Visual processing and BDNF levels in first-episode schizophrenia

ABSTRACT

Objective: Previous studies have shown that patients diagnosed with schizophrenia (SCZ) have deficits in early visual processing, namely contrast processing. These impairments contribute to higher-level dysfunctions associated with abnormal neuronal plasticity. The brain-derived neurotropic factor (BDNF) is an important measure to investigate neuroplasticity in some visual functions like visual learning and visual perception. In this study, we investigated the relationship between contrast processing and BDNF levels in first-episode SCZ patients. Methods: Thirty-nine healthy controls and 43 first-episode SCZ patients were enrolled. Contrast sensitivity measurements were conducted using spatial frequencies ranging from 0.2 to 16 cycles per degree (cpd). Results: Our results suggested that the SCZ group had higher contrast sensitivity than healthy controls for all frequencies, except for the middles. They also showed decreased BDNF levels compared to controls. Surprisingly, significant negative correlations were found between BDNF levels and contrast sensitivity for female patients for middle and high spatial frequencies. Conclusions: Our results provide support for (i) the association of SCZ with alterations of magno- and parvocellular pathway functioning and for (ii) decreased BDNF levels in first-episode SCZ patients.

Keywords: Schizophrenia; contrast processing; visual functions; brain-derived neurotrophic factor; first-episode.

1. Introduction

Schizophrenia (SCZ) is a severe psychiatric disease, associated with significant health, social, and economic concerns (1). SCZ is also complex and heterogeneous, encompassing several symptoms like hallucinations or delusions, paranoia, disorganized thought or behavior, affective blunting, perceptual and cognitive dysfunctions. Attempts have been made to find reliable neurobiological markers for SCZ (Fernandes et al., 2018; Peng et al., 2007; Tomasik et al., 2016).

Low-level visual processing could serve as a biomarker since SCZ patients show impairments in contrast processing (Fernandes et al., 2019; Zemon et al., 2020) and color discrimination (Fernandes et al., 2018; Shuwairi et al., 2002). These impairments reflect dysfunctions in two main visual pathways – the magnocellular and parvocellular pathways. The magnocellular pathway processes low-resolution visual information (less than 3 cpd) which is forwarded to neurons in the dorsal visual pathway responsible for processing low contrast and moving stimuli (Fernandes et al., 2018; Merigan and Maunsell, 1993). Neurons of the parvocellular pathway relay high spatial frequencies and chromatic information to neurons primarily within the ventral visual pathway (Merigan and Maunsell, 1993). These pathways show a great deal of interplay between each other in cortex.

Results of contrast sensitivity and color processing studies, however, were often mixed due to the use of antipsychotics or other medication to treat SCZ to treat schizophrenia. Some studies reported that SCZ patients taking antipsychotics had impairments for contrast and color processing (6,7,10). Other studies found that unmedicated SCZ patients had better contrast processing than medicated patients (11), but that both group showed worse performance than controls (12). Such findings need to be considered carefully, though, as the sample size of unmedicated SCZ patients was often small,

which could have affected the findings. It is also important to mention, however, that studies investigating first-episode are scarcely, and then the picture is not that simple. Also, there is a consistency in studies showing that patients on later stages of the disease have visual impairments, which is still matter of study on first-episode SCZ.

There is dysfunction in the magno- and parvocellular systems in SCZ (13–15), which increases the level of internal noise in the perceptual system (16). The nature of the mismatch and the level of internal noise is determined by the stage of the disease. Most studies report a dysfunction of the magno- and parvocellular systems in SCZ (Doniger et al., 2002; Fernandes et al., 2019; Kantrowitz et al., 2009; Zemon et al., 2020). Nevertheless, a better visual contrast sensitivity of first-episode patients, in the low range of spatial frequencies, has been found using low spatial frequencies or different techniques. Then, it is essential to evaluate a wide range of spatial frequencies (13,19).

An important role in ensuring neuroplasticity is played by the brain derived neurotrophic factor (BDNF), which is widely found in the neocortex, hippocampus, amygdala, and cerebellum (20). BDNF is one of the most widely studied molecules in psychiatric disorders (21). BDNF is involved in the transmission of nerve signals, enhancing synaptic transmission, and maintaining normal brain functions (22,23).

The use of BDNF as a clinical marker of SCZ has been discussed in previous studies (21,24–26). Many studies have shown lower levels of BDNF in the serum and plasma of SCZ patients compared to control groups, even in SCZ patients who did not receive pharmacological treatment (Buckley et al., 2007; Chen et al., 2009; Chiou and Huang, 2017; Durany et al., 2001; Rizos et al., 2008; Toyooka et al., 2002). For example, Chen and colleagues (2009) reported that the BDNF levels of 88 patients who experienced their first episode and who had never taken medication were significantly lower than healthy age- and gender matched control subjects. In addition, lower levels of

BDNF were observed in patients with the paranoid subtype of SCZ (ref?). Similar results were reported in studies with SCZ patients treated with neuroleptics (24,29,32,33). In their meta-analysis of 41 studies, Fernandes et al., (2015) found that BDNF levels was accentuated with disease duration, but not correlated with the severity of symptoms. This might be explained by differences in BDNF levels in serum and plasma. The level of BDNF is considered as a marker of the stage of the disease, with more lower levels of BDNF indicating a later stage of SCZ (Fernandes et al., 2015).

