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Color vision impairments in schizophrenia and the role of antipsychotic medication type

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ABSTRACT

Schizophrenia patients (SCZ) demonstrate deficits in many domains of mental functioning, including visual perception. An issue that has been relatively unexplored, in terms of explaining variation in visual function in SCZ, however, is medication use. The present study explored potential medication effects on color vision in SCZ, a process that is strongly linked to dopaminergic function in the retina. SCZ patients who had clear-cut either typical ($n = 29$) or atypical ($n = 29$) monotherapy, without any other concurrent medication, and a group of age- and gender-matched healthy controls participated in the study. Color vision was assessed by the Cambridge Colour Test, using the Trivector and Ellipse subtests. The results demonstrated impaired color perception in patients with schizophrenia, especially in those receiving typical antipsychotics, but these deficits were subtle and not generalized to all parameters. Our findings are consistent with the known neurophysiology of the retina and visual pathways, and with the effects of dopamine blocking medications, but the results should be carefully interpreted.

1. Introduction

There is a well-established literature documenting multiple aspects of visual processing impairment in schizophrenia, ranging from low- to high-level changes (for reviews see Silverstein (2016), and Silverstein & Rosen (2015). What has been relatively unexplored, however, is the issue of the effects of different antipsychotic medication on visual function. This is an important issue because: 1) typical vs. atypical antipsychotic medications have differing effects on neurotransmitter systems (Richtand et al., 2008); 2) certain disorders, such as Parkinson's disease provide human models demonstrating that changes in neurotransmitter levels (e.g., in dopamine) in both the brain and retina are associated with meaningful changes in visual function, including in color vision (Brandies and Yehuda, 2008; Djamgoz et al., 1997; Witkovsky, 2004); and 3) studies in healthy humans and animals demonstrate that augmentation of levels of neurotransmitters such as dopamine by administration of drugs such as L-DOPA enhances visual functions that are impaired in people with neurological and psychiatric disorders, including schizophrenia (Brandies and Yehuda, 2008; Caravaggio et al., 2018; Djamgoz et al., 1997; Nasser et al., 2013; Witkovsky, 2004). Regarding point 1 above, one of the main differences between atypical and typical medication is their pharmacology. Typical medications have strong affinity for dopaminergic D_1-D_2 receptors, causing several adverse effects and impairing visual sensitivity in part due to action on muscarinic acetylcholine receptors (Meltzer, 2013). On the other hand, atypical antipsychotics have a higher affinity for serotonergic 5-hydroxytryptamine-2A (5-HT_{2A}) than for D_1, causing less side effects and less overall reduction of dopamine.

Studies investigating the effects of medication on visual function in SCZ have generated mixed findings. Major concerns regarding these studies, however, were small sample sizes for each subgroup (e.g., Chen et al., 2003, $n = 8$ typical, $n = 25$ atypical), polypharmacy (e.g., Cadenhead et al., 2013; $n = 41$, taking concurrent drugs), and differences in disease course (e.g., Shoshina et al., 2014, patients in remission, incomplete remission and subremission). Furthermore, color vision in SCZ was not a focus for most of these, even though cone function and daytime vision in general is heavily determined by retinal dopamine (Witkovsky, 2004). Although Cadenhead et al. (2013) investigated chromatic thresholds for red/green stimuli, subjects were tested under isoluminance and investigation of specific color systems (e.g., Protan, Deutan and Tritan) was not possible.

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Shuwairi et al. (2002) investigated color discrimination in 16 patients with SCZ and 14 healthy subjects. They observed that SCZ patients had reduced color discrimination, and that this was unrelated to chlorpromazine equivalent doses. However, this study had several limitations including: 1) low power due to small samples sizes; 2) a variable duration for completion of all color vision tests ranging from one day to two months; 3) inclusion of tests (e.g., Lanthony D-15) with low reliability (Good, Schepler, & Nichols, 2005, 2015); and 4) the use of tests that assessed only suprathreshold performance, increasing the risk of confounds from low IQ (Cranwell, Pearce, Loveridge, & Hurlbert, 2015; Paramei, 2016; Paramei and Bimler, 2016) and generalized deficit factors such as poor motivation, sedation, and attentional impairment (Strauss, 2001).

An alternative assessment procedure is the Cambridge Colour Test (CCT) (Mollon and Regan, 2000), a computerized test that allows for control over the parameters of the stimuli, and the use of a psychophysical staircase procedure for estimating reliable discrimination thresholds, using repeated measurements (Paramei, 2012; Paramei and Oakley, 2014). The CCT tests have less within-subject variability in color discrimination when compared to other tests (Good, Schepler, & Nichols, 2005, 2005), and may be less susceptible to generalized deficit confounds related to loss of motivation or attention. The CCT has demonstrated validity in populations with retinal, subcortical and cortical dysfunction (Fernandes et al., 2017a, 2017b, 2018a, 2018b; Kumaran et al., 2018; Zachi et al., 2017; Feitosa-Santana et al., 2010). However, no studies have reported on color vision in SCZ using the CCT. The CCT assess color vision using two subtests: Trivector (three vectors corresponding to Protan, Deutan and Tritan confusion lines) and Ellipse (the use of MacAdam's ellipses corresponding to regions on a chromaticity diagram).

In this study, we used the CCT to test whether: 1) schizophrenia patients demonstrate abnormal color vision; and 2) medication type (typical vs. atypical antipsychotic medication) is differentially related to color vision. In Study 1, we investigated color discrimination using the Trivector test and a short version of the Ellipse test (to obtain a baseline) in 66 SCZ patients regardless of antipsychotic use. In Study 2, we examined 58 patients not included in Study 1, who had either clear cut typical or atypical antipsychotic monotherapy without any other concurrent medication, again using the Trivector and Ellipse tests.

2. Materials and methods

2.1. Ethics statement

The present study followed the ethical principles of the Declaration of Helsinki and was approved by the Committee of Ethics (registration number CCAE: 45774715.9.0000.5188) from the Federal University of Paraiba. Written informed consent was obtained from all of the participants.

