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RESEARCH

Role of medication adherence in the relationship between neuroticism and functioning in patients with bipolar disorder

Bipolar bozuklukta nevrotiklik ve işlevsellik arasındaki ilişkide ilaç uyumunun rolü

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Abstract

Purpose: This study examined the relationship between neuroticism, medication adherence, and functioning in Bipolar disorder (BD) patients. Furthermore, the role of medication adherence as a mediator between neuroticism and functioning was investigated.

Materials and Methods: The study included 71 patients with BD and 44 healthy controls. All participants were assessed using the Eysenck Personality Inventory (EPI), Brief Functional Assessment Scale (FAST), and Medication Adherence Rating Scale (MARS). Anxiety and depression levels were assessed using the Hamilton Anxiety (HAM-A) and Depression (HAM-D) Rating Scales.

Results: Patients with bipolar disorder showed higher neuroticism scores compared with healthy controls (mean 2.61 vs. 1.66) and poorer functioning (FAST: 13.70 vs. 7.74). Within the patient group, neuroticism was moderately associated with worse functioning ($r = .43$) and lower medication adherence ($r = –.28$). Medication adherence showed a strong association with better functioning ($r = –.50$). In the mediation analysis, higher neuroticism predicted lower adherence (standardized $\beta = –0.29$), and lower adherence predicted poorer functioning ($\beta = –0.35$), indicating a significant indirect pathway from neuroticism to functional impairment through medication adherence.

Conclusion: Neuroticism negatively affects the functioning of patients with BD through poor medication adherence. Thus, personality traits should be considered when planning treatments aimed at improving functioning in patients with BD. Interventions aimed at increasing medication adherence in patients with high levels of neuroticism may lead to better functioning-related outcomes.

Keywords:. Bipolar disorder, functionality, medication adherence, neuroticism, personality.

Öz

Amaç: Bu çalışmada, Bipolar bozukluk (BB) tanılı bireylerde nevrotiklik, ilaç uyumu ve işlevsellik arasındaki ilişkilerin incelenmesi amaçlanmıştır. Ek olarak, ilaç uyumunun nevrotiklik ile işlevsellik arasındaki ilişkide aracı rolü araştırılmıştır.

Gereç ve Yöntem: Bu çalışmaya 44 sağlıklı kontrol ile birlikte 71 BB hastası dahil edilmiştir. Katılımcılara Eysenck Kişilik Envanteri (EKE), Kısa İşlevsellik Değerlendirme Testi (KİDT) ve İlaç Uyum Derecelendirme Ölçeği (İUDÖ) uygulanmıştır. Anksiyete ve depresyon düzeyleri Hamilton Anksiyete (HAM-A) ve Depresyon (HAM-D) Derecelendirme Ölçekleri ile değerlendirilmiştir.

Bulgular: BB hastaları, sağlıklı kontrollere kıyasla daha yüksek nevrotiklik puanlarına (ort. 2.,61 vs. 1.,66) ve daha kötü işlevselliğe (KİDT: 13.,70 vs. 7.,74) sahipti. Hasta grubunda nevrotiklik, işlevsellik ile orta düzeyde pozitif (r=.,43) ve ilaç uyumu ile negatif yönde ilişkiliydi (r=–.,28). İlaç uyumu, daha iyi işlevsellik ile güçlü bir ilişki gösterdi (r=–.,50). Mediyasyon analizinde yüksek nevrotikliğin daha düşük ilaç uyumunu yordadığı (standart β=–0.,29) ve düşük uyumun daha kötü işlevsellik ile ilişkili olduğu (β=–0.,35) görüldü; bu bulgular, nevrotiklik ile işlevsellik arasındaki ilişkinin ilaç uyumu üzerinden dolaylı olarak gerçekleştiğini gösterdi.

Sonuç: Nevrotiklik, BB'de işlevselliği olumsuz etkilemekte ve bu etki düşük ilaç uyumu aracılığıyla dolaylı olarak ortaya çıkmaktadır. Bulgularımız, BB'de işlevselliği artırmaya yönelik tedavi planlamasında kişilik özelliklerinin dikkate alınması gerektiğini göstermektedir. Yüksek nevrotiklik düzeyine sahip hastalarda ilaç uyumunu artırmaya yönelik müdahalelerin işlevsellikle ilgili sonuçları olumlu etkileyebilir.

Anahtar kelimeler: Bipolar bozukluk, ilaç uyumu, işlevsellik, kişilik, nevrotiklik.