Studies of the level of BDNF in patients with the first episode of SCZ (Chen et al., 2009) and who did not receive long-term treatment suggest the possibility that decreased levels of BDNF may be a marker of SCZ, which in turn may be related to impaired visual performance. Visual dysfunctions in SCZ, in particular contrast sensitivity, has already been shown to serve as a marker of the stage of illness. However, despite some studies on first-episode SCZ patients, to this date there is no report of a study comparing a range of spatial frequencies and the association of BDNF levels with visual processing. To goal of the present study is address this gap in the literature. Our main hypotheses are that unmedicated first-episode SCZ patients (1) will show increased contrast sensitivity compared to controls; and (2) will show decreased levels of BDNF compared to controls; and (3) will have a negative correlation between BDNF levels and contrast sensitivity.

2. Method

2.1 Participants

Thirty-nine healthy controls (HCs; mean age = 21.3 years, *SD* = 3.0 years) and 43 first-episode patients diagnosed with schizophrenia (SCZ; mean age = 21.4 years, *SD* = 2.8 years) in the 18-48 year old age range were enrolled for this study.

The SCZ group were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (34). The exclusion criteria were: (a) current use of any antipsychotic medication, (b) presence of comorbidities (psychiatric, cardiovascular, vascular, etc.) (Fernandes et al., 2018), and (c) current history of a neurological disorder (other than SCZ), cardiovascular disease, history of head trauma, history of contact with substances such as solvents, current or previous drug or substance abuse, and current use of medications that may affect visual processing and cognition (e.g., mood stabilizers). Patients were recruited from private clinics and never exposed to neuroleptics at the time of admission to the study and the HCs were recruited from the general population. The HCs had no neuropsychiatric disorders according to the Structured Clinical Interview for the DSM (35). For patients who used benzodiazepines (21 patients), we stipulated that the maximum dosage should be 20 mg/day (diazepam dose equivalent).

All SCZ patients underwent evaluation with structured interview including the Scale for the Assessment of Negative Symptoms (SANS) (36), the Positive and Negative Syndrome Scale (PANSS) (37), and the Brief Psychiatry Rating Scale (BPRS) (38). They rated according to their symptoms during the month before intake of any medication. This evaluation was further correlated with contrast values.

All participants had a corrected or uncorrected acuity of at least 20/20 (binocular viewing) as assessed using a Snellen chart. Participants had no retinal abnormalities on fundoscopic examination or optical coherence tomography.

2.2 Brain-derived neurotrophic factor - BDNF

We measured BDNF in serum samples as they are more reliable than plasma samples (39). The serum was centrifuged within 20 minutes and stored at -50°C until analysis (IRBLleida Biobanc). BDNF serum levels were measured with an enzyme immuno-

assay (ELISA) kit (R&D Systems, Germany) according to the manufacturer's instructions. Results were expressed as ng/ml. Coefficients for intra- and inter-assay were <10%. We followed the manufacturer's instructions to limit cross-reactivity (there were no cross-reactivity).

2.3 Stimuli and Apparatus

The stimuli were linear, vertically oriented sine-wave gratings with spatial frequencies of 0.6; 2.8; 4.5; 8.0 and 16.0 cpd. Each grating pattern subtended 6.0 º deg at the viewing distance. They were presented at 2.5 º deg spatial offset from the fixation cross (left or right). The stimuli were presented on a 21.5" Apple iMac monitor (MHK23BZ/A) with a display resolution of 1920 × 1080 pixels and a refresh rate of 60 Hz. All measurements were performed with binocular vision. The CS-100A Chroma Meter (Konica Minolta, Japan) was used for the gamma-correction. Mean luminance was 59 cd/m² and used as the background luminance. The viewing distance was 1.7 m. The participant's head were stabilized using forehead and chin rests.

2.4 Procedures

Detailed task instructions were provided to the participants prior to the start of the tests, and the need of accuracy over speed was emphasized. A practice session to familiarize participants with the procedure and to avoid misunderstanding was performed (5 minutes). This procedure was conducted in a quiet, comfortable, room. Each session lasted from 20 to 25 minutes. To avoid fatigue, participants were encouraged to take breaks at their discretion.

The participants responded whether the grating was presented on either the left or right side of the computer screen (2-AFC). The task was easily grasped by the participants. An adaptive staircase procedure varied the stimuli, which was computer con-

trolled and depended on the participant's response. After two consecutive correct responses, contrast was decreased by 0.6 log units, and after every incorrect response, contrast was increased by 1.0 log units. The staircase ended after 10 contrast reversals using the smallest step size (0.2 log units). The software calculated the contrast threshold for each spatial frequency taking the mid-point between the mean for peaks and troughs. The average square of the deviations was used to calculate the peak variance, and the square root of variances was calculated and averaged. The average of the last 10 reversals were used to determine the threshold for each spatial frequency.