2.2. Eligibility criteria

The SCZ patients were recruited from the Psychosocial Care Center, a community-based outpatient clinic. Psychiatrists at the same institution diagnosed SCZ according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013). The exclusion criteria for SCZ patients were: (a) antipsychotic polypharmacy, (b) presence of psychiatric comorbidities, and (c) discontinuation of medication at any time. See below for additional exclusion criteria for all subjects. All study patients had either used the same class of antipsychotic medication for at least five years, or, in the case of younger patients, had used the same class of medication since the first psychotic episode. The following typical antipsychotics were used: haloperidol ($n = 19$), chlorpromazine ($n = 9$), and levomepromazine ($n = 1$). The following atypical antipsychotics were used: quetiapine ($n = 11$), olanzapine ($n = 8$), risperidone ($n = 7$), clozapine ($n = 2$), and ziprasidone ($n = 1$). Chlorpromazine equivalents were calculated using conversion factors described previously (Danivas and Venkatasubramanian, 2013; Kreyenbuhl et al., 2010; Woods, 2003).

We also used tobacco use disorder (Fernandes et al., 2018b) as an exclusion criterion, as assessed by Fagerström Test for Nicotine Dependence (score > 6; Heatherton et al., 1991) and by the DSM-5. The healthy controls (HC) had no Axis I or II disorders according to the Structured Clinical Interview for the DSM-5 (SCID-5; American Psychiatric Association, 2013) and were recruited from the general population. The experimental procedures occurred at the Federal University of Paraiba. Participants did not receive monetary compensation for their completion of study procedures.

General exclusion criteria were: <25 old or >45 years old (aging in the visual system could bias the results; Santos et al., 2003), current history of neurological and cardiovascular disease, history of head trauma and contact with such substances as solvents, and current use of medications that may affect visual processing and cognition (e.g., benzodiazepines).

Participants had no retinal abnormalities on fundoscopic examination or optical coherence tomography. All of the observers were screened for color blindness using Ishihara's tests for color deficiency (Ishihara, 1972), and had normal or corrected-to-normal (20/20) vision as determined by a Snellen chart. The Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) was used to evaluate illness severity. The Addenbrooke's Cognitive Examination Revised (ACE-R; Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006) was used to screen for possible cognitive impairment.

2.3. Stimuli and apparatus

CCT stimuli are pattern of small circles randomly varying in diameter with no spatial structure: variation was 5.7° arcmin in external diameter and 2.8° arcmin in internal diameter, and from 8 to 18 cd/m^2 in luminance (Paramei and Oakley, 2014). The targets, pseudoisochromatic stimuli (Landolt C-shaped) defined by test colors that are to be discriminated on an achromatic background, were defined by a superimposed chromatic contrast. The luminance variation on each trial prevents learning effects.

The Trivector, a short (3–5 min) test, estimates sensitivity to short, medium, and long wavelengths through the Protan, Deutan, and Tritan confusion lines, respectively (Mollon and Regan, 2000; Regan et al., 1994). Pairs of staircases related to each of the three confusion lines were run simultaneously in an interleaved and random procedure (for details see Paramei and Oakley, 2014, p. A377). A 1 up/1 down staircase rule was used, with a step size of 20% of the average chromaticity. The Ellipse test maps three MacAdam Ellipses in different regions of the CIE u′v′ chromaticity diagram along a Tritan line. The area of the ellipses represents color discrimination in the u′v′ units. That is, the smaller the ellipse, the better the discrimination ability. We used each ellipse's area to quantify possible losses in color discrimination. The Landolt-like "C" had an opening at 1.25° of visual angle, and 6 s response time for each trial.

2.4. Procedures

Prior to the start of the tests, detailed task instructions were provided. Accuracy over speed was emphasized. A practice session to familiarize participants with the procedure and to avoid misunderstanding was performed. The CCT software incorporates a check on the validity of the data by using catch trials to detect random responding. Catch trials consist of a saturated color at the maximum of the CRT gamut, and these stimuli can be easily discriminated even by patients with severe congenital and acquired color vision impairment. Catch stimuli were presented at pseudo-random intervals during the test session and constituted approximately 10% of the stimuli (for further details about CCT catch trials, see Costa et al., 2007). Accuracy was 100% for both healthy controls and patients with SCZ on the catch trials, suggesting that

patients and controls were fully engaged in the tasks. All participants were dark-adapted upon testing, and were seated in the testing room for at least 10 min under constant illumination prior to completing the first color test. They were tested binocularly, positioned at 3 m from the monitor.

After 12 staircase reversals, thresholds along each vector were computed. A four-alternative forced-choice (4-AFC) method was used, and the subjects' task was to identify, using a remote control response box, whether the target was presented with its gap to the left, right, top, or bottom of the "C" (Fig. 1). The participants were also instructed to indicate if they could not identify the stimulus gap (Regan et al., 1994). Each session of the CCT lasted from five to 45 min. The participants were encouraged to take breaks between each block of measurements to avoid fatigue. The dependent variables for CCT are Protan, Deutan and Tritan color confusion lines (Trivector test), and length of major axis (u′v′ units), axis ratio, and angle of the major axis (Ellipse). The length of the major axis (diameters) indicates the thresholds for each vector of the MacAdam Ellipses; the angle of the major axis indicates the inclination of the Ellipse on the color space, and the axis ratio indicates the difference between the minor (not measurable with CCT) and major lengths. Then, the Ellipse is calculated using these variables.

2.5. Statistical analysis

Kruskal-Wallis tests were used to determine whether between-group differences existed, and Mann-Whitney *U* tests were used as post hoc tests to identify specific pairwise group differences. Ellipse area was calculated using the formula [Area = π × angle × axis ratio × length of the major axis]. In addition, for each ellipse the eccentricity parameter was calculated using the formula [Eccentricity = $\sqrt{1 - (\text{axis ratio})^2}$]. If the eccentricity values are ≅0, this indicates less color discrimination.

Spearman's rho (ρ) correlations were used to assess relationships between the biosociodemographic variables (e.g., age, gender, level of education) and visual performance on CCT tests. We considered effect sizes (w^2) for Kruskal-Wallis H test values that were >0.80 to be large effects. The effect size (r) for pairwise comparisons was estimated based on z-score conversion (using absolute values) (Field, 2013) and values >0.50 were considered medium-to-large effects. The data are presented using boxplots with the center line representing the median.

3. Results

3.1. Study 1

3.1.1. Participants

Sixty-six SCZ patients and 64 healthy controls participated in the first study. The sample characteristics of the participants are summarized in Table 1. The groups did not differ in age, or the ratio of males to females. There were differences regarding level of education. There were no significant correlations between CPZ equivalents and color measures.

