Acta Psychiatrica Scandinavica

WILEY

Acta Psychiatrica Scandinavica

ORIGINAL ARTICLE OPEN ACCESS

Influence of Sex and Diagnosis on Clinical Variables and Neurocognitive Performance in Severe Mental Illness. Results From the PsyCourse Study

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Received: 29 April 2025 | **Revised:** 21 July 2025 | **Accepted:** 5 August 2025

Funding: This work was supported by the Deutsche Forschungsgemeinschaft.

Keywords: bipolar disorder | neurocognition | psychosocial functioning | quality of life | schizophrenia | sex differences | somatic disease

ABSTRACT

Introduction: Bipolar disorder (BD) and schizophrenia (SZ) are serious mental illnesses (SMI) with overlapping symptoms but distinct differences in onset and course. Sex differences are an area of growing interest in SMI. This study aims to examine potential interactions between sex and diagnosis across a broad range of variables, to compare males and females within SZ and BD, and to investigate sex-specific group differences.

Methods: A total of 1516 individuals were included in a cross-sectional study using baseline data from the multicenter PsyCourse Study, including BD ($n = 543$), SZ ($n = 517$), and healthy controls (HC) ($n = 456$). Sociodemographic characteristics, clinical symptoms, psychosocial functioning, quality of life, neurocognitive performance, and somatic comorbidities were assessed. Generalized linear models were used to analyze differences between groups and sexes. False Discovery Rate (FDR) and Bonferroni post hoc comparisons were performed.

Results: Significant interactions were identified in age ($p = 0.001$), age at treatment ($p = 0.05$), illness duration ($p = 0.03$), illicit drug use ($p = 0.01$), and smoking ($p = 0.05$). Differences in substance use were observed across groups and sexes, with the highest rates found in males with SZ. The BD group showed better functioning and neurocognitive performance compared with the SZ group. Within the BD group, females reported better performance in verbal memory ($p = 0.003$) and psychomotor speed ($p < 0.001$) than males. Moreover, both females and males with SMI showed higher rates of thyroid alterations compared with HC ($p = 0.01$ for females and $p = 0.002$ for males).

Conclusions: Significant sex differences were observed in substance use and somatic comorbidities. Interactions between diagnosis and sex underscore the importance of considering both factors in clinical assessments. These findings highlight the need to tailor sex-specific treatment for each patient. Further research is needed to explore the role of sex hormones and other biological and societal factors in the presentation and course of these disorders.

Maria Serra-Navarro and Maria Heilbronner contributed equally to this article.

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For affiliations refer to page 16.

Summary

- Significant outcomes
  - Interactions between sex and diagnosis were found in age at treatment onset, illness duration, illicit drug use, and tobacco smoking.
  - Sex-sensitive treatment is crucial for better clinical outcomes, healthy habits, and comorbidity management, as our findings reveal.
  - Future research should explore the role of sex, gender, and hormones in disease presentation, course, and treatment response.
- Limitations
  - Data on females' reproductive life events and gender were not collected, which may significantly influence clinical and disease course in severe mental illness.
  - The present study should be considered exploratory. Medical comorbidity data were collected though self-reports, assuming a potential subjective bias. However, participants were asked whether a medical doctor had ever provided the diagnosis, which may help mitigate this concern.

1 | Introduction

Bipolar disorder (BD) and schizophrenia (SZ) are both serious mental illnesses (SMI) that share overlapping symptoms, such as psychotic features and cognitive impairments [1, 2]. Likewise, a remarkable genetic overlap between both disorders has been extensively described [3, 4]. However, they also differ significantly in their onset, course, and underlying neurobiological mechanisms [5, 6]. One emerging area of interest is the role of sex differences in the clinical presentation, neuropsychological, and psychosocial performance in both disorders.

Sex influences the course of SZ, especially in terms of age of onset and symptomatology. SZ is more prevalent in males under 40, while females show two distinct peaks of incidence, with an initial peak between 20 and 39 years and a secondary increase after 40 [7]. Men with SZ show more negative symptoms and more severe clinical features, whereas women exhibit more affective symptoms [8]. BD also shows sex differences: females are at higher risk of bipolar II and hypomania, while males are more prone to mania and substance abuse [9–11]. Findings of age of onset are mixed, with some studies reporting later onset in females, while others found no significant differences [10–13].

