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Colour Vision Impairments in Bipolar Disorder: A Systematic Review

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HIGHLIGHTS

- Ongoing evidence of colour vision impairment in mild to moderate mania of bipolar disorder I.
- Low evidence of genetic linkage between colour blindness and bipolar disorder.
- Future studies require rigorous methodologies (i.e., biomarkers, adjusting to confounders) to validate findings.

ABSTRACT

Visual impairments are common in patients with bipolar disorder (BD), and the neuropathophysiology may suggest a potential influence on colour vision. This systematic review aimed to assess existing data of colour vision impairment, including chromatic discrimination and colour blindness in patients with BD. Comprehensive literature search compliant with PRISMA 2020 was conducted in Medline, Embase, and Google Scholar from inception to February 28th, 2023. Our inclusion criteria were: (1) patients with a diagnosis of bipolar I or II disorder based on DSM, ICD, or clinical diagnosis, and (2) study investigating colour vision (i.e., including colour blindness and discrimination), with (3) no restrictions on the condition of the comparator group. Study quality appraisal was performed using the NIH Study Quality Assessment Tool. Five studies from Brazil, Netherlands, and USA, with 338 patients were included. Three cross-sectional studies assessed chromatic discrimination and two case-series assessed colour blindness in patients with BD. The three cross-sectional studies support reduced chromatic discrimination during mild to moderate mania in BD when compared to healthy comparators. The latter two articles presented low evidence of an X-linked inheritance of BD. Our review indicates evidence of reduced chromatic discrimination in mild to moderate mania. However, further research is needed to validate these findings and to extend to other mood states in BD given current limitations. Future studies can benefit from further multi-institutional data, larger sample sizes, appropriate blinding, the use of biomarkers, and statistical adjustment to confounders to fully elucidate the role of chromatic discrimination in BD.

Keywords: bipolar disorder, mania, color vision, color blindness, chromatic discrimination; vision changes

ABBREVIATIONS

BD, Bipolar Disorder; BD-I, Bipolar Disorder I; BD-II, Bipolar Disorder II; CCT, Cambridge Colour Test; DSM-5, Diagnostic and Statistical Manual of Mental Disorders-Fifth edition; NIH, National Institute of Health-Quality Assessment Tools**;** SADS, Schedule for Affective Disorders and Schizophrenia; YMRS, Young Mania Rating Scale

1.0 INTRODUCTION

Bipolar disorder (BD) is a chronic, affective disorder characterized by recurrent manic/hypomanic and depressive episodes with complex neuropathophysiology. Visual disturbances are not a rare phenomenon in BD with reports of 32% of patients describing heightened colour vibrancy during manic/hypomanic episodes and 20% that is experiencing duller colour perception during depressive episodes[1]. Colour vision is facilitated when light within the visible spectrum enters the eye, reaching the retina. The retina, with its various layers, includes cone cells in the photoreceptor layer, that capture wavelengths of coloured light and transmit signals through the optic nerve to the visual cortex for visual and cognitive processing[2]. The colour pathway is characterized by red-green processing (i.e., parvocellular pathway) and blue-yellow processing (i.e., koniocellular pathway). Chromatic deficits are seen with disruptions in the colour pathway and can be congenital or acquired whereby the latter is attributed to ophthalmic, neurological, or systemic conditions[2].

There is evidence of accelerated pre-frontal cortical thinning in patients with BD, including in the occipital cortex responsible for visual processing[3]. Moreover, the dysregulation of monoamine neurotransmitters (e.g., dopamine), commonly observed in BD, primary psychotic illnesses, and administration of typical antipsychotics, leads to the distortion of dopaminergic visual pathways that are crucial for colour perception[4,5]. Furthermore, patients with BD exhibit significant retinal and brain atrophy with distortion to both red-green and blue-yellow systems[6]. Though, comorbidities such as smoking, diabetes, and hypertension have yet to be clearly elucidated in confounding these findings[7]. Current literature postulates that the depressive symptoms observed in Parkinson's disorder and seasonal affective disorders may be sequelae of atrophy to cortical regions including the occipital cortex and abnormalities in retinal photoreceptors[8,9]. Similarly, BD patients during depressive states demonstrated impairments in the magnocellular and parvocellular pathways responsible for visual contrast[10]. This raises the question as to whether aberrancies to the visual pathway found in BD patients have a role in the pathophysiology of the disease.