3.1.2. Trivector test

Significant differences in discrimination thresholds along the three vectors were found between groups. The results of the Trivector test are shown in Fig. 2. SCZ group had higher thresholds along the Protan ($U = 36, p < .01, r = 0.54$), Deutan ($U = 36, p < .01, r = 0.51$) and Tritan ($U = 39, p < .01, r = 0.62$) vectors when compared with HCs.

3.1.3. Ellipse test

The results of the Ellipse measurements are shown in Fig. 3. There were significant differences in the areas of Ellipse 1, [$U = 8$, $p < 001, r = 0.51$], Ellipse 2, [$U = 15, p = .007, r = 0.33$] and Ellipse 3, [$U = 10, p < .001, r = 0.45$] between groups.

3.1.4. Correlation analysis in schizophrenia groups

The BPRS scale was positively correlated with Trivector test scores (Table 2). No significant correlations were found between age, gender, and level of education for Trivector and Ellipse.

Nonparametric regression analyses were conducted to investigate the effect of BPRS on chromatic discrimination in SCZ (Table 3). The nonparametric regression analysis showed a relationship between BPRS and Trivector values. Several factors such the drug dosage, illness duration, or medication type are in principle capable to modulate the relationship between BPRS and visual outcomes (since were considering the whole group). However, we only found degree of correlation in the Trivector test with $r < 0.035$.

3.2. Study 2

3.2.1. Participants

Fifty healthy controls, 29 patients who were diagnosed with SCZ and using typical antipsychotics, and 29 patients who were diagnosed with

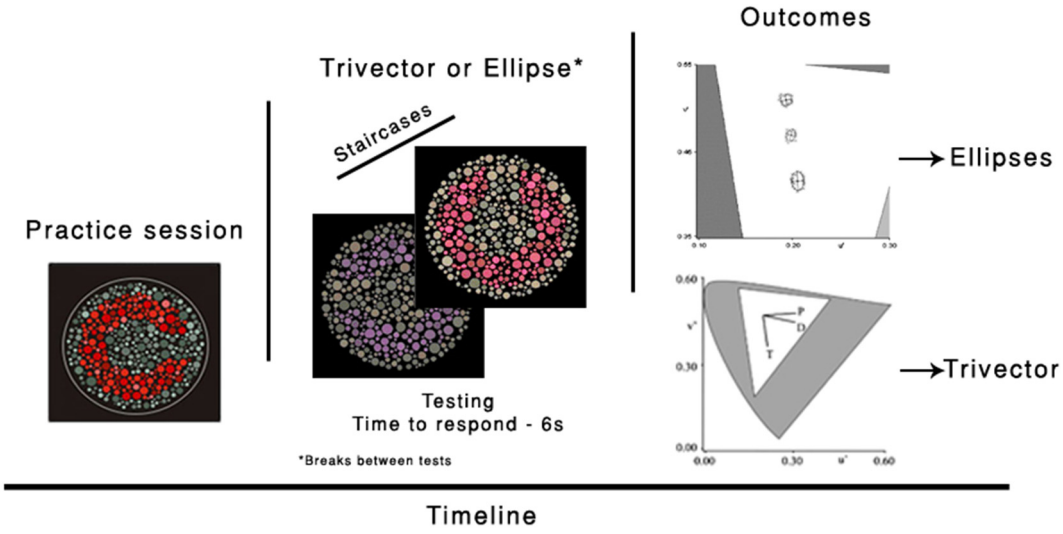

Fig. 1. Cambridge Colour Test. The subjects' task was to identify, using a remote control response box, whether the stimuli was presented with its gaps randomized in one of four positions (left, right, up, or bottom). A practice session was performed for the individuals grasp the test. Then, the participant was tested at Trivector or Ellipse subtests.

Table 1
Sample characteristics of Study 1 participants.

Variable	HC ($n = 64$)	SCZ ($n = 66$)
Gender		
Male	37	37
Female	27	29
Age		
Age, years (SD)	35.7 (7.8)	34.5 (8.9)
Level of education, years (SD)	10.6 (2.4)	9.68 (2.8)
Age of onset, years (SD)	–	18.5 (2.0)
Number of hospitalizations	–	6.6 (4.2)
Comorbidities	–	–
Brief psychiatric rating scale (total score; mean/SD)	–	42.5 (7.4)
Hamilton rating scale for depression	1.8 (1.2)	7.59 (1.5)
Typical/atypical medication	–	37/29
CPZ	–	591 (625.3)

HC - healthy controls, SCZ - schizophrenia patients, CPZ - Chlorpromazine Equivalent. Hamilton Rating Scale for Depression (score < 7; no depression).

SCZ and were using atypical antipsychotics participated in Study 2. Characteristics of the participants are summarized in Table 4. The groups did not differ in age, level of education, and the ratio of males to females. No differences in scores on the BPRS and Hamilton Rating Scale for Depression were found between SCZ subgroups. In addition, there were no differences in illness duration. There were no significant correlations between CPZ equivalents and color measures.

3.2.2. Trivector test

There were significant differences in discrimination thresholds along the three vector axes between groups ($p < .001$). The SCZ typical group had higher chromatic discrimination thresholds than the HCs group along the Protan, Deutan, and Tritan axes (all p-values < .001; all r-values > 0.70). The SCZ atypical group had higher chromatic discrimination thresholds than the HCs group along the Protan axis ($U = 27$, $p < .001$, $r = 0.57$), Deutan axis ($U = 11$, $p = .001$, $r = 0.79$), and Tritan axis ($U = 32$, $p = .008$, $r = 0.43$). Comparisons between the SCZ typical and atypical groups revealed differences in chromatic discrimination thresholds for the Protan axis ($U = 48$, $p = .007$, $r = 0.41$) and Tritan axis ($U = 31$, $p = .001$, $r = 0.30$), with no difference for the Deutan axis ($U = 65$, $p = .089$). The results of the Trivector test are shown in Fig. 4.