In neurocognition, sex differences have been studied in the general population and in SMI. In the general population, females performed better on verbal memory and social cognition tasks, while males performed better on spatial processing and motor speed [14]. In SMI, findings remain inconsistent. In SZ, several studies indicate that females exhibit superior cognitive abilities, particularly in language, executive function, and memory domains [15], with this advantage linked to differences in brain structure and function [16]. In contrast, males tend to experience greater cognitive impairment [17, 18] in verbal learning and memory, with these deficits already apparent at first-episode psychosis [19]. Nevertheless, some studies report poorer cognitive functioning in females [20–22] or find no significant sex differences [18, 23]. In BD, cognitive deficits are typically less severe than in SZ but affect various domains, including executive function, attention, and verbal memory [2, 24]. Males performed better than females in working memory tasks, whereas females outperformed males in verbal learning and memory recognition tasks [12, 25]. Cognitive deficits in both disorders are associated with poorer functional outcome [5] and reduced Quality of Life (QoL) [26]. Patients with SMI reported worse QoL compared to HC [26], with individuals with BD reporting a higher QoL than those with SZ [26]. In BD, females have better social relationships [26] but worse physical QoL [10, 27].

Cardiovascular risk factors, such as hypertension and diabetes, along with migraine and cancer, are more prevalent in individuals with SMI [28–34]. Sex differences in BD and SZ in somatic comorbidities are inconclusive. In the general population and in BD, males show a higher risk of hypertension while females have more thyroid alterations [10, 34]. Diabetes is reported to be more prevalent in females with SZ, though some studies found higher rates in males across both BD and SZ [31, 35] as in the general population [36]. Migraine is more common in females in the general population and specifically more frequent in individuals with BD [31, 37–40]. Finally, controversial results have been found regarding sex and cancer in individuals with SMI. In the general population, cancer incidence is higher in males than females [41], a pattern observed in BD but not consistently in SZ [42]. To the best of our knowledge, this is the first study to investigate sex differences between BD and SZ in a large patient sample.

1.1 | Aims

This study aims to: (a) examine potential sex-by-diagnosis interactions; (b) investigate sex-specific diagnostic differences in clinical variables and neurocognitive performance in individuals with BD and SZ compared to HC; and (c) explore sex differences within BD and SZ separately, comparing males and females across all assessed outcomes. This approach will offer a more comprehensive understanding of how sex influences the course and presentation of these psychiatric disorders, helping to identify distinct patterns that could guide sex-sensitive treatment strategies and enhance clinical outcomes.

2 | Material and Methods

2.1 | Sample

A total of 1516 participants were included in this cross-sectional study, with data obtained from the multicenter, longitudinal, naturalistic, transdiagnostic PsyCourse Study, conducted across 20 clinical sites in Germany and Austria (www.PsyCourse.de). We used data from the baseline assessment (Visit 1) and the Verbal Learning Memory Test (VLMT) [43] in the following visit (Visit 2). All data were extracted from the PsyCourse dataset Version 5.0 (https://data.ub.uni-muenchen.de/251/) [44]. The

design and other properties of the PsyCourse Study are well described elsewhere [45].

Inclusion criteria for patients were: (1) aged ≥18 years; (2) diagnosed with SZ (F20.x) and BD (F31.x), according to ICD-10 criteria (confirmed within the corresponding DSM-IV diagnostic framework); (3) proficiency in the German language. For the purposes of the present study, only patients with SZ and BD were included.

Controls were recruited at four clinical centers: UMG Göttingen, LMU Munich, Medical University of Graz, and from the MImicSS study. These were contacted, for example, via mail using address lists obtained from the local Residents' Registration Office, or through advertisements in public areas.

The inclusion criteria for controls were: (1) no history of affective or psychotic illness, assessed by a brief diagnostic interview for mental disorders [46]; specifically, control participants were excluded from the study if they had ever been treated as inpatients for one of the investigated ICD-10 diagnoses; (2) proficiency in German language. Control participants followed a protocol similar to that of clinical participants.

The study was approved by the responsible Ethics Committees at the individual recruitment centers and was carried out according to the Declaration of Helsinki. All participants provided written informed consent.

2.2 | Assessments

2.2.1 | Sociodemographic and Clinical Data

Sociodemographic data comprised age, sex, living arrangement, and employment. Clinical information included diagnosis, age at first outpatient treatment, disease duration, psychiatric family history, alcohol consumption, lifetime use of illicit drugs, current medication only in patient groups (number of antipsychotics, antidepressants, mood stabilizers, and tranquilizers), psychopathology, neurocognitive performance, and functioning. The *PsyCourse Codebook* [47] provides detailed information on phenotypic variables.