Clinically, acquired colour vision deficits found in individuals with BD may hold prognostic value with greater insight of the pathophysiology or clinical sequelae of the disorder. As such, we aim to systematically evaluate the presence of atypical colour perception, including difficulties in chromatic discrimination and colour blindness, in BD patients with attention towards bias, quality, and methodological limitations.

2.0 METHODS

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[11]. The protocol was uploaded to Open Science Framework *a priori* at *https://osf.io/8dja4/.*

2.1 Search Strategy and inclusion criteria

In collaboration with a library information specialist (RS), an extensive literature search from 1947 to February 28, 2023, was conducted, in Medline (OVID) and Embase for articles investigating colour vision in the BD population with no restriction on study type and date of publication **(Supplementary Table 1)**. We also conducted a manual search on Google Scholar using Boolean operators of keywords including "bipolar disorder or mania or manic" and "colour vision or colour blindness or colour perception" and references of eligible records throughout full-text eligibility.

Our inclusion criteria were the following: (1) participants with a diagnosis of bipolar I or II disorder (BD-I, BD-II) based on DSM, ICD (any version) or clinical diagnosis and (2) study investigating colour vision (e.g., Cambridge colour test, Lanthony D-15d test, etc.), with (3) no restrictions on the condition of the comparator group. The above criteria (i.e., any version of DSM/ICD, no restriction of comparator group) were established to optimize exploration and inclusion of available studies given the limited literature on BD and colour vision seen on preliminary search.

2.2 Study Screening

Studies were imported into Covidence[12] whereby title/abstract and full-text screening was conducted by four independent reviewers (KL, VD, IL, SW). Any disagreements were resolved with consensus or consulting a third-party author (JT, AG).

2.3 Data Extraction

Two investigators (IYZM, SL) independently extracted relevant data from included articles onto Microsoft Excel spreadsheet designed *a priori.* Our primary outcomes were general findings of chromatic discrimination and/or colour blindness. We extracted measures of the primary outcome as reported by authors and collected comprehensive demographic data and information regarding diagnostic criteria, symptom severity scales, study design, and control group types.

2.4 Quality Assessment/Risk of Bias

Quality assessment was independently conducted by two investigators (IYZM, SL) using the NIH Study Quality Assessment Tool[13]. Conflicts in the quality assessment were discussed to reach a consensus.

2.5 Statistical Analysis

We performed descriptive statistics such as mean, range and measure of variance (e.g., standard deviations, 95% confidence interval) where applicable. We determined a meta-analysis was not feasible due to the heterogeneity of study outcomes (i.e., measures of effect size) and inaccessibility of raw data (i.e., trivector thresholds). Therefore, the findings are summarized in a narrative format.

3.0 RESULTS

3.1 Study and Participants Characteristics

The literature search resulted in 2957 records **(Fig. 1)**. After excluding 551 duplicates, 2406 were screened. We excluded 2271 studies due to incongruencies to predetermined inclusion criteria. Of the 95 full-text studies, 90 were excluded leaving 5 included papers[14–18]. Three articles were cross-sectional studies[14,17,18], and 2 were case-series assessing linkage analyses[15,16]. The country of origins included Brazil (n=3) [14,17,18], Belgium (n=1)[15], and the United States (n=1)[16]. In these articles, BD-I, BD-II and cyclothymia were diagnosed using the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) in 3 articles and Schedule for Affective Disorders and Schizophrenia (SADS) in 2 articles **(Table 1)**. The symptom severity of mania was assessed using the Young Mania Rating Scale (YMRS) in 3 studies, all of which assessed chromatic discrimination (YMRS>19 as mania, YMRS=13-19 as hypomania, YMRS≤12 as remission[19]). Importantly, distinctions between mania and hypomania are based on DSM-5 and not YMRS cut-offs. In total, 338 patients were included with a mean age of 36.9 ± 9.5 and 37.9% (n = 128) females **(Table 1)**.

3.2 Chromatic discrimination

Three studies (n=127) assessed chromatic discrimination in outpatients with BD-I in mild to moderate mania[14,17,18]. All three articles used the Cambridge Colour Test (CCT), specifically the Trivector subtest to evaluate chromatic discrimination **(Table 2)**. The CCT is a brief (<5 mins), computerized test administered as a veridical measuring tool for congenital and acquired colour vision impairment[20]. The Trivector test measures thresholds of the Protan, Deutan, and Tritan vectors (red, green, and blue wavelengths, respectively). Across the three studies, chromatic discrimination was worse in BD patients when compared to healthy comparators (HC), as detailed in the ensuing paragraphs.