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INTRODUCTION

Bipolar disorder (BD) is a serious public health issue worldwide and is among the leading causes of disability[1]. BD is characterized by chronic and cyclical mood swings that significantly impact the quality of life and functioning in individuals. Impairments in cognitive and social functioning can be observed even during remission periods[2,3]. Adherence to psychotropic medication is one of the cornerstones of BD management. According to the World Health Organization, this refers to the extent to which a person's behavior complies with the recommendations of healthcare providers[4]. Non-adherence to medication is a common problem that affects approximately 50% of patients with mental disorders[5]. Among patients with BD, this rate varies from 20% to 70%. Non-adherence can increase the risk of relapse and trigger hospitalization, thereby reducing the quality of life[4–7].

Personality traits are consistent patterns of thoughts, feelings, and behaviors that can influence the development and progression of mental health conditions[8]. Neuroticism is a trait that is defined in various personality models and is frequently observed in patients with BD[9–11]. High neuroticism has been linked to an increased susceptibility to negative emotions, difficulty in coping with stress, and a heightened risk of psychopathology[12,13]. Some studies have suggested a direct link between neuroticism and functioning[11,14]. High levels of neuroticism have also been associated with cognitive impairment in BD patients, particularly in verbal memory[3]. Furthermore, various studies have demonstrated that neuroticism can negatively impact medication adherence[15–17]. Specifically, high neuroticism has been associated with lower medication adherence when assessed via self-report[15,17,18]. Some studies suggest that this negative relationship may be mediated by factors such as beliefs about medication and low self-efficacy[17,19]. However, other studies suggest that personality traits are not related to medication adherence[15].

From a theoretical perspective, the relationship between neuroticism and functional outcomes in BD can be interpreted within the framework of stress vulnerability and self-regulation. Individuals with higher levels of neuroticism are more prone to emotional instability, maladaptive coping, cognitive biases and may exhibit increased sensitivity to side effects, greater health-related anxiety, and more negative beliefs about medications that can hinder consistent use of prescribed medications[11–15,19]. Poor adherence, in turn, is associated with increased symptom recurrence, reduced psychosocial functioning, and poorer long-term outcomes[4–7]. Therefore, these behavioral tendencies may provide a plausible pathway through which neuroticism may indirectly contribute to worse functional outcomes in BD.

Although previous studies have demonstrated that personality traits such as neuroticism are associated with medication adherence and functional outcomes in BD, the mechanisms linking these factors remain unclear. In particular, the potential mediating role of medication adherence in the relationship between neuroticism and functioning has not been systematically evaluated. The present study was designed to address this gap by examining whether medication adherence mediates the association between neuroticism and functional impairment in clinically stable patients with BD. Based on existing evidence, we hypothesized that higher levels of neuroticism would be associated with worse functioning, and that this relationship would be mediated by lower medication adherence. Elucidating this mediating mechanism could inform the development of more effective and personalized intervention strategies for BD treatment.

MATERIALS AND METHODS

Sample

The current study included 115 participants, including 71 patients diagnosed with BD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and 44 healthy controls. Euthymic BD patients were consecutively recruited from the psychiatry outpatient clinic. Euthymic periods were defined as Hamilton Depression Rating Scale (HAM-D) score < 7, Young Mania Rating Scale (YMRS) score < 7, and no mood episode or psychiatric hospitalization during the preceding six months according to medical records. Participants aged 18–60 years were included in the study. The exclusion criteria were a YMRS score of ≥ 7, HAM-D score of ≥ 7, and the presence of psychiatric comorbidities. Participants were enrolled between May and July 2025. Initially, 110 patients were enrolled; however, 25 patients were excluded

due to the presence of a psychiatric comorbidity and 14 due to a HAM-D score > 7, resulting in a final sample of 71 BD patients under remission.

The healthy control group consisted of volunteers recruited from among the hospital staff and the local community who did not have a history of psychiatric illnesses, as confirmed by a brief psychiatric interview conducted by a resident in psychiatry (MFS). Individuals with a family history of major psychiatric disorders or current use of psychotropic medication were excluded.

Procedure

The current study was conducted in accordance with the Declaration of Helsinki for research involving human participants and was approved by the Necmettin Erbakan University Ethics Committee for Non-Drug and Non-Medical Device Research (IRB date and number: 07.06.2024/5023).

All participants who met the inclusion criteria were administered the HAM-D, Hamilton Anxiety Rating Scale (HAM-A), Functional Assessment Short Test (FAST), and Eysenck Personality Inventory (EPI). Additionally, the YMRS and Medication Adherence Rating Scale (MARS) were applied to the patient group. Psychiatric evaluations were conducted in a room with adequate sound insulation. The clinician-rated scales (HAM-D, HAM-A, FAST, and YMRS) were administered directly by the psychiatrist conducting the study (HB). The self-report instruments were completed by the participants under the supervision of the same psychiatrist to ensure comprehension and consistent data quality.

