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Ph.D. THESIS

Mapping the Relationships of Potential Psychological Mechanisms and Psychiatric Comorbidities for Bipolar Disorder Severity

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Notes._____

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CHAPTER I. THEORETICAL BACKGROUND

1.1. Introduction and Research Topic

Bipolar Disorder (BD) is one of the leading contributors of disability globally. The World Health Organization (WHO, 2011) has ranked it as the second most obtrusive factor in impaired day-to-day functioning, due to the severe cognitive and functional degeneration. While fluctuations in mood might be normal every now and then, habitual and sudden mood swings might be signaling a chronic affective disorder (Grande et al., 2016). Impacting roughly 40 million individuals globally, a 12-month prevalence survey conducted by the WHO - World Mental Health Survey Initiative estimated that approximately 1.5% of the population was affected by a Bipolar Spectrum Disorder (BSD), 0.4% by Bipolar Disorder type I (BD-I), 0.3% by Bipolar Disorder type II (BD-II), and 0.8% do not meet full criteria for BD-I or BD-II (e.g. *met only one symptom of mania*) (Singh et al., 2025). Early studies classed the disorder as affecting up to 5% of the population in some settings. An example of this is the inclusion of cyclothymic disorder in prevalence research (Berk & Dodd, 2005).

A worldwide study conducted by Lai et al. (2024) observed that cases of Bipolar Disorder have been rising in recent years, with an increase of 59.3% from 1990 to 2019. Amongst all age groups, the highest incidence risk is observed in the 15-19 age group. The highest 'years lived with disability' impact occurred in males aged 20-24 and females aged 25-29. Simply put, young adults (namely in their 20s) lose the most of their healthy years of life due to Bipolar Disorder. Current research urges for discovery of methods to identify those at high risk for developing the disorder in order to (1) have a chance at amending risk factors and (2) achieve prompt diagnosis and intervention (Vieta et al., 2018; Niu et al., 2022; Lai et al., 2024).

However, bipolar disorder diagnosis is oftentimes delayed by up to 15 years due to diagnostic complexity (Lublóy et al., 2020). Studies observed an incidence of misdiagnosis of 52%, 69% and even up to 76.8% (Knežević; & Nedić, 2013; Shen et al., 2018). Some reports note that only 20% of individuals with bipolar disorder are accurately diagnosed in the first year of treatment (Kaya et al., 2023). Misdiagnosis isn't felt only at a personal level, but also nationwide. Every misdiagnosed bipolar patient costs healthcare $18,286 (including hospitalizations, ER visits and outpatient visits) every year in the U.S.A (McIntyre et al., 2022).

But why is diagnosing bipolar disorder so perplexing? More often than not, individuals seek out treatment during depressive episodes, rather than manic (or hypomanic) episodes, being wrongfully diagnosed with major depressive disorder (Stiles et al., 2019). A different diagnosis is inopportune since it follows inaccurate treatment. Major Depressive Disorder (MDD) is treated with antidepressants, which unfortunately in the BD population is associated with profound consequences, such as increased hospitalizations and more suicide attempts (Stiles et al., 2019). Unfortunately, patients are less likely to report hypomanic and manic symptoms due to the productive and even enjoyable symptoms that accompany the 'highs' of BD (Berk et al., 2025; Stiles et al., 2019).

Diagnosing BD is likewise complicated by "multiaxial comorbidity" furthermore masking a BD diagnosis (McIntyre et al., 2004). The high prevalence of comorbidities in

bipolar disorder (Amerio et al., 2015; Amerio et al., 2016; Di Florio et al., 2024; Dong et al., 2020; Ferentinos et al., 2020; Fornaro et al., 2016; Fornaro et al., 2021; Hu et al., 2023; Hunt et al., 2016; Khoso et al., 2023; Lega-Rego et al., 2024; Nabavi et al., 2015; Novick et al., 2010; Pavlova et al., 2015; Pavlova et al., 2017; Pedro et al., 2023; Pinto et al., 2019; Preti et al., 2016; Preti et al., 2018; Sandstrom et al., 2021; Schiweck et al., 2021; Tondo et al., 2016; Trott et al., 2024; Yapici et al., 2018; Yapici et al., 2020) might obscure symptoms of bipolar disorders.

For example, 31% of patients with bipolar I disorder are wrongfully diagnosed with schizophrenia or substance induced psychotic disorder due to psychotic symptoms (Meyer & Meyer, 2009; Gonzalez-Pinto et al., 1998). The high comorbidity with substance use disorders might play a role in misdiagnosis (Hunt et al., 2016). Borderline personality disorder (BPD) in particular can be mistaken for bipolar disorder. This is thought to be due to an overlap in symptoms (Frias et al., 2016). In clinical settings, diagnosing both disorders is a rare phenomenon, as the symptoms of one of the disorders can obscure the diagnosis of the other (Parker et al., 2022) and professionals typically prefer diagnostic parsimony.

Besides the difficulty of diagnosis, the high psychiatric comorbidity rates amongst this population are more of a rule rather than the exception. Research has shown that about 66% of individuals with bipolar disorder face an additional psychiatric comorbidity (Pavlova et al., 2015, Wang et al., 2025). Looking at lifetime estimates, these percentages hike up to an astonishing 92% of individuals with BD facing other mental disorders as well (Merikangas et al., 2007). These high rates of comorbidity for an additional disorder signify the high probability that bipolar disorder patients not only face one additional comorbidity, but more probably face an array of comorbidities and even more so subclinical symptomatology. Comorbid anxiety disorder, for example, is 4.6 times more prevalent in bipolar disorder samples than the general population. A working theory in this sense is the common co-occurrence of depression and anxiety disorders. As depressive episodes occur in bipolar disorder, there might be common risk factors tying them together (Léda-Rêgo et al., 2023). This is a relationship observed by studies conducted in the present thesis as well (Studies 3 & 4), in a smaller sample network analysis on the Romanian population (Study 3 in this thesis), as well as a larger sample encapsulating multiple global regions in another network analysis, we conducted cross-nationally (Study 4 in this thesis).

Childhood maltreatment has been consistently associated with mental health disorders across one's lifetime (Scott et al., 2023). Epidemiological studies indicate that up to almost a third of psychiatric disorders that emerge may be attributed to childhood maltreatment (Kessler et al., 2010). These wide associations with multiple psychiatric disorders would signify that maltreatment confers a risk for psychopathology. Even so, associations are often studied in isolation (Keyes et al., 2012).

In studies of childhood maltreatment in bipolar disorder, more than half of those diagnosed report to have experienced at least one form of severe childhood maltreatment (Struck et al., 2020). Childhood maltreatment has been associated with an earlier age of onset, a higher risk of a rapid cycling form, more manic and depressive episodes and a higher risk for suicide attempts (Agnew-Blais & Danese, 2016; Daruy‐Filho et al., 2011; Laroche et al., 2022). Even so, a small number of studies have differentiated by types of childhood maltreatment, emotional abuse being sparsely considered. Evidence that does exist indicates

that emotional abuse and neglect are the most frequently reported types of childhood maltreatment, with emotional abuse being the strongest associated with BD development (Etain et al., 2010; Palmier-Claus et al., 2016). Maltreatment has been further associated with a 2.63 higher occurrence in individuals with bipolar disorder (Palmier-Claus et al., 2016).

Emotional abuse is the most prevalent form of abuse identified in individuals with bipolar disorder (Palmier-Claus et al., 2016). Findings show that emotional abuse is far greater in BD samples than the general population and the strongest associated with a more convoluted course (Etain et al., 2008). Recent research considers the strong relationship between emotional abuse and severe bipolar disorder might be explained by the action of high levels of affective instability (Taylor et al., 2021). When compared to controls, bipolar disorder individuals have higher rates of affective instability, as well reported higher rates of maltreatment. When investigated via path analyses, it would seem that affective instability mediates the relationship between childhood trauma and a diverse range of clinical features in BD, such as early age of onset, more episodes (as well as mixed), suicide attempts and anxiety disorders (Marwaha et al., 2019; Hett et al., 2022).

On a cognitive level, childhood maltreatment (excluding emotional neglect) is linked to poorer global cognition and intelligence, as well as other various cognitive impairments: learning, verbal memory, working memory, executive functions, verbal fluency (*see* Fares-Otero et al., 2025). Although cognitive deficits are common in BD, the level of functioning differs substantially across individuals. This could be due to a mechanism such as inflammation, which occurs following maltreatment. Inflammation might be caused by the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, due to a prolonged activation of the HPA axis and persistent cortisol activation as a consequence of chronic stress. A pro-inflammatory state is triggered by excessive cortisol which impedes on the immune system homeostasis promoting a state which creates vulnerability for cognitive decline (Majd et al., 2025).

About one third of people diagnosed with BD experience impairment for multiple cognitive domains, such as attention, verbal memory and executive function, while another third experience deficits in attention, memory, processing speed and executive function which persists in euthymic periods, while a final third remain relatively unaffected (Majd et al., 2025). A key cognitive mechanism explored in the context of Bipolar Disorder is Attentional Bias. Attentional Bias is defined as the "*preferentially attending to information that is related to the content of the emotional concerns of patients*" (Crombez et al., 2013; pp. 3). The construct also reflects the process through which specific information is preferentially processed at the expense of other information (Azriel & Bar-Haim, 2020). At any point in time, an individual processes tens if not hundreds of stimuli simultaneously. Even so, detailed processing can be conducted only for a set of stimuli (e.g., an ambulance sounding in the background, the sentence you're reading right now etc.), to reduce the mental load. The human mind blocks out several seemingly irrelevant stimuli, choosing those that can be utilized in the control of human behavior (Azriel & Bar-Haim, 2020).

Garcia-Blanco et al. (2013a) investigated mood congruency amongst the different episodes of bipolar disorder. Mood-Congruency Attentional Bias would entail manic individuals demonstrating faster response rates to "happy" stimuli, while BD patients in a depressed state would show a preference for "sad" stimuli, while a prolonged euthymic mood

state would not show an attentional bias for either stimuli. Murphy et al. (1999) similarly tested this hypothesis in manic and depressed individuals, observing that manic patients responded quicker to positive stimuli, while depressed individuals responded faster to negative stimuli (Elliott et al., 2004 and Erickson et al., 2005 report similar findings).

CHAPTER II. OBJECTIVES AND GENERAL METHODOLOGY

This thesis attempted to tackle a number of theoretical, practical and methodological aspects related to bipolar disorder as well as individuals at risk of developing the disorder. The objectives of this thesis were derived from an exhaustive analysis of the scientific literature, building upon the findings presented in the preceding sections.

The first objective of this thesis was to systematically review and quantify the experimental data regarding attentional biases in bipolar patients or individuals at-risk, regardless of episode (depressed, euthymic or manic). Therefore, we conducted a quantitative meta-analysis, employing a multilevel model, in order to assess positive and negative emotional attentional biases in this population. We included observational data from experimental studies in order to investigate these variables in the target population. A number of moderators were tested in a metaregression and in subgroups analyses in order to investigate the variables as exhaustively as was feasible up to this point in time.

Our second objective was to investigate the extent of pooled prevalences of psychiatric comorbidities in the hope of quantifying into a clear-cut percentage every type of psychiatric comorbidity in bipolar disorder. Similarly, we hoped to observe if certain psychiatric comorbidities predicted earlier age of onset, more suicide attempts, higher incidence and severity of episodes and more hospitalizations in people with bipolar disorder. To achieve this objective, we conducted a quantitative meta-analysis.

Our third objective was to analyse the correlational relationship between variables that promote a clinical severity of the diagnosis of bipolar disorder using a network analysis. In this sense, we conducted a network analysis and a Bayesian network analysis using directed acyclic graphs (DAGs) in order to show a possible predictive pathway between maltreatment and frequent bipolar disorder comorbidities (e.g., anxiety disorders, eating disorders).

Our fourth objective was to investigate these correlations and possible causations using a larger, globally representative sample, compared to our restricted Romanian sample, in order to see if across cultures we would find the same associations, communities and DAGs.

Our fifth objective was to adapt and establish the psychometric validity and reliability of a scientific instrument, designed to assess the risk of developing bipolar spectrum disorders in the Romanian population. In this sense, we conducted this study with the aim of facilitating the process of identifying individuals up to 50 years old who are at risk of having or developing the disorder.

Finally, we propose an answer for the limitations of psychiatric comorbidity and maltreatment longitudinal research in bipolar disorder, fundamenting an innovative method

which is scarcely used, microsimulation. Microsimulation offers a backbone to observe how various variables behave where longitudinal research is rare and difficult to implement.

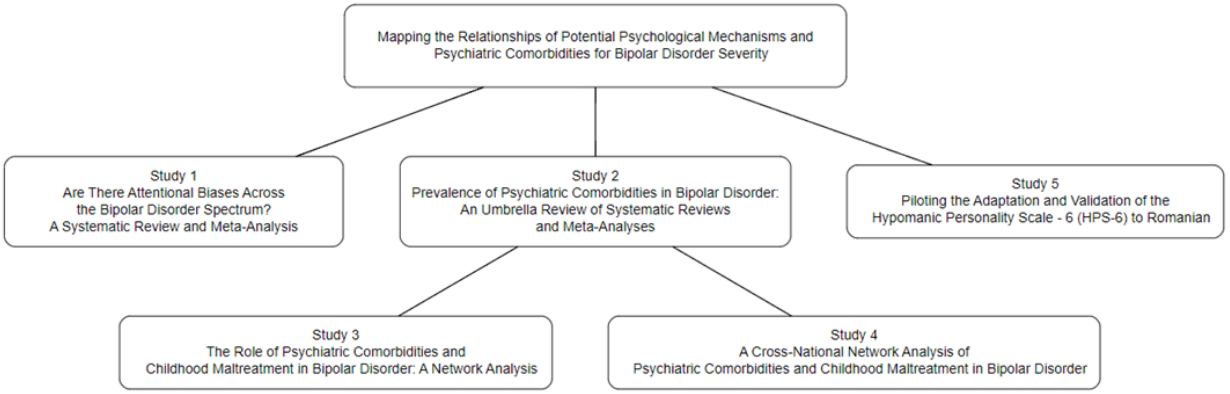

Figure 1. A Graphical Representation of the Structure of the Thesis

CHAPTER III. ORIGINAL RESEARCH

Study 1. Are there Attentional Biases Across the Bipolar Disorder Spectrum? A Systematic Review and Meta-Analysis

3.1.1. Introduction

Bipolar Disorder (BD) is one of the leading causes of disability worldwide, World Health Organization (2011) surveys ranking it as the second most determinant component impairing daily functioning.

Research has focused on finding potential factors and determinants of the onset of BD (see Rowland & Marwaha, 2018; Pinto et al., 2019; Hamdani et al., 2013; Li et al., 2016; Uemura et al., 2015; Mellerup et al., 2017; Palmier-Claus et al., 2016; Aas et al., 2019). Disturbances in general information processing have been linked to a more unfavorable course of BD (e.g., executive and declarative memory impairments) (Robinson et al., 2006; Tsapekos et al., 2021). It affects cognitive processes such as emotion regulation or reward salience that in turn exacerbate symptoms and influence relapse risk (Peckham et al., 2017; Mason et al., 2016). These biases are not necessarily related to the onset of bipolar disorder (BD) and could just as plausibly be a consequence of the condition or exacerbator of its severity.

Recent literature has moved on to exploring erroneous emotional information processing (Scot & Pope, 2003 as cited in Leyman, 2009). Attentional biases are defined as *the preferential allocation of attention towards specific information* (Crombez et al., 2013). They serve as a possible link to the severity of mood disorders and other psychopathologies (Pine et al., 2005; Sinclair et al., 2016; Faunce, 2002).

Preferential processing of emotional information has been proposed as a feasible exacerbating factor in BD as well (Garcia-Blanco et al., 2014). A novel idea in this sense is

the possibility of mood-congruent attentional biases in individuals affected with BD (Garcia-Blanco et al., 2013). The construct refers to "manic" individuals responding at a faster rate when "happy words" or emotionally positive stimuli are presented, while BD patients in a "depressive" mood state will respond faster to "sad words". The direction of preferential processing of BD in literature offers mixed data in respect to BSD and its respective mood states. Seeing that attentional bias has been hypothesized as a possible vulnerability in at-risk individuals in the development of BD, implies that understanding this mechanism could prove useful in addressing symptom severity (via attention bias modification training).

The aim of this meta-analysis is to investigate the magnitude of positive & negative attentional biases in those affected or at risk of developing BD. This is in fact the first meta-analysis to our knowledge examining emotional attentional biases in this clinical group.

3.1.2. Methods

The study protocol was registered and updated in PROSPERO, the International Prospective Register of Systematic Reviews (CRD42025644602). This meta-analysis adhered to the PRISMA guidelines recommendations (Higgins & Cochrane Collaboration, 2020). A systematic search (using a string composed of adequate keywords) for relevant published journal articles was conducted in the following electronic databases: Scopus, PubMed, PsycINFO, ProQuest, Web of Science and supplementing with the first 10 pages on Google Scholar for peer-reviewed articles, written in English. Initial search was conducted on February 2nd 2024, and updated on July 15th 2025, January 14th 2025 and 11th of July 2025.

Selection of Studies

Only published, peer-reviewed, studies were included in our meta-analysis. The study included either individuals diagnosed with Bipolar Disorder or at-risk for Bipolar Disorder (whether this be through familial risk or screening-based risk e.g. Hypomanic Personality Scale). The study included a conclusive affective attentional bias probe / task such as Emotional Stroop Task, Affective Go/NoGo, Affective Shifting Task, Emotional Dot Probe, Emotional Free-Viewing Task, Emotional Incidental Recall Task, Affective N-Back and similar tasks or variations of the aforementioned probes. For studies including an intervention (e.g., novel pharmaceutical drug), only pre-intervention data was collected. Studies were required to report data related to positive or negative emotions (e.g., "positive images". "happy target", "negative words", "shift-negative") in comparison to a healthy control group. Articles were excluded if BD (or at risk) individuals had significant cognitive deficits or impairments (e.g., dementia), were pregnant, peri- or post-partum, had an additional schizophrenia diagnosis or Autism Spectrum Disorder in order to exclude confounding variables and reliably attribute results to a homogenous BD sample.