In addition to the CCT, Fernandes et al. (2017) administered the Ellipse subset and the Lanthony d-15D Test to further assess chromatic discrimination[14]. The authors recruited outpatients with BD-I and mania (mean YMRS=20.2 ± 4.3) **(Table 1)**. The authors found that patients with BD (n=12) had significantly reduced chromatic discrimination compared to healthy comparators (n=12) in all domains of

the Trivector ($p<0.001$), Ellipse ($p<0.01$), and D15d tests ($p<0.001$) **(Table 2)**. Patients with BD had higher chromatic discrimination thresholds in the Protan (r=0.65 [0.53-0.72], R^2=0.36), Deutan (r=0.48 [0.39-0.60], R^2=0.1) and Tritan (r=0.55 [0.45-0.60], R^2=0.08) vectors of the Trivector test compared to HC. Patients with BD had significantly greater Ellipse areas (i.e., reduced chromatic discrimination) in the Protan (r=0.84 [0.73-0.87], R^2=0.11), Deutan (r=0.73 [0.60-0.80] R^2=0.3), and Tritan (r=0.6 [0.52-0.72], R^2=0.12) axes of the Ellipse test compared to HC. Moreover, the colour confusion indices for the D15d tests were scored higher (i.e.., reduced chromatic discrimination) among BD patients (r=0.81 [0.72-0.86]) compared to HC.

Fernandes and colleagues (2022) recruited BD-I outpatients in mild to moderate mania with mean YMRS=16.45 ± 5.14[18] **(Table 1)**. The authors found participants with BD (n=20) experienced higher chromatic discrimination thresholds (e.g., reduced chromatic discrimination) for the Protan (Cohen's f=1.18 [0.86-1.50], YMRS R^2=0.35, medication dose R^2=0.52), Deutan (Cohen's f=1.57 [1.20-1.95], YMRS R^2=0.48, medication dose R^2=0.42), and Tritan (Cohen's f=1.37 [CI 1.03-1.73], YMRS R^2=0.38, medication dose R^2=0.77) vectors of the Trivector test compared to healthy comparators (n=25) **(Table 2)**. Multiple mediation models revealed a strong, direct effect of medication dosage (Protan [a1xb1=1.64, *SE*=0.68, *z*= 2.40; 95%BCas 0.30–2.98], Deutan [a1xb1=2.72, *SE*=0.82, *z*=3.43;95%, BCas 1.16–4.26] and Tritan [a1xb1=4.14, *SE*=1.29, *z*=3.21; 95%BCas 1.62–6.77]; $p<0.001$) and moderate-to-high, indirect (mediated) effect of symptom severity (Protan [a2xb2=3.15, *SE*=1.37, *z*=2.31; 95%BCas 0.47–5.85], Deutan [a2xb2=2.67, *SE*=1.38, *z*=1.96; 95%BCas 0.003–5.40] and Tritan [a2xb2=4.85, *SE*=2.35, *z*=2.06; 95%BCas 0.23–9.44]; $p<0.01$) on lower chromatic discrimination. They found no significant correlation between illness duration and chromatic discrimination in participants with BD.

Oliveira and colleagues (2022) recruited BD I outpatients who were active smokers and in acute mania (mean YMRS=17.7 ± 4.4)[17] **(Table 1)**. The team found that those with BD who smoke (n=23) had significantly higher chromatic discrimination thresholds for the Protan (ω^2=0.47 [0.29-0.60]), Deutan (ω^2=0.36 [0.21-0.49]) and Tritan (ω^2=0.19 [0.04-0.34]) vectors of the Trivector test when compared to those with BD who do not smoke (n=23) **(Table 2)**.

3.3 Colour Blindness

Two forty-plus year old studies (n=14 families) investigated the hypothesis of X-linked co-inheritance of BD and colour blindness among inpatients with BD-I, BD-II and their families[15,16]. The disease stage was not described in either paper. As detailed below, these studies present conflicting conclusions despite similar findings.