Electronic medical records from the hospital information system were used to verify diagnoses, illness history, and treatment regimens. The standardized clinical procedures routinely implemented in the psychiatry outpatient clinic ensure the reliability and reproducibility of the collected data. All clinical assessments and data collection procedures were conducted at the Department of Psychiatry, Faculty of Medicine, Necmettin Erbakan University, a tertiary academic medical center with standardized outpatient follow-up protocols for mood disorders.

Measures

Sociodemographic data form

The research team developed a personal information form to collect demographic data from the participants. The participants were asked about their age, sex, marital status, and level of education.

Eysenck Personality Inventory (EPI)

The EPI was created by Francis and colleagues as a revised shortened version of the Eysenck Personality Questionnaire[20,21]. The scale examines personality traits under three main factors: extraversion, neuroticism, and psychoticism, along with a lying factor. In this questionnaire, each personality dimension is assessed through six items, and participants respond to a total of 24 questions in a Yes (1) / No (0) format. The score for each trait ranges from 0 to 6. Although no clinical cut-off scores have been established for the subscales, they are suitable for use in comparative research. The internal consistency coefficients of the Turkish adaptation were reported as 0.78, 0.65, 0.42, and 0.64 for the respective subscales. Test–retest reliability values were 0.84, 0.82, 0.69, and 0.69, indicating satisfactory temporal stability. The Turkish validity and reliability study for this scale was conducted in 2007[22].

Functioning Assessment Short Test (FAST)

FAST was developed by Rosa et al. in 2007[23]. This scale is designed to assess functioning in patients with mental disorders. FAST is a four-point Likert-type scale and comprises 24 items. The FAST can be completed based on a clinical interview with the patient, direct observations made during the assessment, and information obtained from family members when available. Each item is rated on a 0 to 3 scale, where 0 indicates no difficulty and 3 indicates severe impairment. The total score is calculated by summing the ratings across all items, with higher scores reflecting worse functioning. No clinical cut-off scores have been established for the scale; however, it is recommended for use in comparative and research settings. Administration requires familiarity with psychopathology. The Cronbach's alpha value in the internal consistency analysis was 0.96[24]. The Turkish validity and reliability study was conducted by Aydemir and Uykur in 2012.

Medication Adherence Rating Scale (MARS)

MARS was developed by Thompson and colleagues to assess treatment adherence behaviors and attitudes of patients[25]. It comprises 10 questions that can be answered with a 'yes' or 'no' response and has a possible score ranging from 0 to 10. Higher scores

indicate higher medication adherence. A Turkish study focusing on the validity and reliability of the scale reported that a score between 0 and 7 indicates poor adherence, while a score between 8 and 10 indicates good adherence[26]. The Cronbach's alpha coefficient for the Turkish version of the scale was 0.92[26].

Hamilton Anxiety Rating Scale (HAM-A)

HAM-A was developed by Hamilton in 1959 and is designed to measure anxiety levels and symptom distribution in patients[27]. It consists of 14 items and enquires about both psychological and physical symptoms. Each item is scored on a 0–4 scale, yielding a total score ranging from 0 to 56. As no clinical cut-off score has been established, the scale is suitable for use in comparative research. The inter-rater reliability coefficient has been reported as 0.94, indicating excellent agreement between evaluators. It is not a self-report scale and should only be administered by a qualified healthcare professional. The Turkish validity and reliability study was conducted by Yazıcı et al. in 1998[28].

Hamilton Depression Rating Scale (HAM-D)

HAM-D was developed by Hamilton and aims to assess the severity of depressive symptoms[29]. It is not a self-report scale and should be administered by a qualified healthcare professional. The scale consists of 17 items; each item assesses the presence and severity of depressive symptoms related to mood, appetite, sleep, guilt, sexual desire, and anhedonia. The items are rated on Likert-type scales ranging from 0–4 or 0–2, depending on the specific symptom assessed. The total score ranges from 0–52 where higher scores indicate more severe depressive symptoms. The Turkish validity and reliability study was conducted by Akdemir and colleagues[30].

Young Mania Rating Scale (YMRS)

The YMRS was developed by Young and colleagues[31]. The scale measures the severity of manic symptoms experienced over the last week. It consists of 11 items, seven of which use a five-point Likert scale, and the remaining four use a nine-point Likert scale. The scale includes items scored on 0–4 and 0–8 ranges, with higher scores indicating greater severity of manic symptoms. In assessing mania, the clinician's direct observations of the patient's behavior during the interview are essential. Additional information from collateral sources such as family members or the treatment team is also incorporated into the evaluation when available. The validity and reliability of the Turkish version have been reported, with an internal consistency coefficient of 0.79[32].

