of the relationship between continuous variables, and Spearman Correlation analysis was performed when assumptions were not met. Statistical analyzes were performed with SPSS 23.0 (SPSS Inc, Chicago, IL, USA) package program and the level of significance (Type I error rate) was accepted as $p<0.05$.

RESULTS

Participants' Characteristics

In this cross-sectional case-control study, patients with remitted schizophrenia (PG) (n=26, and first-degree relatives of schizophrenia patients (RG) (n=25, 43.88±14.54) and healthy controls (HCG) (n=36, 41.31±12.40) were compared in terms of oxidative stress and neurocognitive tests. The RG was composed of 56% siblings, 32% parents, and 12% children. There was no statistically significant difference between the three groups in terms of gender, age, and duration of education (p=0.380, p=0.611, p=0.194). There was no significant difference between the groups in terms of past major depression and generalized anxiety disorder, existing medical disease, BMI, smoking ($x^2(2) = 1.746$, p=0.418, $x^2(2)$ =0.170, p=0.919, p=0.966, p=0.348). 80.8% of the patients use only second-generation antipsychotics, and 15.4% use both first-generation and second-generation antipsychotics. 3.8% of the patient group use only first-generation antipsychotics. The

Table 1. Sociodemographic and Clinical Features of the Patient, Relative, and Healthy Control Group

	Cases (n = 26) n (%) mean ± SD	**Relatives (n = 25) n (%), mean ± SD**	**Healthy Control (n = 36) n (%) mean ± SD**	**Statistical Analyses**
Age (*year*)	40.46±11.69	43.88±14.54	41.31±12.40	F(2, 84)=0.495 p=0.611[a]
Sex (*female n*)	14 (53.8%)	18 (72%)	21(58.3%)	$x^2(2)$=1.937 p=0.380[c]
Education Status (*year*)	12.15±3.04	11.72±3.90	13.22±4.16	*H*(2)=3.276 p=0.194[a]
Marital Status (*married n*)	5 (19.2%)	15 (60%)	26 (72.2%)	$x^2(2)$=17.728, p=0.000[c]
Smoking (*packs/year*)	14.62±22.06	8.36±13.26	10.81±14.40	*H*(2)=2.109 p=0.348[a]
BMI (kg/m^2)	28.33±4.50	28.16±5.90	28.50±4.78	F(2, 84)=0.035 p=0.966[a]
Duration of disease (*month*)	16.46±11.90			
PANSS score (P)	12.46 ± 4.91			
PANSS score (N)	15.77 ± 6.83			
PANSS score (G)	27.42 ± 7.20			
PANSS score (T)	55.58 ± 14.51			
Equivalant dose (*mg/day*)	509.58± 283.42			

BMI: Body Mass Index, PANSS: Positive and Negative Syndrome Scale, PANSS score (P): PANSS positive symptoms subscale; PANSS score (N): PANSS negative symptoms subscale; PANSS score (G): : PANSS general psychopathological subscale; PANSS score (T): total PANSS score, n: number of cases, %: percentage, p: p value
[a] ANOVA, [b] Kruskal Wallis Test, [c] Chi Square

mean chlorpromazine equivalent dose of the antipsychotics used by the patients was 509.58±283.42 mg/day. The chlorpromazine equivalent drug dose levels in the patient group were normally distributed and homogeneous (p=0.106). **(Table 1)**

Neurocognitive Assessments; Social and Non-Social Cognitions

PG, RG, and HCG groups were compared in terms of Eyes Test scores, there was a statistically significant difference between the groups (F(2, 84)=12.785, p=0.000, η^2_p*=0.233*) **(Table 2)**. According to Tukey-corrected results, the HCG had significantly higher scores than the PG and RG (respectively p=0.000, p=0.014). ANCOVA analysis was performed to determine whether the difference between PG, RG, and HCG in terms of Eyes Test scores would persist after controlling for RPSM and Working Memory (d-prime) scores. Accordingly, the RSPM score had a significant effect on the Eyes Test score (F(1, 82)=13.015, p=0.000, η^2_p=0.137). Working memory (d-prime) scores, on the other hand, were not related to the Eyes Test score (F (1, 82) =1.740, p=0.191, η^2_p=0.021). After controlling for the effect of RSPM, and working memory scores, the statistically significant effect on Eyes Test scores between groups disappeared (F (2, 82) =2.961, p=0.057, η^2_p=0.067). However, this value tends to be significant, and the effect size is medium **(Table 3).** Partial eta square values for RSPM were found to be 0.137. Accordingly, when working memory (d'prime) effects are controlled, the RSPM score explains 13.7% of the variability in the Eyes Test scores. When RSPM was controlled, it was observed that working memory did not have a statistically significant effect on the Eyes Test (p=0.191)

