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Exploring praxia deficits in bipolar disorder: A cross-sectional analysis of functionality and quality of life

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Ethics Committee Approval
The study was approved by the Ethics Committee of Istanbul Bilgi University, Turkey (protocol code 2023-40162-033 and date of approval February 21, 2023).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Patients with bipolar disorder often experience praxia deficits, which might impede their functionality and quality of life. This study sought to delve into praxis defects in these patients, contrasting their praxia performance with healthy controls and illuminating the interrelation between praxia performance, functionality, and quality of life.

Methods: In this cross-sectional study conducted from February to July 2023, we enrolled 203 patients diagnosed with bipolar disorder 1. Participants were recruited from the Ibni Sina and Sifa Community Mental Health Centers, both of which are affiliated with the Istanbul Tuzla State Hospital. Additionally, 201 healthy controls (HC) were recruited, primarily from the friends and relatives of the hospital staff. Patients diagnosed with bipolar disorder 1, between 18 and 65 years of age, were included based on their diagnosis as determined by the Structured Clinical Interview for DSM-5 Clinical Version (SCID-5-CV). Their right-handedness was ascertained via the Edinburgh Handedness Inventory. To minimize the confounding effects of acute mood episodes on praxia deficits, patients were required to score below 5 on the Young Mania Rating Scale (YMRS) and 7 or lower on the 17-item Hamilton Depression Rating Scale (HDRS). This criterion ensured the exclusion of individuals experiencing an active mood episode. Additionally, participants needed to have been in remission for at least six months. Healthy controls, aged 18-65 and confirmed as right-handed, were included, provided they had no personal or familial history of psychiatric conditions. A detailed interview using SCID-5-CV confirmed that the healthy controls had no history or suspicion of bipolar disorder (BD) or any other psychiatric disorder and no relatives with a psychiatric disorder. All participants (203 bipolar disorder patients and 201 healthy controls) underwent evaluations using the Test for Upper Limb Apraxia (TULIA), while the bipolar cohort received the Global Functioning Assessment-Functioning (GAF-F) and the World Health Organization Quality of Life-Brief Version (WHOQOL-BREF). Statistical analyses were conducted using SPSS 22.0.

Results: We identified a critical TULIA score threshold of 217, which differentiates bipolar patients from healthy individuals with a sensitivity of 79.3% and a specificity of 77.1% (area under the curve (AUC) 0.799, $P<0.001$). TULIA scores in bipolar patients were significantly positively correlated with functionality (GAF-F; r=0.502, $P<0.001$) and quality of life-general health (WHOQOL; r=0.389, $P<0.001$). TULIA pantomime subscores (OR=0.92, 95% CI 0.86-0.99, $P=0.022$) and CPZ use of more than 250mg per day (OR=2.24, 95% CI 1.19-4.21, $P=0.012$) were independent predictors of impairment in functioning in bipolar patients.

Conclusion: Praxia deficits in bipolar disorder patients may be intricately tied to specific clinical features that influence both their functionality and life quality. Comprehensive praxia deficit assessments can pave the way for devising tailored interventions, enhancing praxia and, by extension, the quality of life of bipolar patients.

Keywords: apraxia, bipolar disorder, functioning, occupational therapy, quality of life

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Introduction

Bipolar disorder (BD) is a chronic condition characterized by cycles of mania, hypomania, and depression, profoundly impacting patients' quality of life, cognition, and socio-occupational functioning [1]. Despite interventions, following the first manic episode, only about one-third of BD patients regain functionality within a year. A significant proportion (30-60%) find it challenging to return to their former socio-occupational status, underscoring the early onset of functional impairment in BD [2]. Effective management of depressive episodes is pivotal in maintaining functionality and preventing the worsening of manic episodes [3-6]. Contemporary therapeutic approaches emphasize not only symptom alleviation but also the restoration of normal functionality to help BD patients lead a meaningful life [4]. Enhanced well-being is linked with a decreased risk of relapse, pushing researchers and clinicians to value functional recovery alongside clinical remission [5].

Praxia refers to the ability to execute or carry out learned purposeful movements. Despite having the desire and physical ability to perform the movements, this is not always possible for BD patients. It is a neurological condition, distinct from muscle weakness, paralysis, or motor coordination issues. In the realm of psychiatry, the study of praxia and its associated deficits has garnered significant interest, especially given its emerging relevance in disorders like schizophrenia. Nearly half of schizophrenia patients display praxia deficits, affecting upper limb movement patterns such as timing, sequence, and spatial configuration [7-9]. Praxia deficits in these patients have been linked to decreased functionality [10]. While motor deficits in schizophrenia are often attributed to treatments, untreated schizophrenia patients also display signs of parkinsonism and minor neurological symptoms. Notably, reduced motor skills have been detected in those at high risk for psychosis or with a family history of schizophrenia [11].