3.2.3. Ellipse subtest

3.2.3.1. Length of major axis. There were significant difference in the length of the Ellipse 1, [χ^2 (2) = 25.690, $p < .001$, $w^2 = 1.199$], Ellipse 2, [χ^2 (2) = 22.888, $p = .001$, $w^2 = 1.037$] and Ellipse 3, [χ^2 (2) = 14.437, $p = .001$, $w^2 = 0.894$]. The SCZ typical group had higher

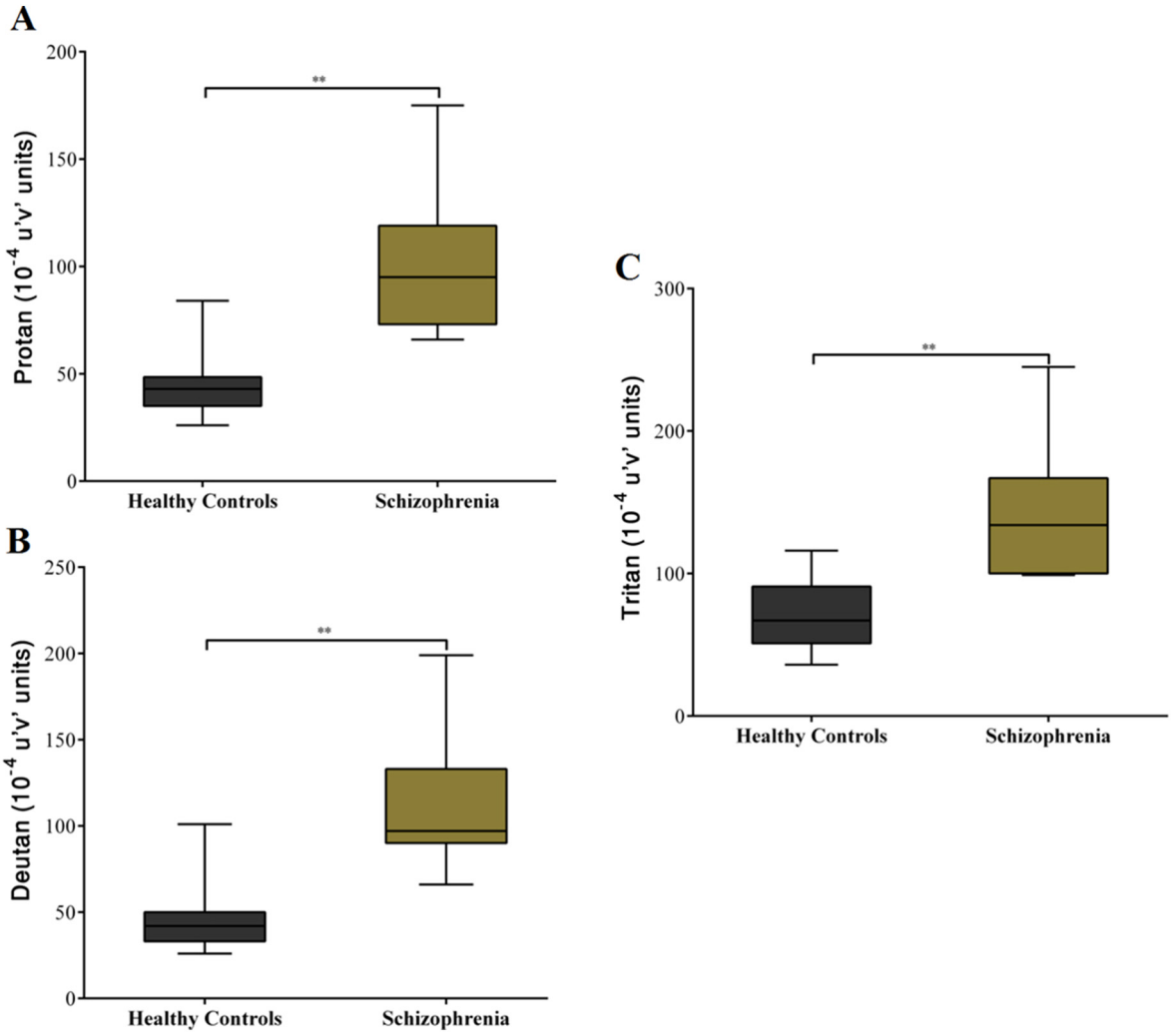

Fig. 2. Boxplots for Trivector color confusion axes for both groups. (A), Protan; (B) Deutan; and (C) Tritan. Data were presented in 10^{-4} u′v′ units of the CIE 1976. **$p < .01$; Box limits indicate the 25th and 75th percentiles. Whiskers extend 1.5-times the interquartile range from the 25th and 75th percentiles. The ends of the whiskers are the maximum and minimum values.