Mendlewicz and colleagues (1979) investigated colour blindness in eight BD inpatients and their relatives from Belgium (n=8 families) for linkage analysis[15]. The group used the Hardy-Rand-Rittler Test, which is a book comprised of a series of colour plates partitioned for screening and diagnosis of colour vision defect, and the Farnsworth-Munsell 100 Hue Test, which is an arrangement task based on coloured cap-sorting to measure chromatic discrimination. Higher lod scores indicate higher likelihood of linkage between two genes (i.e., lod score<-2 suggests no linkage, lod score>3 suggests definite linkage). The authors suggested there is a strong X-linked dominant transmission of BD and colour blindness with both major genes residing close together on the X-chromosome (maximum lod score=1.55 at recombination fraction=0.15). Within the sample, Family 1 demonstrated the highest evidence of X-linkage with the remaining families being inconclusive. There exists high heterogeneity of lod scores within the total sample (X2=15.36, df=7, p=0.3) which is largely accounted for by one pedigree (Family 1) **(Table 2)**.

Gershon and colleagues (1979) used Ishihara plates and anomaloscope to replicate the former study in six BD inpatients and their relatives from the United States (n=6 families)[16]. The group found no linkage between BD and colour blindness as no recombination fraction provided a positive lod score in their sample **(Table 2)**.

3.4 Quality Assessment

In total, four out of five studies were "fair" with one study ranked as "good" in quality **(Supplementary 2)**. All three cross-sectional studies lacked appropriate blinding to the status of participants (e.g., BD vs non-BD) during chromatic discrimination assessment. With both the case-series, it was unclear whether cases were consecutive and of any additional inclusion/exclusion criteria for families to be selected in the study.

4.0 DISCUSSION

This systematic review investigated the relationship between colour vision and BD. Five studies were identified whereby three cross-sectional studies investigated chromatic discrimination and two case-series investigated colour blindness linkage in patients with BD. All three cross-sectional studies indicate evidence of reduced chromatic discrimination in the BD population during mild to moderate mania when compared to HC. Moreover, the hypothesis of an X-linked co-inheritance to BD and colour blindness is unlikely given our contemporary understanding of BD's complex patterns of inheritance.

4.1 Chromatic discrimination

Our review indicates evidence to suggest that individuals with BD exhibit reduced chromatic discrimination across red, blue, and green vectors compared to HC. Colour vision impairment - among

other visual deficits - has been recently associated with schizophrenia and major depressive disorder[21,22]. In two Brazilian multi-site studies, those with schizophrenia (n=66 Study 1, n=68 Study 2) demonstrated reduced acute chromatic discrimination using the CCT with larger differences seen for those using first- instead of second-generation antipsychotics[21]. Impairments were also seen in a small pilot case-control for those in a moderate to severe major depressive episode (n=20) compared to healthy controls (n=32) in the Farnsworth Munsell 100-Hue test[22]. Moreover, growing evidence suggests substantial genetic, biological, and phenomenological overlay between schizophrenia and BD suggesting shared clinical phenotypes[23]. Current research shows that those with BD exhibit evidence of concurrent neurodegeneration and retinal structural damage including reduced thickness of the retinal nerve fibre layer[24], ganglion cell layer [25], and inner plexiform layer[26]. As such, diffuse visual deficits such as contrast sensitivity function[27] and motion perception[28] have been found in BD patients which supports the notion that these degenerative findings can extend to colour perception.

Methodological limitations are to be considered. All participants were mild-moderately manic (average self-report YMRS score=18.1 ± 4.6) throughout the study with likely features of distractibility and flight of ideas during the procedure. The global impairment across Protan, Deutan, and Tritan vectors could be in part secondary to inattention and nonadherence as only one study incorporated selective attention screening before administering colour vision tests[14]. Nonetheless, considering that acquired colour impairment typically initiates with blue-yellow deficiencies before progressing to red-green, the observation of widespread deficits across all three colour vectors appears logical[29].

The three studies were also largely conducted in Brazil, with two papers led by the same research group, and involved cohorts of BD and HC which limits generalizability. The study's small sample sizes and the nature of their cross-sectional design impairs interpretations of causality between chromatic discrimination deficits and BD. Notably, confounding factors known to affect retinal structure should be considered in statistical analysis including the use of antipsychotics, anticonvulsants, lithium, antidepressants, hypertension, diabetes, smoking, and illicit substances[7,30,31]. For instance, antipsychotics have shown to inhibit retinal dopaminergic pathways that can lead to ganglion cell death and subsequent retinal thinning[32]. While comorbid conditions such as type II diabetes mellitus, which is a common sequelae of second-generation antipsychotics, have demonstrated increased prevalence of impaired colour vision, especially those with greater duration of the disease[33]. Furthermore, retinal dystrophies, genetic conditions characterized by degeneration of photoreceptors, present with heterogenous visual defects including colour impairment which poses as a potential confounding issue[34]. Current literature surrounding the relationship between retinal genetic disorders and bipolar disorder are scarce and have yet to be considered in statistical adjustments in these studies. Among our included studies, Oliveira

and colleagues (2022) found smokers with BD had worse chromatic discrimination even when compared to controls with heavier smoking histories[17]. While, Fernandes and colleagues (2022) recruited patients strictly on lithium and showed a strong, direct association between lithium and chromatic discrimination[18]. As such, the absence of a comprehensive study accounting for all these confounding factors concurrently poses a significant challenge in translating these findings into the clinical setting.