2.2.2 | Neurocognition

Standardized neuropsychological tests were performed by trained raters. Crystalized intelligence was assessed by the vocabulary intelligence test (MWT-B) [48]. Cognitive domains evaluated included executive function with the Trail Making Test (TMT Part B) [49], short-term and working memory with the Verbal Digit Span(VDS) [50] Maria Serra-Navarro and Maria Heilbronner contributed equally to this article. Monika Budde and Silvia Amoretti should be considered joint last authors? (forward and backward), psychomotor speed with the Digit Symbol Test (DST) [51] and TMT Part A, and verbal learning and memory with VLMT [43]. The TMT measures multiple cognitive domains, including visual attention (Parts A and B), psychomotor speed (Part A), and task switching (Part B).

2.2.3 | Psychopathology, Level of Functioning, and Quality of Life

Severity of SZ symptoms was evaluated with the Positive and Negative Syndrome Scale (PANSS), using positive, negative, general, and total scores [52]; severity of depressive symptoms, with the clinician-rated Inventory of Depressive Symptomatology (IDS-C_{30}) [53] and the self-rated Beck Depression Inventory II (BDI-II) [54]; severity of manic symptoms, with the Young Mania Rating Scale (YMRS) [55]; severity of illness, with the Clinical Global Impression Scale (CGI) [56]; level of functioning, with the Global Assessment of Functioning (GAF) [57], and QoL with the World Health Organization QoL Questionnaire, brief version (WHOQoL-BREF), using scores for the domains global QoL, physical health, psychological health, social relationships, and environment [58].

2.2.4 | Somatic Diseases

The presence of somatic comorbidities has been gathered through the clinical interview. Interviews were mainly conducted by research/clinical psychologists; participants were asked whether a physician had ever diagnosed any of the following conditions: hypertension, diabetes, hyperthyroidism, hypothyroidism, cancer, and migraine.

2.3 | Statistical Analysis

All neuropsychological variables were log-transformed to normalize their distribution. For socio-demographic characteristics, clinical features, somatic disease, QoL, and neurocognitive and functional performance, generalized linear models (GLM) were performed separately for males and females, using group as the main effect (SZ, BD, and HC). False Discovery Rate (FDR) for multiple testing corrections was performed. In case of significant differences, the Bonferroni post hoc testing strategy was performed. In a second step, variables were all compared through GLM with sex (males and females) and diagnosis (SZ and BD) as main factors, as well as the interaction between diagnosis and sex. FDR for multiple testing correction was applied to all models except for interaction analysis. Center was included as a covariate in all analyses. Effect sizes of the comparison were analyzed with Cohen's d. Additionally, age was included as a covariate in the duration of illness, age at first outpatient treatment, and in all neurocognitive variables analyzed. In all GLM, Estimated Marginal Means, or adjusted prevalence, and the 95% Interval of confidence (IC) were reported for each variable of interest. The Statistical Package for the Social Sciences (SPSS) version 30 and R 4.0.5 software were used to analyze data. All statistical tests were conducted two-tailed, with an alpha level of significance at $p < 0.05$.

3 | Results

The study sample consisted of $N = 1516$ participants. Of $n = 1060$ patients with a mean (range) age of 42.20 (18–78) years; 42.8% were female ($n = 454$), and of 456 HC with a mean (range) age

of 36.14 (18–77) years; 58.8% were female ($n = 268$). Nearly half of the individuals were diagnosed with a SZ-spectrum disorder (48.8%; $n = 517$), while the other half were diagnosed with BD (51.2%; $n = 543$).

3.1 | Interaction Diagnosis (BD and SZ) × Sex

Results regarding diagnosis by sex interactions and sex differences in the BD and SZ groups are presented in Table 1. There were several Diagnosis × Sex interactions in terms of age, age at first outpatient treatment, duration of illness, rates of illicit drug use, and cigarette smoking. Females with SZ were older than males at first outpatient treatment compared to females with BD. Moreover, those who were older at first outpatient treatment presented a longer duration of illness. Regarding both illicit drug and cigarette use, being female was a protective factor, and males with SZ exhibited the highest risk for substance use.