The effect of the Group variable on Working Memory (d-prime) scores were checked with Kruskal-Wallis one-way ANOVA. It was found a statistically significant difference among the groups (*H* (2) =16.771, p=0.000). It was found that the HCG got significantly higher scores than the PG and the RG, according to the post hoc (Mann-Whitney U) tests (respectively U=223.00, z=-3.593, p=0.001; U= 224.00, z=-3.277, p=0.003). There

Table 2. The Comparison Between the Groups about Clinical and Biochemical Measurements

	Cases (mean ± SD)	Relatives (mean ± SD)	Controls (mean ± SD)	P value
Eyes Test	18±3.97	20.32±5.321	23.69±4.111	0.000[a] *F*(2,84) = 12.785 *η2p* = 0.233*
Working Memory (*d'prime*)	1.05±0.64	1.10 ± 0.58	1.76±0.78	0.000 [b] *H*(2) = 16.771
RSPM Score	32.31±9.83	42.28±9.99	46.06±10.25	0.000 [b] *H*(2) = 21.233
T.Glutathione (*μM*)	1.60±0.84	2.07±1.62	1.91± 0.84	0.104 [b] *H*(2) = 4.525
Catalase (*μM*)	76.53±27.13	71.62±33.45	95.64±48.2	0.096 [b] *H*(2) = 4.691
SOD (*U/mL*)	0.023±0.008	0.027 ± 0.006	0.024 ±0.01	0.157 [b] *H*(2) = 3.700
MDA (*μM*)	4.51± 2.62	3.82±2.46	5.63± 6.03	0.527 [b] *H*(2) = 1.282
Nitrate (*μM*)	15.53±9.70	12.41± 9.72	13.03± 14.41	0.095 [b] *H*(2) = 4.710
Nitrite (*μM*)	11.97± 3.01	11.62± 3.15	12.41± 7.96	0.212 [b] *H*(2) = 3.099
NO (*μM*)	27.44±12.71	24.03±12.42	25.45±21.80	0.102 [b] *H*(2) = 4.569
GPx (*pg/ml*)	2113.51±763.82	1849.34±701.04	1105.60±764.63	0.000 [a] F(2, 84) = 19.704

Eyes Test: Reading in the Mind in the Eyes Test, RSPM: Raven Standard Progressive Matrices, T.Glutathione: Total Glutathione, SOD: Superoxide Dismutase, MDA: Malondialdehyde, NO: Nitric Oxide, GPx: Glutathione Peroxidase, SD: Standart Deviation a ANOVA b Kruskal Wallis Test, *R Squared =.233 (Adjusted R Squared =.215), Anova, Posthoc Tukey

Table 3. Effect of Group Variable on Eyes Test Measurement when RSPM and Working Memory (d'prime) Scores Controlled

	Sum of Square	df	Mean Square	F	p[a]	Partial Eta Value
Working Memory	28.360	1	28.360	1.740	.191	.021
RSPM	212.104	1	212.104	13.015	.001	.137
Group	96.506	2	48.253	2.961	**.057**	.067
Error	1336.358	82	16.297			

RSPM: Raven Standard Progressive Matrices, df: degree of freedom, F: F value, p: p value
* R2 =0.385 (Adjusted R2 =0.355), [a]: ANCOVA, Dependent variable; Eyes Test Score, Covariance; RSPM score, Working Memory

was no statistically significant difference between PG and RG (U=307.00, z=-0.339, p=0.734).

It was found a statistically significant difference in terms of the RSPM score (H(2)=21.233, p=0.000). In the pairwise comparisons, it was observed that the patient group had a statistically lower RSPM score than the RG and HCG (respectively U=145.50, z=-3.385, p=0,001; U=163.00, z=-4.355, p=0.000). There was no statistically significant difference between RG and HCG (U=371.00, z=-1.160, p=0.246).

Oxidative Stress Parameters

There was no statistically significant difference between groups in terms of Total Glutathione, CAT, SOD, MDA, Nitrite, Nitrate, and NO level; (respectively p=0.104, p=0.096, p=0.157, p=0.527, p=0.095, p=0.212, p=0.102) **(Table 2).** Conversely, there was a statistically significant difference in terms of GPx values (p=0.000). According to the results of the Tukey HSD corrected post-hoc tests, the HCG had statistically lower GPx values than the PG and RG. There was a statistically significant difference between PG and HG, and the RG and HG (respectively p=0.000, p=0.000). However, there was no statistically significant difference between PG and RG (p=0.992).