Statistical analysis

All statistical analyses were carried out using IBM SPSS (version 23) and Jamovi (version 2.6.44) software. Descriptive statistics are presented as mean ± standard deviation (median where appropriate) for continuous variables and as percentages for categorical variables. Normality of continuous variables was assessed using the Shapiro–Wilk test together with histograms and Q–Q plots. Based on the normality test results, independent samples t-test or Mann-Whitney U test were applied to compare the sociodemographic and clinical variables between BD patients and healthy controls. The chi-square test was used to compare the categorical variables. For between-group comparisons, effect sizes were reported as follows: Cohen's d for normally distributed variables analyzed with independent-samples t-tests (age only), rank-biserial correlation (rbc) for Mann–Whitney U tests, and Cramér's V for chi-square tests. Spearman's correlation analyses were carried out to evaluate the relationship between personality traits, medication adherence and functioning.

The mediation model was used to examine whether the effect of neuroticism on functional impairment was transmitted indirectly through medication adherence. The mediation analysis was carried out using a general linear model in Jamovi. In the mediation model, neuroticism was defined as the independent variable, and functioning was defined as the dependent variable. MARS, HAM-A, and HAM-D scores were included in the model as potential mediators. Multicollinearity was evaluated using Variance Inflation Factors (VIF < 2.0 for all predictors). The mediation analysis reported standardized beta coefficients, confidence intervals, and p-values. A significance level of $p < 0.05$ was accepted for all statistical results. In addition, to improve the robustness of the mediation analysis, bootstrap resampling (5000 resamples) was conducted.

For the regression models within the mediation framework, R^2 values were reported, and 95% bootstrap confidence intervals (5000 resamples) were used for indirect effects. A power analysis was conducted using G-Power (version 3.1) to determine

the minimum sample size required for the study. Assuming an effect size of 0.5, an alpha error probability of 0.05, and power (1–β) of 0.80 for detecting medium-to-large effects, the required minimum total sample size was 102 participants. The final sample of 115 participants (71 patients with BD and 44 healthy controls) exceeded this requirement, confirming adequate statistical power for the analyses carried out.

RESULTS

Evaluation of the sociodemographic characteristics indicated that the level of education in the BD group was significantly lower than that of the healthy controls (p = 0.010). Additionally, the prevalence of smoking was significantly higher in the BD group than in the control group (p = 0.036). No significant differences were found in the other sociodemographic characteristics between the two groups (Table 1).

Patients with BD exhibited significantly higher neuroticism (p = 0.007) and FAST scores (p = 0.002) compared to the healthy controls. However, the BD group scored significantly higher on the EPI-Lie subscale (p < 0.001). Table 2 presents the comparative data on psychometric test outcomes. Effect sizes for group comparisons are provided as Cohen's d (age), rbc (Mann–Whitney U), and Cramér's V (chi-square), as appropriate in Table 1 and Table 2.

Table 1. Comparison of sociodemographic characteristics between patients with bipolar disorder and controls.

Variables (Mean ± SD)		**BD (n=71)**	**Controls (n=44)**	**Cohen's d / rbc / V**	**t / Z / X^2**	**p**
Age [a]		42.62 ± 13.44	37.39 ± 14.22	-0.38	-1.959	0.053
Gender	Female	36 (50.7%)	29 (65.9%)	0.149	1.974	0.125
	Male	35 (49.3%)	15 (34.1%)			
Place of residency	Urban	66 (93%)	37 (84.1%)	0.141	1.435	0.208
	Rural	5 (7%)	7 (15.9%)			
Smoking status	Yes	27 (38%)	8 (18.2%)	0.21	4.160	**0.036**
Year of education (median)		10.45 ± 4.46 (12)	12.48 ± 5.47 (12)	-0.28	-2.586	**0.010**
Marital status	Married	43 (60.6%)	28 (63.6%)	0.21	0.017	0.844
	Single	28 (39.4%)	16 (36.4%)			
Occupational status	Yes	28 (39.4%)	17 (38.6%)	0.08	0.000	1.000
Duration of marriage (median)		14.84 ±14.62 (12)	13.39 ±14.37 (10)	0.07	-0.679	0.497
Number of children (median)		1.75 ±1.65 (2)	1.66 ±1.73 (2)	0.03	-0.295	0.768

Bold values indicate p<0.05. Chi-square and Mann-Whitney U tests were used. [a] Independent Sample t-test was applied due to normally distributed data. BD: bipolar disorder; SD: standard deviation. Effect sizes were reported as follows: Cohen's d for normally distributed variables analyzed with independent-samples t-tests (age only), rank-biserial correlation (rbc) for Mann–Whitney U tests, and Cramér's V (V) for chi-square tests.