3.2 | Sex Differences in BD and SZ

Females with SZ were significantly older ($d' = 0.36$) than males with SZ. In terms of functioning and QoL, no sex differences were found. Regarding neurocognitive outcomes, sex differences were found in psychomotor speed ($d' = 0.29$) and verbal learning ($d' = 0.27$) and memory ($d' = 0.30$) in the BD group. In BD, females outperformed males in psychomotor speed and in verbal learning and memory. Concerning clinical features, no differences were found between males and females with SMI. Pharmacological treatment did not differ between sexes. As for substance use, sex differences were only observed in SZ. Males reported higher rates of lifetime tobacco use ($d' = 0.32$) and use of illicit drugs ($d' = 0.44$) than females. In relation to somatic disease, females in both groups (BD and SZ) reported higher rates of thyroid alterations ($d' = 0.35$ and $d' = 0.36$, respectively).

3.3 | Differences Between Groups Among Females and Males

This section presents group comparisons conducted separately within female (Table 2) and male (Table 3) subsamples of the HC, BD, and SZ groups.

3.3.1 | Sociodemographic Characteristics

Among females, those with SMI were significantly older, more likely to report a family history of psychiatric illness, less often lived alone, and more frequently had less paid employment compared with HC females. The BD female group reported higher rates of family history of psychiatric disorder than females with SZ. Conversely, BD males were significantly older than SZ and HC males. Compared to HC males, fewer males with SMI lived alone. The proportion of males with a family history of psychiatric illness was significantly different between the three groups, with a gradient from BD to SZ to HC. There was a lower rate of paid employment in male participants with SZ compared to those with BD. As expected, HC males demonstrated the highest rates of employment.

3.3.2 | Neurocognitive Functioning

Several differences were observed in neurocognitive performance. In both sexes, the HC group outperformed participants with SMI. Moreover, within both the male and female subgroups, the BD group outperformed the SZ group across the remaining neurocognitive variables analyzed (see Figure 1). However, among males, no differences in verbal memory or task switching were observed between the SZ and BD groups.

3.3.3 | Clinical Characteristics

The SZ group, in both sexes, was significantly younger at first outpatient treatment and showed greater clinical severity compared to the BD group assessed by PANSS and CGI. No significant differences were found between diagnoses in depressive symptoms and duration of the illness within males and females. Moreover, individuals with BD exhibited more manic symptoms compared to the SZ group in both subgroups. As expected, participants with SMI exhibited more clinical symptoms than HC.

Differences across groups were found in substance use. Females with SMI exhibited higher rates of lifetime tobacco use than HC females. Moreover, the rate of lifetime alcohol abuse was significantly higher in females with BD than in HC. While in males, the BD group showed significantly lower rates of lifetime illicit drug use than HC and SZ males. Besides, males with SMI presented higher rates of alcohol abuse than the HC group. No differences between the BD and SZ groups were found. With respect to lifetime tobacco use, males with SMI showed higher smoking rates compared to HC, and the SZ group exhibited the highest rate of consumption overall. In pharmacological treatment, as expected, the BD group uses the most antidepressants, mood stabilizers, and lithium. In contrast, the SZ group uses more antipsychotics and tranquilizers than the BD group. Regarding somatic comorbidities, females with SMI presented higher hypertension rates compared to HC females. The BD group, males and females, exhibited significantly higher rates of thyroid alterations compared to both SZ and HC groups.

3.3.4 | Functioning and QoL

In both sexes, post hoc analysis confirmed that the BD group exhibited superior functioning compared to the SZ group. The BD group demonstrated significantly higher environmental QoL than the SZ group within the male and female subgroups. As expected, HC participants in both subgroups exhibited the highest levels of functioning and QoL.

4 | Discussion

Our study identified several significant patterns and sex-based differences in both BD and SZ. First, interactions between sex and diagnosis have a significant effect on age, duration of illness, age at first outpatient treatment, tobacco, and illicit drug use. Second, sex differences were found in SZ and BD. Third, both male and female participants exhibited similar trends across different groups.

TABLE 1 | Sex differences and interaction group × sex in bipolar disorder and schizophrenia.