Regression Analyses

A high level of correlation was found between the Eyes Test scores and the RSPM scores for all participants (r_s=0.564, p=0.000). Besides, there was also a statistically significant correlation ($r_{p=}$0.425, p=0.000) between the Eyes Test scores and the Working Memory (d'prime) scores. A multiple linear regression analysis with an enter method was performed to explore the predictive power of RSPM and Working Memory scores on the Eyes Test scores. Accordingly, there was a significant model (F (2, 84) =24.724, p=0.000). R square value indicated that 35.6% of the variation in the Eyes Test scores were explained by those two variables. Moreover, both RSPM scores (F (1,85)=37,076 p=0.000) and Working Memory scores (F(1,85)=18,791 p=0.000) significantly predicted Eyes Test scores.

When the correlation patterns were examined between oxidative stress parameters and Working Memory (d'prime) and Eyes Test scores, there was a moderate level positive correlation between the Eyes Test score and SOD (r_s=0.302, p=0.004), and a moderate level negative correlation with NO (rs=-0.307, p=0.004). The correlation coefficients between Working Memory scores and any oxidative stress parameters were found to be insignificant. In addition, a multiple linear regression analysis was performed to measure the effect of NO and SOD levels on the Eyes Test. There was no significant model predicting Eyes Test scores from SOD and NO variables (F (2, 84)=2.754, p=0.069).

DISCUSSION

Since endophenotypic markers are measurable indicators of genetic susceptibility, they are very useful in the understanding of the etiology of complex neuropsychiatric disorders. When the marker is close to the genetic origin, there is a higher probability of detection in first-degree relatives (Beauchaine & Marsh 2006). Determining these often overlooked, discreet sensitivity traits via various measurement tools have numerous benefits, including early detection of psychopathology and the development of more specific treatment agents. In this study, we examined the differences in biochemical measures and neuropsychiatric measures among PG and RG, who appear to have genetic markers for the disorder, and HCG. It is an advantage for our study that there is no significant difference between the groups in terms of age, gender,

education period, BMI, and smoking history, which are known to have effects on neuropsychiatric measurements and oxidative stress parameters. We found a moderate-level positive relationship between NO and Eyes Test, and a moderate-level negative relationship between SOD and the Eyes Test. We did not find any significant relationship between social cognition and other oxidative stress parameters. There was not any relationship between working memory scores and oxidative stress parameters. It has been reported that free radicals may accumulate in the prefrontal cortex, causing neuron damage and ultimately leading to cognitive symptoms (Maas et al. 2017). In various studies with different methodologies, improvement in cognitive functions with N-acetylcysteine treatment in patients with schizophrenia (Yolland et al. 2020), relationship between greater lipid peroxidation (assessed by TBARS) and impaired working memory (Cruz et al. 2021) an also significant relationship between SOD levels and cognitive dysfunction in late-age schizophrenia was shown (Huo et al. 2021) Besides the small number of publications stating that there is no link between oxidative stress and social cognition, others claim that there is (Xie et al. 2019). Oxidative stress markers used in the studies are also different may affect the results. In this study, the lack of a significant relationship between social cognition, working memory, and oxidative stress parameters might be related to the sample group's clinical features or the tasks selected. Furthermore, the absence of any relationship between social cognition and oxidative stress may be due to the normalization of oxidant and antioxidant levels with compensatory mechanisms (Gonzalez-Liencres et al. 2014). Thereafter, increased GPX may be an indicator of increased oxidative stress has been stated, and may be an indicator of low basal cognitive function or cognitive deterioration (Espinosa-Diez et al 2015, Ahmed et al. 2021).

In this study, social cognition was found to reveal a moderate correlation between working memory, and general intellectual skills. However, this issue is controversial in the literature. According to Green and Nuechterlein, social cognition and neurocognition cannot be evaluated independently of each other (Green & Nuechterlein 1999). On the other hand, neurocognitive areas such as language and memory are spared in people with a frontal or prefrontal injury who display some social behavior impairments, and there is the preservation of neurocognitive areas in prosopagnosia, which is known as face recognition disorder. Both disorders are examples of the discrepancy between social cognition and neurocognition (Anderson et al. 1999). These clinical examples also suggest that different neuroanatomical circuits are regulating these regions. According to Fett et al "Even if social cognition is based on neurocognition, it is largely different from neurocognition" (Fett et al. 2011). Also, Sergi et al. stated that neurocognition and social cognition are different but highly related constructs (Sergi et al. 2007).