Data extraction

The following data was extracted: demographic characteristics pertaining to the BD and control samples, such as age and percentage of females, characteristics pertaining to the BD diagnosis were represented by illness duration, age of onset, number of total episodes (whether these manic, hypomanic, mixed or depressive added up), number of depressive,

manic, hypomanic or mixed episodes assessed independently, anxiety scores, percentage with comorbid ADHD, percent of patients on medication, percent of patients on the following medication: lithium, antiepileptics, antipsychotics, antidepressants, anxiolytics. If the study did not present overall medication use, the highest percentage of usage was put as overall medication use. We also extracted the percentage of patients in euthymic, manic, hypomanic, depressive or mixed states as well as the percentage that were diagnosed with BD-I or BD-II. The following extracted data pertains to the type of probe used its characteristics and outcomes: the type of probe / instrument that was used (e.g. Affective Go/NoGo, Emotional Stroop, Antisaccade, Emotional Dot Probe etc.), what type of bias was assessed (positive versus negative attentional emotional bias), the type of presentation (physical versus digital), the exposure type (subliminal versus supraliminal), the exposure time (subliminal, 500ms or over 1000ms), the type of stimulus used (words versus pictures versus films), the design of the task (blocked versus random).

The coding system was chosen according to the recommendations outlined by Bar-Haim et al. (2007) on studying attentional biases. Pertaining to the study itself, we extracted whether the study was conducted on a risk population (individuals with familial risk for BD or assessed via the Hypomanic Personality Scale, Eckblad & Chapman, 1987) and whether the study was of pediatric nature. We coded the bipolar type (euthymic, manic or depressed) for subgroup analyses.

Study Quality

Study quality was assessed using Risk of Bias in Non-Randomized Studies of Exposure (Higgins et al., published online Mar. 24 2024). The instrument is based on algorithms for each domain that dictate whether the study is of very high risk of bias, high risk of bias, some concerns or low risk of bias. Six studies had some concerns, while 37 were coded as low risk of bias (except for concerns about uncontrolled confounding). One study was excluded for a very high risk of bias as it did not make any attempt to control confounding, not reporting demographic data or similar indices (matched). Our favorable ratings are due to risk of bias instruments being mostly catered towards data with multiple measurements, while our data was composed of experimental data, with no post-testing or pre-testing of attentional bias measures.

Data analysis

Data analysis was performed using “R” statistical software version 2022.12.0+353 and a variety of R packages were utilized. The most accurate and currently considered ‘relevant’ method of presenting attentional biases is an interference score; one method of calculation is by subtracting the reaction time (RT) for neutral words from the RT for emotional words (Kaiser et al., 2017). If the data was not clearly reported (e.g. simply states “not significant”), but interference scores could be calculated, it was calculated manually and a pooled standard deviation was computed in MiniTab for the new std. dev. interference scores. Hedges’ g effect sizes were calculated via Comprehensive Meta-analysis V3 (Borenstein, 2023) using the mean and standard deviations of the clinical and healthy control groups. The effect direction was coded as negative effect sizes representing bias, while positive effect sizes representing lack of bias.

Our meta-analysis was conducted using a multilevel random-effects model to account for the heterogeneity expected between studies, with effect sizes reported as Hedges'g coefficients along with their associated p-values and confidence intervals. An aggregated model was conducted as well to assess overall emotional attentional bias and for publication bias which is not appropriate for a multilevel dataset. Analyses were run on an overall level of emotional attentional bias in BD, per outcome (positive emotional bias versus negative emotional bias) and per subgroup in order to capture the full phenomenon.

Heterogeneity was estimated using I^2, H^2 and prediction intervals (95%). I^2 quantifies the proportion of total variability due to true differences between studies. The following proportions were interpreted as follows; 25% - low heterogeneity, 50% - moderate heterogeneity, 75% - high heterogeneity (Higgins & Thompson, 2002). H^2 indicates how much the observed variability exceeded what would be expected from sampling error. It is in a direct relationship with I^2 as $I^2 = H^2 - 1/ H^2$ (Higgins & Thompson, 2002). Complete homogeneity is assessed at H=1. There aren't status quos on interpreting as low or high H^2 scores, with significant values larger than 1 to infinity representing heterogeneity (Pathak et al., 2017). A 95% prediction interval estimates the range of the true effect size of approximately 95% of where future studies are expected to fall into, accounting for observed heterogeneity (Borenstein, 2023).

To explore sources of heterogeneity, we conducted subgroup, moderator and meta-regression analyses.We conducted analyses for potential outliers using Cook's distance and standardized residuals. Studies high on either indicator were flagged and removed. For Cook's distance, we used a cut-off of a distance bigger than 4/n (n representing the number of studies) to assess outliers (Cook, 1977). Standardized residuals were interpreted using a normal distribution (-2/+2 standard deviations). If studies exceeded two standard deviations they were flagged and removed (Serdahl, 1996). Effect sizes that exceeded these distances were flagged and remove and the model was ran again. AIC (Akaike Information Criterion) and BIC (Bayesian Information Criterion) values of the models were compared to see if the removal of outliers led to a better or worse fit.

3.1.3. Results

Our initial search on February 2nd, 2024 yielded 2925 references, of which 1261 were eliminated due to being duplicates. Our first step had the first author screen the title and abstracts of the retrieved studies for our keywords of interest. Overall, 255 references were sought for retrieval, nine of which could not be retrieved. As such, 246 reports were included in our full-text analysis and were read by a second reviewer as well. Disagreements over inclusion were resolved by consensus. 206 articles were excluded due to not meeting our inclusion criteria. Articles were excluded as well if they did not offer data separately or a comparison that could be used for positive or negative emotional bias. The search was updated on July 15th, 2024, 14th of January 2025 and on the 11th of July, 2025. See **Figure 1** for details on the study selection process.

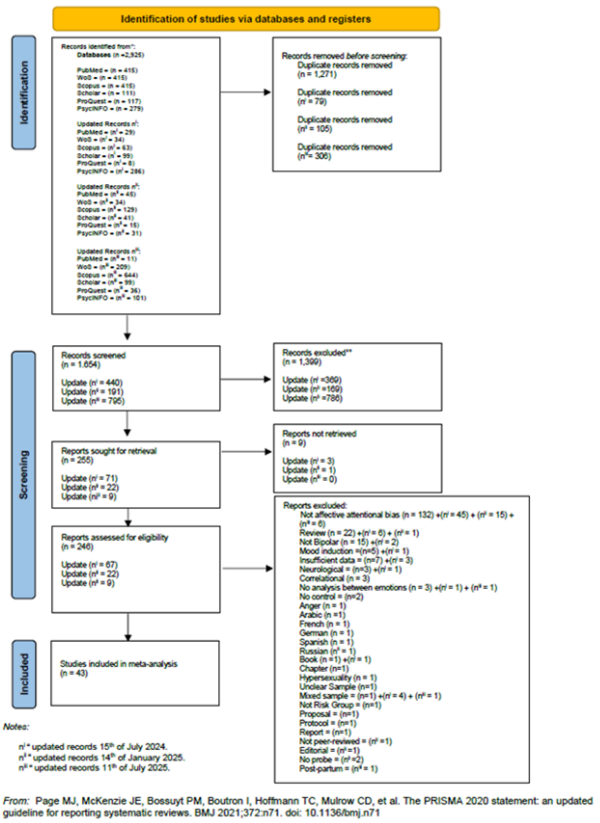

Figure 1. Flowchart of the Study Selection Process (PRISMA)

Characteristics

The included 43 studies had a total sample size of 3522 and 186 comparisons. Weighted mean age of the entire sample was 36.17 (years). Weighted mean age BD sample was 36.82 (years), the weighted mean age of the healthy control sample was 35.52 (years). The weighted mean percentage of females per the entire sample was 50.57. Weighted mean percentage of females in the BD sample was 49.68 (%), while the healthy control sample had a percentage of 51.48 (%). 13 studies had a depressed subgroup (30.23%), 23 had a euthymic subgroup (53.58%) and 12 had a manic subgroup (27.9%). 29 studies (67.44%) reported medication use. All the studies reported clearly whether the sample was pediatric or not, of the studies included, 6 (15.38%) were pediatric. Sample sizes ranged from 16 to 256.

Aggregated Attentional Biases towards Emotions across the Bipolar Disorder Spectrum

In a meta-analysis including 65 effect sizes of aggregated data, the overall effect size was estimated at g = -0.949 with a confidence interval (CI) ranging from -0.2333 to 0.0436 (p=0.1793), indicating no significant difference in attentional bias between the BD group and the control group. The I^2 statistic of 42.97% suggests that approximately 42.97% of the total variance observed in the aggregated model was attributable to true heterogeneity rather than simply sampling error; this represents a close to moderate heterogeneity. The H^2 value was 1.75 further pointing towards heterogeneity. Prediction interval (*PI*) of this model was -.793; .603. Our next step was to conduct analyses for potential outliers using Cook's distance and standardized residuals. Thus, we identified studies with standardized residuals higher or

lower than 2 standard deviations or high on Cook's distance. Three effect sizes were flagged and removed, and the model was rerun.

New effect size was estimated at g = -0.0552 with a 95% confidence interval (CI) ranging from --0.1928 to 0.0824 (p=.4317), indicating that the difference in attentional bias between the BD group and the control was not significant. Comparing AIC and BIC values indicated that the exclusion of outliers improved the fit of the model. The model without outliers had lower AIC (118.0599) and BIC (122.2486) values when compared to the model that included all data, which had AIC (128.0762) and BIC (132.3940). Lower values on the model without outliers suggests that the removal of outliers lead to a more parsimonious model with better data fit.

Multilevel Attentional Biases towards Emotions across the Bipolar Disorder Spectrum

In a multilevel meta-analysis including 186 effect sizes, the overall effect was estimated at g = -0.1310 with a 95% confidence interval (CI) ranging from -0.2846 to 0.0227 (p=0.0943), indicating that the difference in attentional bias between the BD group and the control group was not significant. Heterogeneity generated by I^2 was 90.74% while the prediction interval (*PI*) for this model was -2.138; 1.876.

Our next step was to conduct analyses for potential outliers using Cook's distance and standardized residuals. Nine effect sizes were flagged and removed, and the model was reran. New overall effect size was estimated at g = -0.0954 (95% CI: [-0.21; 0.02], p=0.1). Comparing AIC and BIC values, the exclusion of outliers did not improve model fit in this case. The model without outliers had lower AIC (296.8933) and BIC (303.2343) values when compared to the model that included all data, which had AIC (595.9315) and BIC (605.5926). Lower values on the model without outliers suggests that the removal of outliers lead to a more parsimonious model. With these in mind, the model without outliers was used in further analyses.

Metaregression on Attentional Biases towards Emotions across the Bipolar Disorder Spectrum

We conducted a multivariate metaregression analysis (k=107) with the following variables: age of the BD group, percentage of females in the BD group, percentage of patients on psychiatric medication and study quality. The calculated I^2 of 42.18%, indicated that over 42.18% of the observed variance was due to true heterogeneity rather than sampling error. The omnibus test of moderators was statistically significant QM(4) = 9.8495, *p=0.0430,* suggesting that the included predictors accounted for between-study variability. Of the four moderators, only the percentage of female participants was statistically significant (β = -0.0173, *p=0.0121*), indicating that studies with a higher proportion of female participants tended to report attentional emotional bias in the BD sample. Age of the BD group (β = 0.0077, *p=0.3418*), on-medication percentage (β = -.0005, *p=0.8691*), and study quality (β = -0.1117, *p = 0.5412*) were not statistically significant predictors in the model.

To further explore these relationships, prediction intervals (95%) and predicted effect sizes were calculated across values for each moderator, while holding covariates constant. Increasing the percentage of BD participants on medication was associated with increasingly negative effects, with significant effects observed at 80% (g = -0.289; 95% CI: [-0.49; -0.08])

and 100% (g = -0.366; 95% CI: [-0.69; -0.04]) BD participants. Similarly, studies with a higher percentage of female participants showed an increase in effect size of attentional bias and BD association for each level, becoming statistically significant from samples comprising 60% females and upward (g = -0.455; 95% CI: [0.73; 0.176]). For participant age, younger samples were associated with significant negative effect sizes of attentional bias and bipolar disorder association (g = -0.70; 95% CI: [-1.337; -0.068]), whereas older samples (e.g., age 70) showed not significant results. Study quality also showed a tendency towards negative effect sizes, but this result did not reach statistical significance in the regression model.

Subgroup analyses

Subgroup analyses were conducted to assess whether subgroups acted differently between the two types of attentional biases.

For the positive emotional attentional bias outcome (k=71), the test of moderators was significant, QM(2) = 21.1416, *p<.0001.* The depressed subgroup (g = .6856, 95% CI [0.31; 1.053], *p<.0003*) differed significantly from both the manic (*p<.0001*) and euthymic subgroups (*p<.0003*). However, the manic and euthymic subgroups did not differ significantly from each other (*p = .8534*) in terms of attentional bias. The overall effect of attentional bias for the euthymic group was significant (g= -0.3048, 95% CI [-0.57; -0.03], *p < .03*), indicating a positive attentional bias when no subgroup moderators are accounted for.

For the negative emotional attentional bias outcome (k=55), the test of moderators was not statistically significant, QM(2) = 5.52, *p=.06.* However, within the model, the depressed subgroup showed a significant negative attention bias (g = -0.7135, 95% CI [-1.376; -0.05]*, p=.0349*) and differed significantly from the euthymic subgroup (*p= .0239*). The manic (*p = .2545*) and euthymic (*p= .7689*) subgroups did not differ significantly from each other in terms of attentional bias.

Publication Bias

Egger's test was not significant (*p= 0.77*) and Duval & Tweedie's trim-n-fill procedure resulted in an adjusted effect size of g = -.0602 (95% CI: [-.2075; .0872]), which was still not significant (*p= .42*). This indicates that the distribution of the studies is likely to be symmetric, there being no evidence of publication bias. We have also plotted a funnel plot for visual inspection which can be consulted via supplementary materials.

We've conducted a fail-safe N analysis to calculate the robustness of our results. We've used the general approach based on Orwin and Rosenberg (Viechtbauer, 2024) to estimate how many studies with null results would need to be added to reduce the observed effect size. Fail-safe N calculated for this outcome as 0 means that no additional studies would be needed to render null the significance of the current results.

3.1.4. Discussion

In this meta-analysis we have aimed to clarify the complex relationship between attentional bias towards emotional stimuli and the targeted population. The results provide insight into the phenomenon though the evidence remains mixed. The findings are discussed in detail below.

In the aggregated model analysis examining attentional biases in BD, the effect size was of low magnitude and not statistically significant. The heterogeneity observed indicates that the results vary considerably depending on study characteristics. Similarly, when using a more complex multilevel model incorporating samples based on the type of BD episode, the overall effect size remained negative and low, but also did not reach statistical significance. Heterogeneity in the model was high, which further points to variability in the data and the need for further exploration of variables.

In our metaregression analyses, one moderator was identified that appeared to influence attentional biases in BD patients. Female BD patients demonstrated low, but overall significant emotional attentional biases, which could be indicative of gender differences in BD specific attentional processes. This link could be due to sensitivity to emotional stimuli that results in greater attentional biases. Pintzinger et al. (2016) showed that women demonstrate protective attentional biases in response to heavily negative stimuli.

There is extensive evidence linking childhood maltreatment with BD, pointing to more frequent psychiatric comorbidities when present (Agnew-Blais & Danese, 2016). As such, maltreatment, an important predictor of severity and development, may help account for some of the heterogeneity observed in our analyses. However, further research is needed to investigate this variable in relation to attentional biases. The substantial heterogeneity in our analysis points to moderators we were not able to include, as there was differential and limited reporting.

The influence of mood state on attentional biases was another focus. The subgroups did not reveal significant differences when comparing positive or negative attentional biases across the three mood states. The variability in effect sizes suggests that other factors may influence the results and stresses the need for additional studies with more exhaustive reporting data (e.g., illness duration, age of onset, types of medication).

Limits pertaining to our meta-analysis are that the analyses were restricted by small samples sizes within studies, 70% of sample sizes being under 25 individuals. Amongst all studies, there are none that replicated their findings by retesting their samples at another time-point, one singly study verifying bias by using another probe. The probes themselves are ambiguously interpreted in literature, errors or accuracy being simultaneously considered a method of signaling attentional bias in some cases. Until clarity is given and verified through the scientific method on interpreting attentional bias, we can neither imply or deny its existence with certainty. Authors presented interference indices scarcely, which at present are the superior method of attentional bias presentation as it takes into account intrapersonal and interpersonal variations. Comparing Reaction Times (RT) of psychiatric patients to healthy controls will evidently result in high RTs as their cognitive performance is affected due to medication or the diagnosis itself.

Future studies using experimental data assessed at a single time point should consider employing an instrument better suited for this type of evaluation. While ROBINS-E (Higgins et al., 2024) is a rigorous and comprehensive tool for assessing studies with multiple time points, it is less effective when applied to single time-point experimental data. Improved reporting standards are necessary in order to synthesize literature accurately, as is a larger usage of the interference indices and clear reporting of methodology.

Studies assessing attentional biases should use an additional method or probe and multiple assessment points in order to expand generalizability. ADHD and/or anxiety as well as maltreatment might affect emotional processing in those with BD, but we were not able to analyze this quantitatively due to limited reporting. Future studies exploring this relationship could help clarify both the severity of diagnosis and associated emotional processing deficits. Furthermore, longitudinal studies are necessary to effectively study attentional biases as a mechanism in BSD severity.

In summary, while a low magnitude of attentional biases in BD are suggested by the data, especially in women, the evidence is inconclusive so far. The effect of medication warrants further attention. Future research should focus on standardization of measures of attentional biases and exploring variability.

Study 2. Prevalence of Psychiatric Comorbidities in Bipolar Disorder: An Umbrella Review of Systematic Reviews and Meta-Analyses

3.2.1. Introduction

Diagnosis of BD is delayed up to 10-15 years from onset. One of the main mechanisms responsible for the delay in diagnosis is the presence of psychiatric comorbidities, which complicate the clinical evaluation process and the accurate establishment of a diagnosis (Lublóy et al., 2020).

Approximately 90% of individuals with BD experience comorbid anxiety disorders (Altinbaş, 2021), while 35.7% present with substance use disorders (Hunt et al., 2016). When tobacco use disorders are included, this prevalence increases to 46.3% (Fornaro et al., 2022). Furthermore, up to 60% of individuals with BD experience eating disorders (Yakovleva et al., 2023), 73% may meet criteria for attention-deficit/hyperactivity disorder (ADHD) (Sandstrom, 2021), and 37.7% may receive a diagnosis of borderline personality disorder (Fornaro et al., 2016). Additionally, BD faces large rates of suicide ideation (48%, Hu et al., 2023), suicide attempts (36.3%, Novick et al., 2010) and suicide deaths (1.8%, Hu et al., 2023).