This staircase procedure translates to an accuracy of target detection of 75% on a psychometric function (40). The initial contrast for each spatial frequency was above threshold. Each stimulus had an exposure time of 600 ms with an intertrial interval of 300 ms (note: participants had an unlimited amount of time to respond before the intertrial interval).

2.5 Statistical Analysis

The data distribution for each spatial frequency within each group was assessed using measures of central tendency and measures of dispersion. Distributions for each group were compared using the Monte Carlo method for skewness and kurtosis, and the cut-off value was >1.96.(41,42).

Both groups' data were characterized by normal distributions, and so parametric tests were performed to analyse continuous data. For comparisons between groups (bio-socio-demographic), the *t*-test for independent measures was conducted.

A general linear model was used to analyse the data from CSF measurements. Absence of multivariate outliers was checked assessing Cook's Distance ($\frac{4}{n-k-1}$). There were no outliers. Canonical discriminant analysis was used as a post hoc test. Omega squared (ω^2) was used to assess effect sizes (for small sample sizes, ω^2 reduces bias)

(43). Bonferroni's correction was applied to adjust the *p*-value and reduce the probability of Type 1 errors. Product-moment and point-biserial correlation analysis were performed to investigate determine any associations between demographics and the CSF results.

2.6 Ethics statement

The present study followed the ethical principles of the Declaration of Helsinki and was approved by the Committee of Ethics. Written informed consent was obtained from all of the participants.

3. Results

3.1 Demographics characteristics

The characteristics of the participants are summarized in Table 1. The groups did not differ in age [t (80) = 0.32, p = 0.08], level of education [t (80) = 0.17, p = 0.86], or the ratio of males to females [χ^2 (1) = 0.09, p = 0.92].

Table 1. Demographics characteristics of the sample

	Controls (N = 39)		**First-onset SCZ (N = 43)**		
	Mean (SD)	**Median (sIQR)**	**Mean (SD)**	**Median (sIQR)**	t / χ^2
Age, years	21.4 (2.8)	20.0 (4.5)	21.3 (3.2)	20.0 (5.5)	0.320
Education, years	12.2 (1.8)	12.0 (2.5)	12.4 (1.9)	12.0 (2.5)	0.172
Male/Female	28/15	-	25/14	-	0.009
BPRS Total	0.0	0.0	35.0 (5.3)	34.0 (10.5)	22.4*
SANS	0.0	0.0	4.9 (2.1)	5.0 (6.5)	14.1*
PANSS Positive	0.0	0.0	8.7 (1.4)	8.4 (3.0)	41.3*
PANSS Negative	0.0	0.0	7.2 (1.0)	7.0 (5.5)	52.3*
PANSS Total	0.0	0.0	55.0 (8.9)	54.0 (19.5)	38.9*

BDNF (ml)	15.4 (1.3)	15.5 (2.9)	7.2 (2.8)	6.5 (5.5)	17.0*

Note: *p < 0.001

3.2 Contrast processing

Identical statistical conclusions were obtained when patients treated with benzodiazepines were excluded from the analysis, and so we will report the results in the whole group of patients.

The results of the CSF measurements are shown in Figure 1. There was statistically significant difference between the groups, (F (5, 76) = 42.97, p < 0.001; Pillai's trace = 0.74, $\omega 2$ = 0.72 with a 95% CI of 0.63 to 0.78). Post hoc testing revealed significant differences at all frequencies, except 4.5 cpd (p = 0.10). The first-episode SCZ group had better performance for the 0.6 cpd (p < 0.001, Hedges' g = 1.76 with a 95% CI of 1.26 to 2.30), 2.8 cpd (p = 0.034, Hedges' g = 0.47 with a 95% CI of 0.04 to 0.92), 8.0 cpd (p < 0.001, Hedges' g = 1.99 with a 95% CI of 1.47 to 2.54) and 16 cpd (p = 0.006, Hedges' g = 0.62 with a 95% CI of 0.18 to 1.06) compared to HCs.