Although this study found a correlation between neurocognition and general intellectual skills. It was found that approximately 18% of the variations in social cognitive performance can be attributed to working memory and 30.4% to general intellectual skills. Both of these factors can account for 35.6 percent of the variance in the Eyes Test. This rate is very low when compared to Vauth et al's assumption. In that study, non-social cognition accounts for 83 percent of the disparities in social cognition performance. It's possible that the difference in results is due to the type of social cognition scales used (Vauth et al. 2004). Because Vauth et al. used the Situational Feature Recognition Test and the Schema Component Sequencing Task-Revised. However the Eyes Test gives information regarding ToM and emotion recognition skills while requiring relatively fewer language skills. In this regard, we believe it is more sensitive when testing social cognition in mental diseases where language skills are impaired, such as schizophrenia. According to the findings of our study, social cognition, neurocognition, and general intellectual skills are different but strongly related constructs.

Endophenotypic deficits are present in first-degree relatives of patients as well as in patients themselves (Greenwood et al. 2007). One of the endophenotype criteria specified by Gottesman and Gould is that the patient's first-degree relatives differ significantly from the control cases (Snitz et al. 2006). In our study, in addition to the criterion of being detected more frequently in first-degree relatives of patients than in the general population, the parameters exhibiting significant differences between patients and controls were defined as an endophenotype. The working memory (d'prime) value and Eyes Test were found to be significantly lower in RG than in HCG. There was no difference between PG and the RG. This finding is compatible with studies in the literature (Glahn et al. 2014, Park & Gooding 2014, Tikka et al 2020). It is important that these differences are found among similar groups in terms of age, gender, educational status, cigarette consumption, and BMI, all of which have been shown to influence social cognition and neurocognition. These results suggest that both tests can be evaluated as endophenotypes according to the criteria of Gottesman and Gould. The difference in social cognition that was exhibited between the groups disappeared when working memory and general intellectual skills were adjusted. However, due to the group variable's middle-range effect size (partial eta square = 0.067), we believe that both working memory and social cognition can be evaluated as endophenotypes.

In addition to that, the group differences in Eyes Test scores became insignificant which may be due to the insufficient number of samples. Furthermore, in disorders such as schizophrenia, in which semantic and syntactic speech abnormalities and deficiencies in pragmatic language use are seen, the Eyes Test employed in this study is a suitable test to evaluate social cognition independent of language skills. According to some publications, the Eyes Test may not be a sensitive enough assessment to evaluate first-degree relatives of schizophrenia who have not yet reached the diagnostic threshold (Kelemen et al. 2004). Because we believe that when the test difficulty increases, the difference between RG and HCG will increase with the second-order ToM tests. However, when working memory and RSPM were controlled, the Eyes Tests revealed reduced discrimination, implying a superficial endophenotype. The probability of detection in first-degree relatives decreases as the marker moves away from its genetic origin. Another explanation is that neurocognition and social cognition share genetic susceptibility genes.

There was no significant difference when the PG, RG, and HCG were compared to evaluate the oxidative stress measured in terms of Total Glutathione, CAT, SOD, MDA, and NO values. Furthermore, the HCG had lower GPx values than the PG and RG. There was no statistically significant difference between the PG and the RG. The usual expectation in oxidative stress studies on schizophrenia patients (Akyol et al. 2002, Dadheech et al. 2006, Miljevic et al. 2018, Raffa et al. 2011, Zhang et al. 2003), relatives of patients, early stage of psychosis or ultra-high risk psychosis (Zeni-Graiff et al, 2019, Ventriglio et al. 2021) is an increase in oxidative stress and a decrease in antioxidant mechanisms our findings appear to contradict the literature. Nevertheless, there are also findings different from the decrease in antioxidants in studies. For example, Buosi et al. (2021) displayed higher CAT levels and lower SOD levels in schizophrenia patients compared to healthy controls. They argued that this difference between antioxidants may be related to the different effects of various cigarette ingredients on antioxidants. Conus et al. (2018) also stated that elevation in antioxidant levels can be detected during the first period of the psychosis (FEP) or in a particular patient subgroup. Besides, they said that the patients who have higher baseline GPx activity may show better improvement during antioxidant treatment. The patients included in our study are not FEP patients, but they may be from a particular subgroup of patients. Identifying different subgroups in terms of oxidative stress is important in terms of identifying individuals who could improve with antioxidant treatments and in this sense, applying targeted treatments (Ermakov et al. 2021). Another explanation for the higher level of GPX in this study may be the participants were selected from patients who received long-term regular treatment. Consistent with this explanation, it was reported an increase in GPx levels and a reduction in serum antioxidants in patients who did not receive medication treatment somewhat reverted after antipsychotic treatment (Tsai et al. 2013, Xuan et al. 2011). It has even been reported that oxidative damage may increase especially in the use of typical group antipsychotics, and there may be various differences in terms of oxidative damage depending on which antipsychotic is used (Ermakov et al. 2021).

