Title: Combined influence of medication and symptom severity on visual processing in bipolar disorder

Running head: clinical variables and visual processing

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Abstract

Earlier studies have reported visual impairments in patients with bipolar disorder (BPD), but it is not clear which clinical variables are associated with those disturbances. Here, we investigate the relationship between visual functioning, in terms of chromatic discrimination, and the impact of BPD duration, mood state, and the patients' medication. Forty-five participants (25-45 years old) were recruited for this study. Chromatic discrimination was performed using the Trivector subtest of the Cambridge Colour Test. A serial multiple mediation analysis was carried out to investigate the assumption of association between chromatic discrimination and the BPD clinical variables. Our findings showed that compared with healthy controls, BPD patients' performance was worse for the Protan ($p < .001$), Deutan ($p < .001$), and Tritan ($p < .001$) (red, green, and blue, respectively) vectors. In addition, mediation analysis revealed a strong direct ($p < .001$) and moderate-to-high indirect effects ($p < .01$) on chromatic discrimination. This study indicated a relationship between clinical variables and chromatic discrimination in BPD. It highlights the importance of examining the wider clinical context of an affective disorder to understand how it affects visual processing in that population.

Keywords: Bipolar disorder; medication; mood state; visual processing; color discrimination; chromatic discrimination.

1. Introduction

Bipolar disorder (BPD) is a severe affective mental condition associated with cognitive (Bora and Pantelis, 2015; Holmes et al., 2008) and sensory processing impairments (Fernandes et al., 2017; O'Bryan et al., 2014; Schallmo et al., 2015). Several studies investigated visual processing disturbances in illness such as schizophrenia (Fernandes et al., 2019; Silverstein, 2016; Zemon et al., 2021), major depressive disorder (Bubl et al., 2015, 2012) and other psychotic disorders (Keane et al., 2016), while the only findings related to BPD suggest impairments in low-level visual processing (Fernandes et al., 2017; Moser et al., 2020; O'Bryan et al., 2014; Oliveira et al., 2021). Moser et al. (2020) reported that BPD patients had increased visual contrast thresholds, but nothing is known about their chromatic discrimination, for example. Furthermore, symptom severity, mood state, illness duration, and the medication use in BPD patients were confounding factors in those studies, revealing the need to examine and understand their role in visual processing (Fernandes et al., 2018; Shoshina et al., 2021b; Shoshina and Shelepin, 2015).

Studies demonstrated that the cognitive impairments observed in BPD patients are present during acute manic episodes and during the remission period (Bora and Pantelis, 2015). Among the cognitive deficits related to BPD are verbal memory, attention and executive functioning (Lackner et al., 2016). It is also suggested that stressful episodes can lead to a modulation of brain circuits, causing structural brain abnormalities and cognitive impairment (Cardoso et al., 2015). Recent findings did not refer to the association between impairments in visual processing and clinical variables in BPD patients. The existence of such association is essential to the understanding of selective or indirect effects of medication

and the duration of the disease, for example, such as reported for other psychiatric conditions (Almeida et al., 2020; Silva et al., 2021a, 2021b; Zemon et al., 2021).

It is known that antipsychotics and mood stabilizers can affect cognitive (Karson et al., 2016; Rybakowski, 2016) and visual performance, but it is unclear to which extent those drugs help or impair cognitive functioning. Some studies showed that atypical antipsychotics preserved some visual functions in patients with schizophrenia (Fernandes et al., 2019; Shoshina et al., 2021; Zemon et al., 2021). However, the effects of mood stabilizers in BPD have not been investigated using reliable and robust statistical approaches.

Earlier studies did not investigate the influence of mood state and medication use on visual processing in BPD patients. Yang et al. (2013) investigated a heterogeneous sample of BPD and schizophrenia patients and found impairments for some stimuli discrimination (e.g., size, orientation and motion direction). O'Bryan et al. (2014) also investigated motion perception in BPD patients who showed abnormalities in dot motion trajectory. Using a spatial frequency of 2 cpd and circular gratings, Schallmo et al. (2015) showed a weak surround suppression in BPD patients. Fernandes et al. (2017) investigate color processing in type 1 BPD and found increase in thresholds (i.e., worse discrimination) when compared to healthy controls, while Fernandes et al. (2019) reported lower contrast discrimination for low and high spatial frequencies. Although relevant, those studies included heterogeneous samples, and the lack of control of variables such as the effects of illness duration, mood state or symptom severity.