As we delve deeper into the realms of praxia performance, it is vital to dissect the intricate functionalities governed by praxis into more precise categories: namely, imitation and pantomime performances, each further subdivided into non-symbolic, intransitive, and transitive actions. Imitation involves the replication of observed actions, a skill that is indispensable in learning and executing routine tasks efficiently. Pantomime, on the other hand, entails the symbolic representation of actions without the involvement of objects, a facet pivotal in non-verbal communication and the smooth navigation of social contexts. Breaking it down further, non-symbolic actions are characterized by gestures devoid of a direct reference. Intransitive actions involve movements not directed toward an object but they bear a specific meaning, while transitive actions involve interactions with objects to convey meaning. These distinct yet intertwined realms of praxis performance embed themselves in everyday functionalities, governing a range of actions from basic self-care routines to complex occupational tasks. A deficit in any of these subcategories could potentially disrupt the fluidity of daily activities, rendering seemingly straightforward tasks cumbersome and impeding effective communication. Therefore, a nuanced understanding of praxia performance is not merely academic; it bears substantial implications for daily functioning and thereby the quality of life for individuals with bipolar disorder, delineating avenues for targeted therapeutic interventions that can foster enhanced daily living and well-being [7-9].

Given the shared spectrum of BD and schizophrenia in the DSM-5, coupled with their significant overlaps, it becomes imperative to explore praxia deficits noted in schizophrenia within the BD demographic. Although in-depth studies specifically focusing on praxia performance in BD are limited [12], there is a growing body of research that suggests areas of proximate concern. Notably, potential disturbances in frontal-executive functions have been observed during hypomanic phases, and there are indications of slight cognitive impairments during euthymic periods in BD patients. While these findings do not directly imply praxia deficits, they inhabit a closely related research domain, hinting at overlapping neuropsychological facets. It is also worth noting that medications, particularly antipsychotics and mood stabilizers, might influence these observations, given that some are known to induce motor side effects [13].

Consequently, this study embarks on a cross-sectional investigation of praxia deficits in BD patients, contrasting their outcomes with healthy controls. Furthermore, it delves into the relationship between praxia deficits, functionality, and quality of life. We hypothesize a discernible decline in praxis performance in BD patients relative to controls and posit that this deterioration correlates with diminished functionality and life quality in the BD cohort.

Materials and methods

Study design and participants

In this cross-sectional study, we enrolled 203 patients diagnosed with bipolar disorder 1 from the Ibni Sina and Sifa Community Mental Health Centers, affiliated with the Istanbul Tuzla State Hospital. Additionally, 201 healthy controls (HC) were recruited, primarily from friends and relatives of the hospital staff.

Patients diagnosed with bipolar disorder 1, aged between 18-65, were included based on their diagnosis as determined by the Structured Clinical Interview for DSM-5 Clinical Version (SCID-5-CV). Their right-handedness was ascertained via the Edinburgh Handedness Inventory. To minimize the confounding effects of acute mood episodes on praxia deficits, patients were required to score below 5 on the Young Mania Rating Scale (YMRS) and 7 or lower on the 17-item Hamilton Depression Rating Scale (HDRS). This criterion ensured the exclusion of individuals experiencing an active mood episode. Additionally, participants needed to have been in remission for at least six months. Healthy controls, aged 18-65 and confirmed as right-handed, were included, provided they had no personal or familial history of psychiatric conditions. A detailed interview using SCID-5-CV confirmed that the healthy controls had no history or suspicion of BD or any other psychiatric disorder and no relatives with a psychiatric disorder.

The exclusion criteria for all participants included illiteracy, pregnancy, lactation, substance abuse, specific

neurological conditions, recent head trauma, motor abnormalities, recent electroconvulsive treatments, certain organic mental disorders, and the inability to provide informed consent. Additionally, any patient with coexisting psychiatric disorders was excluded from the study.

Data collection

Over the span from February to July 2023, every patient who sought care at the Community Mental Health Centers was evaluated as a potential participant for the study, ensuring an unbiased, consecutive sampling approach to mitigate selection bias. Patients were initially approached based on their diagnoses of bipolar disorder 1, as ascertained by the SCID-5-CV. The application of strict inclusion and exclusion criteria, which were meticulously established to minimize confounding variables, were utilized to refine our participant pool. This strategy also aimed to maintain the integrity of our findings by limiting inclusion. Furthermore, our healthy controls, largely recruited from acquaintances of the hospital staff, underwent a detailed interview utilizing the SCID-5-CV to ensure no history or familial linkage to psychiatric disorders, thereby establishing a robust comparative baseline. To shield against measurement bias, evaluators, blinded to participant group assignments, underwent standardized training to ensure uniformity in data collection procedures.