The fact that a drug-free period was not provided in our study is a limitation. Nevertheless, the fact that this difference was also found in relatives of patients who did not receive any treatment in our study indicates that this difference is due to genetic sensitivity rather than medication treatment. In addition, the absence of a relationship between oxidative stress and social cognition was explained by the compensatory mechanisms (Gonzalez-Liencres et al. 2014). Similarly, elevated antioxidant levels in schizophrenia and high-risk psychosis may be associated with compensation was reported (Espinosa-Diez et. al 2015, Ahmed et al 2021). Therefore increase in GPx level was thought to be a result of a compensatory mechanism in response to increased oxidative stress in patients and patients' relatives in our study. Furthermore, our groups were similar in terms of age, smoking, body mass index, and the absence of additional psychiatric disease histories, reducing the effect of oxidative stress from these parameters to lower levels. In this sense, we concluded that our assessment was correct and that the increase in GPx level represents an important endophenotype.

Limitations

The burden of caregivers in the RG was not measured in this study, which is a significant limitation. Although no such study has been identified among relatives of schizophrenia patients, there have been articles showing that caregivers of Alzheimer's patients had higher psychological morbidity (González-Salvador et al. 1999). Considering that schizophrenia can cause severe disability in patients, caregiver burden may affect cognitive functions and oxidative stress parameters. To control for this factor, relatives were also assessed for current psychiatric diseases, and those with additional diseases were excluded from the study. Furthermore, the subjects in the patient group were on regular medications. The use of measurement tools that can provide quantitative data on the level of caregiver burden, on the other hand, would provide more accurate results.

Another limitation is that the patient's family is not homogeneous in terms of siblings, parents, and children. Endophenotype studies with a homogeneous group of children of schizophrenia patients have been reported to yield more accurate results. In this study the majority of the participants were siblings. This could have resulted in an existing marker not being detected. However, according to a comprehensive meta-analysis, the type of relative had no significant effect on the variables (Lavoie et al. 2013).

Another significant limitation is that serum oxidative stress parameters have only been studied. It is questionable whether serum values fully reflect oxidative stress in the central nervous system. Moreover, oxidative stress markers may affect by many confounders such as the oxidant effect of antipsychotics, diet, unhealthy lifestyle, ethnicity, and genetic factors (Ballesteros et al. 2013) although some factors were controlled.

N-back and Eyes test which are widely used instruments in neurocognitive assessment, could not assess all of the social and non-social cognitive domains that may be impaired in patients. In future studies, it was suggested further addition more tests to measure the relationship between oxidative stress and cognitive impairment.

In our study, some of the 'relatives' rejection of participating in the study may be related to paranoid personality traits or sub-threshold psychotic symptoms. Since these individuals were not evaluated, the relative sample may have performed better than expected. This could have resulted in an inability to generalize the results and a failure to demonstrate an existing relationship.

CONCLUSION

We concluded in this study that social cognition, neurocognition, and general intellectual skills are different but strongly related constructs besides, GPx levels, social cognition as measured by the Eyes Test, and working memory as measured by the n-back task can be used as endophenotypes. Identifying the GPx level as a strong and highly specific endophenotype in our study is critical. Endophenotypes guide treatment targets even after the disease has developed. In this regard, it is important to assume that, in addition to psychopharmacological treatments, interventions to reduce oxidative stress and approaches to improve cognitive skills will have a positive impact on the disease's progression. We hope that this study and future studies will determine the endophenotypes for psychiatric disorders to develop targeted prevention and treatment programs.

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Correspondence:
Dr Selma Cilem Kizilpinar, Department of Psychiatry,
Adana City Research and Training Hospital,
Adana, Turkey,
uygurcilem@gmail.com, +90 506 800 41 99