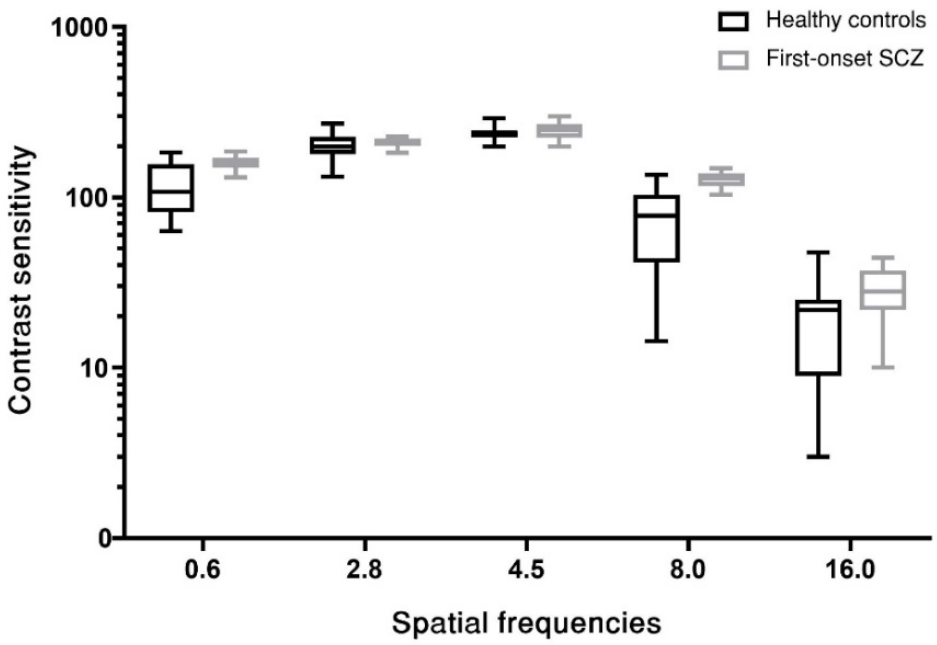

Fig. 1. **Contrast sensitivity values for the two groups (healthy controls and first-onset SCZ patients).** Solid lines represent mean sensitivity, the boxes represent the quartiles and the whiskers represent the range.

3.3 Correlation analysis

3.3.1 Correlation analysis between contrast sensitivity and BDNF

No significant correlations between contrast sensitivity and BDNF levels in healthy controls were found. In the SCZ group, significant correlations between the level of BDNF and contrast sensitivity were observed only when they were divided by gender. A statistically significant negative correlation between the BDNF level and contrast sensitivity was found in female patients for 4.5 cpd and 16 cpd (r = -0.58; r = -0.53, $p < 0.05$) (Figure 2).

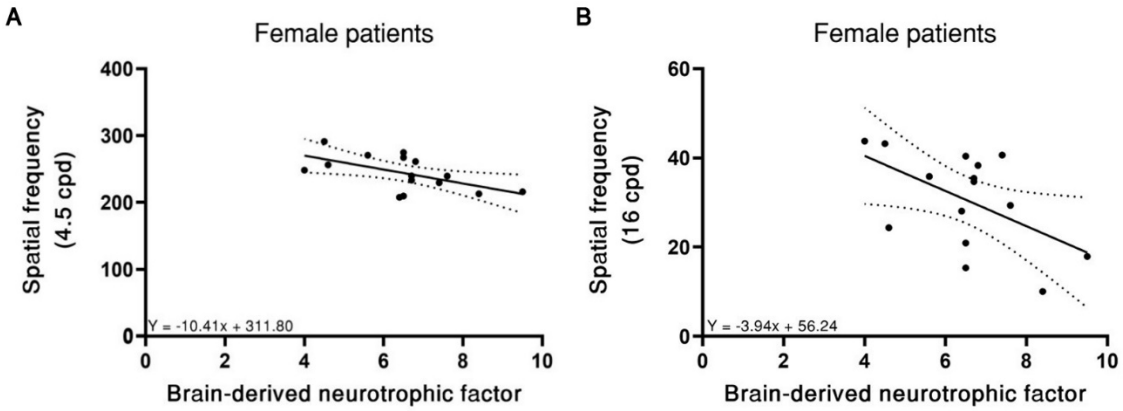

Fig. 2. Correlation between the BDNF levels and contrast sensitivity in female patients for 4.5 cpd (A) and 16 cpd (B).

3.3.2 Correlation analysis between contrast sensitivity, BDNF and clinical variables

A significant correlation was found between CS at low spatial frequency (0.6 cpd) and negative symptoms assessed with the SANS in males (r = 0.48, n = 28, $p < 0.05$) and females (r = 0.58, n = 15), $p < 0.05$). There was also a significant correlation between CS

at high spatial frequency (16.0 cpd). Females also showed a significant correlation between CS at high spatial frequency (16.0 cpd) and SANS score ($r = 0.55$, $p < 0.05$) as well as a pronounced inverse correlation between negative symptoms and the level of BDNF ($r = -0.72$, $p < 0.05$). A significant correlation was found between duration of disease and PANSS total score ($r = 0.48$, $p < 0.001$) as well as duration of disease and CS at mid-spatial frequency (give spatial frequency, $r = 0.6$, $p < 0.05$).

In connection with the detection of sex differences and the influence of the duration of the disease, a correlation analysis of contrast sensitivity and BDNF levels was performed for subgroups of patients with a disease duration of up to 3 months (0-3 months, n = 25) and more than 3 months (3-6 months, n = 18). All patients with a disease duration of less than 3 months showed a significant correlation between contrast sensitivity in the range of low spatial frequencies (0.6 cpd) and the severity of both positive and negative symptoms ($r = 0.49$, $p = 0.01$; $r = 0.40$, $p = 0.05$).