During the recruitment of patients with bipolar disorder, 37 individuals were precluded due to various reasons such as illiteracy, pregnancy, lactation, and substance abuse. Subsequently, 31 individuals faced exclusion due to the existence of specific neurological conditions, recent incidents of head trauma, or discernible motor abnormalities. A further scrutiny led to the exclusion of six individuals due to their recent history of undergoing electroconvulsive treatments or having certain identifiable organic mental disorders. In the final tier of exclusion, 23 individuals were eliminated due to their inability to provide informed consent or due to the presence of coexisting psychiatric disorders. Furthermore, 29 patients were unable to complete the procedure and were thus omitted from the study. Consequently, the final analytical phase was conducted with a robust sample of 203 patients, substantiating the strength and precision of the results derived from our exploration.

In recruiting HCs, our rigorous screening and selection strategy was sequentially implemented to uphold the validity of our findings. Twenty-two individuals were immediately excluded due to various factors including illiteracy, pregnancy, lactation, and a history of substance abuse. Subsequently, an additional 14 candidates were excluded, attributed to the identification of distinct neurological conditions, recent head trauma incidents, or apparent motor abnormalities. In the third and final stage of our exclusion strategy, eight participants were disqualified due to not providing informed consent or a diagnosis of coexisting psychiatric disorders. Additionally, 17 participants were unable to successfully conclude the procedure and were thus also excluded. Consequently, the final analysis was rigorously conducted with a substantiated and reliable sample of 201 HCs, ensuring that the subsequent findings were rooted in a meticulously curated dataset.

After data collection, retrospective power analyses were performed to validate the robustness and reliability of our findings. With an observed standard effect size varying between 0.71 and 0.95 across different outcomes, a sample size of 200 participants per group facilitated a robust study power, anchoring at an approximate 99% with an allowable 5% margin of error. This post-hoc validation serves to confirm that our study was adequately powered to detect significant effects and differences, bolstering the reliability and validity of the results obtained, despite the post-hoc nature of the power analysis.

Measures

Sociodemographic and Clinical Information: A structured questionnaire was designed to gather participants' sociodemographic data, clinical information, and medication history. Information, such as age, gender, education level, occupation, duration of illness, and medication type and dose were recorded.

Edinburgh Handedness Inventory: This was used to assess hand preference in daily activities to determine dominant hand usage [8].

Test for Upper Limb Apraxia (TULIA): Proven sensitive to detect upper extremity movement disorders in schizophrenia, TULIA offers a comprehensive motion performance evaluation in imitation and pantomime areas, each with three subcategories focusing on intransitive (actions without objects), transitive (actions involving objects), and meaningless movements. The imitation and pantomime tests aim to assess patients' ability to reproduce observed actions and express particular actions without the aid of verbal instruction, respectively. Performance in these areas can be critical markers of an individual’s daily functioning capacity, reflecting their ability to understand and carry out essential tasks that influence their quality of life. The tests evaluate individuals on a scale ranging from 0 to 5 based on content and temporospatial errors, where higher scores signify superior performance and, by extension, fewer praxia deficits. TULIA scores vary between 0 to 240. Its Turkish standardization, validity, and reliability were completed in 2019 [14].

YMRS is an 11-item scale quantifying manic state severity and validated for Turkish audiences by Karadağ et al. [15]. HDRS is a 17-item scale gauging depression severity, validated for Turkish use by Akdemir et al. [16]. GAF-F evaluates general functionality on a 0-100 scale, with higher scores indicating better functionality [17]. WHOQOL-BREF is a condensed WHOQOL-100 version gauging quality of life, validated in Turkey by Eser et al [18].

Ethical considerations

The Ethics Committee of Istanbul Bilgi University (protocol code 2023-40162-033; approval date February 21, 2023) approved this study. It is performed in accordance with the Declaration of Helsinki. All patients provided written informed consent.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences for Windows (SPSS) version 22.0. The normal distribution of the variables was determined through the Kolmogorov-Smirnov test and Skewness-Kurtosis values. Descriptive statistics provided insights into demographic data. Depending on data distribution, the Student’s T-test or Mann-Whitney U-test was implemented for comparing independent

groups. Pearson and Spearman correlation tests ascertained correlations of normally and non-normally distributed data, respectively. To identify independent factors forecasting functionality in BD patients, univariate and multivariate logistic regression analyses were utilized. The receiver operating characteristic (ROC) analysis showcased the application of TULIA subscores in distinguishing BD patients from healthy controls. Statistical significance was deemed at *P*-level <0.05. Only patients with complete datasets were incorporated in the analysis, ensuring no missing data.