Table 2. Comparison of psychometric test scores between groups (Mean ± SD (median)).

	BD (n=71)	**Controls (n=44)**	**rbc**	**Z**	**p**
EPI-Neuroticism	2.61 ± 1.81 (2)	1.66 ± 1.20 (2)	0.30	-2.714	**0.007**
FAST	13.70 ± 12.26 (10)	7.74 ± 6.74 (6)	0.34	-3.054	**0.002**
MARS	7.68 ±1.80 (8)	-	-	-	**-**
HAM-A	5.11 ± 6.81 (2)	3.18 ± 3.51 (2)	0.13	-1.198	0.231
HAM-D	1.45 ± 1.58 (1)	1.45 ± 1.55 (1)	-0.01	-0.108	0.914
YMRS	0.32 ± 1.13 (0)	-	-	-	**-**
EPI-Extraversion	3.21 ± 1.93 (3)	2.98 ± 1.76 (3)	0.07	-0.710	0.478
EPI-Psychoticism	0.99 ± 0.93 (1)	1.32 ± 1.22 (1)	-0.13	-1.231	0.218
EPI-Lie Scale	5.15 ± 1.06 (5)	3.48 ± 1.71 (3.5)	0.58	-5.485	**<0.001**

Bold values indicate p<0.05 (Mann-Whitney U test). BD: Bipolar disorder; EPI: Eysenck Personality Inventory; FAST: Functioning Assessment Short Test; MARS: Medication Adherence Rating Scale; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale; YMRS: Young Mania Rating Scale; SD: standard deviation. Effect sizes were reported as rank-biserial correlation (rbc).

Evaluation of the psychometric test scores within the patient group indicated a positive and significant correlation between neuroticism levels and FAST as well as HAM-D scores ($p < 0.01$ for both). A negative and significant correlation was found between neuroticism and MARS scores ($p < 0.05$). MARS scores were negatively correlated with FAST scores ($p < .01$), indicating that higher medication adherence was associated with better overall functioning. MARS scores were also negatively correlated with HAM-A and HAM-D scores ($p < 0.05$ for both). Additionally, a positive and significant relationship was observed between age and MARS scores ($p < 0.01$). Table 3 presents detailed comparisons of psychometric test scores and sociodemographic data within the patient group.

Table 3. Correlations between sociodemographic features and psychometric test scores among the patients.

BD patients (n=71)	**Age**	**MARS**	**EPI-Neuroticism**	**FAST**	**HAM-A**	**HAM-D**	**EPI-Extraversion**	**EPI-Psychoticism**	**EPI-Lie Scale**
Age	1								
MARS	.31**	1							
EPI-Neuroticism	.05	-.28*	1						
FAST	-.16	-.50**	.43**	1					
HAM-A	-.18	-.24*	.23	.40**	1				
HAM-D	-.12	-.27*	.31**	.33**	.42**	1			
EPI-Extraversion	-.18	.14	-.18	-.21	-.04	-.16	1		
EPI-Psychoticism	-.25*	-.10	.10	-.13	-.15	-.16	.07	1	
EPI-Lie Scale	.34**	.25*	.03	-.22	.06	-.06	.02	-.02	1

*$p<0.05$, ** $p<0.01$, Spearman's correlation test was carried out. BD: Bipolar disorder, EPI: Eysenck Personality Inventory, FAST: Functioning Assessment Short Test, MARS: Medication Adherence Rating Scale, HAM-A: Hamilton Anxiety Rating Scale, HAM-D: Hamilton Depression Rating Scale.

A regression model predicting medication adherence from neuroticism explained 14% of the variance ($R^2 = 0.14$), whereas the model predicting functioning from both neuroticism and adherence explained 35% of the variance ($R^2 = 0.35$). A VIF < 2.0 for all predictors indicated the lack of any multicollinearity. The mediation analysis revealed that the effect of neuroticism on functionality was significant indirectly via the MARS ($p = 0.042$). Medication adherence showed a decrease as the neuroticism levels increased ($p = 0.011$), and this decrease in adherence was associated with impaired functioning ($p < 0.001$). Although the total effect of neuroticism on functioning was significant ($p = 0.001$), the direct effect did not reach statistical significance ($p = 0.052$).