However, reported comorbidity rates vary considerably across studies. Such variability underscores the need to systematically synthesize evidence in order to more accurately characterize the psychiatric burden in this population. Addressing this heterogeneity is essential for improving phenotypic characterization and for informing personalized interventions tailored to the heterogeneous manifestations of bipolar spectrum disorders (BSDs) and their comorbidities. Such approaches may also help reduce the persistent risk of misdiagnosis experienced by individuals with BSDs.

To address these gaps, we aimed to conduct an umbrella review of systematic reviews and meta-analyses in order to systematically quantify the pooled prevalence of comorbid psychiatric disorders amongst individuals with BSDs.

3.2.2 Materials and methods

Search strategy of the review

For this umbrella review of systematic reviews and meta-analyses, we have adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and JBI (Joanna Briggs Institute; Aromataris et al., 2020) methodology for umbrella reviews. A study protocol was preregistered and updated in PROSPERO (the International Prospective Register of Systematic Reviews) with the following ID: CRD420251273878.

A systematic search was conducted for relevant peer-reviewed, published, journal articles, written in English, in the following electronic databases; PubMed, Web of Science, PsycINFO and ProQuest on the 9th of January 2026. We have developed a string to represent best practices in each database. MeSH terms were used where applicable. There were no restrictions applied to the date or interval of the published articles. Citations were extracted from each database and introduced into EndNote 20 in order to find and remove duplicates. After duplication removal, the remaining citations were uploaded to Rayyan (an AI, web-based tool used to efficiently aid researchers in literature reviews) for dual-rater appraisal.

Inclusion and exclusion criteria

We included systematically conducted meta-analytic reviews that reported the lifetime, current or combined pooled prevalence of psychiatric comorbidities in BSDs. Mental health conditions were included if they were defined in either DSM (Diagnostic and Statistical Manual) or ICD (International Classification of Diseases) classification, therefore disorders such as Tobacco Use Disorder being included in this umbrella review as well. Another aspect we deemed of the utmost importance were suicide-related indices, such as suicide ideation, attempts and deaths, which were included alongside psychiatric comorbidities. The meta-analyses were included if they fulfilled our inclusion criteria and excluded systematically if they conflicted with either of our exclusion criteria.

Two authors evaluated all the retrieved articles systematically including or excluding them based on preregistered criteria. Consequently, we included studies conducted on individuals diagnosed with BD (BD-I, BD-II or BD-NOS), whether they were conducted on adult or pediatric populations. Studies with mixed populations (e.g., BD and schizophrenia) were included only if the BD data could be separated. The study had to be systematic reviews & meta-analyses conducted psychiatric disorders and reported pooled prevalences of the psychiatric disorder investigated in relation to BD.

As for exclusion criteria, we did not include studies that did not include individuals with a formal diagnosis, had mixed data (e.g., mood disorders) or focused on physical and medical comorbidities. Primary studies, narrative reviews, editorials, or reviews without sufficient methodology reporting were not included. Following the initial screening of the articles, disagreements were resolved through discussion and, when necessary, consultation with a third author until a consensus was reached.

Data extraction

We based our construct extraction based on the JBI extraction tool as well as variables relevant in BSD studies (e.g., current episode, type of BSD). The authors extracted the following data: study author, study full title, year of publication, databases searched in the

meta-analysis, age ranges of participants, sample ranges, countries of studies included in the meta-analysis, setting of the studies, whether the outcome was primary or secondary, the overall objectives of each studies as stated either in the abstract or within the full-text, the type of analysis done (e.g., random effects / fixed effects / using individual study data etc.), number of studies included in the meta-analysis, data on subgroups (if possible and delimitated), whether the study was done on pediatric, adult or both, the current episode of the participants, the type of BD, which instrument was used to confirm the diagnosis of BD (e.g., DSM-5 / ICD-11 etc.), the total number of BD participants, the percentage of females included in the meta-analysis, the mean age of participants, the mean age of onset, the pooled prevalence of the comorbidity within the meta-analysis, the confidence interval of the pooled prevalence, and data on heterogeneity (I^2, Q-test, df, p-value, CIs).

3.2.3 Results

We retrieved 1722 articles from the aforementioned databases. After removing duplicates using EndNote 20 and checking manually as well, 1213 articles were left which were screened by title and abstract. After initial screening, 154 articles were deemed appropriate to be evaluated full text as well. A total of 26 articles were included in this umbrella meta-analysis. The complete PRISMA Flowchart of the study selection process is presented in **Figure 1**.

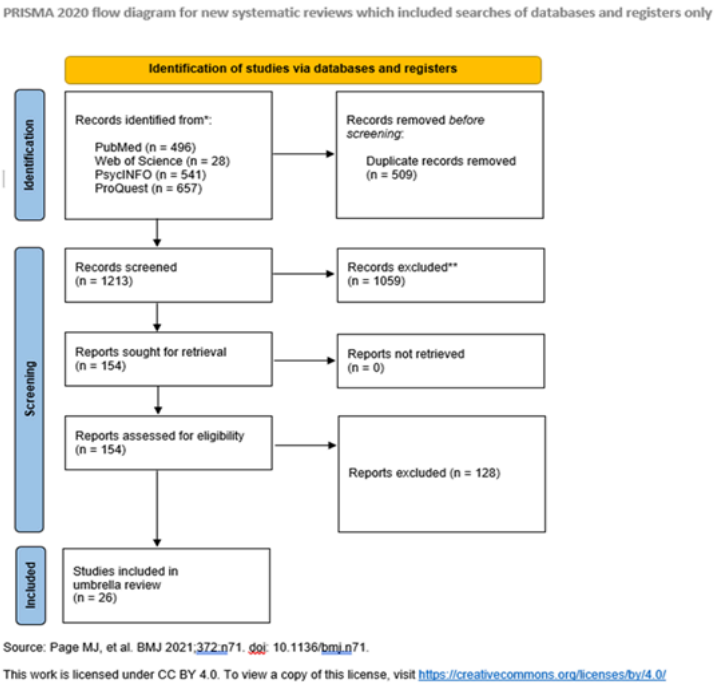

Figure 1. Study Selection Flowchart (PRISMA)

Corrected Covered Area calculation for overlapping area

We calculated the corrected covered area (CCA) in order to provide data on the overlap of primary studies included in the meta-analyses where similar outcomes under similar statistical procedures and methods were used. All analyses were run in "R" version 4.5.1 (2025-06-13, ucrt build) using "RStudio" version 2025.5.1 (Build 513). We

implemented the code and 'R' package developed by Boungioukas et al. 2021, '*ccaR'*. The formula shown in **Figure 2** was applied to calculate the of studies between systematic reviews and meta-analyses.

$$CCA = \frac{N - r}{(r \times c) - r},$$

Figure 2. Corrected Covered Area Formula (formula from Hennessy & Johnson, 2021)

Therefore, we calculated the CCA for the following six outcomes: lifetime anxiety, current anxiety, lifetime OCD, lifetime ADHD, lifetime suicide attempts and lifetime eating disorders. N represents the total number of occurrences of primary studies, while r represents the total number of unique publications, c represents the number of meta-analyses. Highest overlap was for ADHD lifetime outcome (14.3%), while the lowest was for the suicide attempts outcome (4.9%). When consulting 1:1 overlap matrices, these indices rise up to 53.3% for lifetime Anxiety and 10.1% for suicide attempts.

Study Quality Assessment

Overall methodological quality of the included meta-analyses was assessed using the AMSTAR-2 tool (Shea et al., 2017) and plotted graphically using the R package '*amstar2Vis'* (Bougioukas et al., 2024). AMSTAR-2 contains 16 items which assess study quality, using both critical and non-critical items, categorizing systematic reviews and meta-analyses into 'critically low', 'low', 'moderate', and 'high' methodological quality. Two raters evaluated the methodological quality independently, dissensions were discussed by both raters and resolved through consensus where needed. Across studies 18 were deemed high quality, 0 moderate quality, 5 low quality and 3 critically low quality.

Certainty of Evidence

We used the GRADE system to quantify the certainty of our primary outcomes. Secondary outcomes and subgroups were too sparse and heterogeneous to warrant systematic mentioning but can be consulted via *supplementary materials*. This decision was made to improve readability and focus attention on dependable outcomes. Subgroups (type of BD, gender) were evaluated using GRADE if no other aggregated outcome was available. The GRADE system contains five categories that can upgrade or downgrade a study from high quality of evidence to low quality of evidence. As observational studies start from a very low certainty of evidence, it isn't surprising that 93 of our outcomes were ultimately rated as low certainty, while 7 were rated as very low and 6 were rated as moderate certainty.

Characteristics of the included meta-analyses

Two meta-analyses were published before 2015 (Novick et al., 2010; Di Florio et al., 2014). The other 10 were published in the last 10 years (Amerio et al., 2015; Amerio 2016; Dong et al., 2020; Ferentinos et al., 2020; Fornaro et al., 2016; Fornaro et al., 2021; Fornaro et al., 2022; Hu et al., 2023; Hunt et al., 2016; Khoso et al., 2023; Leda-Rego et al., 2024;

Nabavi et al., 2015; Pavlova et al., 2015; Pavlova et al., 2017; Pedro et al., 2023; Pinto et al., 2019; Preti et al., 2016; Preti et al., 2018; Sandstrom et al., 2021; Schiweck et al., 2021; Tondo et al., 2016; Trott et al., 2024; Yapici et al., 2018; Yapici et al., 2020). The range of primary studies included in the meta-analyses varied from three to 101 (Amerio et al., 2016; Tondo et al., 2016). Sample ranges of the primary studies included in the meta-analyses varied from 10 to 73496 (Yapici et al., 2020; Trott et al., 2024).

Prevalence of psychiatric disorders in BSDs

Six meta-analyses reported the overall prevalence of any anxiety disorder within a bipolar sample (Leda-Rego et al., 2024; Pavlova et al., 2015; Pavlova et al., 2017; Yapici et al., 2018; Yapici et al., 2020; Nabavi et al., 2015). For example, Leda-Rego et al. (2024) evaluated lifetime anxiety disorders amongst BD individuals in a sample size totaling 23.276, observing a prevalence of 40.4% [95% CI: 34.97-46.06] of any anxiety disorder.

Seven meta-analyses reported the prevalence of Generalized Anxiety Disorder (GAD) in BD samples (Leda-Rego et al., 2024; Nabavi et al., 2015; Pavlova et al., 2015; Pavlova et al., 2017; Preti et al., 2016; Yapici et al., 2018; Yapici et al., 2020). In the largest sample (N = 21.847 adults) in this umbrella meta-analysis, the observed pooled lifetime prevalence, observed in an adult population, was 13.08% [95% CI: 10.32-16.45].

Seven meta-analyses reported the prevalence of Panic Disorder in BSD samples (Leda-Rego et al., 2024; Nabavi et al., 2015; Pavlova et al., 2015; Pavlova et al., 2017; Preti et al., 2016; Yapici et al., 2018; Yapici et al., 2020). In the largest sample analyzed in this study (N = 28.786 adults) a pooled prevalence of 14.86% [95% CI: 12.18-18.01] was identified when considering a lifetime panic disorder diagnosis (Leda-Rego et al., 2024).

Six meta-analyses reported the prevalence of Social Anxiety Disorder (SAD) (Leda-Rego et al., 2024; Nabavi et al., 2015; Pavlova et al., 2015; Pavlova et al., 2017; Yapici et al., 2018; Yapici et al., 2020). In the largest sample size analyzed in this study (N = 25.378 adults), a pooled prevalence of 10.63% [95% CI: 8.42-13.33] was identified when considering lifetime SAD (Leda-Rego et al., 2024).

Four meta-analyses reported the prevalence of Agoraphobia in BSD samples (Leda-Rego et al., 2024; Nabavi et al., 2015; Pavlova et al., 2015; Pavlova et al., 2017). In the largest sample size (N = 20.691 adults), a pooled prevalence of 5.4% [95% CI: 3.67-7.88] was identified, considering a lifetime diagnosis of Agoraphobia.

Separation Anxiety Disorder was reported in one meta-analysis (Yapici et al., 2020). The sample was composed of 2.351 pediatric BSD and reported a pooled prevalence of 26.1% [95% CI: 19.9-33.5] for comorbid lifetime Separation Anxiety Disorder (Yapici et al., 2020).

Four meta-analyses reported the prevalence of Specific Phobia in BSD samples (Leda-Rego et al., 2024; Nabavi et al., 2015; Pavlova et al., 2015; Pavlova et al., 2017). In the largest sample size analyzed (N = 19.399 adults), a pooled prevalence of 9.23% [95% CI: 7.16-11.82] was identified.

Nine meta-analyses reported the prevalence of OCD in BSD samples (Amerio et al., 2015; Amerio et al., 2016; Ferentinos et al., 2020; Leda-Rego et al., 2024; Nabavi et al., 2015; Pavlova et al., 2015; Pavlova et al., 2017; Yapici et al., 2018; Yapici et al., 2020). In the

largest sample size analyzed (N = 27.191), a pooled prevalence of 9.8% was identified considering a lifetime OCD diagnosis [95% CI: 7.48 - 12.73] (Leda-Rego et al., 2024).

Any eating disorder was assessed in two meta-analyses (Fornaro et al., 2021; Leda-Rego et al., 2024). Prevalences were similar, with Fornaro et al. (2021) observing a pooled lifetime prevalence of 9.5% [95% CI: 7-13] (N = 4.856) for BSD individuals of any age, and Leda-Rego et al. (2024) who identified a pooled prevalence of 9.31% [95% CI: 6.45 - 13.25].

Two meta-analyses evaluated lifetime Anorexia Nervosa prevalence in BSD samples. (Leda-Rego et al., 2024; Fornaro et al., 2021). Prevalences were similar, with Leda-Rego et al. (2024) observing a pooled prevalence of 3.05% [95% CI: 2 - 4.64] and Fornaro et al. (2021) identifying a pooled prevalence of 3.8% [95% CI: 2-6].

Two meta-analyses evaluated Bulimia Nervosa lifetime prevalence (Leda-Rego et al., 2024; Fornaro et al., 2021). Leda-Rego et al. (2024) observed a pooled prevalence of 5.08% [95% CI: 4.12-6.24], while Fornaro et al. (2021) identified a pooled prevalence of 7.4% [95% CI: 6-10].

Two meta-analyses evaluated lifetime Binge Eating Disorder prevalence (Leda-Rego et al., 2024; Fornaro et al., 2021). Leda-Rego et al. (2024) observed a pooled prevalence of 7.75% [95% CI: 5.11-11.61] in a sample of 2.135, while Fornaro et al. (2021) found a prevalence of 12.5% [95% CI: 9.4-16.6] in 7.089 individuals.

One meta-analysis assessed Substance Use Disorder (SUD) directly (Leda-Rego et al., 2024). The pooled prevalence was 30.7% [95% CI: 23.73–38.73] in an adult sample of 20.352 looking at lifetime SUDs. Hunt et al. (2016) evaluated any lifetime substance abuse or substance use disorders, observing the largest pooled prevalence in men, totaling 51.1% [95% CI: 40.3-61.9] (N = 7.397) and the lowest in a BD-II sample with 28.1% [95% CI: 21.8-34.3] (N = 1.474).

Three meta-analyses reported on alcohol use disorder (AUD) (Di Florio et al., 2014; Pedro et al., 2023; Hunt et al., 2016). In the largest sample size included in this umbrella review (N = 31.271), a pooled prevalence of 29.12% [95% CI: 18.96-40.46] was identified when considering lifetime AUDs in adults (Pedro et al., 2023).

Two meta-analyses assessed Cannabis Use and Cannabis Use Disorders (CUD) (Pinto et al., 2019; Hunt et al., 2016). Hunt et al., 2016 looked at CUDs per gender, with men totaling a pooled prevalence of 32.8% [95%CI: 19.9-45.8] and women - 18.1% [95%CI: 8.9-27.2]. Pinto et al., 2019 assessed use, abuse and disorders altogether revealing a pooled prevalence of 24% [95%CI:18-29] for a sample size of 51.756 regarding cannabis use or any type of CUD comorbidity.

Tobacco Use Disorder (TUD) was evaluated in one meta-analysis (Fornaro et al., 2022). Pooled prevalence of lifetime TUD was 46.30% [95%CI:33.9–59.2 %] in a sample evaluating both current and lifetime TUDs regardless of age (N = 2.703).

Three meta-analyses evaluated ADHD in BSD samples (Leda-Rego et al., 2024; Sandstrom et al., 2021; Schiweck et al., 2021). In the largest sample included in this umbrella review (N = 401.108 individuals over the age of 15), a pooled prevalence of 17.11% [95% CI: 13.05-21.59] was observed for current and lifetime ADHD (Schiweck et al., 2021).

Borderline Personality Disorder (BPD) was assessed in a single meta-analysis (Fornaro et al., 2016). The pooled prevalence observed was 21.6% [95% CI: 17.0 - 27.1] in a sample of 5.273 adult individuals when looking at lifetime prevalence for BPD.

Four meta-analyses reported prevalence of Post-Traumatic Stress Disorder (PTSD) (Leda-Rego et al., 2024; Nabavi et al., 2015; Pavlova et al., 2015; Pavlova et al., 2017). Largest sample size ,21.444, observed a pooled prevalence of 8.15% [95% CI: 5.83 - 11.28] in an adult sample looking at lifetime PTSD.

Two meta-analyses reported suicide ideation (Hu et al., 2023; Khoso et a., 2023). One of the meta-analyses reported pooled prevalence per gender, with male gender having a pooled prevalence of 48% [95% CI: 44-52] and female gender of 44% [95% CI: 40-49] when looking at both pediatric and adult samples lifetime ideation (Hu et al., 2023). The second meta-analysis reported suicidal ideation indifferent to gender, revealing a pooled prevalence of 52% [95% CI: 34-70] (Khoso et al., 2023).

Five meta-analyses reported pooled prevalence for suicide attempts (Hu et al., 2023; Dong et al., 2020; Khoso et al., 2023; Novick et al., 2010; Tondo et al., 2016). In the largest sample size included in this umbrella review (N = 79.937 adults), a pooled prevalence of 31.1% [95% CI: 27.9-34.3] was observed when taking into consideration lifetime suicide attempts.