Results

Table 1 presents the demographic and clinical characteristics of the study participants, including patients diagnosed with bipolar disorder and healthy controls.

Table 1: Sociodemographic and clinical features

	Patients with Bipolar Disorder (n=203)	Healthy Controls (n=201)	*P*-value
Age, mean (SD)	39.1 (9.4)	40.3 (8.9)	0.14
Gender, n (%)			
Female	103 (51.7)	97 (48.3)	0.72
Male	98 (48.3)	104 (51.7)	
Marital status, n (%)			
Single / divorced/widowed	108(53.2)	105 (52.2)	0.35
Married	95(46.8)	96 (47.8)	
Smoking, n (%)			
Yes	120 (59.1)	103 (51.2)	0.11
No	83 (40.9)	98 (48.8)	
Education year, mean (SD)	9.2 (3.0)	8.7 (2.2)	0.06
Family History of Psychiatric Illness, n (%)			
Yes	63 (31)		
No/Unknown	140 (69)		
Duration of illness (years), mean (SD)	6.3 (3.3)		
	Med (min-max)		
Number of Hospitalizations	1.98 (0-5)		
Total Number of Episodes	4 (1-35)		
Number of Depressive Episodes	1 (0-15)		
Number of Manic Episodes	2 (1-20)		
Number of Episodes with mixed Features	0 (0-5)		

SD: Standard Deviation, Med (min-max): median (minimum-maximum)

Healthy controls had significantly higher TULIA scores, TULIA imitation and TULIA pandomime subscores compared to patients with bipolar disorder (*P*<0.001) (Table 2).

Table 2: Comparison of TULIA scores between patients with bipolar disorder and healthy controls

	Patients with Bipolar Disorder (n=203)	Healthy Controls (n=201)	*P*-value
TULIA	213.1 (10.8)	221.5 (6.7)	<0.001
TULIA Imitation	107.9 (4.9)	111.2 (4.4)	<0.001
TULIA Pandomime	105.2 (6.7)	110.3 (3.5)	<0.001

TULIA: Test for Upper Limb Apraxia, Values are given mean (SD)

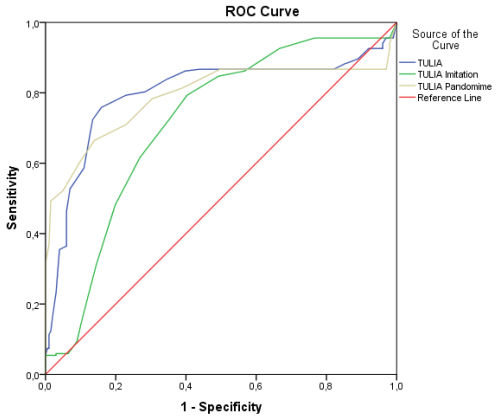
The ROC analysis revealed that using a TULIA score lower than 217 as a cut-off, differentiating patients with bipolar disorder from healthy controls resultedin a sensitivity of 79.3% and a specificity of 77.1% (area under the curve (AUC) 0.799, *P*<0.001). Using 109 as a cut-off value for the TULIA imitation subscore differentiated patients with bipolar disorder from healthy controls with a sensitivity of 71.9% and a specificity of 65.2% (area under the curve (AUC) 0.715, *P*<0.001). When 108 was the cut-off value for the TULIA pandomime subscore differentiating patients with bipolar disorder from healthy controls, a sensitivity of 70.9% and a specificity of 77.1% (area under the curve (AUC) 0.791, *P*<0.001) was revealed. (Table 3, Figure 1).

Table 3: Receiver operating characteristic (ROC) analysis of inflammation biomarkers for predicting patients with bipolar disorder vs. healthy control group distinction

	AUC	*P*-value	Lower Bound	Upper Bound	Cut-off point	Sens (%)	Spec (%)
TULIA	0.799	<0.001	0.752	0.847	217	79.3	77.1
TULIA Imitation	0.715	<0.001	0.664	0.766	109	71.9	65.2
TULIA Pandomime	0.791	<0.001	0.743	0.839	108	70.9	77.1

AUCArea under curve, Sens: sensitivity, Spec: Specificity, TULIA: Test for Upper Limb Apraxia

Figure 1: ROC curve analysis of TULIA, TULIA Imitation and TULIA Pandomime differentiating patients with bipolar disorder from healthy controls (cut-off scores were found 217, 109 and 108, and Area-Under-Curves 0.799, 0.715 and 0.791 respectively)