No significant indirect effects were detected via HAM-A or HAM-D ($p = 0.187$ and $p = 0.449$, respectively). Since the patient group showed higher scores on the EPI-Lie (social desirability) subscale, the mediation model was re-estimated using the PROCESS macro (Model 4, version 4.2) in SPSS to examine whether the EPI_Lie subscale, which differed significantly between the patient and control groups, could influence the results. In this supplementary analysis, neuroticism predicted functionality through three parallel mediators—treatment adherence (MARS), anxiety (HAM-A), and depressive symptoms (HAM-D)—while EPI_Lie was included as a covariate. Consistent with the original model, the indirect effect of neuroticism on functionality through treatment adherence remained statistically significant (BootCI [.0686, 1.5513], $p < 0.05$), whereas the indirect effects through anxiety and depressive symptoms were not significant ($p > 0.05$ for both). The total effect of neuroticism on functionality was maintained ($B = 2.51$, $p = 0.001$), and the direct effect remained marginal ($B = 1.40$, p

= 0.058). Thus, the mediation pattern was robust to adjustment for social desirability. The data related to the mediation analysis are presented in Table 4 and Figure 1.

Table 4. Mediation analysis examining the indirect effect of medication adherence on the relationship between neuroticism and functional impairment.

Type	Effect	Estimate	SE	95% CI Lower	95% CI Upper	β	z	P
Indirect	EPI-Neuroticism ⇒ MARS ⇒ FAST	0.678	0.3336	0.0239	1.3315	0.1000	2.031	**0.042**
	EPI-Neuroticism ⇒ HAM-A ⇒ FAST	0.304	0.2305	-0.1477	0.7557	0.0448	1.319	0.187
	EPI-Neuroticism ⇒ HAM-D ⇒ FAST	0.146	0.1926	-0.2317	0.5234	0.0215	0.757	0.449
Component	EPI-Neuroticism ⇒ MARS	-0.289	0.1132	-0.5105	-0.0666	-0.2895	-2.548	**0.011**
	MARS ⇒ FAST	-2.348	0.6978	-3.7161	-0.9807	-0.3453	-3.365	**<0.001**
	EPI-Neuroticism ⇒ HAM-A	0.691	0.4389	-0.1695	1.5510	0.1836	1.574	0.116
	HAM-A ⇒ FAST	0.440	0.1820	0.0835	0.7968	0.2442	2.419	**0.016**
	EPI-Neuroticism ⇒ HAM-D	0.225	0.0998	0.0298	0.4211	0.2589	2.259	**0.024**
	HAM-D ⇒ FAST	0.647	0.8050	-0.9309	2.2245	0.0831	0.804	0.422
Direct	EPI-Neuroticism ⇒ FAST	1.343	0.6926	-0.0140	2.7007	0.1981	1.940	0.052
Total	EPI-Neuroticism ⇒ FAST	2.471	0.7546	0.9918	3.9499	0.3644	3.274	**0.001**

Bold values indicate p<0.05. Mediation analysis was conducted using the Jamovi software. Confidence intervals were computed with the bootstrap corrected (5000 resamples) method. Betas are completely standardized effect sizes. EPI: Eysenck Personality Inventory; FAST: Functioning Assessment Short Test; MARS: Medication Adherence Rating Scale; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale; CI: Confidence Interval. $R^2 = 0.35$. When EPI_Lie scores were included as a covariate, no changes were observed in the significance levels of the statistical effects.

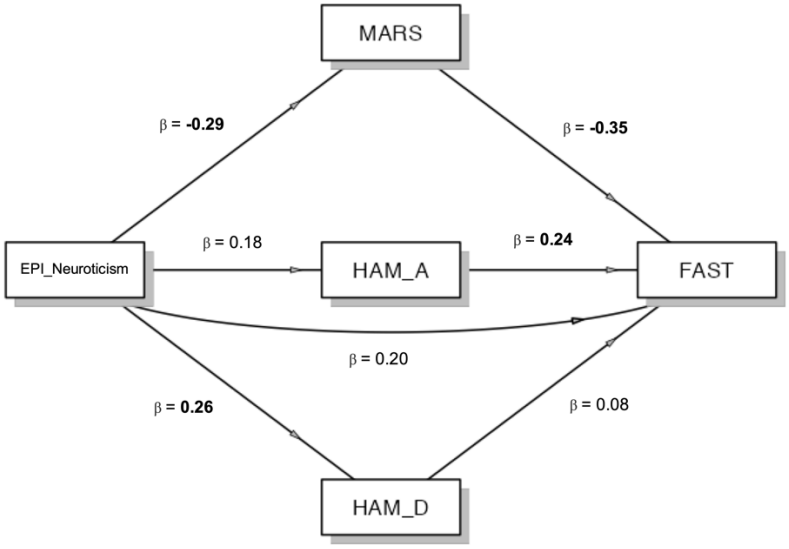


Figure 1. Path diagram.

Bold means statistically significant; EPI: Eysenck Personality Inventroy, FAST: Functionning Assessment Short Test, MARS: Medication Adherence Rating Scale, HAM-A: Hamilton Anxiety Rating Scale, HAM-D: Hamilton Depression Rating Scale.