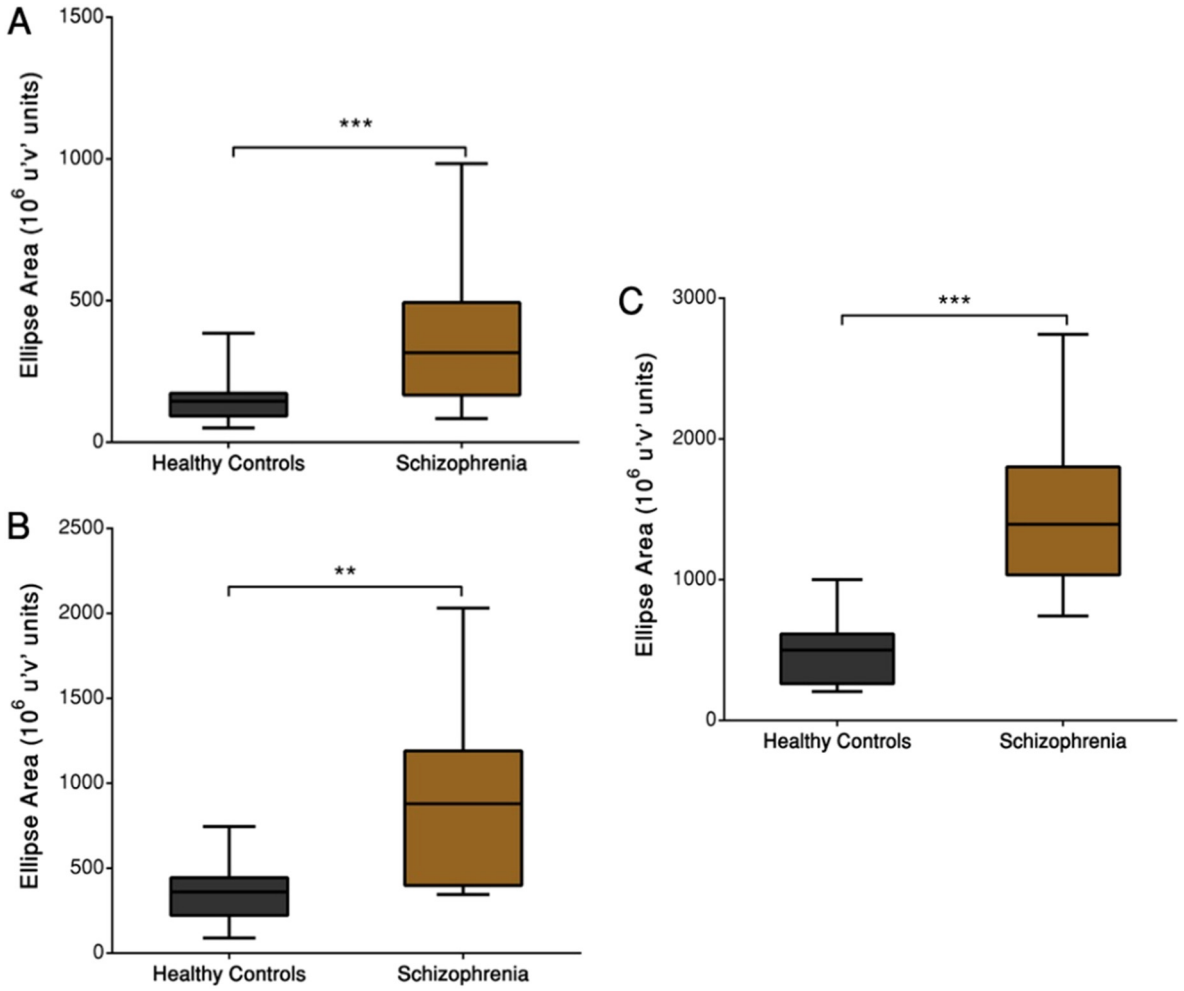

Fig. 3. Area of Ellipse 1 (A), Ellipse 2 (B) and Ellipse 3 (C) for the healthy controls and schizophrenia groups. Data were presented in 10^{-6} u′v′ units of the CIE 1976. ***$p < .001$, **$p < .01$; Box limits indicate the 25th and 75th percentiles. Whiskers extend 1.5-times the interquartile range from the 25th and 75th percentiles. The ends of the whiskers are the maximum and minimum values.

length's thresholds than the HCs group along Ellipse 1 ($U = 16$, $r = 0.84$), Ellipse 2 ($U = 12$, $r = 0.69$), and Ellipse 3 ($U = 32$, $r = 0.44$; all p-values < .001). The same tendency was observed between SCZ atypical and HC groups for Ellipse 1 ($U = 2$, $r = 0.85$), Ellipse 2 ($U = 13$, $r = 0.56$), and Ellipse 3 ($U = 29$, $r = 0.43$; p-values < .001). There were differences between the SCZ typical and SCZ atypical for Ellipse 2 ($U = 74$, $p = .011$, $r = 0.36$), and Ellipse 3 ($U = 86$, $p = .033$, $r = 0.31$). There were no differences between SCZ groups for Ellipse 1. The results are shown in Fig. 5.

3.2.3.2. Ellipse angle. There were significant difference in the angle of the Ellipse 1, [χ^2 (2) = 48.41, $p < .001$, $w^2 = 1.78$], Ellipse 2, [χ^2 (2) = 68.03, $p < .001$, $w^2 = 2.15$] and Ellipse 3, [χ^2 (2) = 26.49, $p < .001$, $w^2 = 1.11$]. There were differences between the angle for typical and HCs group along Ellipse 1 ($p < .001$, $r = 0.70$), Ellipse 2 ($p < .001$, $r = 0.78$), and Ellipse 3 ($p = .008$, $r = 0.53$). The same tendency was observed between SCZ atypical and HC groups for Ellipse 1 ($p < .001$, $r = 0.53$), Ellipse 2 ($p < .001$, $r = 0.68$), and Ellipse 3 ($p = .001$, $r = 0.38$). There were differences between the SCZ typical and SCZ atypical for Ellipse 1 ($p = .040$, $r = 0.27$), Ellipse 2 ($p = .001$, $r = 0.42$) and Ellipse 3 ($p = .031$, $r = 0.28$).

3.2.3.3. Eccentricity. Significant differences were observed in the eccentricity of the ellipses between the three groups along Ellipse 1 (χ^2 (2) = 19.96, $p < .001$, $r = 0.90$), Ellipse 2 (χ^2 (2) = 27.14, $p < .001$, $r = 1.12$) and Ellipse 3 (χ^2 (2) = 19.75, $p < .001$, $r = 0.90$). SCZ groups had lower eccentricities values compared to HC (all p-values < .001). Both SCZ groups had eccentricities values closer to

Table 2
Correlation of chromatic discrimination tests and BPRS.

	Protan	Deutan	Tritan	Ellipse 1	Ellipse 2	Ellipse 3
Study 1						
SCZ	0.47*	0.52*	0.42*	0.19	0.22	0.11
Study 2						
Typical	0.28	0.11	0.27	0.17	0.36	0.05
Atypical	0.10	0.23	−0.20	−0.50	0.27	0.04

* $p < .05$

Table 3
Nonparametric regression analyses of the relationship between BPRS and chromatic discrimination tests.

Variables	Adjusted R^2 of model	β	*t*-Value	*p*-Value
Study 1				
Protan	0.33	0.54	7.19	0.01
Deutan	0.09	0.13	3.01	0.05
Tritan	0.21	0.42	8.55	0.01
Study 2				
Protan	0.10	0.41	1.22	0.12
Deutan	0.06	0.74	0.38	0.75
Tritan	0.02	0.02	0.93	0.92

Table 4
Sample characteristics of Study 2 participants.

Variable	HC ($n = 50$)	SCZ typical ($n = 29$)	SCZ atypical ($n = 29$)
Gender			
Male	26	17	17
Female	24	12	12
Age			
Age, years (SD)	36.1 (7.3)	35.3 (5.2)	35.6 (6.0)
Level of education, years (SD)	11.4 (2.1)	9.3 (2.8)	8.8 (2.4)
Age of onset, years (SD)	–	19.3 (2.4)	21.1 (3.0)
Number of hospitalizations	–	6.4 (4.0)	6.2 (2.1)
Comorbidities	–	–	–
Brief psychiatric rating scale score	–	41.1 (8.0)	43.3 (7.5)
Hamilton rating scale for depression	1.3 (0.6)	5.77 (1.5)	6.21 (1.8)
CPZ	–	561 (441.8)	619 (681.3)

HC - healthy controls, SCZ - schizophrenia patients, CPZ - Chlorpromazine Equivalent. Hamilton Rating Scale for Depression (score < 7; no depression).