Mean (confidence interval)	SZ				BD				Sex × diagnosis	
	Females ($N=181$)	Males ($N=336$)	F	p (FDR)	Females ($N=273$)	Males ($N=270$)	F	p (FDR)	Statistic	p
Sociodemographic variables										
Age	42.08 (40.33, 43.84)	37.77 (36.48, 39.06)	15.06	**<0.001 (0.01)**	44.55 (42.99, 46.12)	45.48 (43.91, 47.05)	0.67	0.41 (0.69)	10.82	**0.001**
Living alone, yes (%)	77 (42.54%)	154 (45.83%)	0.52	0.47 (0.71)	93 (34.07%)	101 (37.41%)	0.66	0.42 (0.69)	0.002	0.97
Family history, yes (%)	108 (59.67%)	175 (52.08%)	1.33	0.25 (0.56)	215 (78.39%)	193 (70.74%)	3.91	0.05 (0.23)	0.37	0.54
Currently paid employment, yes (%)	53 (29.28%)	95 (28.27%)	0.08	0.78 (0.86)	110 (40.29%)	119 (44.07%)	0.75	0.39 (0.69)	0.59	0.44
Neurocognitive variables										
Verbal intelligence (MWT-B)	26.53 (25.65, 27.42)	27.03 (26.38, 27.68)	0.88	0.35 (0.57)	29.13 (28.57, 29.69)	28.82 (28.24, 29.40)	0.78	0.38 (0.69)	0.78	0.38
TMT-A	41.74 (39.14, 44.34)	39.51 (37.61, 41.41)	0.92	0.34 (0.57)	35.32 (33.57, 37.08)	36.22 (34.43, 38.02)	0.38	0.54 (0.71)	0.74	0.39
TMT-B	90.06 (83.32, 96.79)	94.70 (90.06, 99.34)	0.86	0.35 (0.57)	84.24 (79.48, 89.01)	87.17 (82.27, 92.08)	0.26	0.61 (0.74)	0.37	0.55
VDS forward digit span	8.72 (8.39, 9.05)	8.69 (8.45, 8.93)	0.06	0.81 (0.87)	9.35 (9.09, 9.60)	9.33 (9.07, 9.59)	0.15	0.79 (0.89)	0.02	0.88
VDS backward digit span	5.47 (5.16, 5.78)	5.45 (5.23, 5.67)	0.15	0.70 (0.84)	6.00 (5.75, 6.25)	6.18 (5.93, 6.43)	0.80	0.37 (0.69)	0.88	0.35
DST	56.02 (53.74, 58.29)	51.16 (49.49, 52.84)	9.45	0.02 (0.12)	64.33 (62.35, 66.32)	59.43 (57.41, 61.45)	11.00	**<0.001 (0.02)**	0.10	0.76
VLMT correctly recalled words	44.16 (41.78, 46.53)	42.35 (40.62, 44.08)	0.93	0.33 (0.57)	49.88 (48.28, 51.48)	46.35 (44.78, 47.93)	8.66	**0.003 (0.03)**	0.56	0.46
VLMT recognition	10.32 (9.32, 11.32)	10.13 (9.40, 10.86)	0.00	0.99 (0.99)	12.22 (11.69, 12.76)	10.88 (10.35, 11.42)	9.83	**0.002 (0.03)**	2.48	0.12

(Continues)

TABLE 1 | (Continued)