4.2 Colour Blindness

This review also explored the hypothesis proposing the existence of a singular, prominent gene for BD that resides closely to Protan/Deutan gene arrays located on the X-chromosome. Mendlewicz and colleagues (1979) found their pedigree analysis to support co-transmission of BD and colour blindness while a replication study published by Gershon et al. (1979) refuted their conclusion[15,16]. Criticisms to the former study includes potential sampling bias given the lack of reported inclusion criteria as eight out of 110 BD patients were selected, and that all male probands (the BD patient initially recruited to investigate colour blindness within their family) had colour blindness with majority of the selected families having both colour blindness and BD. Contrastingly, these concerns did not present in the second study with further methodological improvements including using multiple, blinded interviewers, whereas the former study relied on a single interviewer.

Recent research reinforces a genetic aetiology of BD; however, studies have yet to find a Mendelian pattern of transmission, including evidence of X-linked inheritance, indicating that complex mechanisms of heritability are likely involved[35]. Linkage methodologies, such as the two studies included in our review, fails to generate reliable, replicable results when tasked to interpret disorders of complex heritability including BD. Importantly, tools at the time of these two studies were limited as genome-wide association study (GWAS), the approach of identifying allelic variation associated with a particular disease, was first introduced decades afterwards. Recent GWAS of 40,000 BD patients indicated 64 associated genomic loci with convergence on several biological pathways demonstrating considerable complexity of BD's genetic aetiology[36]. As such, the hypothesis whereby a single major gene responsible for BD residing proximal to Protan/Deutan gene arrays on the X-chromosome is not consistent with contemporary knowledge of BD genetics.

4.3 Implications and Limitations

Colour vision deficits in high-risk populations have the potential to pose as clinical markers in screening for BD via retinal imaging and targets for novel therapies. There is evidence that colour/light exposure in early life can influence the risk and age of onset of manic episodes[37,38]. Future studies

dedicated to elucidating basic mechanisms of colour vision deficits in BD and their clinical utilities play a role in enhancing patient care.

To note, our review and the included studies have limitations. Firstly, our review solely provided descriptive statistics and did not generate pooled chromatic discrimination threshold values across our studies which would have offered further insight. Although there was serious consideration for conducting a meta-analysis, the heterogeneity in study outcomes (i.e., reported effect sizes) and the absence of raw data (i.e., trivector thresholds of total sample) hindered its execution. Moreover, the interpretability of the meta-analysis would be of low quality as several articles do not account for global deficits of inattention/distractibility seen in mania. Finally, our literature search is limited to Medline and Embase which can be more thoroughly expanded to other databases. For limitations of included studies, all cross-sectional studies investigating chromatic discrimination were not blinded rendering high risk of bias. Finally, all participants from the chromatic discrimination studies were outpatients from private clinics in Brazil which makes it challenging to interpret on a broader scale.

Future studies would benefit from rigorous adjustment to confounding factors including use and duration of medications (e.g., antipsychotics, anticonvulsants, lithium, antidepressants), comorbid conditions (e.g., hypertension, diabetes, smoking, and substance use disorder), and underlying genetic disorders (e.g., retinal dystrophies). Particularly, significant insight can be gathered by systemically recording the above patient data, stratifying between sexes, and determining whether overt phenotypes (i.e., chromatic discrimination and colour blindness) vary depending on medications taken over their lifetime. Moreover, future studies can use retinal imaging (e.g., electrodiagnostic technology and optical coherence tomography) as biomarkers to correlate retinal function and structure with clinical performance of chromatic discrimination.