0.2 indicating that the ellipses for the two groups were circular in shape.

3.2.3.4. Area of the ellipses. There were significant between-group differences in the areas of Ellipse 1, [χ^2 (2) = 43.05, $p < .001$, $w^2 = 1.60$], Ellipse 2, [χ^2 (2) = 63.81, $p < .001$, $w^2 = 2.39$] and Ellipse 3, [χ^2 (2) = 52.57, $p < .001$, $w^2 = 1.93$]. The SCZ typical group had larger ellipses than the HC group along Ellipse 1, Ellipse 2 and Ellipse 3 (all *p*-values < .001; all *r*-values > 0.70) indicating lower color discrimination. The SCZ atypical group demonstrated enlargement of the three ellipses compared with HCs along Ellipse 1 ($p < .001$, $r = 0.68$), Ellipse 2 ($p < .001$, $r = 0.65$), and Ellipse 3 ($p < .001$, $r = 0.73$), also indicating poorer color discrimination. There were also differences between the SCZ atypical group and SCZ typical groups for Ellipse 1 ($p < .001$, $r = 0.58$), Ellipse 2 ($p = .040$, $r = 0.25$) and Ellipse 3 ($p = .012$, $r = 0.33$). The results are shown in Fig. 6.

3.2.4. Correlation analysis in schizophrenia groups

No significant correlations were found between age, gender, and level of education for either SCZ group in the Trivector or Ellipse tests. The BPRS total score was not correlated with chromatic discrimination in both SCZ groups (Tables 2, 3).

4. Discussion

Across two studies, SCZ patients demonstrated poorer color discrimination (higher thresholds) than HCs, and in multiple cases patients taking typical antipsychotic medications demonstrated poorer performance than patients taking atypical medications. These results suggest that SCZ may affect color vision, and/or that antipsychotic medication affects color vision in the disorder. Of note, our results suggest a subtle, but a reduction in thresholds for short, medium and high wavelengths, replicating an earlier finding from Shuwairi et al. (2002).

Despite differences in the pharmacological characteristics of atypical antipsychotics, they may all come from groups of benzisoxazoles. These

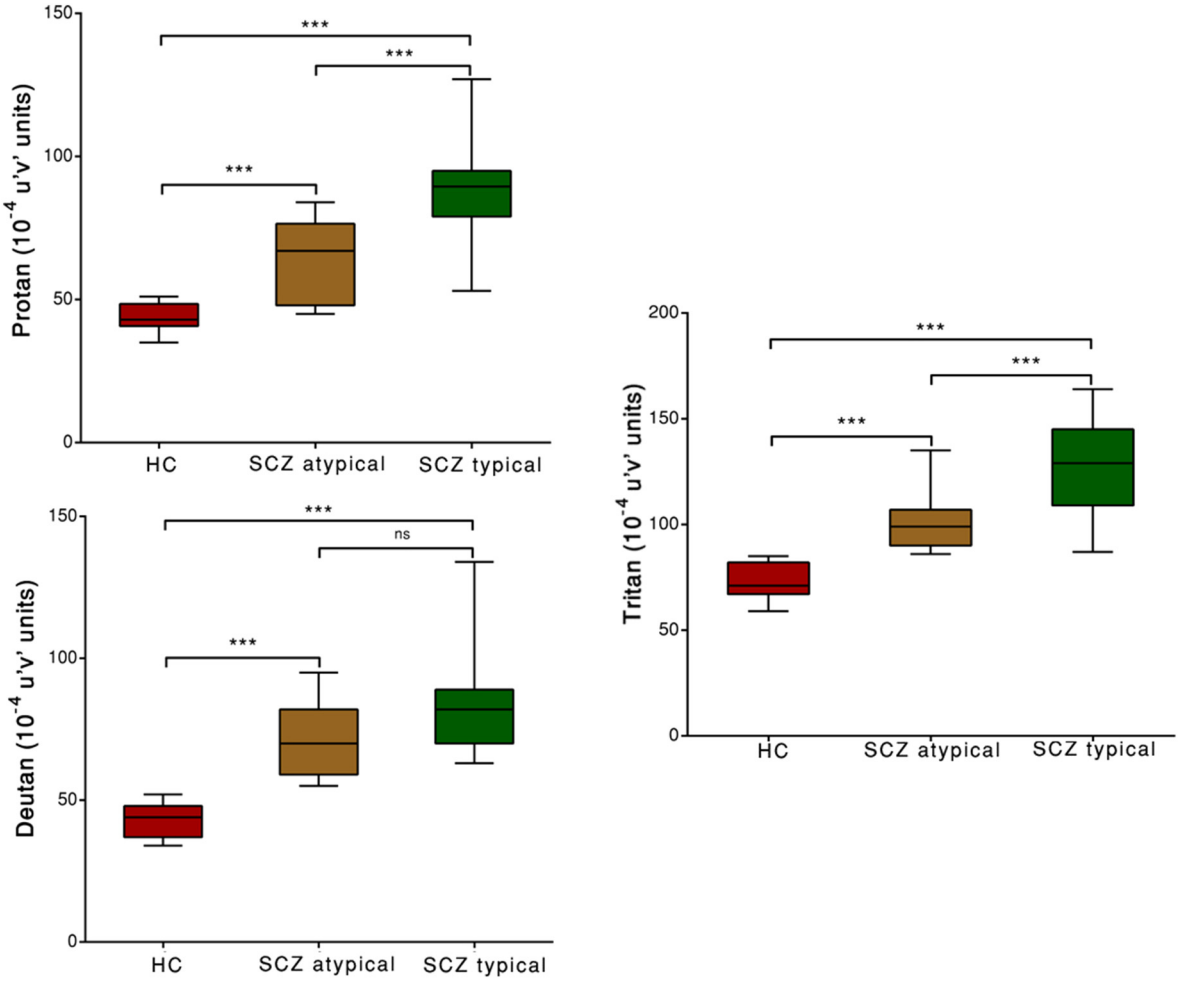

Fig. 4. Boxplots for Trivector color confusion axes. (A), Deutan; (B) Protan; and (C) Tritan. Data were presented in 10^{-4} u′v′ units of the CIE 1976. ***$p < .001$; Box limits indicate the 25th and 75th percentiles. Whiskers extend 1.5-times the interquartile range from the 25th and 75th percentiles. The ends of the whiskers are the maximum and minimum values.