Mean (confidence interval)	SZ				BD				Sex × diagnosis	
	Females ($N=181$)	Males ($N=336$)	F	p (FDR)	Females ($N=273$)	Males ($N=270$)	F	p (FDR)	Statistic	p
Clinical features										
Age at first outpatient treatment	27.19 (25.76, 28.61)	25.66 (24.62, 26.71)	2.87	0.09 (0.31)	29.77 (28.31, 31.23)	30.99 (29.53, 32.46)	1.34	0.25 (0.60)	3.80	**0.05**
Duration of illness	12.63 (11.44, 13.81)	12.33 (11.48, 13.19)	0.16	0.69 (0.84)	12.43 (11.06, 13.81)	12.63 (11.23, 14.04)	0.05	0.83 (0.89)	4.77	**0.03**
IDS-C_{30}	13.13 (11.54, 14.71)	12.73 (11.58, 13.88)	0.15	0.70 (0.84)	14.09 (12.71, 15.47)	12.63 (11.25, 14.02)	2.12	0.15 (0.38)	0.56	0.46
YMRS	2.04 (1.45, 2.64)	2.47 (2.01, 2.93)	1.25	0.26 (0.56)	3.96 (3.23, 4.68)	3.63 (2.90, 4.35)	0.40	0.53 (0.71)	1.26	0.26
BDI	13.83 (12.03, 15.62)	12.49 (11.22, 13.76)	1.43	0.23 (0.55)	14.58 (13.06, 16.10)	12.70 (11.17, 14.23)	2.92	0.09 (0.30)	0.12	0.73
CGI	4.22 (4.07, 4.36)	4.38 (4.28, 4.49)	3.32	0.07 (0.29)	3.84 (3.72, 3.96)	3.86 (3.73, 3.98)	0.04	0.83 (0.89)	1.33	0.25
PANSS positive	13.65 (12.81, 14.49)	14.46 (13.84, 15.08)	2.31	0.13 (0.41)	9.24 (8.84, 9.64)	9.25 (8.85, 9.66)	0.003	0.96 (0.96)	1.78	0.18
PANSS negative	15.98 (15.00, 16.96)	16.27 (15.55, 16.99)	0.23	0.64 (0.84)	9.94 (9.47, 10.42)	10.33 (9.84, 10.81)	1.21	0.27 (0.62)	0.02	0.90
PANSS general	30.57 (29.14, 32.01)	29.96 (28.90, 31.02)	0.45	0.50 (0.73)	23.38 (22.58, 24.18)	23.30 (22.49, 24.12)	0.02	0.90 (0.92)	0.26	0.61
PANSS total	60.17 (57.23, 62.57)	60.76 (58.60, 62.93)	0.10	0.75 (0.86)	42.32 (40.93, 43.71)	43.00 (41.59, 44.41)	0.46	0.50 (0.71)	0.002	0.97
Substance use										
Ever smoked cigarettes, yes (%)	86 (46.96%)	214 (63.10%)	12.78	**< 0.001 (0.01)**	134 (49.08%)	144 (53.33%)	1.10	0.29 (0.63)	3.72	**0.05**
Lifetime alcohol abuse, yes (%)	8 (4.42%)	35 (10.12%)	5.34	0.02 (0.12)	22 (8.06%)	32 (11.85%)	2.53	0.11 (0.30)	0.89	0.35
Ever take illicit drugs, yes (%)	50 (27.62%)	156 (46.13%)	24.52	**< 0.001 (0.01)**	92 (33.77%)	109 (40.37%)	2.96	0.09 (0.30)	6.72	**0.01**
Pharmacological treatment										
Number of antidepressants	0.32 (0.24, 0.39)	0.25 (0.20, 0.31)	1.94	0.16 (0.47)	0.56 (0.48, 0.64)	0.59 (0.52, 0.67)	0.31	0.58 (0.72)	1.65	0.20
Number of antipsychotics	1.76 (1.62, 1.89)	1.77 (1.67, 1.87)	0.02	0.90 (0.95)	0.99 (0.89, 1.09)	0.93 (0.82, 1.03)	0.74	0.39 (0.69)	0.44	0.51

(Continues)

TABLE 1 | (Continued)

Mean (confidence interval)	SZ				BD				Sex × diagnosis	
	Females ($N=181$)	Males ($N=336$)	F	p (FDR)	Females ($N=273$)	Males ($N=270$)	F	p (FDR)	Statistic	p
Number of mood stabilizers	0.06 (0.01, 0.10)	0.08 (0.05, 0.12)	1.07	0.30 (0.57)	0.75 (0.68, 0.82)	0.79 (0.72, 0.86)	0.55	0.46 (0.71)	0.03	0.87
Number of tranquilizers	0.29 (0.22, 0.37)	0.29 (0.24, 0.34)	0.07	0.93 (0.95)	0.18 (0.13, 0.23)	0.13 (0.08, 0.18)	2.55	0.11 (0.30)	0.84	0.36
Lithium	8 (4.42%)	10 (2.98%)	0.67	0.41 (0.65)	93 (34.07%)	105 (38.89%)	0.31	0.58 (0.72)	0.70	0.40
Somatic disease										
Hypertension, yes (%)	24 (13.26%)	55 (16.36%)	1.58	0.21 (0.55)	51 (18.68%)	69 (25.56%)	3.84	0.05 (0.23)	0.05	0.82
Diabetes, yes (%)	16 (8.84%)	24 (7.14%)	0.27	0.60 (0.82)	17 (6.23%)	21 (7.78%)	0.42	0.52 (0.72)	0.68	0.41
Hyper-hypothyroidism, yes (%)	30 (16.57%)	18 (5.36%)	15.73	**<0.001 (0.01)**	78 (28.57%)	39 (14.44%)	15.83	**<0.001 (0.02)**	0.96	0.33
Cancer, yes (%)	7 (3.87%)	4 (1.19%)	3.31	0.07 (0.29)	24 (8.96%)	14 (5.19%)	2.70	0.10 (0.30)	0.65	0.42
Migraine, yes (%)	16 (8.84%)	11 (3.27%)	6.01	0.02 (0.12)	34 (12.45%)	17 (6.30%)	5.66	0.02 (0.14)	0.26	0.61
Functioning and quality of life										
GAF	53.69 (51.78, 55.59)	51.65 (50.26, 53.05)	2.84	0.09 (0.31)	61.07 (59.56, 62.58)	61.81 (60.29, 63.33)	0.46	0.50 (0.71)	2.91	0.09
Global quality of life (WHOQoL-BREF)	12.59 (11.99, 13.19)	12.70 (12.25, 13.15)	0.08	0.78 (0.86)	12.89 (12.41, 13.37)	12.83 (12.33, 13.32)	0.04	0.85 (0.89)	0.12	0.74
Physical health (WHOQoL-BREF)	13.60 (13.17, 14.03)	13.75 (13.42, 14.08)	0.29	0.59 (0.82)	13.58 (13.22, 13.95)	14.19 (13.81, 14.57)	5.00	0.03 (0.18)	1.33	0.25
Psychological health (WHOQoL-BREF)	12.91 (12.40, 13.43)	13.26 (12.88, 13.64)	1.10	0.29 (0.57)	12.84 (12.42, 13.26)	13.37 (12.93, 13.81)	2.94	0.09 (0.30)	0.17	0.68