The main purpose of this study was to investigate the mediation effects of the medication and mood state of BPD patients on visual processing in terms of chromatic discrimination. We hypothesized that BPD patients would present impairments for chromatic discrimination. which would be associated to the medication dosage and manic state. We

predict that both clinical variables would be associated with a worse chromatic discrimination with a moderate-to-strong effect.

2. Methods

2.1 Participants

There were 25 healthy controls (HCs; mean age = 32.12 years; *SD* = 5.10 years) and 20 BPD patients (mean age = 35.60 years; SD = 6.77 years). They were recruited from the general population (HCs) or from private clinics (BPD patients). Participants were aged between 20 and 45 years, and did not have retinal nor eye impairments as presented in self-reports and based in previous examinations. All participants were above the cut-off point of the Mini-Mental State Examination (Folstein et al., 1975)**.**

BPD patients met the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (American Psychiatric Association, 2015) criteria for type 1 BPD. We also evaluated the patients using the Young Mania Rating Scale (YMRS; Young et al., 1978). Most of the BPD patients were acutely manic during the study. The only medication the BPD patients were taking was lithium. The HCs had no neuropsychiatric disorders or additional health conditions that could have affected the results (Almeida et al., 2020; Silva et al., 2021a, 2021b). An initial screening for eligibility was conducted and after assessed for eligibility, the groups were classified and matched to gender, age and education level. More details about eligibility criteria and the sample characterization format can be found in Fernandes et al. (2017, 2020). All participants had a corrected or normal-to-corrected acuity of at least 20/20 (binocular viewing) as assessed using a Snellen chart. All participants were free from color blindness (Ishihara, 1972). Sample was calculated using the following equation:

Equation 1: $S = \frac{\left(\frac{\sigma_1^2+\sigma_2^2}{K}\right) x \left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2}{\frac{\Delta^2}{K x n_1}}$

where,

S = sample
σ = variance of the means
α = 0.05
β = 0.20
z = Z value for α or β
K = ratio of sample for both groups
Δ = difference between two means
More details about the methods can be found in Supplementary Material 1.

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.

2.2 Stimuli

Here we used the Cambridge Colour Test (CCT) subtest Trivector. The CCT stimulus is a C-shaped Landolt ring displayed within a differently colored background. The position of the opening in the ring was presented randomly in one of four positions (top, bottom, left and right). The chromatic contrast varied until reached a threshold [(for more details, see Fernandes et al. (2020)]. In our setting, the "ring" had an opening of 1.25° of visual angle at 3-meter viewing distance. To ensure that the break in the ring is identified based only chromatic information, luminance noise was added by subdividing the background and stimulus into small circles randomly varying in size (between 2.8° arcmin and 5.7° arcmin in diameter), and randomly varying in luminance (min: 8 cm/m², max: 18 cd/m^2). Three different stimuli were used to measure thresholds the Protan, Deutan, and Tritan vectors (corresponding to red, green and blue, respectively). Thresholds for these three stimuli are determined primarily by the L-, M- and S-cone, respectively (long, mid- and short-cone) (Mollon and Regan, 2000; Regan et al., 1994). The background was achromatic, and located

at u’ = 0.1977, v' = 0.4689 (CIE 1976 chromaticity diagram).

2.3 Procedure

The participants were dark adapted for 10 minutes (Pirenne, 1962) and then tested. The four-alternative forced-choice (4-AFC) method was used, and the subjects’ task was to identify, using a remote-control response box, whether the opening of the “ring” was presented on the left, right, top, or bottom of the monitor (Fig. 1). The participants were also encouraged to respond whether they could not identify the opening of the “ring” (Mollon and Regan, 2000). The CCT uses the staircase rule to obtain thresholds, considering the increase or decrease in the intensity (or contrast) of the stimulus (Treutwein, 1995). For each of the three vectors, the CCT algorithm implemented two interleaved staircases presented in a random order using a weighted a one up/one down staircase rule, with a ratio of 1/3 to converge on the 75% threshold. The staircase rule helps to determine the thresholds, with an increase (up) or decrease (down) of contrast after a number of responses (e.g., 1/3, one up, three down). Accuracy over speed was emphasized in the instruction (Fernandes et al., 2019). The CCT is a reliable test used worldwide over the past 30 years. Higher thresholds indicated worse performance or worse chromatic discrimination [for extensive details of the procedures, see Fernandes et al. (2020), Paramei (2012), Paramei and Oakley (2014)]. The test procedure is presented in Fig 1.