DISCUSSION

The primary finding of the current study was that individuals with BD exhibited higher levels of neuroticism and significantly worse functioning compared to healthy controls. Among the BD patients, positive correlations were observed between neuroticism, functioning, and depression scores, and a negative correlation was identified between neuroticism and medication adherence. Furthermore, negative correlations were observed between medication adherence and functioning, anxiety, and depression. We report here that medication adherence mediated the relationship between neuroticism and functional impairment in BD patients. While this association reached statistical significance, its practical implications should be interpreted with caution, considering the modest effect sizes observed.

As per the study design, the control group was matched in age and sex with the patients. Consequently, there were no significant intergroup differences. No significant differences were identified in the marital status between the two groups in the current study, although the literature contains conflicting results. For instance, Aydın and colleagues reported no significant differences in age and sex between BD patients and healthy controls but found that a significantly higher proportion of individuals in the BD group were single, widowed, or divorced[11]. This suggests that demographic distributions may vary across different populations or when different matching strategies are used.

Our finding that individuals in the BD group had a lower level of education is consistent with the literature, suggesting that chronic mental illnesses are associated with cognitive and functional limitations that may affect educational achievement[2,3]. However, previous studies also emphasize that the effect on education may vary depending on the illness, age of the population, and cultural context[13]. We observed that smoking was significantly more prevalent in the BD group; this outcome is consistent with the high prevalence of nicotine dependence reported among individuals with mental disorders[3]. However, previous studies have not found a significant relationship between smoking and medication nonadherence[6]. BD patients can encounter notable difficulties, especially in occupational performance and job retention. Employment rates also tend to be lower for this demographic group[33]. The absence of a significant difference in employment status between the BD group and healthy controls in the current study may be related to the sample being an outpatient population that was euthymic and clinically stable.

We found significant positive correlations between neuroticism, impaired functioning, and depression symptoms. These results reinforce the established detrimental impact of neuroticism on mental health and functioning[12,34,35]. High levels of neuroticism have been associated with worse general cognitive functioning and impaired executive functioning[36,37]. Furthermore, neuroticism has been found to be negatively correlated with depression symptoms[12,34], and perceived general health status[16,38]. The presence of higher levels of neuroticism in patients with BD compared to healthy controls has been attributed to the disorder itself in some studies[35,39].

Neuroticism levels were significantly negatively correlated with medication adherence in the current study, indicating that adherence decreases as neuroticism levels increase, corroborating the findings of other studies[40]. This negative correlation suggests that individuals with high levels of neuroticism may experience greater anxiety about medication or perceive the side effects as more intense[16,19,34,41,42]. Furthermore, high neuroticism has been found to negatively impact medication adherence scores, as measured by self-reports[15,17,18]. A systematic review noted that neuroticism was one of the most frequently studied personality traits associated with medication non-adherence, with an increase in neuroticism being associated with a higher likelihood of non-adherence[40]. An epidemiological study of individuals with chronic illnesses also revealed a negative correlation between neuroticism and medication adherence[43,44]. Similarly, high neuroticism scores have been associated with low medication adherence in older populations[18,45] and patients with type 2 diabetes[17,42]. Neuroticism may negatively affect medication adherence by increasing the concerns of patients about the treatment[34,44] and causing them to perceive more intense side effects[16].

Medication adherence in patients with BD was significantly and negatively associated with functional, anxiety, and depression scores in the current study. This highlights the potential role of treatment adherence in clinical outcomes and overall functioning of the patients. High medication

adherence has been associated with better functioning and lower disability levels in patients with BD[7]. Conversely, medication non-adherence may lead to a worsening of symptoms, relapses, re-admissions, and a decline in the quality of life[4,5]. These relationships demonstrate that medication adherence is a fundamental factor for both symptom control and overall quality of life and social functioning of the patients. We also found that individuals with BD had significantly higher levels of neuroticism and functional impairment than the healthy controls. This is consistent with the existing literature, indicating that neuroticism is a prominent feature of BD and has negative effects on functioning[3,9–11].

The main finding of the current study was a significant indirect effect of neuroticism on impaired functioning in patients with BD through medication adherence, as suggested by mediation analysis. Emotional sensitivity and negative emotional tendencies in individuals with high neuroticism may negatively affect overall functioning by reducing medication adherence. A previous study carried out on individuals with chronic illnesses also found that neuroticism was negatively associated with medication adherence[43]. Thus, although studies have shown that neuroticism affects medication adherence, information on whether this mediates impairment in functioning is limited. The difficulties caused by neuroticism may negatively impact disease control and an individual's performance in daily life by affecting treatment adherence. We also found that the total effect of neuroticism on functioning was statistically significant. Furthermore, the mediation analysis revealed that anxiety or depression symptoms did not play a significant role in the relationship between neuroticism and functioning. A recent study indicated that neuroticism could indirectly affect suicide risk in BD patients through depressive symptoms alone[46]. Thus, clinical symptoms such as depression may mediate the relationship between neuroticism and other clinical outcomes (e.g., suicide).