(Continues)

TABLE 1 | (Continued)

Mean (confidence interval)	SZ				BD				Sex × diagnosis	
	Females ($N = 181$)	Males ($N = 336$)	F	p (FDR)	Females ($N = 273$)	Males ($N = 270$)	F	p (FDR)	Statistic	p
Social relationships (WHOQoL-BREF)	13.17 (12.58, 13.77)	12.49 (12.04, 12.94)	3.28	0.07 (0.29)	13.58 (13.16, 14.01)	12.88 (12.44, 13.31)	5.20	0.02 (0.14)	0.001	0.97
Environment (WHOQoL-BREF)	14.41 (13.93, 14.88)	14.04 (13.68, 14.39)	1.48	0.22 (0.55)	15.45 (15.13, 15.78)	15.35 (15.01, 15.69)	0.19	0.67 (0.78)	0.48	0.49

Abbreviations: BDI, Beck Depression Inventory; CGI, Clinical Global Impression Scale; DST, Digit Symbol Test; FDR, false discovery rate; GAF, global assessment of functioning; IDS-C30, Inventory of Depressive Symptomatology; MWT-B, Vocabulary Intelligence Test; PANSS, Positive and Negative Symptom Scale; TMT, Trail Making Test; VDS, Verbal Digit Span; VLMT, Verbal Learning Memory Test; WHOQoL-BREF, World Health Organization Quality of Life Questionnaire, brief version; YMRS, Young Mania Rating Scale. Significant differences ($p < 0.05$) are marked in bold.

Our results indicated that individuals with BD exhibit a more favorable neurocognitive profile compared to those with SZ. These findings are widely reproduced in the literature [24, 59]. Data from our sample reveal a continuum of crystallized intelligence, wherein HCs represent one end and individuals with SZ the other. This finding is consistently reported in the literature [12, 60–62]. Moreover, previous studies described significant deficits and impaired premorbid intellectual function in SZ [63]. However, the evidence regarding premorbid function in BD is equivocal, presenting more heterogeneity, with some studies indicating an exceptional intellectual ability in at least some of these patients [64]. Regarding sex differences, females with BD consistently demonstrated better performance on processing speed and verbal memory tasks. Several studies support the finding that females outperform males in verbal memory [12, 65–66]. However, the findings regarding processing speed contrast with those of a recent meta-analysis in individuals with BD and in the general population [14, 25]. It is important to note that the magnitude of the differences in these cognitive domains is small and should be interpreted with caution. These findings may help inform the development of sex-specific cognitive interventions aimed at addressing domain-specific deficits.

Our data confirmed that the SZ group showed a more severe clinical profile. These findings align with existing literature that suggests a continuum of severity, placing BD closer to HC and SZ at the more severe end of the spectrum [24, 67–69]. Significant group-by-sex interactions were observed in clinical features specifically indicating that sex differences in treatment onset vary by diagnosis. In BD, previous studies have suggested that women may experience a later onset and, consequently, a later initiation of treatment [10, 13]. This may be due to women seeking treatment for other psychiatric conditions more frequently or different prodromes [70]. The duration of illness was also longer in those who started treatment at an older age, indicating potential delays in diagnosis and interventions [10, 13]. The observed interactions between sex and diagnosis emphasize the importance of considering this factor in clinical assessments. The differences observed between these groups highlight the distinct neurobiological and clinical trajectories associated with each disorder [6, 71].