A second order meta-analysis (or meta-metaanalysis) could be run for the suicide attempts outcome using three meta-analyses (Dong et al., 2020; Khoso et al., 2023; Tondo et al., 2016) since our corrected covered area calculation showed an overlap of 10.1%. In order to achieve this, we ran our analysis in 'R' using the following packages: *'metafor'*. We used the primary outcome (without subgroups or gender differences) to calculate a singular pooled prevalence of suicide attempts in BSDs. We then performed a random-effects meta-analysis on the logit-transformed prevalence estimates and then back-transformed them to the original prevalence percentages. Heterogeneity between meta-analyses was assessed using I^2. The three meta-analyses showed consistent results, the newly calculated pooled prevalence was 31.8% [95% CI: 28–35], while I^2 was moderate at 38.9%, but not significant, p = .1302.

Suicide Deaths

Suicide deaths pooled prevalence was reported by one meta-analysis reporting on gender differences (Hu et al., 2023). The meta-analyses included participants regardless of age, observing a pooled prevalence of 1.8% [95% CI: 1.7 %–2.0 %] in suicide deaths for the male gender (N = 19.427) and 0.8% [95% CI: 0.7 %–0.9 %] for females (N = 30.645).

Any Psychiatric Comorbidity

Any psychiatric comorbidity was reported in one meta-analysis (Leda-Rego et al., 2024). Pooled prevalence observed was 38.1% [95% CI: 35.24–42.70] for lifetime comorbidity in adults.

3.2.4. Discussion

In this umbrella review of systematic reviews and meta-analyses, we integrated evidence regarding the prevalence of comorbid psychiatric disorders in BSD populations. Our

findings reemphasize the excessive additional burden of anxiety disorders, substance abuse disorders, ADHD, BPD, suicidal ideation & attempts, eating disorders and related disorders in the BSD population. These high rates are tremendous compared to the general population (Leda-Rego et al., 2024). Anxiety disorders for example, were revealed to be 4.6 times higher in BSD populations comparative to the general population (Pavlova et al., 2017). Comorbidities have been shown to lead to a more severe course of BSD, suffering from more frequent episodes which are more severe, lower treatment adherence and a reduced response to medications (Fountoulakis et al., 2025).

Our umbrella review emphasizes the limitations of the traditional categorical framework of mental disorders. The substantial prevalences observed across anxiety disorders, substance use, and other comorbidities suggest there are underlying vulnerabilities and overlapping psychopathological processes. These findings support that psychiatric comorbidity are a constraint of the current diagnostic systems which create boundaries for dimensional phenomena (Kotov et al., 2017; Clark et al., 2017). As such, it would be beneficial to incorporate dimensional models such as the Hierarchical Taxonomy of Psychopathology (HiTOP) and the Research Domain Criteria (RDoC).

Similarly, the high comorbidity of burden draws attention to important implications in treatment of BSD. These results emphasize the need for transdiagnostic and process-based interventions. Acceptance and Commitment Therapy (ACT) focuses on fundamental psychological processes (e.g., emotion regulation, cognitive flexibility) that stand across diagnostic categories (Hofmann & Hayes, 2019; Hayes et al., 2020).

In a National Comorbidity Survey realized by Kessler et al. (1995), 95% of the BSD respondents met criteria for at least three lifetime psychiatric disorders (Sagman et al., 2012). SUDs may onset before BSD symptoms, concealing the diagnosis (Winokur et al., 1995), ADHD similarly obscures symptoms due to similarities, such as impulsivity, overactivity, rapid speech, emotional lability and other symptoms which mirror both disorders (Massat et al., 2008). This overlap emphasizes the need for diagnostic precision and the development of diagnostic tools to help differentiate disorders with similar symptomatology.

The heterogeneity observed across studies, such as the age groups and types of BD assessed might stand to reason for the various pooled prevalences observed. In ADHD for example, Sandstrom et al. (2021) revealed an astonishing rate of 73% [95% CI: 66-79] of pediatric samples qualifying for an additional ADHD diagnosis, while 17% [95% CI: 14-20] of adults met criteria within the same meta-analysis.

An important aspect which was not assessed within these meta-analyses was the cumulative burden of comorbidities, namely how many of the participants within these samples met criteria for multiple comorbidities at the same time. This umbrella review of systematic reviews and meta-analyses revealed that almost half of the BSD patients face additional burden of ADs, SUD, ADHD, or AUDs. Furthermore, our umbrella meta-analyses revealed reliably that over a third (up to 36.3% according to Novick et al., 2010) of BSD diagnosed individuals attempt suicide. However, with the information at hand we do not know dosage effects. For instance, of the almost 50% of BSDs with an additional AD, how many of these face SUD, ADHD simultaneously or another psychiatric comorbidity as well?

To the best of our knowledge, this is the first umbrella review tackling the issue of the prevalence of psychiatric comorbidities in BSDs. This review offers strong evidence of the

additional burden this population faces and the overbearing need for personalized treatment, better diagnostic precision and research into adequate treatment for BSD individuals who face other psychiatric comorbidities as well.

While we initially aimed to meta-analyze all primary psychiatric comorbidity outcomes, CCA overlap rightfully did not permit us to do so. Although such an analysis would have been statistically feasible, the results would likely have been biased due to repeated inclusion of the same primary studies - in some cases duplicated up to five times - thereby artificially inflating or deflating prevalence rates. Given these limitations, we strongly encourage greater transparency and broader data accessibility to facilitate timely and cost-efficient conduct of umbrella reviews and meta-analyses. Future research should aim to extract and analyze individual-level data from the primary studies outlined in this umbrella review of systematic reviews and meta-analyses in order to enable more granular analyses and improve the precision of prevalence estimates.

Study 3. The Role of Psychiatric Comorbidities and Childhood Maltreatment in Bipolar Disorder: A Network Analysis

3.3.1. Introduction

Up to 60% of BD individuals have faced at least one type of childhood maltreatment (Quide et al., 2020). Childhood maltreatment is a well-studied risk factor as well as course altering cause, acting as predictor of BD development as well as of its severity, bringing on longer episodes, tighter euthymic periods between episodes, more hospitalizations, lower efficacy of medications, more complex comorbidity profiles and more suicide attempts (Daruy-Filho et al., 2011, Aas et al., 2020, Agnew-Blais & Danese, 2016, Kefeli et al., 2018, Levandowski et al., 2018; Palmier-Claus et al., 2016; Hett et al., 2022).

Across childhood maltreatment types, emotional abuse seems to be the most common type of childhood maltreatment in BD individuals, with rates being far greater than compared to the general population and the strongest predictor of a complex course of the disorder (Etain et al., 2008). Sexual abuse, similarly, has been consistently linked to greater illness severity, higher rates of comorbidities, such as substance use disorders, and an increased likelihood of post-traumatic stress disorder (PTSD) (Maniglio, 2013). Physical abuse, on the other hand, is associated with poorer treatment response, including reduced effectiveness of mood stabilizers such as lithium (Cascino et al., 2021).

To boot, BD is characterized by high psychiatric comorbidity, with approximately 50% to 66% of individuals with BD facing an additional psychiatric disorder (Pavlova et al., 2015, Wang et al., 2025). Research has shown that up to 92% of individuals with BD report having suffered from at least one other comorbid mental disorder at some point in their lifetime (Merikangas et al., 2007). Childhood maltreatment may represent a key pathway through which the high rates of psychiatric comorbidity emerge in BD patients. Exposure to childhood maltreatment has been frequently linked to an increased vulnerability to various psychiatric conditions that often co-occur with BD. Findings from the Stanley Foundation Bipolar Treatment Outcome Network (n = 631) demonstrated that individuals exposed to childhood physical or sexual abuse exhibited an earlier onset of BD, a greater number of Axis

I and II comorbid disorders, and increased rates of suicide attempts (Leverich et al., 2002; Post et al., 2003).

Importantly, childhood maltreatment is strongly linked to comorbid conditions, all of which contribute to a more complex and severe clinical presentation. Psychiatric comorbidities contribute to illness severity, treatment resistance, and poorer overall prognosis in BD (Krishnan, 2005, Leda-Rego et al., 2023). Taken together, these findings suggest that childhood maltreatment might play a critical role in shaping comorbidity profile in BD.

One approach to visualizing the associations between our constructs and exploring potential underlying mechanisms is the network paradigm. Network theory postulates that mental disorders are states of interacting features that can become self-sustaining (Borsboom, 2017). This feature might explain overlapping comorbidities which can mutually activate symptom clusters rather than sovereign entities that might fail to capture the relationships with childhood maltreatment types. Network analysis offers a useful framework for addressing this by conceptualizing psychopathology as a system of interacting variables. Hence, different childhood maltreatment subtypes and comorbidities are modeled as mutually dependent nodes, allowing for the identification of associations between comorbidities themselves or between comorbidities and childhood maltreatment subtypes that might subsequently highlight comorbidity profiles.

By examining these factors simultaneously, network analysis can help generate hypotheses about potential mechanisms underlying complex clinical profiles. Despite lengthy evidence linking childhood childhood maltreatment to BD risk and to worse BD course, childhood maltreatment is often treated as a single aggregated exposure even though subtype-specific associations (e.g., sexual abuse and lifetime PTSD) suggest that aggregation can conceal differentiated patterns (Palmier-Claus et al., 2016; Laroche et al., 2022; Duarte et al., 2020). Large-scale research suggests that childhood maltreatment is associated with a greater prevalence of psychiatric comorbidities and with a faster accumulation of comorbidities prior to BD onset, this pattern suggests a developmental cascade (Agnew-Blais & Danese, 2016; Laroche et al., 2022).

The current study aims to examine the network structure linking childhood maltreatment and frequent psychiatric comorbidities in individuals with BD. Using network analysis, we will explore how different forms of childhood maltreatment (e.g., emotional abuse, physical neglect) are connected to comorbid conditions (e.g., anxiety disorders, eating disorders) and whether certain comorbidities act as bridge nodes to complex clinical presentations or form distinct communities (or clusters) (Radicchi et al., 2004). We seek to identify potential targets for interventions and clarify potential pathways through which childhood maltreatment types shape clinical severity in BD.

3.3.2. Methods

Participants

The data used in this study was collected through the World Health Organization-World Mental Health International College Student (WMH-ICS) initiative. Participants in the current study were first-year college students from participating universities in Romania. Informed consent was obtained in accordance with each institution's

ethical procedures in accordance with national legislation. Our final sample consisted of 317 participants who met criteria for lifetime BD using the Composite International Diagnostic Interview for DSM-5 (CIDI-5), with a mean age of 20.11 years (SD = 4.1), ranging from 18 to 36 years. In terms of gender, 82 participants (25.87%) identified as male, 227 (71.61%) as female, and 8 (2.52%) reported a different gender identity. Descriptive statistics were computed using JASP version 0.19.3.0.

Measures

In order to capture symptomatology, lifetime prevalence of DSM-5 disorders (anxiety disorders, major depressive episode) was assessed using the Composite International Diagnostic Interview Screening Scales, Version 3.2 (CIDI-SC V3.2; Kessler et al., 2013). Lifetime assessments of BD and drug use disorder (DUD) were based on CIDI-5 modified for self-report administration (Mason et al., 2025). Alcohol abuse was assessed using the Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al., 1993). Self-harm was assessed using the Non-Suicidal Self-Injury Scale (NSSI) (Whitlock et al., 2014). An instrument developed within the consortium was used to assess eating disorders (Strid et al., 2025. Childhood maltreatment was assessed using selected items from CIDI-3.0 and the Adverse Childhood Experiences International Questionnaire, which assessed emotional abuse, physical abuse, sexual abuse and neglect before age 17. Per WMH survey standards, each childhood maltreatment variable was coded as present or absent based on conventional thresholds. For full details *see* Myers et al., (2021).

Data Analysis

All analyses were conducted using the statistical software "R" version 4.5.1., using the graphical interface RStudio 2025.5.1.513. The network was constructed using the aforementioned variables as nodes (four types of childhood maltreatment, as well as six mental health comorbidities). The dataset included binary data (1=present, 0=absent) for childhood maltreatment experiences and psychiatric comorbidities. There was no missing data in our database.

We estimated sample size using a power analysis via the *powerly* package (recommended sample size was 311 participants). A network of regularized partial correlations was estimated using the EBICglasso algorithm from the *bootnet* package which was applied to binary data via a nonparanormal transformation (corMethod = "npn").

Methodologically, we estimated a network of childhood maltreatment subtypes and psychiatric comorbidities in BD using a Gaussian Graphical Model (GGM) based on polychloric correlations using EBICglasso. We assessed the accuracy of edge weights and the stability of centrality indices (strength, expected influence, closeness and betweenness) using nonparametric bootstrapping with 1,000 iterations and case-dropping to evaluate centrality stability. In addition to network estimation, we conducted several additional analyses. We further conducted bootstrap-based edge-weight difference tests and centrality strength difference tests, summarized via edge difference matrices, to avoid overinterpreting small or unstable differences between connections and nodes.

To assess a hierarchy of nodes we estimated node predictability (R^2) using the *mgm* package to evaluate how well each node could be predicted by adjacent nodes. Redundant variables were assessed using the *goldbricker* function from the *networktools* package. In addition, we applied Walktrap community detection to identify clusters of tightly connected nodes, allowing us to examine whether specific childhood maltreatment subtypes and comorbidities form meaningful subgroups within the network structure.

Finally, given that GGMs are undirected and cannot imply causality, we constructed a Bayesian network estimation using directed acyclic graphs (DAGs) to explore plausible directional relationships among childhood maltreatment and comorbidity variables using the Hill-Climbing algorithm via the *bnlearn* package. While these models do not establish causal effects, particularly in cross-sectional data, they allow for hypothesis generation for future research in BD.

3.3.3. Results

Network estimation

A Gaussian Graphical Model was estimated using the EBICglasso method via the estimateNetwork() function from the *bootnet* package (see **Figure 1**). This framework generates unique associations between variables while controlling for all others, improving interpretability as it shrinks small edge weights to zero. Given the binary nature of the variables, a nonparanormal transformation was applied (corMethod = "npn"). This method approximates normality preserving the structure of the data. Redundancy analysis using the *goldbricker* function did not offer any suggestions.

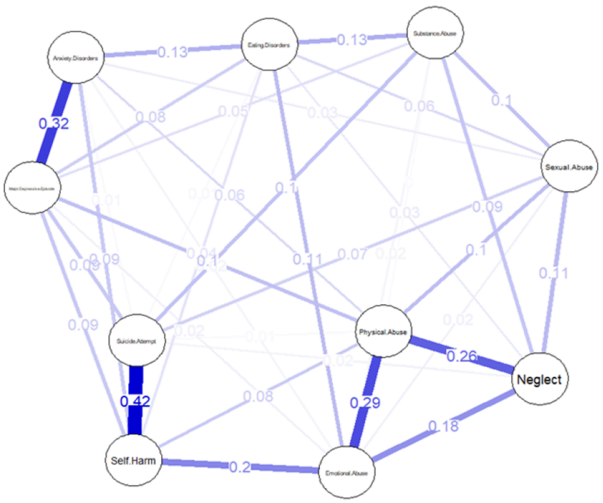

Figure 1. Network estimation of 10 nodes (4 = childhood maltreatment types, 6 = psychiatric comorbidities) of adults on the Bipolar Disorder Spectrum (BSD) (N =317).

The network illustrates associations between childhood maltreatment subtypes and psychiatric comorbidities in BD individuals. The strongest association observed was between Self-Harm and Suicide Attempt (= .42). This highlights a close link between the two

behaviors. Maltreatment subtypes were tightly connected between each other, suggesting substantial co-occurence (= .29, = .26, = .18), which is to be expected. Emotional abuse emerged with a moderate association to self-harm (= .20), pointing to a possible link between early emotional abuse and Non-Suicidal Self-Injury.

Within our comorbidities, strong associations were observed between major depressive episodes and anxiety disorders (= .32). Connections between direct maltreatment subtypes and direct comorbidities were weaker, retaining distinct structures within the network. Hence, community detection and Directed Acyclic Graphs (DAGs) may help clarify bridges and more direct associations between nodes.

Network accuracy and stability

Our next step was to evaluate the robustness of the network. We conducted bootstrap-based analyses of edge-weight accuracy, centrality stability, and edge weight differences in order to achieve this. Edge weight accuracy and stability was assessed through bootstrapping procedures. Wider intervals in edge weights suggest less reliable associations between nodes. The Suicide Attempt-Self Harm edge surfaced as the strongest and most stable edge. We computed an edge difference test matrix to identify which connections between nodes were significantly stronger than other connections. We identified strong associations between Suicide Attempts and Self-Harm, Physical Abuse and Emotional Abuse and Anxiety Disorder and Major Depression. These edges showed the most statistically significant differences compared to other edges in the network.

Centrality & Node Predictability

The correlation stability (CS) coefficient was used to assess centrality stability. This represents the proportion of the sample that can be dropped while maintaining a correlation of at least .7 to the original centrality estimates. According to Epskamp et al. (2018), a CS coefficient above .50 is acceptable, values below .25 are considered inadequate, while values between .25 and .50 require caution in interpretation. In the current study, strength and expected influence had a CS coefficient of .67 and .59 respectively, indicating stability and interpretability on these two centrality indices. Betweenness (.05) and closeness (.28) did not meet the recommended .50 threshold and were thus excluded from our interpretation.

We continued by computing strength centrality scores and node predictability (R^2). Strength centrality scores reflect how intensely each variable is connected to the rest. Values ranged from .49 to .93. Self-Harm had the highest strength (.93), suggesting it to be central and well-connected within our network. Other highly central nodes were Physical Abuse (.86) and Emotional Abuse (.92). These results highlight self-harm, emotional and physical abuse as playing a central role in the comorbidity structure of individuals with BD.

We calculated node predictability (R^2) in order to assess how well each variable could be predicted based on its direct neighbors. The highest predictability was observed for Self-Harm (R^2 = .37), followed by Physical Abuse (R^2 = .33), Suicide Attempt (R^2 = .29), and Emotional Abuse (R^2 = .32). Sexual Abuse (R^2 = .11 and Substance Abuse (R^2 = .10) had the lowest predictability in our network.

Community Detection

A walktrap algorithm was performed to detect clusters of communities. As such, four communities were highlighted. A childhood maltreatment cluster, internalizing cluster, behavioral cluster and self-harm cluster. The childhood maltreatment cluster included physical abuse, emotional abuse, sexual abuse and neglect, while the internalizing cluster included depression and anxiety. The behavioral cluster included eating disorders and substance abuse, while the self-harm cluster included self-harm and suicidal attempts.