Female SCZ patients with less than 3 months of disease had a strong correlation between BDNF levels and contrast sensitivity for mid-spatial frequency (4.5 cpd; Figure 3A; r = -0.73, p = 0.04), as well as negative symptoms (r = -0.72, p = 0.04). In the subgroup of women suffering from the disease for more than 3 months, the level of the BDNF correlated with contrast sensitivity at 16 cpd (Figure 3B; r = -0.79, p = 0.03), the severity of positive (r = 0.79, p = 0.03) and negative symptoms (r = 0.86, p = 0.01). There was also a correlation between negative symptoms and contrast sensitivity at 16 cpd (r = -0.81, p < 0.05).

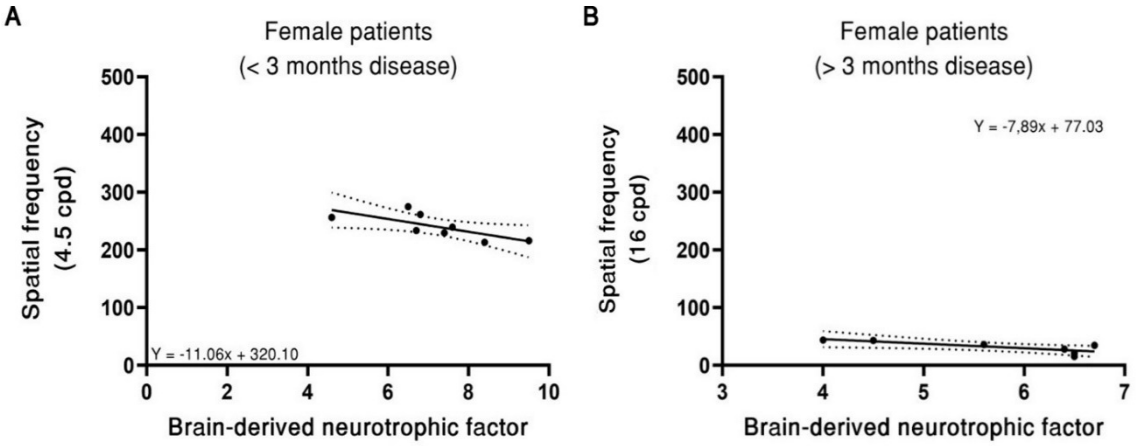

Fig. 3. Correlation between BDNF levels and contrast sensitivity in female patients suffering from SCZ for less than 3 months (A) and more than 3 months (B).

Male SCZ patients (n = 17) with less than 3 months of disease presented also a strong correlation between negative and positive symptoms at 0.2 cpd ($r = 0.70$, $p = 0.002$; $r = 0.58$, $p = 0.01$). In a subgroup of men suffering from SCZ for more than 3 months (n = 11), there was a correlation between negative symptoms and contrast sensitivity at 16 cpd ($r = -0.81$, $p < 0.05$).

4. Discussion

First episode patients with schizophrenia showed better contrast sensitivity than controls. Increased CS in the low-spatial frequency range indicates association with the magnocellular pathway and increased CS in the high-spatial frequency range association with the parvocellular pathway. Previous studies performed conducted on untreated first-time episodes of SCZ have shown an increase in sensitivity only in the low spatial frequencies (5,14). High spatial frequencies have not been previously examined in first episode SCS to our knowledge.

Kéri and Benedek (44) also observed an increase in contrast sensitivity to magnocellular system-specific stimuli in people at high risk for psychosis compared to healthy controls. Contrast sensitivity at the lower spatial frequencies is believe to be mediated by the magnocellular system. The magnocellular system also mediates peripheral vision and

motion perception (13,45). An increase in contrast sensitivity in the low spatial frequency range in the untreated first episode of SCZ, compared with a healthy control, was shown by the authors in the task of comparing two Gabor elements (13,45). Cadenhead et al. (46) reported that untreated SCZ (n = 5) showed an enhancement of sensitivity for achromatic grating pattern that would be detected by the magnocellular system, but a decrease in chromatic sensitivity which is believed to be mediated by the parvocellular system. The parvocellular system provides local image analysis, and according to the authors, a similar violation of the parvocellular system was typical for patients with schizotypal disorder. According to the authors, a similar violation of the parvocellular system was typical for patients with schizotypal disorder. The number of non-treated SCZ patients in those studies was limited, though, which precludes further comparisons.

The increased sensitivity of the parvocellular system in untreated first episode SCZ patients was unexpected, since the literature suggests no change or a reduction in sensitivity (46).

The significant decrease in BDNF in patients with untreated first episode of SCZ, compared to healthy controls, here is also consistent with previous studies (27,28,47,48). Thus, our data provide additional supporting evidence to the idea that low levels of a neurotrophic factor contribute to the abnormal neuron plasticity observed in patients with SCZ. We did not observe any age-related effects on the BDNF levels, but a trend in the influence of the gender of patients, with a large decrease in BDNF levels of patients with SCZ.