[Fig. 1]

2.4 Data analysis

Distributions for each group were compared using the Monte Carlo method for skewness and kurtosis, and the cut-off value was > 1.96 (Antonius, 2003; Tabachnick and Fidell, 2007). Statistical analysis was performed using SPSS 25.0 and MATLAB R2018b (mathworks.com).

A chi-squared (2 x 2) test was used to compare gender, while the two groups were compared, for the other variables, using the Mann-Whitney U test. Bonferroni's correction was applied to adjust the *p*-value and prevent type 1 errors. Spearman's rank correlation coefficients (rho) were used to assess the existence of an association between outcomes of the test and biosociodemographic variables, such as age, gender, level of education, illness duration (years), medication (mg) and mood state (YMRS). The effect size (Cohen's *f)* was estimated based on the transformation of η^2, following the formulae by McGraw and Wong (McGraw and Wong, 1992). Cohen's *f* was calculated using the following equation:

Equation 2: $f = \sqrt{\frac{\omega_p^2}{1-\omega_p^2}}$

Mediation analysis and the bootstrapping method were applied (Hayes, 2013). Model 4 of Hayes' PROCESS for SPSS using 5,000 bootstrap simulations was used. BPD group was dummy coded and entered in the model. YMRS and lithium dosage were entered in the model separately. The regression assumptions were first checked and there were no multicollinearity (Tolerance / VIF < .01 and 10, respectively). No data influenced the results according to Mahalanobis' and Cook's distances or according to leverage values. The variables were centered to avoid bias, and the interaction effect was observed. We conducted a serial multiple medication considering medication dosage and mood state (YMRS) as mediators (Fig. 2).

[Fig. 2]

3. Results

3.1 Sample characteristics

The characteristics of the participants are summarized in Table 1. The groups did not differ in age, [$U = 168$, $p = .060$], level of education, [$U = 234.500$, $p = .723$] or comparing

the results of the MEEM [$U = 190$, $p = .077$]. A 2 x 2 chi-square was conducted to compare the differences between males and females, and the results indicated no significant differences, [χ (1) = .844, $p = .221$].

[Table 1]

3.2 Trivector test

Patients with BPD had worse chromatic discrimination (higher thresholds) for the Protan, [$U = 20$, $p < .001$, Z = - 5.258, Cohen's $f^2 = 1.178$ (95% CIs: .859 – 1.504], Deutan [$U = 7$, $p < .001$, Z = - 5.676, Cohen's $f^2 = 1.572$ (95% CIs: 1.201 – 1.945], and Tritan [$U = 2$, $p < .001$, Z = - 5.722, Cohen's $f^2 = 1.368$ (95% CIs: 1.025 – 1.726]. The results of these tests are summarized in Fig. 3

[Fig. 3]

3.3 Correlation Analyses in the BPD group

Separate analyses were performed. No significant relationships between any of the pairs of variables were found in the control group (all p-values > .05). In the BDP group, no significant correlations were found between age (all p-values > .05) or level of education (all p-values > .05) and the Trivector outcomes. Detailed descriptions of the analyses can be found in Supplementary Material 2.

3.3.1 Illness duration

No significant correlation was found between the duration of disease and the Protan ($rho = .302$, $p = .196$), Deutan ($rho = .420$, $p = .064$) and Tritan ($rho = .332$, $p = .152$) vectors.

3.3.2 Medication dosage

There were correlations between medication dosage and the Protan [*rho* = .812, $p <$ .001; 95% CIs: .574 – .922], Deutan [*rho* = .791, $p <$ .001; 95% CIs: .480 – .900] and Tritan [*rho* = .543, p = .014; 95% CIs: .133 – .765] vectors.