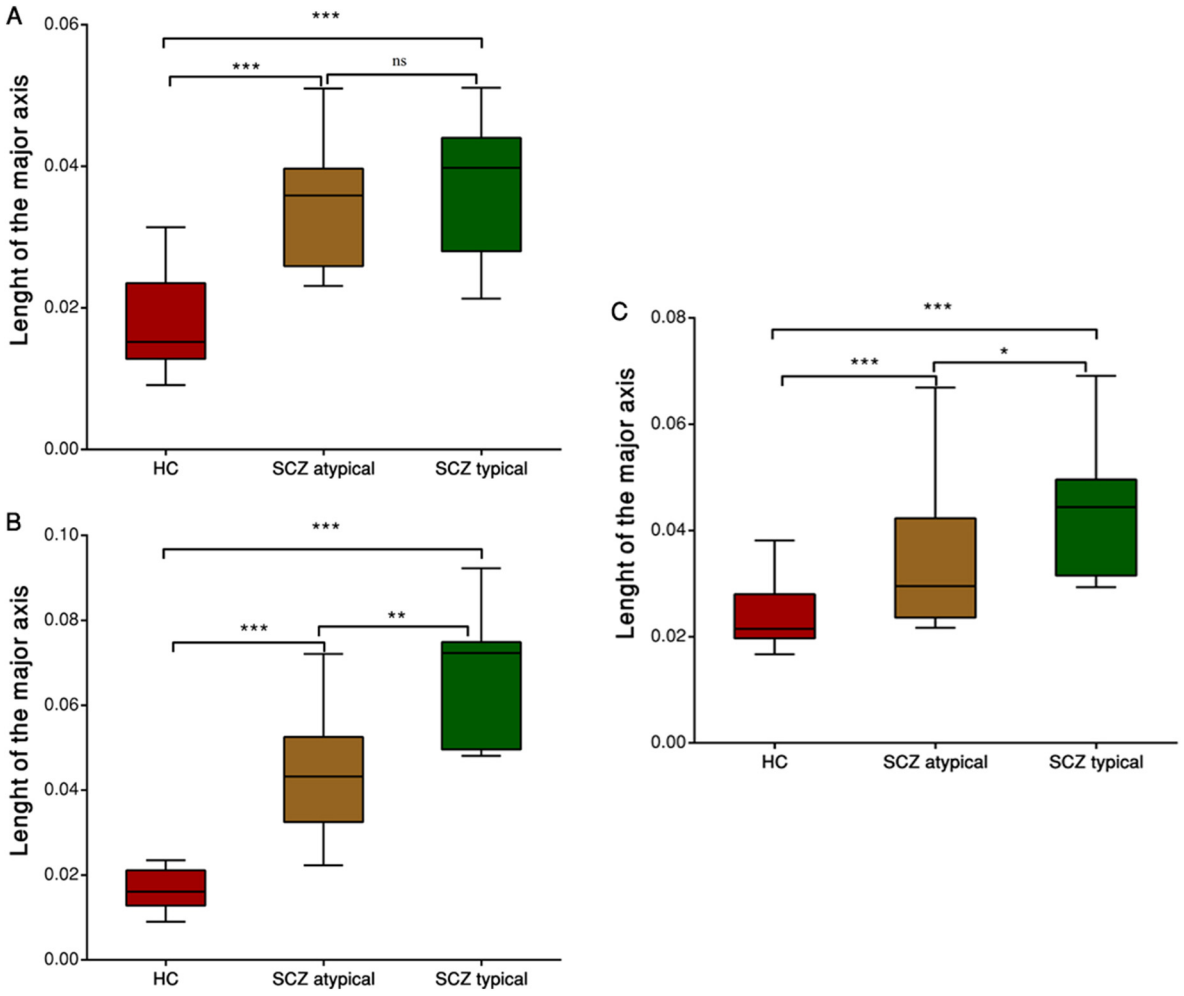

Fig. 5. Boxplots for lengths of the major axis. Ellipse 1 (A), Ellipse 2 (B), and Ellipse 3 (C). ***$p < .001$, **$p < 01$, *$p < .05$; Box limits indicate the 25th and 75th percentiles. Whiskers extend 1.5-times the interquartile range from the 25th and 75th percentiles. The ends of the whiskers are the maximum and minimum values.

drugs do not present substantially different mechanisms of action, thus suggesting that this is not an intervening variable. Similarly, most of the typical antipsychotic medications prescribed for patients in this study were of the same class (i.e., butyrophenones and phenothiazines). To further minimize possible effects of medication-related variables, the equivalent dosages were similar between patient groups. However, it is still possible that differences between the two SCZ groups in Study 2 (mainly for the short and long wavelengths) could have been due to differences in the overall length of time that patients were receiving antipsychotic medication, total lifetime exposure to these drugs, total duration of psychotic disorder or other aspects of illness heterogeneity. We were unable to obtain data on these variables, and this is an important issue that needs to be examined further in future studies. It is important to point out, however, that differential extent of between-group differences is not unexpected, given the nature of the tests we used. For example, for the Trivector test, it is not necessarily the case that similar changes on all axes are expected. Many eye diseases initially present with Tritan defects only. At more advanced stages, red-green abnormalities often emerge. According to Kollner's rule, the Tritan defect manifests (in most cases) due to retinal lesions, whereas the additional red-green abnormality implies that, apart from the retina, damage the optic nerve is also involved.