Following our initial comparison between sociodemographic data and TULIA scores of bipolar disorder patients and healthy controls, we delved deeper into the BD patient cohort. Our primary objective was to understand the interplay between disease-specific characteristics and praxia deficits. This more granular investigation aimed to shed light on how intrinsic factors of the disorder might influence praxia performance. With this focus in mind, we present our findings as follows:

In our study, we evaluated TULIA, GAF-F and WHOQOL-BREF Scale scores of patients with bipolar disorder. The mean TULIA score was found to be 213.12 (0.84), with the subscores of TULIA imitation being 107.90 (4.95) and TULIA pandomime being 105.22 (6.70). The mean GAF-F score was determined as 80.20 (8.25). The WHOQOL-BREF general health subscore was found to be 69.89 (14.16), and the median WHOQOL physical health subscore was 67.86 (ranging from 0 to 100). The median WHOQOL psychological subscore was 50.00 (ranging from 0 to 95.8); the median WHOQOL social relationships subscore was 50.00 (ranging from 0 to 100); and the median WHOQOL environment subscore was 59.38 (ranging from 0 to 100).

A correlation analysis was conducted to investigate the relationships between TULIA, GAF-F, and WHOQOL-BREF scores, as well as the severity of symptoms measured by YMRS and HDRS. These results are shown in Table 4.

Table 4: Correlation Analysis between TULIA, TULIA Imitation, TULIA Pandomime, GAF-F, YMDS, HDRS, WHOQOL-BREF scores and subscores

	TULIA	TULIA Imitation	TULIA Pandomime	GAF
GAF-F[a]	0.502**	0.459**	0.473**	1.000
WHOQOL General Health[a]	0.389**	0.387**	0.344**	0.216**
WHOQOL Physical Health[b]	0.303**	0.239**	0.281**	0.090
WHOQOL Psychological[b]	0.320**	0.298**	0.283**	0.203**
WHOQOL Social Relationships[b]	0.172*	0.146*	0.239**	0.153*
WHOQOL Environment[b]	0.048	0.44	0.093	0.169*
YMRS[b]	-0.107	-0.137	-0.064	-0.010
HDRS[b]	-0.164*	-0.138*	-0.185**	-0.156*

[a]Pearson, [b]Spearman's Correlation Analysis. *P<0,05, **P<0,01; GAF-F: Global Functioning Assessment-Functioning, HDRS: Hamilton Depression Rating Scale, TULIA: Test for Upper Limb Apraxia, WHOQOL-BREF: World Health Organization Quality of Life-Brief Version, YMRS: Young Mania Rating Scale

To ensure standardized comparisons among various antipsychotic dosages, we utilized the chlorpromazine equivalent method. This method equates the potency of different antipsychotics to that of chlorpromazine, a commonly used benchmark in psychopharmacology. Through this approach, we achieved a uniform reference point, facilitating a more coherent analysis of the potential impacts of different antipsychotic

dosages on praxia performance. A weak negative correlation was found between mean five-year chlorpromazine (CPZ) dosage and TULIA imitation, TULIA pandomime and TULIA scores (r=-0.175, *P*=0.012; r=-0.140, *P*=0.046; r=-0.172, *P*=0.014, respectively).

We aimed to investigate the potential impact of mood stabilizers, specifically lithium and valproate, on TULIA, TULIA imitation, and TULIA pandomime scores among bipolar disorder patients. We found no statistically significant difference in TULIA, TULIA imitation and TULIA pandomime scores among patients with bipolar disorder who were treated with valproate (n=81), lithium (n=78), a combination of valproate and lithium (n=21), or none of these (n=23) (*P*=0.099, *P*=0.394 and *P*=0.376, respectively.)

For the purposes of this study, patients were categorized based on their usage of specific long-acting antipsychotics (LAIAs). The LAIAs considered in the study were aripiprazole, risperidone and paliperidone. Dosages for these antipsychotics varied. Our findings revealed that patients not on LAIAs (n=109) exhibited statistically significant lower TULIA (211.2 vs. 215.3), TULIA imitation (107.2 vs. 108.7), and TULIA pantomime (104.0 vs. 106.6) scores in comparison to those on LAIAs (n=94). The p-values associated with these differences were *P*=0.006, *P*=0.029, and *P*=0.005, respectively.