3.3.3 Mood state (YMRS)

There were correlations between medication dosage and the Protan [*rho* = .482, $p <$ .001; 95% CIs: .052 – .762], Deutan [*rho* = .472, p = .026; 95% CIs: .016 – .757] and Tritan [*rho* = .686, $p <$ .001; 95% CIs: .350 – .866] vectors.

3.4 Mediation Analyses in the BPD group

Considering the absence of correlations between disease duration and Trivector outcomes, we opted to avoid model inflation using only a serial multiple moderation with medication dosage and mood state (M_1 = medication dosage; M_2 = YMRS).

3.4.1 Medication dosage

There were indirect effects for the Protan [a^1 x b^1 = 1.638, *SE* = .683, z-value = 2.396; 95% BCas .298 – 2.977], Deutan [a^1 x b^1 = 2.722, *SE* = .820, z-value = 3.425; 95% BCas 1.159 – 4.262] and Tritan [a^1 x b^1 = 4.144, *SE* = 1.287, z-value = 3.219; 95% BCas 1.621 –6.767] vectors. From these results, we conclude that medication dosage had a moderate-do-high significant influence on the outcomes (adjusted R^2 for Protan, Deutan and Tritan were .522, .422 and .770, respectively).

3.4.2 Mood state (YMRS)

There were indirect effects for the Protan [a^2 x b^2 = 3.153, *SE* = 1.367, z-value = 2.305; 95% BCas .472 – 5.845], Deutan [a^2 x b^2 = 2.670, *SE* = 1.376, z-value = 1.962; 95% BCas .003 – 5.396] and Tritan [a^2 x b^2 = 4.846, *SE* = 2.350, z-value = 2.058; 95% BCas .231 –9.441] vectors. From these results, we conclude that the mood state, alone, had a

low-to-moderate significant influence on the outcomes (adjusted R^2 for Protan, Deutan and Tritan were .349, .484 and .380, respectively).

3.4.3 Multiple mediation: medication dosage and YMRS

The parameters of the underlying nonparametric multiple regression (and multiple mediation) are summarized in Table 2. The total indirect effects (combining medication dosage and YMRS) were found for the Protan [$a^1 \times b^1 + a^2 + b^2 = 3.142$, *SE* = 1.482, z-value = 2.120; 95% BCas .237 – 6.046], Deutan [$a^1 \times b^1 + a^2 + b^2 = 2.895$, *SE* = .660, z-value = 1.943; 95% BCas .360 – 6.150] and Tritan [$a^1 \times b^1 + a^2 + b^2 = 2.166$, *SE* = 0.840, z-value = 2.512; 95% BCas .476 – 3.857] vectors. All the graphs for the multiple mediation can be found in Supplementary Material 2.

The multiple mediation showed mitigating influence of the medication dosage and the YMRS; however, Adjusted R^2 and estimates were higher for the medication than for the YMRS.

[Table 2]

4. Discussion

This study investigated a possible association between medication and mood state on chromatic discrimination disturbances in BPD patients. Our results supported the hypothesis that BPD may be associated with impairments in visual processing. The main novel aspect of the present study was the use of robust approaches (serial multiple mediation analyses) to examine the influence of clinical variables in BPD patients. Another feature of this study is that all of the patients were mostly acutely manic at the time of the study, differing from other studies that assessed only euthymic patients. Patients with BPD had worse discrimination (i.e., higher thresholds) when compared to HCs (Fig. 3) this was related both to medication dosage (all p-values < 0.001) and to greater severity of manic symptoms (all p-values < 0.01).

We observed that, for the Protan, Deutan, and Tritan vectors, the BPD patients presented worse color discrimination than the healthy controls. These differences were not specific to color vision or to any of its specific axes. Since the human visual system presents a combination of additive and opponent cone signals (L+M), L−M, and [S−(L+M)] it is a difficult task to segregate the signals of visual pathways (Klistorner et al., 1997; Roy et al., 2009). It is unclear how the parvo-, magno- and koniocellular are being affected by the losses in the wavelengths (Fernandes et al., 2021). In this case, we can only hypothesize that there is a diffuse impairment and may involve one or all of the pathways. Since the S-cones generate slower responses than the other cones (L- and M-cones), this is a possible explanation of why Tritan have higher thresholds than Protan and Deutan. Also, a slower response indicates a lower sensitivity and differences in interpreting visual function (Baudin et al., 2019). This suggests that although the S-cones may be the first affected in some diseases (Fernandes et al, 2019), when the impairment is general or extensive, it is difficult to segregate these diffuse impairments.