Bayesian Estimation using Directed Acyclic Graphs

We performed a Bayesian network estimation with directed acyclic graphs using the Hill-Climbing algorithm with 1,000 bootstrap samples (see **Figure 2**). Therefore, edges were kept only if they appeared in at least 85% of the bootstrapped networks. Models were evaluated using the Bayesian Information Criterion (BIC). A Bayesian Directed Acyclic Graph (DAG) model was used in order to visualize possible directional relationships based on the underlying data structure. The strongest pathway observed was Emotional Abuse->Non-Suicidal Self-Injury followed by Suicide Attempts. Major Depressive Episode was presented as a possible precursor of Anxiety Disorders.

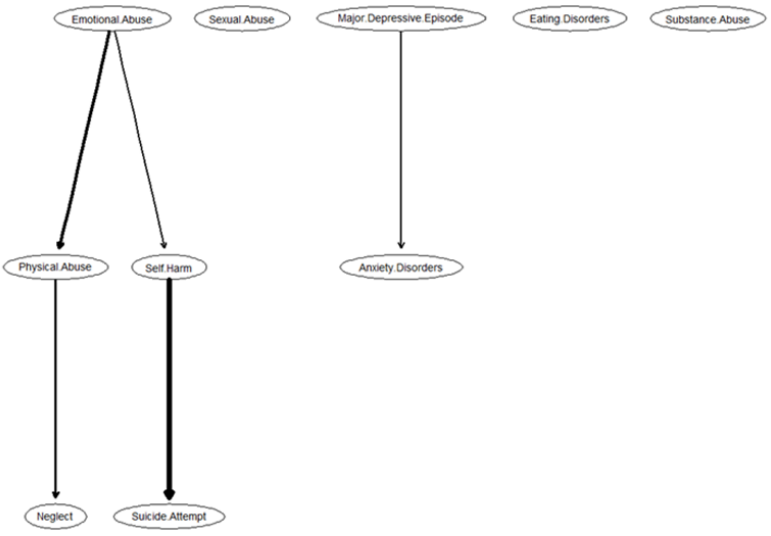

Figure 2. Bayesian Directed Acyclic Graph of associations between childhood maltreatment and comorbidities. Arrows show possible predictive direction, thicker lines highlight higher BIC values.

3.3.4 Discussion

The network structure revealed tight-knit communities of nodes, indicating that abuse types and comorbidities might group into clear-cut clusters rather than a diffuse anatomy. All childhood maltreatment types clustered together while depression and anxiety grouped together into an internalizing symptoms cluster. Non-Suicidal Self-Injury (NSSI) and suicide attempts grouped into a separate community, underlining the link between self-harm and

suicidal acts. Surprisingly, eating disorders and substance abuse clustered together, suggesting a shared behavioral or reward processing dysregulation component based on "self-medication", underlying a possible dysfunctional coping mechanism.

The childhood maltreatment variables are all interconnected, emotional abuse in particular showed a strong association in the network, which is in accordance with previous findings that emotional abuse is the most influential form of abuse and the best predictor of symptomatology severity (Palmier-Claus et al., 2016; Budania et al., 2024; Haussleiter et al., 2020; Hett et al., 2022). Likewise, the anxiety-depression pairing in the internalizing cluster echoes a well-documented comorbidity in BD (with roughly 40% of BD patients experiencing an anxiety disorder during their lifetime) (Laroche et al., 2022a; 2022b). The grouping of eating disorders with substance misuse is consistent with models of patients who struggle with impulse control and reward processing which may be exacerbated by bipolar mood instability (Bart et al., 2021).

We did not find evidence that a single comorbidity or relationship acts as a central bridge across clusters. Instead, the network suggests that conditions tend to form autonomous communities. Childhood maltreatment, in turn, has been associated with a faster accumulation of multiple comorbid disorders prior to BD onset. This implies that early trauma can set the stage for a more complex clinical presentation involving several comorbidity clusters. Indeed, even though our network estimation separates communities for clarity, in practice more severe childhood maltreatment could provide a different structure, compared to BD patients with low or no childhood maltreatment. This observation is in line with a large-scale study where emotional and sexual abuse emerged as key determinants of developing a high-comorbidity profile and suicidality in BD (Laroche et al., 2022a).

Within our network, Self-Harm (NSSI) showed the highest strength centrality in the entire network. The strongest connection identified was between NSSI and Suicide Attempts, a relationship significantly stronger than most other connections. This is consistent with prior evidence that NSSI increased the risk of consequential suicide attempts (Lee et al., 2021). Our data supports an association between emotional abuse and self-harm and furthermore to suicide attempts, creating a bridge from early-life trauma to eventual suicidality. This is in agreement with reports in BD youth that emotional abuse is an independent predictor of self-harm, and that individuals with self-harm have suffered from an increased exposure to abuse (Janiri et al., 2024).

In a study involving over 3,000 BD patients, emotional abuse (along with sexual abuse) was the strongest predictor whether individuals developed comorbid disorders and attempted suicide (Laroche et al., 2022a). Hett et al. (2022) reported that emotional abuse was positioned at the core of a network linking childhood trauma with BD comorbidities, similarly our study observed emotional abuse as the best connected childhood maltreatment node. Sexual abuse went underreported in our study, it's possible that the Romanian population is overall skeptical of reporting previous sexual abuse. This might affect the structure of our network, as the low frequency of sexual abuse limits its ability to form stable associations with other nodes.

An interesting aspect within our network was the separation between the internalizing cluster and behavioral cluster. There were few direct connections between these two communities. Some trauma-exposed individuals may gravitate toward internalizing

symptoms, whereas others might turn to externalized coping (substance abuse or binge eating) to manage distress. It is possible that additional comorbidities not included in our network may act as bridging nodes between these domains. Future research incorporating the underlying mechanisms of comorbidities could further improve interpretability and elucidate the associations among symptoms that cluster within comorbid conditions. Additionally, it would be of value to observe how the network of comorbidities evolves according to childhood maltreatment severity by types. At present, our sample was not large enough to split by severity or maltreatment types. Furthermore, moving forward, large-scale longitudinal samples that can mirror comorbidity accumulation throughout adulthood would prove useful in investigating developmental patterns.

The present study conceptualized BD within a network framework, offering clinicians a more nuanced understanding of the cascading interactions between nodes. For instance, interventions targeting NSSI behaviors (e.g., promoting adaptive coping strategies) may weaken their role in suicidal behaviors, potentially reducing suicide risk. Similarly, addressing central nodes such as emotional abuse through appropriate therapeutic interventions may contribute to broader improvements in symptomatology.

Our exploratory directed acyclic model suggests a path from emotional abuse to self-harm and furthermore to suicide attempts, nevertheless longitudinal data would be needed to confirm this temporal sequence. Our study observed the importance of emotional abuse as a bridge towards self-harm and suicide risk and the possibility of two distinct facets of comorbidity (e.g., a predominantly internalizing versus externalizing group). Future studies that might split samples into high and low childhood maltreatment types might offer different structures.

Study 4: A Cross-National Network Analysis of Psychiatric Comorbidities and Childhood Maltreatment in Bipolar Disorder

3.4.1 Introduction

BD is characterised by episodes oscillating from mania or hypomania to depression (Grande et al., 2016). Timely intervention (and prevention) help manage the disorder efficiently, but diagnosis is often delayed by 10 to 15 years (Lublóy et al., 2020). A prior diagnosis of unipolar depression, substance disorders (which can mask manic symptoms), anxiety disorders, personality disorders or schizophrenia are strongly associated with the diagnostic delay of BD (Lublóy et al., 2020). Timely treatment may help reduce suicide risk in this population where over a third report at least one suicide attempt (Dong et al., 2020).

Comorbidities, whether these be medical or psychiatric, seem to be significantly influenced by childhood maltreatment (Laroche et al., 2022). Half of patients with BD report childhood abuse and neglect, with emotional abuse being reported by 37% of bipolar patients (Daruy-Filho et al., 2011). Higher levels of maltreatment not only led to BD participants reporting various comorbidities but was associated with a faster accumulation of these prior to BD (Laroche et al., 2022). Similarly, maltreatment seems to predict a far more severe tableau of BD, characterized by earlier symptomatology onset, poorer response to treatment, a higher risk for suicide attempts, more mood episodes and a higher risk for a rapid cyclic

course (Etain & Aas, 2021; Aas et al., 2016; Etain et al., 2017; Nemeroff et al., 2016; Williams et al., 2016; Garno et al., 2005).

The aim of this network analysis was to model the relationship between comorbidities in BD at a cross-national level in order to accurately observe the intricate associations between additional comorbidities and types of childhood maltreatment. Our second aim was to create Directed Acyclic Graphs to show possible causal pathways between types of maltreatment and comorbidities. Our third and final aim was to investigate whether low and high maltreatment structures of psychiatric comorbidities were dissimilar.

3.4.2. Methods

Participants

The data included in this study was acquired through the World Health Organization-World Mental Health International College Student (WMH-ICS) initiative. The project aims at collecting global data on the mental health of university students. Participants in the current study were recruited globally. Informed consent was obtained in line with each institution's ethical procedures and in compliance with national legislation.

The final sample consisted of 3544 participants who satisfied the criteria for lifetime BD as assessed by the CIDI-5 instrument. The sample was predominantly female (69.7%), with males comprising 27.8% and individuals identifying as other - 2.%. Mean age was 20.39 (SD = 3.61). On average, participants reported 5.02 comorbid conditions (SD = 2.43), indicating a substantial burden of comorbidity.

Measures

In order to assess symptomatology, lifetime prevalence of DSM-5 disorders were evaluated using the Composite International Diagnostic Interview Screening Scales, Version 3.2 (CIDI-SC V3.2; Kessler et al., 2013). In the case of eating disorders, an instrument developed within the WHM-ICS was utilized (Strid et al., 2025). The Non-Suicidal Self-Injury scale (NSSI) was used to measure self-harm (Whitlock et al., 2014). Childhood maltreatment was measured using relevant items from the CIDI-3.0 and the Adverse Childhood Experiences International Questionnaire, assessing childhood maltreatment before age 17. In line with WMH-ICS survey standards, each maltreatment variable was coded from absent to severe, utilizing a Likert Scale with 5 points. For full details, see Myers et al. (2021).

Data analysis

The analyses were conducted using "R" version 4.5.3., using the graphical interface RStudio 2024.12.1+.563. We constructed the network using the variables outlined previously. The dataset included binary variables (1=presence, 0=absence) for psychiatric comorbidities. The analysis was conducted using multiply imputed datasets to account for missing data and improve the robustness of findings.

We examined the relationships between our variables using network analysis. Networks were estimated as Gaussian Graphical Models (GGM) based on polychloric correlation matrices, with regularization implemented using the EBICglasso algorithm. This

method improves interpretability, yielding a sparse network of partial correlations where associations between nodes represent unique relationships once account for all other nodes. This approach aligns conceptually with latent Gaussian copula methods, which enable a method for estimating network structures for non-normally distributed and heterogeneous data (Fan et al., 2017; Gobbler et al., 2024). It does so by assuming an underlying continuous latent structure of variables. Psychiatric comorbidities reflect continuous dimensions of symptoms and severity; therefore we cannot class them as simply discrete variables.

In order to evaluate the reliability of the estimated network, we conducted bootstrap procedures (with 1000 iterations) in order to generate confidence intervals for edge weights. We assessed the stability of centrality indices using case-dropping bootstrap procedure, which evaluated whether centrality estimates remained consistent when subsets of the sample were removed.

Our next step was to examine whether observed differences between edges and nodes centrality metrics were statistically meaningful using bootstrapped-based differences testing. Node predictability was calculated using the *mgm* package. Furthermore, we assessed redundancy of nodes using the *goldbricker* function from the *networktools* package in order to assure we were including distinct constructs.

We ran community detection using the walktrap algorithm to explore the presence of substructures within the network. We considered the relevance of cumulative adversity and ran subgroups analyses to estimate separate networks for individuals with lower versus higher levels of childhood maltreatment. Differences in overall connectivity and the network structure will be formally evaluated using a network comparison test, based on permutation testing. In line with this objective, we examined the association between cumulative maltreatment exposure and overall psychiatric burden using a negative binomial regression. This method is appropriate for count outcomes which exhibit overdispersion. Incidence rate ratios (IRRs) were inferred to quantify the relationships between childhood maltreatment and the number of lifetime comorbidities, while accounting for age and gender.

Finally, we estimated a Bayesian network using directed acyclic graphs and the hill-climbing algorithm using the *bnlearn* package. These models can suggest potential directional dependencies, but cannot establish causality in cross-sectional data, and are therefore used as an exploratory method.

3.4.3 Results

Network estimation

The network structure was estimated using Gaussian Graphical Models (GGMs) with EBICglasso regularization across all imputed datasets. This method penalizes spurious associations. Correlations were computed using polychoric correlations, thus being able to handle mixed data (binary as well as continuous). Adjacency matrices representing the estimated networks were extracted from each of the 30 imputations. In order to obtain a singular representative network, we pooled results across imputations. Mean edge weights were calculated and the proportion of times each edge appeared across imputations was computed. We applied a threshold of 70% edge inclusion, therefore only edges present in 70% of imputations were retained in the pooled network. We ran a redundancy analysis using

the *goldbricker* function which did not offer any reduction suggestions. The pooled network structure can be consulted via **Figure 1**.

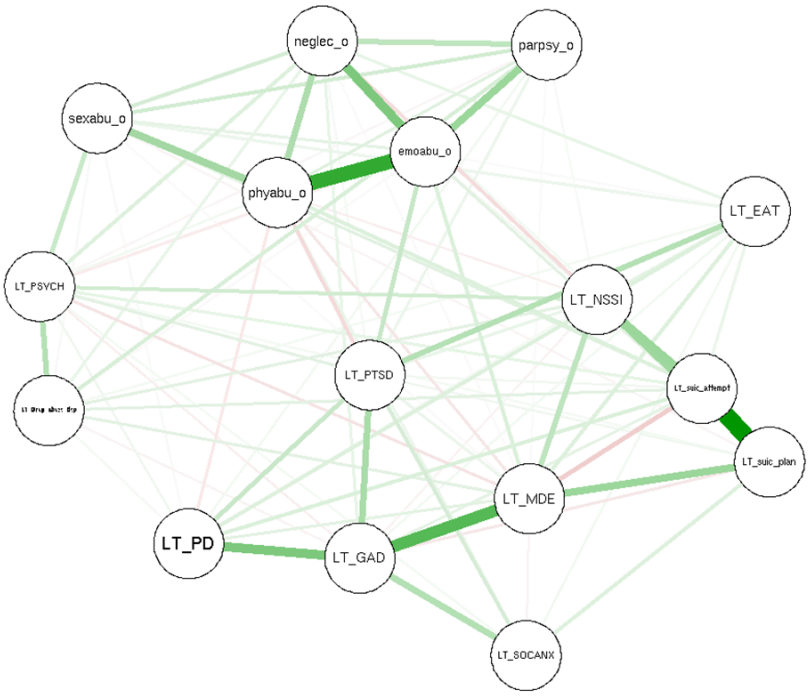

Figure 1. Regularized Partial Correlation Network of Psychiatric Comorbidities and Maltreatment Pooled Across Imputations

Note. Nodes represent the following constructs: LT_MDE - Major Depressive Episode; LT_GAD - Lifetime Generalized Anxiety Disorder; LT_PD - Lifetime Panic Disorder; LT_SOCANX - Lifetime Social Anxiety Disorder; LT_EAT - Lifetime Eating Disorder; LT_PTSD - Lifetime Post-Traumatic Stress Disorder; LT_Drug_abuse_dep - Lifetime Drug Abuse/Dependence; LT_suic_plan - Lifetime Suicide Planning; LT_suic_attempt - Lifetime Suicide Attempts; LT_NSSI - Lifetime Non-Suicidal Self-Injury; LT_PSYCH - Lifetime Psychosis; parpsy_o - parental psychopathology; phyabu_o - childhood physical abuse; emoabu_o = childhood emotional abuse; sexabu_o - childhood sexual abuse; neglec_o - childhood neglect

Network accuracy and stability

We used nonparametric bootstrapping procedures to evaluate network robustness (Supplementary Materials, Figures S1-S2). The confidence intervals around edge weights indicated that stronger edges were estimated with greater precision (e.g., suicide plan-suicide attempt). On the other hand, weaker edges showed wider confidence intervals and should be interpreted cautiously. The connections between suicide plan and suicide attempt, NSSI and suicide attempt and physical abuse and emotional abuse were significantly stronger than various other edges in the network. Centrality stability was similarly assessed using a case-dropping bootstrapped procedure. Correlation stability (CS) coefficients had indicated high stability for strength and expected influence (CS = .75 across all imputations). Closeness (mean CS = .72) and betweenness (mean CS= .66) had moderate stability and must be therefore interpreted cautiously. Strength was thus interpreted as a primary centrality metric, alongside expected influence.

Centrality and node predictability

Our centrality analyses had revealed that suicidal behaviors (plan and attempt) and GAD were amongst the most central nodes in our network. They had high strength values (e.g., suicidal attempt mean strength = 1.29; suicidal plan = 1.28). These nodes would seem to play the greatest role in network connectivity. Emotional abuse and physical abuse similarly demonstrated great connectivity within their own cluster. We ran node predictability analyses which relayed how well nodes were explained by their neighboring nodes. The highest predictability was relayed by emotional abuse (R^2 = .46) and physical abuse (R^2 = .43), followed by suicide attempt (R^2 = .32) and suicidal planning (R^2 = .31). Social anxiety and substance use had the lowest predictability, with R^2 indices under .10. This would indicate they were influenced by constructs outside of our network.

Community Detection

We ran community detection analyses using the walktrap algorithm. This revealed four clusters. The first cluster included internalizing disorders, meaning major depressive episode, generalized anxiety disorder, panic disorder, social anxiety, eating disorder and post-traumatic stress disorder. A second cluster unravelled a self-harm and suicidality clutter, including suicide planning, suicide attempts and non-suicidal self-injury. A third cluster consisted of our childhood maltreatment variables, including parental psychopathology, physical abuse, emotional abuse, sexual abuse, and neglect. Our fourth, and final cluster included externalizing aspects, consisting of drug-abuse / dependence and psychosis. This clustering suggests a clear separation between childhood maltreatment types and psychiatric outcomes, with self-harm behaviors linking the two domains.