In a study by Jindal and colleagues (2010), serum BDNF levels were measured in 41 patients with an untreated first episode of psychosis (24 with SCZ, schizoaffective disorder, or schizophrenic-like disorder, and 17 with psychotic disorders unrelated to SCZ) and 41 their age-matching healthy controls. Patients with SCZ had lower serum

BDNF levels than the control group, while patients with non-schizophrenic psychosis did not differ from the control group. The authors did not observe any age-related effects on the BDNF level but reported a trend in the influence of the gender of patients, with a large decrease in patients with SCZ.

Interestingly, in our study, significant correlations between BDNF levels, contrast sensitivity, and symptoms were observed almost exclusively in female SCZ patients, albeit male SCZ had a few significant correlations too. Similar results were reported in Chinese female patients (49), who had lower levels of BDNF compared to the males and other female patients with SCZ, compared to male patients, as well as women in the control group (50). Thus, gender differences may affect the results of the analysis of BDNF protein levels in patients with SCZ, but the reasons for this phenomenon are unknown and further research is needed.

The influence of the disease duration factor was also established. Patients with a disease duration of less than 3 months showed a correlation of BDNF levels with contrast sensitivity of perception of average spatial frequencies and negative symptoms. At the same time, patients with a disease duration of more than 3 months (3-6 months) showed a correlation between the level of BDNF and the contrast sensitivity of perception of high spatial frequencies and both negative and positive symptoms. The results of a study by Rizos et al. (2010) show that low serum BDNF levels at the onset of SCZ are associated with the duration of untreated psychosis, and this may be associated with an acute neurodegenerative reaction during the untreated phase of psychosis. It is important to mention, however, that we are unable to make such strong assumption between BDNF levels and improvement of contrast sensitivity. This might be related to an increase of dopamine on first-episode, but a longitudinal study can bring light to this discussion. However, our

study was the first to investigate contrast sensitivity, BDNF levels and correlate with clinical variables using different techniques and a range of spatial frequencies.

The main limitation of this study was that the ELISA set used in this study cannot distinguish between the isoforms of BDNF (proBDNF and matureBDNF). Second, some patients took antidepressants (escitalopram, fluoxetine, paroxetine, mirtazapine, and venlafaxine). In addition, since sleep deprivation affects BDNF levels (51), the lack of sleep quality control the night before data collection may also have affected our results. The possibility of generalizing our results may also be limited by the heterogeneity of the sample, since we did not separate patients by the form of SCZ.

Funding: The National Council for Scientific and Technological Development (CNPq), Brazil (305258/2019-2), and Coordination for the Improvement of Higher Education Personnel (CAPES) supported this study

Competing interests: The authors declare that they have no competing interests.

Authors' contributions: IS, NS, JK, AA, FM, PB and TPF helped with data interpretation and helped to draft the manuscript. NS and TF participated in its coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

References

1. Mathers CD, Loncar D. Projections of Global Mortality and Burden of Disease from 2002 to 2030. PLOS Med. 2006 Nov 28;3(11):e442.

2. Fernandes TMP, Andrade MJO de, Santana JB, Nogueira RMTBL, Santos NA dos. Tobacco Use Decreases Visual Sensitivity in Schizophrenia. Front Psychol [Internet]. 2018 [cited 2018 May 17];9. Available from: https://www.frontiersin.org/articles/10.3389/fpsyg.2018.00288/full

3. Peng Z, Chen X, Wei Z. Cryptochrome1 maybe a candidate gene of schizophrenia. Med Hypotheses. 2007;69(4):849–51.

4. Tomasik J, Rahmoune H, Guest PC, Bahn S. Neuroimmune biomarkers in schizophrenia. Schizophr Res. 2016;176(1):3–13.

5. Fernandes TP, Shaqiri A, Brand A, Nogueira RL, Herzog MH, Roinishvili M, et al. Schizophrenia patients using atypical medication perform better in visual tasks than patients using typical medication. Psychiatry Res [Internet]. 2019 Mar 6 [cited 2019

Mar 11]; Available from: http://www.sciencedirect.com/science/article/pii/S0165178118315804

6. Zemon V, Herrera S, Gordon J, Revheim N, Silipo G, Butler PD. Contrast sensitivity deficits in schizophrenia: A psychophysical investigation. Eur J Neurosci [Internet]. [cited 2021 Feb 2];n/a(n/a). Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/ejn.15026

7. Fernandes TMP, Silverstein SM, Butler PD, Kéri S, Santos LG, Nogueira RL, et al. Color vision impairments in schizophrenia and the role of antipsychotic medication type. Schizophr Res [Internet]. 2018 Sep 7 [cited 2018 Oct 2]; Available from: http://www.sciencedirect.com/science/article/pii/S0920996418305516

8. Shuwairi SM, Cronin-Golomb A, McCarley RW, O'Donnell BF. Color discrimination in schizophrenia. Schizophr Res. 2002 May 1;55(1–2):197–204.