Briefly, the mediation analyses indicated three main patterns: (1) although there was influence of the symptom severity on the outcomes, its effects explained an average of > than 40% of the results; (2) the influence of medication on the outcomes suggested that higher the medication dosage, worse the performance (i.e., high influence on the outcomes; > 70%); and (3) the association between symptom severity (YMRS) and medication suggest a worsening on visual functioning in BPD patients (this may be accountable for at least 60% ~ 70% of the results; see adjusted R^2 values); however, should be carefully interpreted.

Regarding the pathophysiology of BD, some biochemical pathways may be involved, namely: (i) neurotransmitters, such as: norepinephrine, serotonin and dopamine; (ii) signalling pathways, such as: cyclic adenosine monophosphate (cAMP), phosphoinositide

and (iii) signal transduction systems coupled with the guaninenucleotide binding protein. Changes in γ-aminobutyric acid (GABA), acetylcholine activity and calcium regulation have also been shown in individuals with BPD (Manji et al., 2001). Scotti-Muzzi et al. (2021) have shown that euthymic type 1 BPD patients had lower Glu/GABA ratio compared to health control, where this was influenced by anticonvulsant and antipsychotic medications, but not lithium. Low GABA values correspond to weak suppression of visual context in perception of contrast in schizophrenia and bipolar disorder (Schallmo et al., 2015; Salmela et al., 2021). Impaired contrast enhancement control is associated with clinical manifestations of the condition. Reduced contrast suppression might be caused by lower retinal contrast gain (Bubl et al., 2012; Bubl et al., 2015; Schwitzer et al., 2017) or by a decreased amount of feedback signal from higher cortical areas (Norton et al., 2016), both of which have different thresholds and gains.

Future studies are needed to compare the cumulative effects of medication, illness duration, and the frequency of shifts between mood states as variables affecting visual processing (for a broad discussion about BPD and mood states, see O'Bryan et al., 2013) in order to fully tease apart trait and state effects.

Research suggests the existence of a relationship between major depressive disorder and BPD with retinal abnormalities, observed in changes in the responses of cones and rods and decreased retinal nerve fiber layer (Tan et al., 2020). BPD patients have significant changes in different layers of the retina, such as the thickness of the peripapillary retinal nerve fiber layer, ganglion cell layer, and internal plexiform layer, which suggests a neurodegenerative factor in those patients (Mehraban et al., 2016; Garcia-Martin et al., 2019; Polo et al., 2019; Lizano et al., 2020; Koman-Wierdak et al., 2021; Sánchez-Morla, et al., 2021; O'Donoghue et al., 2017). A structural analysis of nine retinal layers in patients with

type I BPD and HCs (Sánchez-Morla, et al., 2021) showed a thinning of the retina affecting most layers in BPD compared to the control group. In line with that finding, Alici et al. (2019) showed that the mean thickness of the retinal nerve fiber layer (RNFL) and the mean volume of the ganglion cell layer (GCL) are significantly lower in the group of patients with type 1 BPD than in HCs. Khalil et al. (2017) provided evidence for the relationship between the thickness of the retinal nerve fiber layer and the occurrence of manic episodes in some patients. However, a later study by Khalil et al. (2019) report that the number of episodes, age at onset and severity of disease showed insignificant correlation with OCT parameters. Lizano et al. (2020) did not find a significant relationship with clinical indicators. Kalenderoglu et al. (2016) found a significant negative correlation between a decrease in macular volume corresponding to GCL in patients with BPD and the disease duration, YMRS score, clinical global impression scale, number of hospitalizations, and GCL volume (patients were euthymic at the time of the study, though). The study found that the GCL volume loss was much more prominent than the decrease in the RNFL thickness and suggested that neurodegeneration in bipolar disorder starts in the GCL.