Network Comparison Testing between low and high childhood maltreatment

In order to run a network comparison test we split our sample into low and high childhood maltreatment using those with score under 10 (out of 20 severity points) to comprise the low childhood maltreatment group, and those over 10 to create the high childhood maltreatment group.

We used subgroup analyses to compare individuals with low versus high cumulative maltreatment, revealing differences in overall connectivity. Across imputations, global strength was higher in the low-maltreatment group (mean p = .46, 67% of tests $p<.05$). That indicates that childhood maltreatment and psychiatric comorbidities were better connected in the lower levels of childhood maltreatment. Even so, there were no significant differences in the overall network structure (p = .49).

Thus, the general configuration of the networks was approximately the same. Despite this, certain connections did differ between groups. Connections between suicidal planning and PTSD, and drug abuse and major depressive episode were stronger in the high-maltreatment group. The low maltreatment group had higher associations between GAD and social anxiety, and PTSD and panic disorder. The centrality comparisons similarly indicated that the overall connectivity in the high-maltreatment group was reduced.

Evaluating Comorbidity Burden

Our next objective was to examine the association between the cumulative burden of childhood maltreatment and overall psychiatric comorbidity burden. Our results revealed that higher childhood maltreatment was associated with an increase in lifetime comorbidities. Each additional maltreatment score was significantly associated with an increased comorbidity count ($\beta = 0.039$, $p < .001$). This corresponded to an incidence rate ratio (IRR) of approximately 1.04 indicating a 3.9% increase in comorbidity count for each maltreatment point. Age was not significantly associated with comorbidity burden ($p = .70$), but gender was. Female gender was associated with a 20% increase of comorbidity when compared to males.

Bayesian network (Directed Acyclic Graphs)

We then conducted a Bayesian network using a Hill-Climbing algorithm with bootstrap aggregation (to account for imputations). In this case, edges were retained based on their consistency across bootstrapped samples. Our results suggest plausible directional pathways linking our childhood maltreatment variables to psychiatric comorbidities (see **Figure 2**). We constrained the analysis to not direct psychiatric comorbidities to maltreatment as this is a retroactive variable. Emotional abuse emerged as an important upstream factors influencing NSSI and suicidal attempt and planning. MDE appeared to be a possible precursor to anxiety disorders. While these results might be interesting, causal inferences cannot be drawn until longitudinal analyses are conducted.

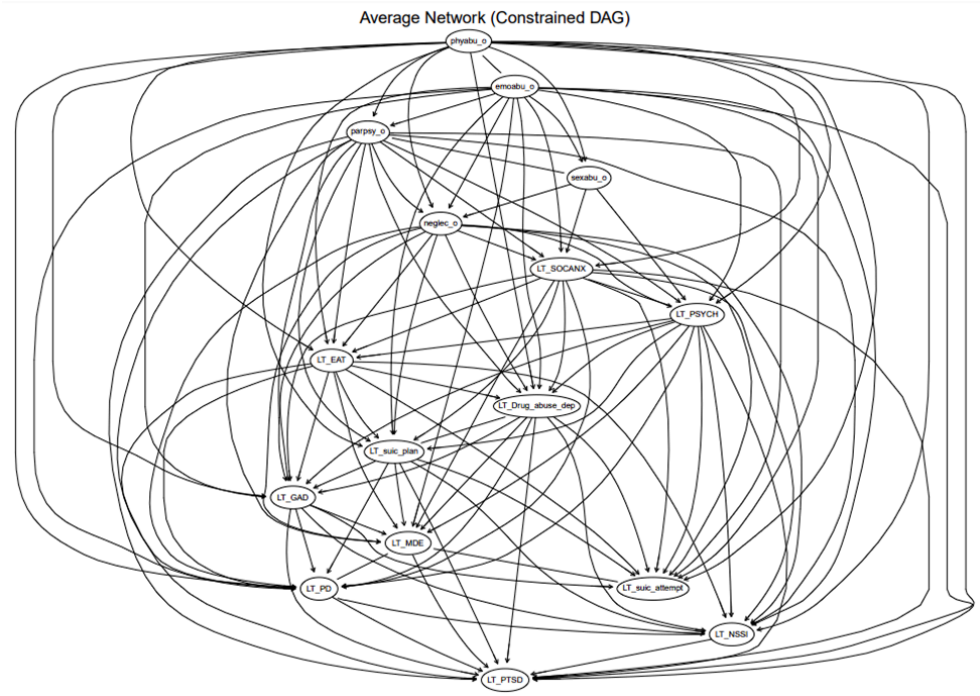

Figure 2. Directed Acyclic Graph (DAG) of Psychiatric Comorbidities and Maltreatment (Constrained Bayesian Network)

3.4.4 Discussion

The following network analysis investigated the relationships between psychiatric comorbidities and childhood maltreatment in a cross-national BD sample. Our results would establish that childhood maltreatment isn't just a correlate of BD but might organize burden and lead to an upstream in comorbidities. A similar finding was related by Laroche et al. (2022), who observed a faster accumulation of comorbidities in those with maltreatment prior to developing BD.

This is consistent with contemporary data that childhood maltreatment is linked to a higher risk of developing psychiatric disorders (Kendler et al., 2000; Phillips et al., 2005; Fergusson et al., 2008; Clark et al., 1997; Green et al., 2010; Johnson et al., 1999; Arseneault et al., 2011; Read et al., 2005). A meta-analysis conducted by Grummitt et al. (2024) quantified that childhood maltreatment accounts for up to 41% of mental health problems. They consider that up to two million cases of depression, anxiety and substance use issues would be erased if not for childhood maltreatment. In BD, childhood maltreatment has been linked to a worse course, with more episodes, a higher risk for suicide attempts and a rapid cycling form (Agnew-Blais & Danese, 2016; Daruy‐Filho et al., 2011; Laroche et al., 2022). Emotional abuse was the strongest link to BD in our sample. A similar finding was observed by Etain et al., 2010 & Palmier-Claus et al. 2016 in their respective studies as well.

Our network comparison analyses indicated that the overall structure and connectivity were somewhat similar between the groups, but the low maltreatment group had better connectivity. This is somewhat surprising, as some studies observed reports of severe maltreatment in half of their BD sample (Garno et al., 2005). We consider this to be due to our high maltreatment group being relatively small (N = 339) compared to the low maltreatment group (N = 2593). We consider the low maltreatment severity to be linked to the population we investigated - university students. College students are usually exposed to less maltreatment, with one study observing that just 20% of students included in their study reported any type of maltreatment (Saed & Talat, 2013). Children that have undergone maltreatment are at an increased risk for school dropout and academic failure (Romano et al., 2015). As such, it's possible that too few individuals with severe or high maltreatment manage to reach higher education.

Our regression analyses demonstrated that cumulative maltreatment exposures were associated with an increased psychiatric burden, highlighting the impact of adversity on the development of psychiatric outcomes. Our Bayesian network analyses revealed plausible directional pathways, emotional abuse, in particular to self-harm and internalizing comorbidities.

Clinically, these results relay the importance of screening and intervening amongst other diagnoses as well, not just the primary BD. Similarly, this points to the severe issue of misdiagnosis in BD. Up to 76.8% of bipolar individuals seem to be wrongly diagnosed at first, with only 20% receiving the correct diagnosis in the first year of treatment (Knežević; & Nedić, 2013; Shen et al., 2018; Kaya et al., 2023).

Several limitations should be considered. First of all, our data was cross-sectional, limiting causal inferences. Although we ran Bayesian analyses with directed acyclic graphs, we cannot establish temporal relationships. Second of all, the imbalance in the high and low maltreatment groups limits the precision of the network comparison results, which we believe skewed our analyses. We would expect different structures amongst higher maltreatment

samples. Third of all, there might be other mechanisms that were not included in the model but might be important in modeling network structures.

Future research should extend these findings using longitudinal models thus clarifying the causal relationships between childhood maltreatment and the development of psychiatric comorbidities as well as structures according to types of maltreatment suffered. Similarly, a network structure of symptoms could offer a more nuanced understanding in observing the interactions in a transdiagnostic manner.

Study 5: Piloting the Adaptation and Validation of the Hypomanic Personality Scale - 6 (HPS-6) to Romanian

3.5.1. Introduction

Bipolar disorder (BD is a chronic, debilitating disorder, affecting approximately 1.5% of the global population (Singh et al., 2025). Accurate diagnosis can span across up to 10-15 years (Lublóy et al., 2020), individuals with BD being incorrectly diagnosed with depression in the first years of treatment (Berk & Dodd, 2005). Inaccurate diagnosis leads to inappropriate management of the disorder, as well as unsuitable medication prescription (Berk et al., 2025; Chen et al., 2024).

Difficulty of diagnosis arises due to various symptomatology presentations as well as individuals seeking out professional help for depressive symptoms rather than the “highs” of the disorder (Stiles et al., 2019). The high rates of comorbidity with substance abuse (Hunt et al., 2016), anxiety disorders (Pavlova et al., 2017), eating disorders (Fornaro et al., 2021) and attention deficit hyperactive disorder (ADHD) (Schiwek et al., 2021), make accurate diagnosis of BD a real challenge.

Similarly, when screening for common mental health disorders, BD is scarcely included in such measures. The Psychiatric Diagnostic Screening Questionnaire (PDSQ; Zimmerman & Matia, 2003), for example, is a screening measure that is used extensively in primary care, and aligns with Diagnostic and Statistical Manual of Mental Disorders (DSM) symptoms, but does not include measures for screening for hypo/manic symptoms (Rogers et al., 2025). The problem of misdiagnosis could be reduced with the help of a short self-report scale meant to screen for BD (Miller et al., 2010).

The average length of stay in the EU for a psychiatric in-patient is 24.3 days while Romania’s average is 17.7 days (Iovu et al., 2019). This is not surprising, as the Romanian healthcare system has a series of limitations, such as poor infrastructure and conditions or lack of qualified personnel. In addition, there are no brief measures to screen for BD in the Romanian language conducted on adequately powered sample sizes. This all the more underscores the importance of easy to use, brief, evidence-based instruments to help accurately diagnose BD patients in a Romanian setting.

Eckblad & Chapman (1986) developed a 48-item instrument with dichotomous reasoning (TRUE/FALSE) in order to detect risk for BSD. The HPS has proven to be a practical tool in assessing BSD and risk for developing BSD. The HPS managed to prove predictive validity for new cases as well as a previous history of hypomania, impulsivity,

grandiose traits and related important risk factors for future BSD (Walsh et al., 2015) as well as predict mania and hypomania in a 13-year follow-up study (Kwapil et al., 2000).

Screening measures for BSD are usually extensive, the full General Behavior Inventory (GBI; Depue et al., 1989) for example, containing 73-items. The original 48-item HPS instrument, although employing a dichotomous answer sheet, can prove to be of substantial length when screening for other diagnoses or psychiatric comorbidities simultaneously. As such, Miller et al. (2011) developed a short version of the HPS, containing only 6 items, which was studied in detail across samples (from both clinical and community settings), which proved to be more efficient than the extensive version of the scale. The shortened version of the scale takes at most 2 minutes to complete and correlates strongly to the original 48-version ($r = .83, p<.001$). Cronbach's alpha in the original adaptation of the 6-item version was $\alpha = .79$.

With these in mind, a brief instrument with high specificity can help navigate specialists towards a correct diagnosis. The HPS-6 could prove to be a noteworthy candidate for screening measures of possible BD diagnosis or high-risk individuals. In this study, we aim to validate and adapt the HPS-6 for the Romanian Population.

3.5.2. Methodology

Participants

Our study comprised two waves of participants from two separate studies. Data for the first study (which focused on our community sample) was collected via the PNRR-III-C9-2023-I8-CF 32/28.07.2023 project. Our first wave of participants was composed of 171 participants. Individuals were recruited from the general Romanian population using online advertisements targeted toward interested parties. Regarding demographic features, our participants were aged between 19-52 years old (M = 25.39, SD = 7.109). Of these, 72.66% were females. Our second wave of subjects (N = 97) was collected independently, through online advertisements. Regarding demographic features, this wave of participants were aged between 19-53 years old (M = 34.02, SD = 9.72). Of these, 82.47% were females.

In order to respect the inclusion criteria, participants had to be over 18 years old, with an upper limit of 50 years old. This upper age limit was selected in order to avoid heterogeneity of responses due to cognitive decline rather than legitimate BD risk and because literature acknowledges a different presentation in older individuals with BD (Beunders et al., 2023). Based on rigorous standards, we aimed to recruit at least 20 participants per item for our scale of interest (Morgado et al., 2017). As such, we aimed to have at least 120 participants per study within our validation and adaptation study.

Measures

Demographics

Participants completed demographic measures such as age, gender, height, weight, education level, occupation, residence environment, civil status, nationality and net monthly income as well as diagnosed psychiatric and chronic physiological issues.

The Hypomanic Personality Scale - 6 item version (HPS-6) was used to assess BSD spectrum disorder risk. A cut-off of three was deemed sufficient to indicate possible risk for BSD in clinical and community samples (Miller et al., 2011). In order to check for convergent validity, the Mood Disorder Questionnaire (MDQ; Hirschfeld et al., 2000) was administered as well. The MDQ is a brief self-report instrument that can be rapidly filled out by the patient or any trained medical / clinician staff, which screens for a history of manic or hypomanic symptoms. The MDQ is a brief instrument with good overall diagnostic accuracy for screening BSDs. The Altman Self-Rating Mania Scale (Altman et al., 1997) evaluates manic symptom presence and severity using 5 items, which are rated on a 4-point Likert scale. Total scores range from 0 to 20, with a score equal or higher than 6 indicating a possible presence of hypomanic or manic symptoms (Meyer et al., 2020). The Patient Health Questionnaire - 9 (PHQ-9; Kroenke et al., 1999) is a diagnostic instrument that assesses depression and common mental disorders faced in primary care, mirroring criteria from the DSM-IV (APA, 1994). The instrument contains nine items, containing a 4-Likert scale ('0-Not at all' vs '3 - Nearly every day'). The Food Neophobia Scale (FNS; Pliner & Hobden, 1992) measures the 'reluctance to eat and/or avoidance of novel foods' as outlined by Pliner & Hobden (1992). The FNS contains 10 items, rated on a 7-point Likert scale. The importance of Olfaction (IOS; Sorokowski et al., 2023) scale investigates primary olfactory functions. It contains 18 items, using a 5-point Likert scale (1 = "*strongly disagree*", 5 = "*strongly agree*"), "The smell of tasty food makes me hungry". The Early University Dropout Intentions Questionnaire - Revised (EUDIQ-R) measures the reasons for which university students are considering dropping out (Bernardo et al., 2022). The scale contains 13 items to measure the overall risk of dropping out, on a 5-point likert scale from 0 - Completely disagree to 5 - completely agree. We used 12 out of the 13 subscales of the Psychiatric Diagnostic Screening Questionnaire (PDSQ) to screen for other diagnoses. The only subscale we did not include was the one assessing for depression as we used the PHQ-9 to assess for severity and participants would undergo a formal clinical evaluation where depression would be evaluated in further detail. Suicide risk was assessed using the Suicidal Behaviors Questionnaire-Revised (SBQ-R; Osman et al., 2001). The SBQ-R is a brief, 4-item scale that assesses suicidal dimensions, generating an overall suicide risk score. Seeing as we want to reach clinically diagnosed bipolar individuals as well, we sought out to exclude only high-risk individuals, using a threshold of 13 (Adelola et al., 2015).

The HPS-48 as well as HPS-6 don't represent a direct possibility of having BD, but create a phenotype for common experiences and behaviors that signify bipolar risk. A direct example for this is reward processing, a deeply researched phenomenon and mechanism that is linked to BD. In particular, BSD individuals experience an excessive and hyperactivated reward-seeking behavioral component in mania, as well as excessive inhibition in depressive episodes (Whitton et al., 2016; Redlich et al., 2015).

The following scales were chosen in order to represent frequently associated characteristics of individuals at risk for bipolar or associated with the disorder itself: The BIS / BAS scales assess two motivational systems, the Behavioral Inhibition System (BIS), 7 items and the Behavioral Activation System, 13 items (BAS) (Carver & White, 1994). They represent avoidance and approach tendencies. Positive Overgeneralization represents the "*tendency to generalize good experiences in one domain to broader aspects of life*" (Eisner et

al., 2008; pp. 8). The Positive Overgeneralization Scale (POG scale; Eisner et al., 2008) contains 3 subscales (lateral generalization, upward generalization and social generalization), comprising altogether 16 items. The UPPS-P Impulsive Behavior scale (Cyders et al., 2007) measures positive and negative emotional urgency as well as various aspects related to impulsivity. Impulsivity is a key feature in BD, causing significant burden. Seeing as the HPS-6 evaluates positive valences, we chose to only administer the Positive Urgency subscale. The Positive and Negative Affect Schedule (PANAS) is a 20-item self-administered measure of positive and negative affect (Watson et al., 1988). It's been hypothesized that positive affect is linked to high BAS, which leads to high goal activation, later on to positive affect and so on (Meyer & Baur, 2009). The Affect Lability Scale (ALS-18; Oliver & Simons, 2004) measures rapid shifts in emotional expressions, using 18 items. The scale measures an individual's tendency to rapidly shift from one emotion or state to another using 18 items and a 3-factor model (Aas et al., 2015).

Procedure

We solicited and obtained approval from the original author of the scale to adapt the HPS-6 to Romanian (Miller et al., 2011). With regard to the adaptation process itself, we followed Gudmundssons's (2012) "forward & backwards" guidelines in order to adequately adapt the HPS-6 item version scale to Romanian. There were divergences regarding the term "giddy", which lead to a third translator, but as divergences persisted, the term was discussed in a panel of nine clinical psychologists and confirmed by the original author of the scale, in order to discern the intention of the construct. Following this, the final Romanian version was translated back to English by two different translators and a final version was developed.