9. Merigan WH, Maunsell JH. How parallel are the primate visual pathways? Annu Rev Neurosci. 1993;16:369–402.

10. Kéri S, Antal A, Szekeres G, Benedek G, Janka Z. Spatiotemporal visual processing in schizophrenia. J Neuropsychiatry Clin Neurosci. 2002;14(2):190–6.

11. Kiss I, Fábián A, Benedek G, Kéri S. When doors of perception open: visual contrast sensitivity in never-medicated, first-episode schizophrenia. J Abnorm Psychol. 2010 Aug;119(3):586–93.

12. Braff DL. Impaired speed of information processing in nonmedicated schizotypal patients. Schizophr Bull. 1981;7(3):499–508.

13. Shoshina II, Shelepin YE, Vershinina EA, Novikova KO. The spatial-frequency characteristics of the visual system in schizophrenia. Hum Physiol. 2015 May 1;41(3):251–60.

14. Shoshina II, Shelepin YE, Semenova NB. Frequency-contrast sensitivity of visual stimulus perception in patients with schizophrenia treated with atypical and typical antipsychotics. Hum Physiol. 2014 Jan 1;40(1):35–9.

15. Shoshina II, Shelepin YuE, Konkina SA, Pronin SV, Bendera AP. Studies of the Parvocellular and Magnocellular Visual Channels in Health and Psychopathology. Neurosci Behav Physiol. 2014 Feb 1;44(2):244–8.

16. Shoshina I, Isajeva E, Mukhitova Y, Tregubenko I, Khan'ko A, Limankin O, et al. The internal noise of the visual system and cognitive functions in schizophrenia. Procedia Comput Sci. 2020 Jan 1;169:813–20.

17. Doniger GM, Foxe JJ, Murray MM, Higgins BA, Javitt DC. Impaired visual object recognition and dorsal/ventral stream interaction in schizophrenia. Arch Gen Psychiatry. 2002 Nov;59(11):1011–20.

18. Kantrowitz JT, Butler PD, Schecter I, Silipo G, Javitt DC. Seeing the world dimly: the impact of early visual deficits on visual experience in schizophrenia. Schizophr Bull. 2009 Nov;35(6):1085–94.

19. Silverstein SM. Visual Perception Disturbances in Schizophrenia: A Unified Model. Neb Symp Motiv Neb Symp Motiv. 2016;63:77–132.

20. Benarroch EE. Brain-derived neurotrophic factor: Regulation, effects, and potential clinical relevance. Neurology. 2015 Apr 21;84(16):1693–704.

21. Harrisberger F, Smieskova R, Schmidt A, Lenz C, Walter A, Wittfeld K, et al. BDNF Val66Met polymorphism and hippocampal volume in neuropsychiatric disorders: A systematic review and meta-analysis. Neurosci Biobehav Rev. 2015 Aug;55:107–18.

22. Fawcett JP, Bamji SX, Causing CG, Aloyz R, Ase AR, Reader TA, et al. Functional evidence that BDNF is an anterograde neuronal trophic factor in the CNS. J Neurosci Off J Soc Neurosci. 1998 Apr 15;18(8):2808–21.

23. Nakajima S, Numakawa T, Adachi N, Ooshima Y, Odaka H, Yoshimura A, et al. Self-amplified BDNF transcription is a regulatory system for synaptic maturation in cultured cortical neurons. Neurochem Int. 2015 Dec 1;91:55–61.

24. Fernandes BS, Steiner J, Berk M, Molendijk ML, Gonzalez-Pinto A, Turck CW, et al. Peripheral brain-derived neurotrophic factor in schizophrenia and the role of antipsychotics: meta-analysis and implications. Mol Psychiatry. 2015 Sep;20(9):1108–19.

25. Libman-Sokołowska M, Drozdowicz E, Nasierowski T. BDNF as a biomarker in the course and treatment of schizophrenia. Psychiatr Pol. 2015;49(6):1149–58.

26. Nurjono M, Lee J, Chong S-A. A Review of Brain-derived Neurotrophic Factor as a Candidate Biomarker in Schizophrenia. Clin Psychopharmacol Neurosci. 2012 Aug;10(2):61–70.

27. Chen DC, Wang J, Wang B, Yang SC, Zhang CX, Zheng YL, et al. Decreased levels of serum brain-derived neurotrophic factor in drug-naïve first-episode schizophrenia: relationship to clinical phenotypes. Psychopharmacology (Berl). 2009 Dec;207(3):375–80.

28. Chiou Y-J, Huang T-L. Serum brain-derived neurotrophic factors in Taiwanese patients with drug-naïve first-episode schizophrenia: Effects of antipsychotics. World J Biol Psychiatry Off J World Fed Soc Biol Psychiatry. 2017 Aug;18(5):382–91.