The present study has limitations. The inferences about neurophysiological mechanisms are in part speculative, since we used a behavioral tool. The inclusion of measures of serum levels of BPD medication would have been helpful for determining the specific effects of different medications on visual performance. Moreover, the use of biological measures such as BDNF (Shoshina et al., 2021) or GDNF would also have been useful to understand the possible association of its levels and the outcomes. Another potential limitation is the narrow range of the duration of BPD, and the use of only YMRS to investigate symptom severity. However, we were able to find moderate-to-strong correlations between manic episodes, medication and color vision.

In summary, the present results showed marked differences in chromatic discrimination between patients with BPD and HCs, which were linked, at least in part, to the patients' manic symptoms and their medication. Further investigations are needed to elucidate the pathophysiological mechanisms that are involved in such sensorial alterations. Also, further studies should investigate medication-free patients to understand the underlying mechanisms related to the absence of medication in larger samples. This will help understand pharmacological mechanisms related to lithium or other medications on visual processing. This study highlights the importance of understanding the association of clinical mediator variables (e.g., mood state, symptom severity, illness duration) with visual functioning, which had been neglected in some BPD studies.

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Authors' contributions: NA, MO, GS, IS, FMF and TPF helped with data interpretation and helped to draft the manuscript. NA helped with data collection and data analysis. NS and TF participated in its coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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Table 1. Demographics characteristics of the sample.

	Healthy controls (*n* = 25)	**BPD (*n* = 20)**
	Mean (SD)	**Mean (SD)**
Age, years	32.12 (5.10)	35.60 (6.78)
Education, years	13.10 (1.90)	12.56 (2.75)
Male/Female	14/11	13/7
Duration of the disease	0.00	11.00 (6.89)
Number of hospitalizations	0.00	1.45 (1.09)
Medication dosage (mg)	0.00	497.50 (361.80)
YMRS	0.00	16.45 (5.14)
MEEM	29.26 (0.30)	29.20 (0.41)

	Standardized			Collinearity		Autocorrelation
Model	**β**	***t*-test**	***p*-value**	**Tolerance**	**VIF**	**Durbin-Watson**
Constant		3.146	< 0.001			
Protan	0.643	3.663	0.001	0.342	1.596	1.195
Deutan	0.798	6.700	< 0.001	0.646	1.358	1.197
Tritan	0.821	8.068	< 0.001	0.760	1.544	0.907

Table 2. Model summary of the multiple regression analysis.

Fig. 1. Schematic representation of the procedures. Initially, the participants were dark adapted for 10 minutes (A) and then tested. Their task was to press the button indicating the opening of the "ring" gap (B). Outcomes for the Trivector test are the variables Protan, Deutan and Tritan (C).