The findings of the current study support the idea that medication adherence is an independent factor in this relationship, as depression and anxiety symptoms did not play a significant mediating role. In other words, medication adherence appears to play a role independent of affective symptoms in the effect of neuroticism on functioning. Although statistically significant, the observed mediation effects accounted for only a moderate proportion of the variance. Thus, while psychological traits such as neuroticism may contribute to non-adherence to medication and reduced functioning, clinical interventions should consider broader biopsychosocial determinants. It is also important to acknowledge ongoing debates regarding the methodological validity of studies linking personality traits to medication adherence. Wouters and colleagues argued that much of the reported association between personality and adherence may stem from the use of self-report instruments rather than objective behavioral assessments[15]. These authors suggested that when adherence was measured through more objective indicators (e.g., pharmacy refill data or serum levels of drugs), the strength of the relationship between personality traits and adherence could diminish. This methodological concern highlights the need for future studies to employ multi-modal assessment strategies to clarify the true extent of these associations.

Previous studies generally support the idea that neuroticism affects areas such as medication beliefs/concerns, social support, self-efficacy, and depressive symptoms[14,17,34]. In fact, neuroticism may not directly impair functioning; rather, it can interact with other factors such as perceived illness control, social support, or insight into illness. These mediating or moderating influences were not directly measured in the current study but should be considered in future research. It is also noteworthy that the direct effect of neuroticism on functioning approached statistical significance ($p = 0.052$, when adjusted for EPI_Lie $p = 0.058$). Although this path was not significant under conventional thresholds, the result may indicate a weak direct association that could emerge more clearly in studies with larger samples. This trend also supports the possibility that neuroticism influences functioning both indirectly through adherence and, to a lesser extent, directly. To our knowledge, no study has shown that the effect of neuroticism on functioning in patients with BD occurs through medication adherence.

The BD patients scored higher on the EPI-Lie subscale compared to the controls, indicating greater social desirability/impression management in self-reports. Given that FAST and MARS are both self-report measures, this tendency could attenuate the observed associations by modestly underestimating the difficulties. To address this, we ran a targeted sensitivity analysis including EPI-Lie as a covariate in

both the mediator and outcome equations. Our analysis revealed that mediation via adherence persisted, suggesting that the central findings are robust to social desirability and likely represent conservative estimates. Because EPI-Lie is conceptually adjacent to personality traits, we interpret covariate-adjusted estimates as conservative and recommend routine consideration of social desirability in future studies.

The current study has some limitations. The cross-sectional design precluded any causal inferences about the identified relationships. The relatively modest sample size and the fact that data were collected from a single center may limit the generalizability of our findings. Furthermore, self-report scales carry the potential for misreporting and recall bias. In addition, other disorder-related factors such as illness duration, number and severity of episodes, side effects, comorbid personality disorders, and insight level were not examined in the current study. These factors may also influence both medication adherence and functional outcomes. Future studies should consider these clinical variables to better elucidate the relationship between personality traits and functional impairment in BD. Future research should also validate the findings of the current study by using larger samples, different populations, and longitudinal designs. Any self-report bias may be mitigated by using objective measures of medication adherence, such as electronic monitoring or pharmacy records.

In summary, the findings of the current study highlight the relevance of personality factors such as neuroticism in understanding functional outcomes in BD, while underscoring the importance of adherence-related mechanisms. Our findings may have significant implications in the treatment strategies for BD. It is critically important to consider personality traits when planning treatment for BD patients who also have high neuroticism. Personalized interventions aimed at improving medication adherence can be developed. such as addressing the beliefs of patients about medications, developing strategies for coping with side effects, and alleviating anxieties related to treatment. Furthermore, psychotherapeutic approaches that target coping with stress and difficulties in emotional regulation associated with neuroticism may indirectly improve medication adherence and overall functioning. Clinicians could utilize motivational interviewing techniques to explore ambivalence towards medication, or provide psychoeducation specifically focused on common concerns regarding side-effects in patients with high neuroticism, framing adherence not just as a clinical necessity but as a tool for improving daily life and personal goals. Future longitudinal and cross-cultural studies incorporating both clinical and psychosocial variables will be essential to clarify causal pathways and enhance the generalizability of our findings.

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