Among patients with bipolar disorder, TULIA scores were negatively correlated with the number of depressive episodes, number of total episodes, and number of hospitalizations (r=-0.245, *P*<0,001; r=-0.185, *P*=0.008; r=–0.292, *P*<0.001, respectively.), whereas TULIA imitation subscores were negatively correlated with number of depressive episodes, number of total episodes. and number of hospitalizations (r=-0.197, *P*=0.005; r=-0.146, *P*=0.037; r=-0.255, *P*<0.001, respectively), and TULIA pandomime subscores were negatively correlated with the number of depressive episodes, number of total episodes, and number of hospitalizations (r=-0.233, *P*=0.001 ;r=-0.167, *P*=0.017 ;r=-0.259, *P*<0.001, respectively). Regarding functionality, GAF-F scores were negatively correlated with number of depressive episodes and number of hospitalizations (r=-0.159, *P*=0.024; r=-0.207, *P*=0.003, respectively). TULIA score, TULIA imitation and TULIA pandomime subscores were negatively correlated with the duration of the illness (r=-0.180, *P*=0.010; r=-0.203, *P*=0.004 and r=-0.141, *P*=0.045, respectively).

Multiple logistic regression analysis was performed to evaluate the factors predicting impairment in functioning in bipolar patients. The dependent variable was impairment in functioning (GAF-F scores < 81), and the independent variables included age, WHOQOL total score, CPZ use, TULIA imitation, and TULIA pantomime subscores. It is important to note that while TULIA (total) was significant in the univariate analysis, only the TULIA pantomime and imitation subscores were considered for the multivariate analysis. This decision was made because TULIA (total) is a composite of both the pantomime and imitation subscores, and as such, it would not be expected to act independently when both of its constituent subscores were already included in the model. The analysis revealed that TULIA pantomime subscores (OR=0.92, 95% CI 0.86-0.99, *P*=0.022) and CPZ use of more than 250 mg per day (OR=2.24, 95% CI 1.19-4.21, *P*=0.012) were independent predictors of impairment in functioning in bipolar patients, after controlling for the effects of other variables. These results suggest that lower TULIA pantomime subscores and CPZ use more than 250 mg per day may increase the risk of impairment in functioning in bipolar patients (Table 5).

Table 5: Univariate and Multivariate Regression Analysis evaluating the factors predicting impairment in functioning (GAF-F score <81) in bipolar patients.

	OR	Lower	Upper	*P*-value
Univariate Regression Analysis				
Age	1.037	1.006	1.069	0.021
Education year	0.932	0.848	1.025	0.146
Duration of illness	1.044	0.960	1.136	0.316
Female vs. Male	0.899	0.518	1.561	0.705
Single vs. married	1.089	0.627	1.892	0.762
Smoking (yes vs no)	1.108	0.632	1.941	0.721
TULIA	0.911	0.875	0.949	<0.001
TULIA Imitation	0.831	0.761	0.908	<0.001
TULIA Pandomime	0.885	0.840	0.934	<0.001
WHOQOL-BREF Total	0.951	0.924	0.980	0.001
CPZ>250mg/day vs.<250mg/day	2.22	1.252	3.928	0.006
Number of depressive episodes <2 vs ≥2	0.973	0.561	1.689	0.923
Multivariate Regression Analysis				
Age	1.030	0.995	1.066	0.094
TULIA Imitation	0.898	0.804	1.004	0.058
TULIA Pandomime	0.922	0.860	0.988	0.022
WHOQOL-BREF Total	0.988	0.953	1.025	0.531
CPZ>250mg/day vs.<250mg/day	2.241	1.193	4.209	0.012

CPZ: Chlorpromazine equivalent dose, GAF-F: Global Functioning Assessment-Functioning, OR: Odds Ratio, TULIA: Test for Upper Limb Apraxia, YMRS: WHOQOL-BREF: World Health Organization Quality of Life Brief Version

Discussion

The current study investigated praxia performance in patients with bipolar disorder and healthy controls, as well as its relationship with clinical variables, functioning, and quality of life among patients with bipolar disorder. Furthermore, a TULIA score higher than 217 showed good sensitivity and specificity in distinguishing healthy controls from patients with bipolar disorder. Our results also showed a negative correlation between TULIA scores and mean five-year chlorpromazine (CPZ) equivalent dosage, as well as a significant effect of the number of depressive episodes on praxia performance in bipolar patients. Importantly, we found that praxia deficits were negatively associated with functionality and quality of life of bipolar patients. Overall, our findings suggest that investigating praxia deficits may provide valuable insights into its relationship with clinical variables and functioning.