We received ethical approval from the university's Ethics Commission and we complied with General Data Protection Regulation (GDPR) and Human Subjects Right in accordance with the national legislation. Our study protocol was registered on ClinicalTrials.Gov with the following ID: NCT07399626

We recruited subjects using a 2-wave approach. The first wave of participants was collected via a larger project, PNRR-III-C9-2023-I8-CF 32/28.07.2023, which used online advertisements to promote the study. Participants completed scales at intake and one-month later in order to test for retest reliability. The aim of the second wave was to test amongst individuals screened and diagnosed for various mental health issues in order to see if the HPS-6 validated and adapted scale could accurately detect bipolar risk and symptomatology and distinguish it from other disorders (e.g., depression). Once participants completed all intake scales, they went through a DSM-5 based semi-structured interview using the SCID-5-CV. Clinical psychologists were blinded from scales, study aims as well as the clinical status of participants. Evaluations took place online (using Google Meet or similar apps) or by telephone and were recorded. Once the participants went through the full SCID-5-CV evaluation, we had another blinded clinical psychologist co-evaluate the participant to confirm symptomatology using the recorded session. If reports were dissimilar, a third clinical psychologist and PI of the study resolved dissensions.

Besides demographics, during intake forms we evaluated suicide risk (using SBQ-R) as well as substance abuse (using the appropriate PDSQ subscale). Regarding suicide risk, we chose the cut-off of 13 (Adelola et al., 2025) to represent high suicide risk. If the cut-off of 13

was met, individuals were not included in the study and were instead given resources to help them manage a crisis and reach out for psychological help. During the study, participants facing current difficulties or deemed in distress were offered resources which were meant to lead participants towards psychotherapy clinics, psychiatrics or even pro bono options tailored to their diagnosis and financial possibilities.

Data Analysis

All analyses were conducted using the statistical software "R" version 4.5.1., using the graphical interface RStudio 2025.5.1.513. Firstly, we computed internal consistency using Cronbach's alpha and Macdonald's Omega. Crobach's α measures how well our items measure a single latent construct using the average correlation between items, with correlations closer to 1 showing higher consistency. Short scales often have lower α cronbach values, but as a rule of thumb, .70 is acceptable (Tavakol & Dennick, 2011). Various psychometricians consider Macdonald's ω to be a more appropriate measure of internal consistency, as it does not consider that all items are proportionally similarly related to the latent trait, estimating more accurately reliability in personality scales, as there is usually a lot of variability in the factor loadings. Alternatively, where there is little variability and a strong factor grouping, α would prove more appropriate (Zinbarg et al., 2005). Seeing as our scale is brief, we did not expect items to load on various factors, thus specifying one factor for the two measures of internal consistency. If the scale offers good reliability, we expect correlation values to be similar. Additionally, we expect test-retest values to be moderate between the two time points in both samples.

Firstly, an Exploratory Factor Analysis (EFA) will be computed in order to establish a hypothesis regarding the factor structure, with a Confirmatory Factor Analysis (CFA) being run on the second wave of participants. Given the binary nature of the target scale ('True', 'False'), we employed the Weighted Least Square Mean and Variance adjusted ("WLSMV") estimator. Li (2015) showed that WLSMV was more accurate in estimating factor loadings than MLR across conditions in Monte Carlo simulations. It models a polychloric correlation matrix amongst items, which is more appropriate for binary items (Verhulst & Neale, 2021), where data is not normally distributed and continuous, and alternatively true correlations can be missed if other estimators are used.

We assessed model fit using Comparative Fit Indices (CFI), Tucker-Lewis Index (TLI), Root Mean Square Error of Approximation (RMSEA) and the Standardized Root Mean Square Residual (SRMR). In line with standard recommendations, model fit was judged acceptable if CFI and TLI .95, RMSEA <.06 and SRMR <.08 (Bentler, 1990; Hu & Bentler, 1999). For local fit evaluation, we examined item residuals, standardized factor loadings and modifications of indices. Loadings that were .50 were considered meaningful in contributing to the latent variable measured (Thoemmes et al., 2018). Once the dimensions of the scale as well as its internal consistency are established, we will be assessing construct validity, using convergent (MDQ & ASRM) as well as divergent measures (FNS & IOS). Thus, we hope to capture high correlations for measures that are conceptually related and low correlations for constructs that are unrelated.

Following this we'll be separating participants into subgroups of diagnosed, risk and other in order to see how well our HPS-6 scale detects diagnosed bipolar, at risk for BD and correctly does not identify those without risk and who did not meet criteria via the SCID-5-CV interview (e.g., depression). We will be employing a Receiver Operating Characteristic (ROC) analysis to assess the specificity and sensitivity of our newly adapted scale. This method is an appropriate method when assessing the diagnostic properties of scales and instruments in order to discriminate between classifications of subjects (Pintea, 2009). Using the previous ROC, we will identify an appropriate threshold and then observe descriptively which diagnoses were a false positive for BD risk.

For our final analysis, we will want to see if the HPS-6 scale correctly detects the "bipolar phenotype". Meaning, how well it predicts high scores on known factors attributed to BD and risk - BIS/BAS scales (Carver & White, 1994), POG (Eisner et al., 2008), UPPS-P-Positive Urgency (Teh et al., 2024), PANAS-Positive (Watson et al., 1998), ALS-18 (Aas et al., 2015). We will be running a series of analyses. First of all, we will be using bivariate correlations to observe primary convergent relationships between constructs. Second of all, we will be running multiple linear regressions for each of the outcome variables in order to see how well HPS-6 predicts well-known constructs related to bipolarity. We will be using age and gender as covariates to control for confounding effects.

3.5.3. Results

The non-clinical sample consisted of 171 participants (M_age = 26.14, SD = 8.95, range = 19–58). The sample was predominantly female (78.36%), with 19.88% male participants and 1.75% identifying as other. Participants reported low to moderate levels of hypomanic traits (HPS_total: M = 2.02, SD = 1.78). Scores on the MDQ indicated moderate levels of mood symptoms (MDQ_total: M = 5.40, SD = 3.41), while depressive symptoms were in the mild to moderate range (PHQ-9: M = 7.57, SD = 5.16). Other measures showed adequate variability (EUDIQ_total: M = 51.3, SD = 8.8; FNS_total: M = 28.06, SD = 10.20; IO_total: M = 66.49, SD = 10.28).

The clinical sample consisted of 97 participants (M_age = 34.02, SD = 9.72, range = 19–50). The sample was predominantly female (82.47%), with 17.53% male participants. Participants reported low to moderate levels of hypomanic traits (HPS_6: M = 1.92, SD = 1.84). Mood-related measures indicated moderate levels of lifetime manic symptoms (MDQ_total: M = 5.27, SD = 3.55) and elevated depressive symptoms (PHQ_total: M = 11.19, SD = 7.23). Current manic symptoms, as measured by the ASRM, were relatively low (M = 2.52, SD = 2.80). Other variables showed adequate variability (FNS_total: M = 32.79, SD = 11.08; IOS_total: M = 65.94, SD = 9.39). For more demographic data please see Supplementary Materials - Table S2.

In our first sample, we computed internal consistency for the HPS-6 scale. The internal consistency was acceptable, with Cronbach's $\alpha = .71$ (95% CI [.64, .77]. Similarly, we computed McDonald's omega which indicated similar acceptable internal consistency ($\omega = .71$). The omega hierarchical coefficient ($\omega h = .71$) suggests that our total score mostly reflects a singular general factor. Factor loadings on the overall factor ranged from .46 to .65. The explained common variance (ECV = 1) further supports the one factor structure. We

verified internal consistency for the clinical sample as well for a double check. The HPS-6 demonstrated acceptable internal consistency in the clinical sample, with Cronbach's alpha of .75 (95% CI [.67, .82]). McDonald's omega total was .76, indicating comparable reliability. Item-total correlations ranged from .35 to .55, suggesting that all items contributed adequately to the scale.

Test–retest reliability was assessed in Sample 1 by examining the association between baseline and retest HPS-6 total scores. Results indicated a significant moderate positive correlation, $r(169) = .43$, $p < .001$, 95% CI [.30, .55], suggesting acceptable temporal stability of the measure over time. For our second sample, we used a similar procedure. The results indicated a strong association, $r(64) = .67$, $p<.001$, 95% CI (.51 - .78), suggesting good temporal stability.

Our next step was to run an EFA to observe how items would load on our scale when adapting it to Romanian. The original factor structure (Miller et al., 2011) had one factor loading, which is expected as it's a short screening scale.

Our EFA results supported the unidimensional structure of the HPS-6. Our items demonstrated moderate to strong loadings (.46–.65) on a single factor. None of the items were below recommended thresholds (<30; Tavakol & Wetzel, 2020). The one factor model accounted for 29.7% of the variance observed in our sample. We attribute this moderate variance might be due to a floor effect, as a large part of our sample reported scant hypomanic symptoms, therefore reducing the variability in our data.

Our next step was to run a CFA. In order to assure independence of samples, we used the data from our second sample (N = 97). The model showed acceptable to good fit to the data, with chi-square = 14.36, df = 9, p = .110, CFI = .975, TLI = .959, RMSEA = .079, 90% confidence interval [.000, .151], and SRMR = .090. All items loaded significantly on the latent factor, with standardized loadings ranging from .53 to .83, thus supporting the unidimensional structure of the scale.

Spearman correlations were conducted to examine the convergent and divergent validity of the HPS-6 (HPS_total). As expected, HPS_total (N = 131) was strongly and positively associated with MDQ_total, r = .56, 95% CI [.43, .67], p < .001, providing clear evidence of convergent validity. This indicates that higher hypomanic phenotype is more robustly related to greater mood disorder symptomatology. Regarding divergent validity, HPS-6 (HPS_total) showed no significant associations with Importance of Olfaction Scale (IOS_total), r = −.02, 95% CI [−.19, .15], p = .82, or Food Neophobia Scale (fns_total), r = .07, 95% CI [−.10, .24], p = .40. These findings support the discriminant validity of the scale, suggesting that hypomanic traits are distinct from these theoretically unrelated constructs. A small but statistically significant positive association was observed between HPS_total and depressive symptoms (phq9_total), r = .23, 95% CI [.06, .38], p = .01. Although not hypothesized, this relationship may reflect shared underlying affective dysregulation across mood-related constructs. Finally, HPS_total was not significantly associated with EUDIQ_total, r = −.08, 95% CI [−.25, .09], p = .34, indicating that hypomanic traits are independent of this construct.

To strengthen our results, we conducted a correlation matrix for our clinical sample as well on baseline data. Spearman correlations were conducted to examine the convergent and divergent validity of the HPS-6 (HPS_total) in a clinical sample (N = 97). As expected,

HPS-6 scores (HPS_total) were strongly and positively associated with MDQ scores (MDQ_total), r = .62, 95% CI [.48, .73], p < .001, indicating robust convergent validity with lifetime mood disorder symptomatology. Additionally, HPS-6 (HPS_total) was moderately associated with ASRM scores, r = .34, 95% CI [.15, .50], p < .001, further supporting convergence with current manic symptom severity. HPS-6 also showed a moderate positive association with depressive symptoms (PHQ_total), r = .47, 95% CI [.30, .62], p < .001. Although not central to the hypothesized pattern, this relationship likely reflects shared affective dysregulation within clinical populations. Regarding divergent validity, HPS-6 (HPS_total) was not significantly associated with food neophobia (FNS_total), r = .03, 95% CI [−.17, .23], p = .79, or importance of olfaction (IOS_total), r = .07, 95% CI [−.14, .26], p = .52. These findings support the discriminant validity of the scale, indicating that hypomanic traits are distinct from social and interpersonal constructs.

Our next analysis was to assess binarily if our adapted HPS-6 instrument correctly detected the clinical bipolar sample, risk sample and correctly discriminated from those without bipolar risk or meeting criteria. Unfortunately, our samples were small within our clinical bipolar sample (N = 10 - either reported by patient or meeting criteria within study evaluation) and risk sample (N = 4). Therefore, we did not find it appropriate to run ROC to assess the specificity and sensitivity of the scale.

Similarly, our next step was to observe if the HPS-6 predicted the bipolar phenotypes we measured. We ran a series of linear regression analyses to see if the HPS-6 predicted constructs associated with bipolarity. Our results were mixed, HPS-6 scores significantly predicted impulsivity (β = 1.18, p = .030) and affective lability (β = 3.2, p<.001). Surprisingly, the HPS-6 scale did not predict other well-studied factors related to bipolar disorder, such as positive overgeneralization and reward processing. See more details in **Table 1**.

Table 1. HPS-6 Regression Results for Bipolar Phenotype Features (N = 66)

outcome	β	SE	t	p
POG	-0.02	0.02	-0.79	.42
UPPS	1.44	0.51	2.83	.006**
PANAS_POS	0.29	0.41	0.71	.47
ALS_18	3.53	0.69	5.07	<.001**
BAS_Drive	0.11	0.17	0.67	.50
BAS_Fun_Seeking	0.17	0.18	0.96	.33
BAS_Reward	0.11	0.19	0.57	.56

Notes. POG - Positive Overgeneralization, UPPS - Positive Urgency - UPPS Impulsive Behavior Scale - Positive Urgency, PANAS_POS - Positive and Negative Affect Schedule, ALS_18 - Affective Lability Scale, BAS_Drive - Behavioral Activation System, Drive Subscale, BAS_Fun_Seeking - Behavioral Activation System - Fun-Seeking Scale, BAS_Reward - Behavioral Activation System

3.5.4 Discussion

Oftentimes, accurate diagnosis of individuals with BD is delayed by up to 15 years (Lublóy et al., 2020). Indices of misdiagnosis vary from 52% to 76.8% (Knežević & Nedić, 2013; Shen et al., 2018). While being diagnosed inaccurately is a pain as of itself, wrongful diagnosis leads to erroneous medication. This can have significant consequences in BD, where antidepressant monotherapy is not advised as it can worsen symptoms and lead to a surge in suicide attempts (Berk et al., 2025; Chen et al., 2024).

The first objective of this study was to investigate the factorial structure of the Hypomanic Personality Scale - 6 in a Romanian sample using an adapted version of the scale. The original factorial structure (Miller et al., 2010) was supported by both our general population sample as well as what was meant to be our clinical sample. All six items loaded on one single latent factor. Model fit indices were generally acceptable, although slightly weaker in our clinical sample (N = 97). This is not surprising as shorter scales, especially screening scales are usually weaker in model fit (D'Urso et al., 2022). Factor loadings were moderate to strong, thus indicating that our items contributed in a meaningful manner to the underlying construct.

Our second objective was to assess the internal consistency of the scale. The HPS-6 demonstrated acceptable reliability in both samples, with Cronbach's alpha and McDonald's omega varying from .71 to .75. These results would signify stable internal consistency despite the scale being quite brief in nature and using binary coding.

Our third objective was to evaluate convergent and divergent validity across study samples. HPS-6 showed a strong association with MDQ in both samples, supporting convergent validity. Similarly, the ASRM scale was positively associated with the HPS-6 scale. Moderate correlations were observed with depressed symptoms (PHQ-9). In contrast, correlations with dissimilar constructs, such as academic drop-out (EUDIQ), food neophobia (FNS) and importance of olfaction did not correlate.

Our fourth objective was to observe if the HPS-6 could correctly detect diagnosed cases of bipolar and bipolar familial risk. Unfortunately, our strictly bipolar sample was very small and an analysis in this sense wouldn't have been valuable, but we encourage future studies to employ ROC to create a threshold for the Romanian version of the scale and evaluate the specificity and sensitivity of the scale in this population.

Our fifth objective was to see if the HPS-6 could be predicted by constructs which can be found in the bipolar phenotype (e.g., reward processing, affective lability). Interestingly, only constructs related to affective lability or impulsivity were predicted well by the HPS-6 scale. This would signify that the scale assesses a specific set of risk behaviors. Although other authors mention the original 48-item scale capturing ambition, we did not observe this relationship in the short version of the scale. It's possible the short version of the scale doesn't grasp this aspect of bipolarity as well.

Several limitations need to be acknowledged, such as the small sample size in the clinical group. Similarly, the low number of diagnosed patients with BD is an important limitation which should be explored further on in future studies. Furthermore, we may mention the small percentage of male included in both our clinical and community samples.

Despite these limitations, the HPS-6 is a promising, brief, evidence-based instrument that can be used in clinical and research settings. Future research should concentrate on validation in a fully clinical and at-risk sample and further investigate its longitudinal stability. Similarly, sensitivity and specificity analyses warrant attention.

CHAPTER IV. GENERAL CONCLUSIONS AND DISCUSSIONS

The current thesis' general objective was to examine the psychological variables involved in the severity of Bipolar Disorder: attentional bias, childhood maltreatment, and psychiatric comorbidities. Furthermore, we aimed to provide practical solutions to reduce the difficulties associated with the diagnosing process and identifying individuals at risk developing bipolar disorder. We expect that this effort would translate into an opportunity for the implementation of early intervention. In order to achieve these objectives, we conducted five original studies.

Firstly, this thesis investigated attentional biases in BD, hoping to enrich literature by providing evidence that phases of BD differ in attentional processing behaviors. Mood-congruency was a promising theory (Garcia-Blanco et al., 2013), and we hoped to observe that attentional processing was congruent to the current mood episode. Our meta-analytic approach used in **Study 1** - unfortunately for us - did not support the idea that attentional biases of any type or during either episode were present in individuals with bipolar disorder. The reasons underlying these results are numerous. Among these, we may mention: 1) attentional biases might not be significantly affected in BD when compared to healthy controls, 2) there is a considerable degree of heterogeneity in literature. In this regard, we have identified the use of multiple probes and assessment methods in investigating attentional biases, coupled with the fact that they are rarely double-validated using a different measure or retested. The third possible reason is that besides the many types of measures used, a large part of studies did not use interference scores, the most accurate method to quantify true attentional biases. Finally, it's possible that an experimental design, used in order to facilitate mood induction, might provide clearer evidence for the presence of this cognitive mechanism.

But alas such is research! To accurately estimate and characterize a population, publishing of null results is just as important as publishing of significant results. Selective reporting, or publication bias, leads to inflated effect sizes (Van Assen et al., 2014), naturally. Science is based on the principle that it is self-correcting. Essentially, false positives or inflated measures will be corrected with time (Munafò & Neill, 2016). In this respect, our meta-analysis guided us towards the presumption that the data does not support emotional attentional biases in BD.

Therefore, **the second objective of this thesis** was to examine the psychiatric comorbidity load this clinical population faces. At least half of individuals with BD seem to be affected by an additional psychiatric comorbidity (Pavlova et al., 2015; Wang et al., 2025) and some reports mention an astounding rate of 96.3% of patients being affected by at least another medical comorbidity (Sylvia et al., 2015). Little research is done on psychiatric multimorbidity and the associations between comorbidities themselves. Although 66% of BD individuals (Pavlova et al., 2015; Wang et al., 2025) report having at least one other

psychiatric comorbidity, percentages concerning two, three or even four psychiatric comorbidities are worrying as well.