5.0 CONCLUSION

In conclusion, our review indicates early evidence of reduced chromatic discrimination in patients with BD which may aid in future prognostic or diagnostic evaluation. However, further research is needed to validate these findings given the notable limitations of small sample sizes, poor generalizability, the nature of cross-sectional design of individuals with mania, and the lack of adjustment to concurrent confounding factors such as medications, medical and genetic comorbidities, smoking, and substance misuse. Additionally, the convoluted heritability of BD from modern research findings refutes the genetic linkage between colour blindness and BD. Future studies can benefit from multi-institutional data, larger sample sizes, appropriate blinding, consideration of BD mood state (i.e., requiring prospective studies),

statistical adjustment to confounders (e.g., medications, comorbid disorders, and genetic conditions), and biomarkers (e.g., retinal imaging), to clarify the role of chromatic discrimination in samples with BD.

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COLLABORATION

MS conceived the study, which was led by JT and AG. KL, VD, IL, and SW completed level I and II screening. IYZM and SL extracted the data and conducted quality appraisal under the supervision of JT. JT, AG, and MS drafted the work, and AG conducted the analyses. RS curated the search strategy. AZ, AS, and SC made substantial contributions to the interpretation of the results. NF made substantial contributions to the discussion. JGF made significant contributions to the revision of the manuscript and methodological appraisal of included studies as bipolar disorder content expert. All authors critically revised the manuscript, approved the final version for publication, and agreed to be accountable for all the aspects of the work. JT and AG had full access to all the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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Figure 1: PRISMA flowchart of included studies