Elucidating the complex relationships within bipolar disorder, this investigation navigates through the intersections of depressive symptoms, praxia deficits, and functional outcomes. The convergence between our findings and established research becomes evident, reinforcing the substantial influence depressive symptoms exert on functional trajectories within this disorder [19-20]. A nuanced understanding is observed in the interplay between praxia performance and the multifaceted domains of quality of life as evaluated through WHOQOL-BREF scores. The interdependence of praxia performance and overall well-being, while intuitively corroborated, incubates possibilities of bidirectional influences, warranting deeper exploration into their causal relationships. Moreover, the non-significant associations of manic symptoms instigate further inquiry into the potential differential impacts of various symptom typologies on functional and praxia outcomes within bipolar disorder. Overall, our findings provide important insights into the relationships between praxia deficits, functioning outcomes, and symptom severity in BD, highlighting the potential impact of depressive

symptoms and praxia deficits on functional and quality-of-life outcomes in this population.

This study illuminates a noteworthy interface between praxia deficits and various clinical attributes, including episode count and hospitalizations, in individuals navigating through the complexities of BP. The elicited connections with TULIA scores convey deeper implications concerning the trajectory and management of the disorder, particularly regarding the deteriorative nature of praxia skills amid its progression.

An intriguing perspective arises when considering the symbiotic relationship between praxia performance and overall functionality, as reflected by GAF-F scores, which kindles a dialogue about the comprehensive impact of mood episodes on patient functionality. The pivotal role of depressive episodes in this context, in particular, accentuates the necessity to strategically address its frequency and severity in treatment plans. Thus, these insights pave the way for future research trajectories, focused not merely on understanding these relationships but also on developing targeted interventions that conscientiously address both the motor and emotional aspects inherent in bipolar disorder management.

The nuanced relationship between motor performance, especially as quantified via TULIA pandomime scores, and functional impairment in bipolar patients, introduces a compelling facet to our understanding of disorder management. Notably, medication-related factors, particularly pertaining to CPZ dosage, warrant a distinct exploration concerning their implicit role in patient functioning. An in-depth exploration into gestural praxis's contributions toward functioning provides a framework for developing targeted interventions and facilitates a deeper exploration into how motor performance intricately intertwines with overall patient functionality and well-being.

The effects of mood stabilizers on subtle neurological symptoms, including praxia, have not been extensively investigated. Based on the current study, we found no statistically significant difference in TULIA scores among patients with bipolar disorder who were treated with valproate, lithium, a combination of valproate and lithium, or none of these. Although there is no study showing the effect of lithium on praxia performance, it has been reported that temporary apraxia has occurred in a few cases of lithium toxicity [21]. On the other hand, no studies in the literature report that valproate may cause praxia defects. The occurrence of dose-dependent tremors in approximately 25% of patients using valproate is well-known, but parkinsonism may develop with cognitive retardation in only a very few cases, and the manifestation improves when the drug is discontinued. A meta-analysis emphasized that treatment with mood stabilizers did not significantly impair verbal and visual memory, attention, executive function, processing speed, or psychomotor performance [22-23]. Overall, our findings suggest that treatment with mood stabilizers, including lithium and valproate, does not appear to have a significant impact on praxia deficits in patients with bipolar disorder. However, further research is needed to confirm these findings and explore potential differences in praxia performance among patients treated with different mood stabilizers.

Understanding the intersection between praxia performance and antipsychotic medications, especially those quantified through CPZ equivalent dosages, enriches the discussion regarding optimized pharmacological intervention in bipolar disorder. This relationship delineates a critical exploration into the dual-faceted impact of antipsychotics, wherein the modulation of motor symptoms, either as a potential therapeutic or side-effect profile, becomes paramount. The observed patterns within CPZ dosages and praxia performance align with some prior investigations [24], yet offer a contrast to others, revealing an intricate landscape where antipsychotic dosages and motor capabilities entwine [25]. This discrepancy underscores the imperative to delve deeper into understanding the subtleties surrounding medication management and its reverberations on motor function.

Similarly, the role of long-acting antipsychotics (LAIA) in shaping praxia performance in bipolar disorder patients provides an intriguing perspective, given their established efficacy in relapse prevention during maintenance treatment [26]. The potential dual benefits concerning relapse mitigation and potentially favorable impacts on motor side effects warrant a further, more granular exploration into delineating the optimal therapeutic strategies employing LAIA, as echoed by several studies [27,28]. Navigating through the multilayered impacts of various antipsychotic treatments on praxia performance underscores a vital aspect of tailored therapeutic strategies and propels the discourse toward a clearer understanding of pharmacological impacts in bipolar disorder management.