The limitations of this study need to be mentioned. For example, unmedicated patients were not included in either study. Longitudinal comparisons of the same patients as they initially receive medication would be especially informative regarding medication effects on color vision. Studying unmedicated SCZ patients would also allow for a determination of the extent to which SCZ itself causes color perception impairments relative to the extent to which antipsychotic medication improves or worsens color vision perception (Kelemen et al., 2013; Kiss et al., 2010). Our assumption is that schizophrenia itself has an effect, however, without comparing medicated patients to a group of unmedicated patients that are matched on important variables (e.g., illness duration and severity), a schizophrenia-related impairment in color vision cannot be assumed. Because patients were not randomly assigned to the medication group (typical vs. atypical), one needs to be careful when making conclusions regarding between-patient-group differences. Additionally, the slight difference in BPRS scores between the SCZ groups in Study 2 may indicate that differences in overall current symptomatology may be more related to color vision ability than medication type. However, the within-subgroup correlations between BPRS-total and color vision tests in Study 2 were not significant, thereby arguing against this interpretation. Also, patients with more severe symptoms can receive higher doses of antipsychotic drugs, which could lead to worse color perception. Finally, it is also possible that severity of specific symptom clusters (e.g., positive or negative symptoms) is driving the between-subgroup effect. This can be investigated in future studies of color vision by characterizing symptomatology using more comprehensive rating scales for specific symptom clusters (e.g., the Positive and Negative Syndrome Scale, the Scales for the Assessment of Positive/Negative Symptoms, the Clinical Assessment Interview for Negative Symptoms).

Despite these limitations, the data from these two studies points to an important direction for future research, the investigation of color

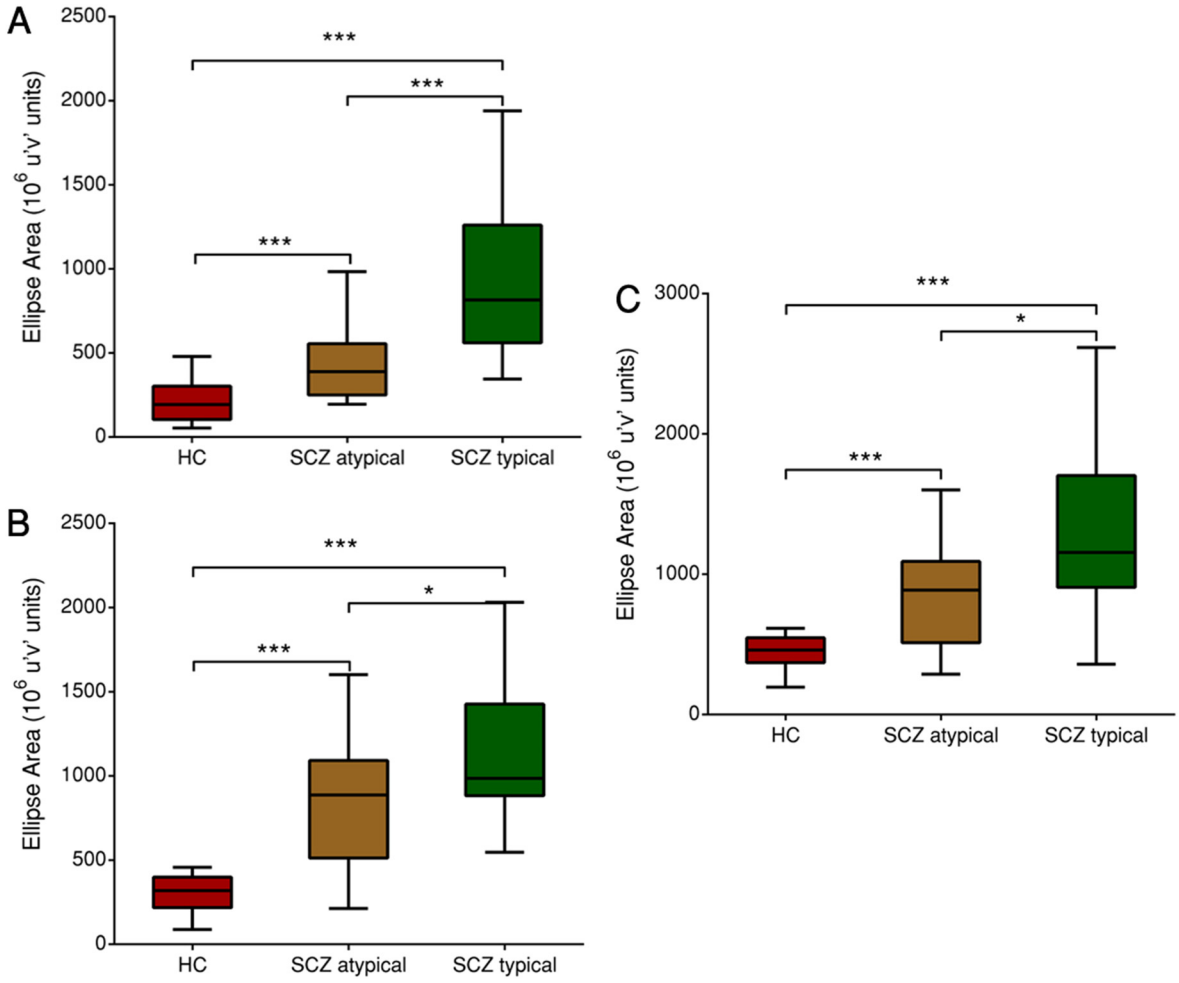

Fig. 6. Area of Ellipse 1 (A), Ellipse 2 (B) and Ellipse 3 (C) for the healthy controls and both schizophrenia groups. Data were presented in 10^{-6} u′v′ units of the CIE 1976. ***$p < .001$, **$p < .01$, *$p < .05$; Box limits indicate the 25th and 75th percentiles. Whiskers extend 1.5-times the interquartile range from the 25th and 75th percentiles. The ends of the whiskers are the maximum and minimum values.

vision impairments in schizophrenia. If it turns out that color vision problems are related to SCZ and not medication, then color vision might be a good non-invasive test to examine dopamine activity. If performance on the tests reflects responsivity to medication, then it could be useful to see if color vision testing after 1–2 weeks on a medication predicts longer term treatment response. Although this is an over-extrapolation of the data, this can helps the quality of life and improve the prognosis of patients, being able to reduce the illness severity due to medication type in some patients. Tests for early detection of eventual treatment response to medications are needed, since currently it can take weeks to determine if a patient responds to a medication.

Conflict of interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Contributors

TMP, RLN and NAS conceived and planned the study. TMP, RLN and LGS carried out the experiments and performed statistical analysis. TMP, SMS, PB, SK and NAS aided in interpreting the results and worked on the manuscript. All authors provided critical feedback and contributed to the final version of the manuscript. All of the authors read and approved the final manuscript.

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