29. Durany N, Michel T, Zöchling R, Boissl KW, Cruz-Sánchez FF, Riederer P, et al. Brain-derived neurotrophic factor and neurotrophin 3 in schizophrenic psychoses. Schizophr Res. 2001 Oct 1;52(1–2):79–86.

30. Rizos EN, Rontos I, Laskos E, Arsenis G, Michalopoulou PG, Vasilopoulos D, et al. Investigation of serum BDNF levels in drug-naive patients with schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2008 Jul 1;32(5):1308–11.

31. Toyooka K, Asama K, Watanabe Y, Muratake T, Takahashi M, Someya T, et al. Decreased levels of brain-derived neurotrophic factor in serum of chronic schizophrenic patients. Psychiatry Res. 2002 Jul 31;110(3):249–57.

32. Buckley PF, Pillai A, Evans D, Stirewalt E, Mahadik S. Brain derived neurotropic factor in first-episode psychosis. Schizophr Res. 2007 Mar;91(1–3):1–5.

33. Zhang XY, Liang J, Chen DC, Xiu MH, Yang FD, Kosten TA, et al. Low BDNF is associated with cognitive impairment in chronic patients with schizophrenia. Psychopharmacology (Berl). 2012 Jul;222(2):277–84.

34. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). American Psychiatric Pub; 2013. 1679 p.

35. American Psychiatric Association. Structured Clinical Interview for DSM-5 (SCID-5) [Internet]. 2015. Available from: https://www.appi.org/products/structured-clinical-interview-for-dsm-5-scid-5

36. Andreasen NC. The Scale for the Assessment of Negative Symptoms (SANS): Conceptual and theoretical foundations. Br J Psychiatry. 1989;155(Suppl 7):49–52.

37. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13(2):261–76.

38. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale , The Brief Psychiatric Rating Scale. Psychol Rep. 1962 Jun 1;10(3):799–812.

39. Tsuchimine S, Sugawara N, Ishioka M, Yasui-Furukori N. Preanalysis storage conditions influence the measurement of brain-derived neurotrophic factor levels in peripheral blood. Neuropsychobiology. 2014;69(2):83–8.

40. Levitt H. Transformed up-down methods in psychoacoustics. J Acoust Soc Am. 1971 Feb;49(2):Suppl 2:467+.

41. Antonius R. Interpreting Quantitative Data with SPSS. SAGE Publications; 2003.

42. Tabachnick BG, Fidell LS. Using multivariate statistics, 5th ed. Boston, MA: Allyn & Bacon/Pearson Education; 2007. xxvii, 980 p. (Using multivariate statistics, 5th ed).

43. Lakens D. Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. Front Psychol [Internet]. 2013 [cited 2017 Mar 10];4. Available from: http://journal.frontiersin.org/article/10.3389/fpsyg.2013.00863/abstract

44. Kéri S, Benedek G. Visual contrast sensitivity alterations in inferred magnocellular pathways and anomalous perceptual experiences in people at high-risk for psychosis. Vis Neurosci. 2007 Apr;24(2):183–9.

45. Shoshina II, Shelepin YE. Contrast Sensitivity in Patients with Schizophrenia of Different Durations of Illness. Neurosci Behav Physiol. 2015 Jun 1;45(5):512–6.

46. Cadenhead KS, Dobkins K, McGovern J, Shafer K. Schizophrenia spectrum participants have reduced visual contrast sensitivity to chromatic (red/green) and luminance (light/dark) stimuli: new insights into information processing, visual channel function, and antipsychotic effects. Front Psychol. 2013;4:535.

47. Jindal RD, Pillai A, Mahadik SP, Eklund K, Montrose DM, Keshavan MS. Decreased BDNF in Patients with Antipsychotic Naïve First Episode Schizophrenia. Schizophr Res. 2010 Jun;119(1–3):47–51.

48. Rizos EN, Michalopoulou PG, Siafakas N, Stefanis N, Douzenis A, Rontos I, et al. Association of serum brain-derived neurotrophic factor and duration of untreated psychosis in first-episode patients with schizophrenia. Neuropsychobiology. 2010;62(2):87–90.

49. Yang Y, Liu Y, Wang G, Hei G, Wang X, Li R, et al. Brain-derived neurotrophic factor is associated with cognitive impairments in first-episode and chronic schizophrenia. Psychiatry Res. 2019 Mar;273:528–36.

50. Weickert CS, Lee CH, Lenroot RK, Bruggemann J, Galletly C, Liu D, et al. Increased plasma Brain-Derived Neurotrophic Factor (BDNF) levels in females with schizophrenia. Schizophr Res. 2019 Jul;209:212–7.

51. Guzman-Marin R, Ying Z, Suntsova N, Methippara M, Bashir T, Szymusiak R, et al. Suppression of hippocampal plasticity-related gene expression by sleep deprivation in rats. J Physiol. 2006 Sep 15;575(Pt 3):807–19.