Given the discernible effect of praxia deficits on the daily functioning and overall life quality in bipolar disorder patients, the role of occupational therapy might emerge as a pivotal component in the holistic management approach. Occupational therapists, with their expertise in enhancing individuals' abilities to perform daily activities, may potentially ameliorate the disruptions caused by praxia deficits in BD patients. Tailored interventions can be devised to foster improvements in the imitation and pantomime domains of praxis, focusing on transitive, intransitive, and non-symbolic actions, respectively, to enhance daily functioning. For instance, guided exercises can be designed to facilitate smoother transitive actions involving objects, aiding patients in regaining competence in essential daily tasks, such as grooming, dressing, and cooking. Moreover, therapy sessions might focus on refining intransitive actions, thereby potentially enhancing non-verbal communication and easing social interactions. The nurturing of non-symbolic actions could further impart a sense of freedom and creativity, cultivating a ground for therapeutic expressions through art or dance. As patients witness improvement in their daily functioning, this could resonate positively with their self-esteem and life satisfaction, forging a pathway toward a more fulfilled life. However, it is essential to approach this with a nuanced understanding, incorporating individualized therapy plans that resonate with the unique needs and preferences of each individual, to truly harness the potential of occupational therapy in nurturing a richer quality of life in bipolar disorder patients [29-30].

Our study underscores the significance of praxia deficits as a pivotal marker of functional capabilities in individuals with bipolar disorder. This entails a compelling call for clinicians to incorporate assessments of praxia performance into their

diagnostic routines. It not only illuminates potential challenges faced by bipolar disorder patients in daily activities but also accentuates the influence of praxia deficits on their overall quality of life. Importantly, our data hint at a distinctive threshold: a TULIA score exceeding 217 might serve as a differentiator between healthy individuals and those with bipolar disorder. Such a differentiation metric could be instrumental in clinical settings, providing a more nuanced understanding of the patient's condition and guiding more tailored interventions. Introducing the TULIA as a routine screening instrument in clinical practices could efficiently pinpoint bipolar disorder patients facing praxia challenges, facilitating early interventions and tailored therapeutic strategies.

Limitations

This study was the one of the first to present real-life data, investigating the relationship among upper limb apraxia, quality of life, and functionality in patients with bipolar disorder. However, there are some limitations. The cross-sectional study design does not allow for comparison before medical treatment. The complex use of various medications and combinations may confound the possible effect of medication on praxia deficits. The use of self-reported measures may be subject to reporting bias and social desirability bias. Additionally, the study had a small sample size and the cross-sectional design limits the ability to draw causal conclusions. Longitudinal studies with larger clinical samples could provide more comprehensive findings.

Conclusions

This research elucidates a tangible intersection between praxia performance and bipolar disorder, unveiling a noteworthy disparity in comparison to healthy controls. A discernible TULIA score threshold surfaces as a potential demarcation line, offering a novel, albeit preliminary, tool for differentiating healthy individuals from those navigating the complexities of bipolar disorder. Inextricably intertwined with quality of life, praxia performance emerges not merely as a metric but a mirror reflecting various facets of the daily functioning and overall well-being of affected individuals. Upon deeper examination, the frequency of depressive episodes unfurls as a potential influencing factor on praxia performance, accentuating a need for further scrutiny in unraveling the multifaceted relationship between mood fluctuations and motor function. Notably, certain parameters, such as TULIA pandomime subscores and specific CPZ equivalent dosage thresholds, forge ahead as possible harbingers of functional impairment, thereby meriting consideration in future predictive models and clinical evaluations.The practical repercussions of these findings permeate various spheres of clinical management in bipolar disorder. The link between praxia, daily functionality, and quality of life underscores the necessity of embedding praxia assessment within the broader evaluative and interventional framework. However, the pathway from research to clinical application is nuanced and demands meticulous validation through further research, particularly in translating TULIA scores into applicable clinical thresholds and understanding the underlying mechanisms connecting depressive episodes to praxia performance.

As we contemplate these findings, numerous avenues for future research unfurl, brimming with potential to deepen and diversify our understanding of bipolar disorder and praxia performance. Investigations exploring the longitudinal impacts of varied antipsychotic medications, deciphering the underlying neurobiological correlates of praxia performance, and constructing refined predictive models encapsulating diverse clinical and demographic variables emerge as pivotal pursuits. Similarly, the horizon looks promising for delving deeper into targeted interventions, such as cognitive remediation therapy and occupational therapy, gauging their efficacy in enhancing praxia performance and, by extension, the functional well-being of bipolar disorder patients. Further explorations could chart the intersections between praxia performance and other facets of bipolar disorder, notably cognitive disruptions and the intricacies of emotional regulation. These holistic inquiries not only promise to validate and refine the preliminary understandings etched out by the present study but also forge pathways toward more holistic, personalized, and efficacious management paradigms. Thus, they harbor the potential to navigate toward more comprehensive, personalized, and efficacious management paradigms for individuals grappling with bipolar disorder, while spotlighting potential risk factors or predictive markers for the onset or exacerbation of the illness.

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