Table 1: Demographics and study characteristics of the included studies

Table 2: Summary of study results

Supplementary 1: Search Strategy

Supplementary 2: NIH Quality Assessment

Figure 1: PRISMA flowchart of included studies

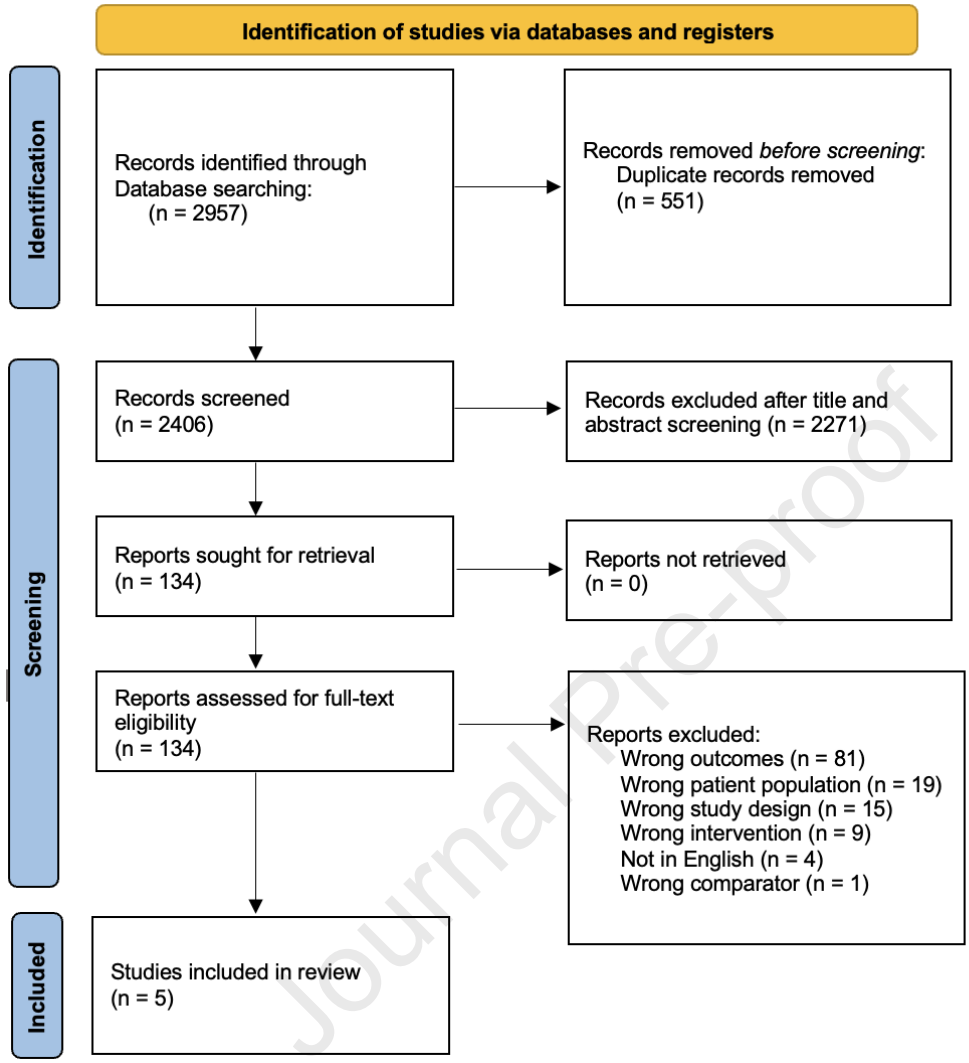

Table 1: Demographics and study characteristics of the included studies

Author, Year (country)	Participant Selection (Age range)	Study Design	Sample Size (N)	Age (years) Mean ± SD	Total Female n (%)	YMRS Mean ± SD	Diagnostic Tool	BD Subtype (Stage)
Chromatic discrimination								
Fernandes, 2022 (Brazil)	Outpatient (20-45 years old)	Cross-sectional	45	BD: 32.12 ± 5.10 Non-BD: 35.60 ± 6.78	18 (40.0)	16.45 ± 5.14	DSM-5	BD I (Mania)
Oliveira, 2021 (Brazil)	Outpatient (25-45 years old)	Cross-sectional	46	BD: 33.2 ± 5.8 Non-BD: 34.3 ± 5.6	19 (41.3)	17.7 ± 4.4	DSM-5	BD I (Mania)
Fernandes, 2017 (Brazil)	Outpatient (25-42 years old)	Cross-sectional	24	BD: 32.3 ± 5.2 Non-BD: 33.6 ± 6.0	10 (41.67)	20.2 ± 4.3	DSM-5	BD I (Mania)
Colour Blindness								
Gershon, 1979 (USA)	Inpatient	Case-series	6 Families (134 total participants) *	Total: 48.61 ± 20.8	55 (41.04)	N/A	SADS	BD I, BD II, and unipolar illnesses (N/A)
Mendlewicz 1979 (Belgium)	Inpatient	Case-series	8 Families (89 total participants) *	Total: 43.92 ± 16.5	26 (29.21)	N/A	SADS	BD I, BD II, and unipolar illnesses, or cyclothymic (N/A)

Abbreviations: BD, Bipolar Disorder; DSM-5, Diagnostic and Statistical Manual of Mental Disorders-fifth edition; SADS, Schedule for Affective Disorders and Schizophrenia; YMRS, Young Mania Rating Scale; *Total number of participants excludes individuals with missing data on colour blindness or BD diagnosis. Stage refers to the patient's disease stage (i.e., mania, hypomania, depression, mixed, or maintenance) during the time of study.

Table 2: Summary of Study Results and Quality Assessment

Author, Year	Colour Vision Tool	Main Findings of BD patients	Comparator Group	Risk of Bias (NIH Score)
Fernandes, 2022	CCT (Trivector)	BD-I patients in acute mania had higher chromatic discrimination thresholds than controls in Protan ($p < 0.001$), Deutan ($p < 0.01$), and Tritan ($p < 0.001$) axes	Healthy general population	Good (12/14)
Oliveira, 2021	CCT (Trivector)	BD-I smokers in acute mania had higher chromatic discrimination thresholds than controls in Protan ($p<0.001$), Deutan ($p<0.001$), and Tritan ($p=0.002$) axes	Heavy Smokers without BD	Fair (10/14)
Fernandes, 2017	CCT (Trivector and Ellipse) Lanthony D-15D	BD-I patients in acute mania had higher chromatic discrimination thresholds than controls in the Trivector ($p<0.001$), Ellipse ($p<0.01$), and D15d tests ($p<0.001$) Trivector: Protan ($p=0.001$), Deutan ($p=0.021$), Tritan ($p=0.007$) axes Ellipse: Protan ($p<0.001$), Deutan ($p<0.001$), and Tritan ($p=0.003$) D15d: colour confusion indices ($p<0.001$)	Healthy general population	Fair (10/14)
Gershon, 1979	Ishihara Plates Anomaloscope	Low evidence of close linkage between BD and colour blindness on X-chromosome (no recombination fraction provided a positive lod score)	N/A	Fair (4/9)
Mendlewicz 1979	Hardy-Rand-Rittler Test Farnsworth-Munsell 100 Hue Test	Evidence of X-linked inheritance of BD gene with linkage of colour blindness loci on the X chromosome. (Maximum lod score=1.55 at recombination fraction=0.15)	N/A	Fair (5/9)

Abbreviations: BD, Bipolar Disorder; CCT, Cambridge Colour Test; NIH, National Institute of Health Quality Assessment Tools.