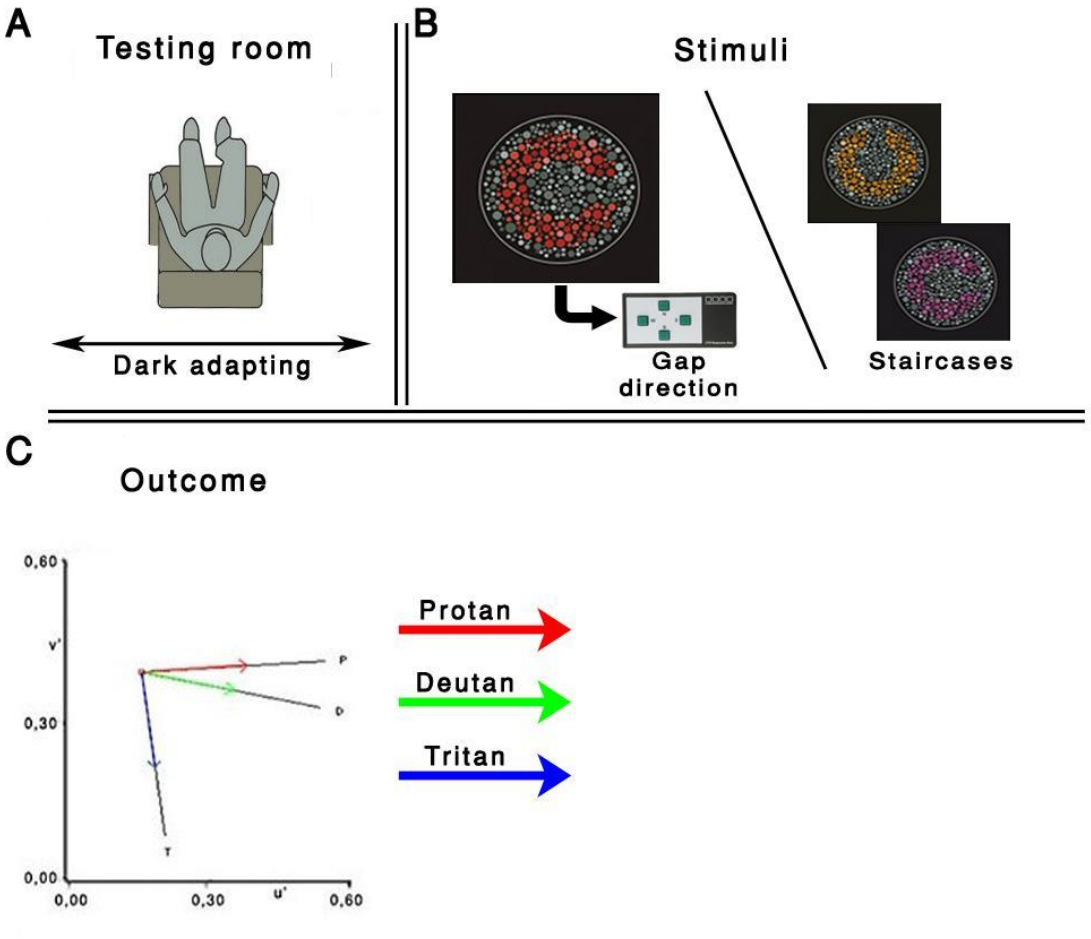

Fig. 2. Schematic representation of the serial multiple mediation (considering the averaged model).

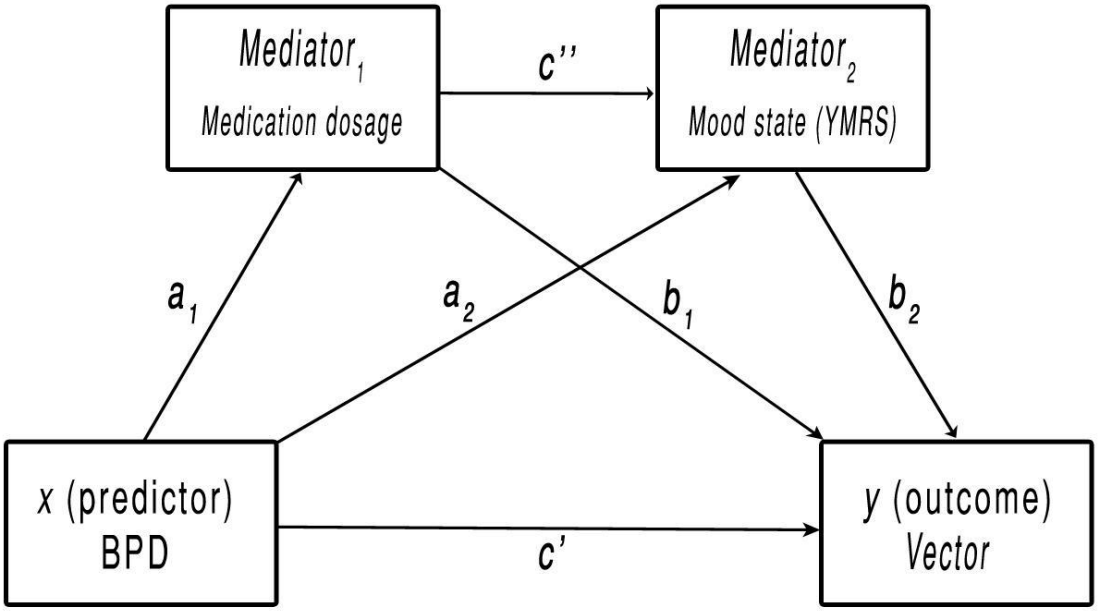

Fig. 3. Violin plots of the Trivector thresholds of healthy controls and BPD groups for the Protan (A), Deutan (B) and Tritan (C) vectors. Inside each violin plot are the individual values (colored dots). The dashed line indicates the mean width over all individuals. The dotted lines indicate the quartiles. Surrounding the dots on each side is a rotated kernel density plot. *** $p < 0.001$