Hence, we decided to conduct an umbrella review hoping to quantify the extensive additional psychiatric burden the bipolar population faces in one singular article that clinicians could consult. Our hope was that corrected covered area analyses (CCA) would be at most 10% to permit us to conduct a second-order meta-analysis and generate an integrated pooled prevalence of all meta-analyses conducted on psychiatric comorbidities. Similarly, we hoped to quantity other measures of burden as well: early age of onset, number of episodes, severity of episodes, rapid cycling, suicide attempts. We managed to fulfil, in part, one of the aims we set out. We systematized pooled prevalences of meta-analyses of psychiatric comorbidities in BD, drawing attention to the severe proportions of additional mental disorders BD individuals face. Further details can be consulted via the manuscript (*see* **Study 2**). We managed to run a second-order meta-analysis on suicide attempts and generated a new pooled prevalence. We recommended future studies go back to primary studies in the hope that more detailed burden (episodes, age of onset etc.) can be extracted and reanalyzed in an integrated manner.

Pondering motives for the large comorbidity percentages in BD we focused on risk factors for psychiatric comorbidities. We chose to analyze the relationship between childhood maltreatment, BD and psychiatric comorbidities. Half of those diagnosed with BD face severe experiences of maltreatment (Kendler et al., 2000; Phillips et al., 2005; Fergusson et al., 2008; Clark et al., 1997; Green et al., 2010; Johnson et al., 1999; Arseneault et al., 2011; Read et al., 2005). Similarly, about half of those with BD have a psychiatric comorbidity (Leda-Rego et al., 2024; Laroche et al., 2022). Maltreatment is a well-known (Scott et al., 2023; Alkema et al., 2024) risk factor for the development as well as for the severity of BD. Another less studied severity factor is the accumulation of psychiatric comorbidities as well the speed of accumulation (Agnew-Blais & Danese, 2016; Laroche et al., 2022).

In the **third and fourth studies** we aimed to enrich literature on psychiatric comorbidity observed in individuals with BD. In order to augment literature on the nature of accumulation of comorbidities, we introduced childhood maltreatment, a well-known risk factor for the development and severity of BD. Similarly, childhood maltreatment seems to lead to a faster accumulation of psychiatric comorbidities among mental disorders (Laroche et al., 2022). In order to achieve this goal, we conducted two network analyses, used to visualize and investigate the structure of comorbidities in individuals with BD. We also aimed to observe the associations between maltreatment subtypes and psychiatric comorbidities. We expected to shed light upon different psychiatric comorbidity associations that might arise depending on the type of maltreatment experienced. Consequently, we observed clustering of maltreatment types, internalizing disorders and externalizing disorders. The externalizing cluster seemed to integrate problematic coping methods (e.g., eating disorders, substance abuse), which piqued our interest and warranted us to replicate our study at a larger scale. As part of the study's replication, we aimed to evaluate whether the same findings hold at a cross-national level. Furthermore, we aimed to expand our initial results, therefore more psychiatric comorbidities were examined. Structures were quite similar in the initial network structure as well as the communities that were formed. Thus, a self-harm and suicide indices cluster, childhood maltreatment and internalizing and externalizing clusters

were identified. In our cross-national network analyses, self-harm and suicide indices were similarly central in our network and emotional abuse was the best-connected childhood maltreatment subtype. In our directed acyclic graph, emotional abuse was deemed a plausible precursor to a multitude of comorbidities and an important construct in self-harm and suicide planning as well as attempts, thus creating a developmental cascade.

Our next study involved tackling another especially severe problem in BD - the misdiagnosis issue. Frequently, it takes at least 8 years till accurate diagnosis, although literature would see time till accurate BD diagnosis going as high as 15 years (Lublóy et al., 2020). Misdiagnosis leads to inaccurate treatment which can worsen symptoms and the overall course of the illness (Berk et al., 2025; Chen et al., 2024). An additional contributor to the diagnostic challenge is the presence of psychiatric comorbidities. Comorbidities can mask bipolar symptoms - such as substance abuse, which can lead to psychotic mania being diagnosed as a short psychotic episode due to substance abuse (Meyer & Meyer, 2009; Gonzalez-Pinto et al., 1998).

In an attempt to mitigate the misdiagnosis issue in the Romanian population, we conducted a **validation and adaptation study** for the Hypomanic Personality Scale 6-item version (HPS-6; Miller et al., 2011). The scale is a short, true or false measure, which can rapidly screen for the presence of BD. Screening measures prove most useful in hospital settings as managing multiple patients simultaneously can lead to overlooking symptoms (Chance et al., 2024; Kim et al., 2023). This issue is often observed in complex clinical situations, such as bipolar individuals presenting in a depressive episode, or manic patients appearing schizophrenic or psychotic, due to substance use. Hence, our fifth aim was to adapt and validate the HPS-6 in order for it to be freely used by mental health specialists in accurately identifying bipolar patients. The adapted scale had good internal consistency ($\propto$ = .71 - .75), but a moderate positive correlation for test-retest reliability in the first sample $r(169) = .43$, $p < .001$, 95% CI [.30, .55] and good reliability in the clinical sample $r(64) = .67$, $p<.001$, 95% CI (.51 - .78). Overall, these findings indicate that HPS-6 is a useful, brief evidence-based instrument that mental health specialists can rely on to identify individuals at risk of developing bipolar disorder.

4.1. Implications

Our thesis has **several strengths**, anchored in the fact that we've used novel, well-founded methods to test our objectives and enrich existing literature.

Our first meta-analytical study has succeeded to test Garcia Blanco et al.'s (2013) mood congruency theory for emotional attentional biases in bipolar disorder using a multilevel meta-analysis method. Regardless of the absence of significant results, from a methodological perspective, we utilized rigorous methodology to quantify the effect and investigate potential moderators. Neither moderators, nor subgrouping revealed noteworthy associations, but nonetheless guides upcoming research.

Our umbrella review of systematic reviews and meta-analyses condenses valuable information that informs professionals and draws attention to the vast amount and diversity of psychiatric comorbidity bipolar disorder individuals face. Similarly, it synthesizes pooled prevalences and runs a second-order meta-analysis to generate a single percentage across

meta-analyses on suicide attempts in bipolar disorder. Unfortunately, we were not able to investigate how age or gender affects onset of psychiatric comorbidity and its accumulation or other aspects of bipolar severity, but we believe it provides a synthesized outlet which can inform primary care providers of the significant additional psychiatric burden this population faces. Similarly, our umbrella review draws attention to the limitations of categorical classification of mental disorders and advocates for transdiagnostic approaches in clinical intervention.

Our two network analyses revealed similar structures of psychiatric comorbidities in bipolar disorder, although these are subject to change if different variables are included to construct the network. Internalizing and externalizing psychiatric diagnoses clustered together, similarly we had a self-harm and suicide cluster and a childhood maltreatment community. Self-harm and suicidality emerged as the most central nodes, bridging communities. Despite differences in overall connectivity of the high maltreatment and low maltreatment networks, the general structure remained similar. Our high maltreatment group was quite dissimilar in sample size to the low maltreatment group which might hinder our findings. Similarly, the overall sample was low in maltreatment. We would expect different structures in a larger high maltreatment sample if divided by quartiles instead of half points. Our two network analyses studies suggest that psychiatric comorbidities in bipolar disorder form a highly interconnected system, with self-harm and suicidal indices as well as internalizing symptoms emerging as central features. From a clinical aspect, this indicates that these features merit attention when intervening in bipolar disorder. Similarly, it points towards the severe misdiagnosis issue we discussed previously. Our sample (N = 3544) met criteria for M = 5.02 (2.43) comorbidities. These findings further emphasize the need for brief screening measures to detect bipolar disorder, as it's a population that is underdiagnosed due to the vast amount of symptoms they face and complex clinical presentations. From a theoretical standpoint, while childhood maltreatment did not have a strong direct effect towards specific comorbidities, these relationships are still subject to change in a severe maltreatment sample. Despite their distal role in both of our networks, it's possible in a transdiagnostic based network their role might be clarified more accurately. This is an effect already being studied by Huang et al. (2025) who observed differential effects by subtype of maltreatment using a transdiagnostic network approach for psychiatric comorbidities. Emotional abuse for example, was linked to depressive symptoms, while physical abuse to excitable symptoms (Huang et al. 2025). Methodologically, these findings support the utility of network analyses for examining complex and overlapping relationships between psychiatric comorbidities and childhood maltreatment. The method allows the identification of central as well as community-based features in a complex psychopathological system.

Finally, our scale validation study provided consistent preliminary evidence for the use of the HPS-6 scale in screening for hypomanic phenotypes in the general population. Internal consistency of the scale was acceptable ($\propto$ = .71-.75). Retest reliability was acceptable in our community sample, $r(169) = .43$, $p < .001$, 95% CI [.30, .55] and good in our clinical sample, $r(64) = .67$, $p<.001$, 95% CI (.51 - .78). The scale proved adequate construct validity for both convergent and divergent indices. Additionally, the Romanian HPS-6 succeeds in predicting affective lability and impulsivity, central constructs in bipolar disorder. Our adapted HPS-6 behaved well, but we urge future studies looking into the Romanian HPS-6 to conduct similar

procedures in other clinical samples. Unfortunately, we did not manage to reach enough clinical or risk subjects to conduct Receiver Operating Characteristic (ROC) (Pintea, 2009) to establish a threshold for the Romanian population.

Despite these limitations, methodologically, we utilized a rigorous method to recruit and formally interview participants using the SCID-5-CV. Although we did not manage to formally validate it in a clinical population, Miller et al. (2011) was reasonably successful in identifying individuals with a history of hypo/manic symptoms in his original study. In a clinical respect, this poses that the HPS-6 is a potentially valuable tool to rapidly screen for hypo/manic symptoms as well, especially since our scale correlated well with the MDQ instrument (Hirschfeld et al., 2000), $r = .56$, 95% CI [.43, .67], $p < .001$. Additionally, we offer the scale within this thesis to be freely used by researchers from all over Romania.

4.2. Limitations

Finally, we address the overall **limitations** of this research. In **the first study** we encountered a small number of participants in almost all of the studies included in our meta-analysis, an aspect which must be taken into consideration when interpreting the results of these primary studies. Furthermore, there is substantial heterogeneity in the assessment of attentional bias, with many primary studies failing to report the most appropriate indicator for measuring this construct. In the absence of such an indicator, the extent to which the obtained results truly reflect reality becomes questionable.

In our **second study**, we were not able to quantify the additional burden of bipolar disorder by psychiatric comorbidity, meaning earlier age of onset, episodes, suicidal indices per psychiatric comorbidity, due to insufficient and inconsistent reporting of data. Subsequently, we were unable to investigate potentially relevant moderators such as the age of onset, the specific subtype of bipolar disorder or the episode type.

In **study 3 and study 4** we encountered the limit of working with cross-sectional nature of data. It is well known that cross-sectional data are severely underpowered to support casual inferences (Baumeister et al., 2026). An additional limitation was the fact that maltreatment was low in both of our network analyses. As a result, we were not allowed to observe how the structure of psychiatric comorbidities modifies in contexts of severe childhood maltreatment experiences.

Finally, in **study 5** the bipolar sample was quite small-scale in our clinical sample. Despite the smaller clinical sample, our scale had good internal consistency and moderate to good reliability across the community and clinical samples. Additional limits are the small percentage of males across the two samples (approximately 20%). Due to a small bipolar and BD risk sample we were unable to run ROC analysis to establish a threshold of bipolar risk for the Romanian Population.

4.3. Future directions

It is our hope that this thesis aids future research. First of all, our meta-analysis on emotional attentional biases shouldn't discourage future researchers from studying this subject. It is possible without proper emotional induction that differences between those diagnosed or at risk for bipolar and the general population aren't significant, but their

responses when aroused by emotional stimuli differ (Kovacs et al., 2025). Similarly, we encourage research on emotional attentional biases to use appropriate methods to formulate bias, specifically the interference method which takes into account reaction times from neutral conditions as well, basically forming a baseline per participant.

Secondly, our umbrella review of systematic reviews and meta-analysis on the prevalence of psychiatric comorbidities in bipolar disorder provides mental health professionals and policy makers with heavy estimates on comorbidities which aren't usually considered in intervention (Ludmir et al., 2018). Our aim was to bring together prevalence estimates and inform future research on the importance of comorbidities in bipolar disorder, a factor which can cast a shadow on appropriate diagnosis. Although we were not able to see moderating effects and additional burden (e.g., earlier age of onset or hospitalizations), this umbrella review does not convey that these associations do not exist.

Regarding our third and fourth studies, we encourage the implementation of the following proposals, which naturally arise from addressing the limitations of our two network studies. First, we recommend replicating the findings from these studies in a population that is not composed exclusively of students. Such research would have an even greater impact if it examined disadvantaged groups, where rates of adverse early-life experiences are known to be higher (Maguire-Jack et al., 2017; Walsh et al., 2019). Similarly, we recommend replicating the findings in samples with a more balanced gender distribution, given the fact that men were underrepresented in studies.

For the fifth study, as future directions, we encourage future researchers to validate the HPS-6 in a purely bipolar and/or risk sample. Our scale behaved well during internal consistency and construct analysis, and adequate in retest reliability analysis. Therefore, it holds as a promising brief measure to screen for bipolar spectrum disorder risk. Even so, it is necessary to evaluate how well it behaves for individuals who meet criteria for the diagnosis or are at an objective high risk for developing the disorder (e.g., genetic risk). Additionally, it is of the utmost importance to evaluate the scale's sensitivity and specificity in detecting 'true' bipolar risk.

Similarly, we consider promising the investigation of childhood maltreatment and psychiatric comorbidities using a dynamic microsimulation approach based on existing literature. Longitudinal bipolar research on maltreatment and psychiatric comorbidities (jointly and separately) is scarce. Although there are studies linking maltreatment to a worsened course of bipolar disorder and a greater incidence of psychiatric comorbidities as well, longitudinal research incorporating both childhood maltreatment and psychiatric comorbidities are missing - at least to our knowledge. Longitudinal research is costly, both in capital as well as time itself. Similarly, it is high risk, high reward. It provides valuable causal data, but if the data doesn't spot significant associations between variables, it becomes unpublishable and for that reason unattractive to researchers, taking us back to the importance of publishing null findings. Thus, we seek to capitalize on the opportunity to offer a solution to this problem, in the hope that this will represent a natural continuation of the efforts undertaken in the present thesis. Consequently, we present below a brief theoretical foundation that may serve as the basis for an innovative line of research.

Agent-based modeling using simulations are a useful method to simulate relationships between variables apriori of real-life testing. The term "agent-based" is subject to debate

(Macal & North, 2009). Here we'll use the definition provided by Gao et al. (2024) to offer readers a basis of the concept. Agents are "*fundamental entities in an agent-based simulation. They represent individuals, entities, or elements in the system being modeled. Each agent has its own set of attributes, behaviors, and decision-making processes.*" (Gao et al., 2024; pp. 2).

Although inspired by agent-based modeling and its beneficial attributes in simulating variables which are difficult to study in vivo (e.g., even if large studies could pinpoint individuals at risk for bipolar disorder and study them from infancy to investigate the effect of maltreatment on psychiatric comorbidities, would the study be viable? Or would it be contaminated due to participants acknowledging they are in a study, therefore rendering maltreatment observation null), the method we consider viable for the nature of this research is dynamic microsimulation. This is due to the fact that we do not expect individuals to influence each other (Arnold et al., 2019). An illustrative example would be the case of agent-based modelling of a traffic jam. The behavior of a select few of agents in the model influences a greater number of agents and their behaviors (Bonabeau, 2002). In our case we do not expect agents to influence each other, but the model could be expanded to include socio-demographic and economic factors which further could extend to agent-based modelling.

Simulation itself is a computational tool which mimics real-word interactions and processes based on formulas, algorithms or computer-generated depictions (Gao et al., 2024; Gürcan et al., 2024). The method is useful for analyzing phenomena which can be difficult, impossible or unrealistic to investigate in real-life (Gao et al., 2024). Microsimulation generates micro-level data, based on aggregated and individual datasets, providing snapshots of data which can further on be analyzed as in conventional data-analysis (Arnold et al., 2019). Consequently, it can provide a basis in order to conduct dynamic microsimulations (in our case useful for generating individual level data as years go). Dynamic microsimulations simulate how distinct individuals behave over time (Arnold et al., 2019).

Dynamic microsimulations necessitate a clear-cut basis on which to work on. Models need to be specified clearly in order to micro-simulate data. In this sense, researchers need to determine "transition probabilities" and other events of interest. For example, in a dynamic microsimulation on how maltreatment influences the development of psychiatric comorbidities, one of the prespecifications would be the prevalences of each comorbidity in the sample (which could be based on our umbrella review in **Study 2** in order to fundament how often each psychiatric comorbidity should emerge. Similarly, these aspects need calibration, as the algorithms used in simulation usually inflate.

In social sciences, agent-based modeling is used to answer and embody theory-driven questions where data is difficult to collect (Arnold et al., 2019). For more details, see Arnold et al's. (2019) paper which explains in greater detail the difference and properties of agent-based modeling, microsimulating modeling and directed acyclic graphs-informed regression modelling. Krijkamp et al. (2018) provide a friendly and appreciable tutorial in R for microsimulation modeling regarding health decisions which helped build the foundation of our dynamic microsimulation model based on literature in this proposal for future research.

Similarly, parameters needed would be the distribution of the age of onset of bipolar disorder, the age of onset of each psychiatric disorder (preferably for bipolar individuals, but elsewise population indices can be used), the proportion of cases of psychiatry comorbidity

appearing before the onset of bipolar versus after the development of bipolar disorder, the prevalence of maltreatment (which can be left as an overall estimate or by type), maltreatment effects on both the acceleration and accumulation of comorbidities as well as effect on comorbidities. Additionally, estimates on suicide attempts, and additional burden (modeling of episodes and severity) could be modelled. Therefore, the proposed design could have considerable theoretical, methodological, and clinical implications in the field of bipolar disorder research. In particular, a dynamic microsimulation design could enable a highly efficient investigation of the ways (especially in terms of financial and time resources) in which childhood maltreatment experiences impact the developmental trajectory of individuals at risk or diagnosed with bipolar disorder, including in relation to the development of psychiatric comorbidities.

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