Supplementary 1: Search strategy

Embase Classic+Embase <1947 to 2023 February 28>

1 exp *schizophrenia spectrum disorder/ 140878

2 schizophren*.tw. 195508

3 (psychosis or psychotic).tw. 110007

4 (schizoaffective or paranoi* or delusion* or paraphrenia).tw. 40345

5 exp *bipolar disorder/ 40144

6 (bipolar or mania or manic).tw. 121914

7 or/1-6 385023

8 color vision defect/ or color vision/ or color blindness/ or contrast sensitivity/ 35926

9 ((colour or colours or color or colors) and (vision or visual or ocular or blind* or discrimination or perception)).tw. 44968

10 Deutan Defect*.tw. 30

11 Achromatopsi*.tw. 967

12 Tritan Defect*.tw. 52

13 dyschromasia.tw. 7

14 dyschromatopsia.tw. 506

15 daltonism.tw. 46

16 visual disorder/ 36382

17 ((vision or visual) adj3 (disorder* or sensitivity)).tw. 10901

18 or/8-17 109123

19 7 and 18 1598

20 (exp animals/ or animal experiment/ or nonhuman/) not exp animals/ 2063550

21 19 not 20 1569

22 visual impairment/ or exp blindness/ or hemianopia/ or low vision/ 120774

23 visual disorder/ or exp amblyopia/ or color blindness/ or color vision defect/ or diplopia/ 84247

24 22 or 23 195747

25 7 and 24 2015

26 (exp animals/ or animal experiment/ or nonhuman/) not exp animals/ 2063550

27 25 not 26 2008

28 21 or 27 2932

29 conference abstract.pt. 4694392

30 28 not 29 2256 without conference abstracts

31 exp *schizophrenia spectrum disorder/ 140878

32 (schizophren* or schizoaffective).tw. 197197

33 exp *bipolar disorder/ 40144

34 bipolar.tw. 108616

35 31 or 32 or 33 or 34 305946 much narrower search of schizophrenia/bipolar

36 18 and 35 1271

37 24 and 35 1341

38 36 or 37 2168

39 (exp animals/ or animal experiment/ or nonhuman/) not exp animals/ 2063550

40 38 not 39 2136

41 40 not 29 1693 without conference abstracts

Supplementary 2: NIH Quality Assessment

CROSS-SECTIONAL	Fernandes 2022	Oliveira 2021	Fernandes 2017
1. Objective clear?	1	1	1
2. Study population clearly defined?	1	1	1
3. Participation rate of eligible persons > 50%?	1	1	1
4. All subjects recruited from same or similar population (& were inclusion/exclusion criteria applied to all?	1	1	1
5. Same size justification, power description, variance, and effect estimates provided?	1	1	1
6. Exposures of interest measured prior to outcomes being measured?	1	1	1
7. Timeframe sufficient to expect association?	NA	NA	NA
8. For exposures that can vary in level, did the study examine different levels of exposure?	1	NA	NA
9.. Exposures measures clearly defined, valid, reliable, and implemented to all?	1	1	1
10. Exposure assessed more than once over time?	NA	NA	NA
11. Outcome measures clearly defined, valid, reliable?	1	1	1
12. Outcome assessors blinded to status of participants?	0	0	0
13. Loss to follow up after baseline <20%?	1	1	1
14. Confounding variables measured and adjusted?	1	0	0
Total Score	**12**	**10**	**10**
Quality Rating 0-5 (Poor), 6-10 (Fair), 11-14 (Good)	**Good**	**Fair**	**Fair**

CASE-SERIES	Gershon 1979	Mendlewicz 1979
Objective clear?	1	1

Study population clearly defined?	1	0
Cases consecutive?	0	0
Subjects comparable?	0	0
Intervention clearly described?	NA	NA
Outcome measures clearly defined, valid, reliable, and implemented consistently to all?	1	1
Length of follow-up adequate?	NA	NA
Stats well described?	1	1
Results well described?	1	1
Total	**5**	**4**
Quality Rating 0-3 (poor), 4-6 (fair), 7-9 (good).	**Fair**	**Fair**

HIGHLIGHTS

- Ongoing evidence of colour vision impairment in mild to moderate mania of bipolar disorder I.
- Low evidence of genetic linkage between colour blindness and bipolar disorder.
- Future studies require rigorous methodologies (i.e., biomarkers, adjusting to confounders) to validate findings.

Conflicts of Interest: We have no conflicts of interest to declare.