Males with SMI showed more substance use in both tobacco and illicit drug use compared to HC [72, 73], except for BD individuals and illicit drug use. Our data is in line with the literature, where men tend to use significantly more substances in both SZ [74] and BD [9, 10]. The literature reports higher rates of tobacco smoking among males with BD [75] and SZ [76]. In our sample, males with BD use significantly less illicit drugs than HC and SZ groups. This finding did not confirm previous findings related to lifetime use of illicit drugs [77], although the role of sex was not explored in these studies. Interactions between sex and diagnosis suggest that being female may have a protective effect against substance use, particularly among women with SZ, who showed significantly lower consumption rates. Meanwhile, males with SZ are at higher risk of engaging in substance use, which may worsen clinical outcomes. Regarding alcohol abuse, we observed a trend in individuals with SMI. As mentioned, males with SMI tend to use more substance [9, 10, 67]. However, results concerning alcohol abuse remain inconclusive; Curtis

TABLE 2 | Group differences among females.

Females						Post hoc analysis		
Mean (confidence interval)	**SZ ($N = 181$) [1]**	**BD ($N = 273$) [2]**	**HC ($N = 268$) [3]**	**Statistic**	***p* (FDR)**	**[1] vs. [2]**	**[2] vs. [3]**	**[1] vs. [3]**
Sociodemographic variables								
Age	42.08 (40.13, 44.03)	44.55 (42.97, 46.14)	36.04 (34.44, 37.64)	57.16	**< 0.001 (0.001)**	[1] = [2] (ns)	**[2] > [3]****	**[1] > [3]****
Living alone, yes (%)	77 (42.54%)	93 (34.07%)	65 (24.25%)	16.79	**< 0.001 (0.001)**	[1] = [2] (ns)	**[2] > [3]***	**[1] > [3]****
Family history of psychiatric illness, yes (%)	108 (59.67%)	214 (78.39%)	136 (50.75%)	52.41	**< 0.001 (0.001)**	**[1] < [2]***	**[2] > [3]****	**[1] > [3]****
Currently paid employment, yes (%)	53 (29.28%)	109 (40.00%)	166 (61.94%)	57.79	**< 0.001 (0.001)**	[1] = [2] (ns)	**[2] < [3]****	**[1] < [3]****
Neurocognitive variables								
Verbal intelligence (MWT-B)	26.93 (26.20, 27.66)	28.69 (28.17, 29.21)	29.92 (29.34, 30.49)	38.62	**< 0.001 (0.001)**	**[1] < [2]****	**[2] < [3]***	**[1] < [3]****
TMT-A	42.45 (40.36, 44.55)	33.60 (31.88, 35.32)	27.83 (28.09, 29.57)	125.14	**< 0.001 (0.001)**	**[1] > [2]****	**[2] > [3]****	**[1] > [3]****
TMT-B	91.91 (86.72, 97.10)	79.98 (79.01, 83.95)	60.30 (56.34, 64.25)	136.42	**< 0.001 (0.001)**	**[1] > [2]***	**[2] > [3]****	**[1] > [3]****
VDS forward digit span	8.64 (8.32, 8.94)	9.42 (9.17, 9.68)	10.04 (9.79, 10.29)	50.33	**< 0.001 (0.001)**	**[1] < [2]****	**[2] < [3]***	**[1] < [3]****
VDS backward digit span	5.46 (5.15, 5.77)	6.06 (5.81, 6.32)	7.46 (7.21, 7.72)	107.28	**< 0.001 (0.001)**	**[1] < [2]***	**[2] < [3]****	**[1] < [3]****
DST	55.64 (53.42, 57.86)	66.76 (64.93, 68.59)	81.34 (79.48, 83.19)	273.73	**< 0.001 (0.001)**	**[1] < [2]****	**[2] < [3]****	**[1] < [3]****
VLMT correctly recalled words	44.22 (42.04, 46.40)	50.66 (49.09, 52.23)	57.01 (55.49, 58.54)	70.67	**< 0.001 (0.001)**	**[1] < [2]****	**[2] < [3]****	**[1] < [3]****
VLMT recognition	10.13 (9.40, 10.87)	12.46 (11.93, 12.99)	13.37 (12.86, 13.87)	38.17	**< 0.001 (0.001)**	**[1] < [2]****	[2] = [3] (ns)	**[1] < [3]****
Clinical features								
Age at first outpatient treatment	27.19 (25.48, 28.90)	29.77 (28.41, 31.13)	—	5.36	**0.02 (0.02)**	**[1] < [2]***	—	—
Duration of illness	14.31 (12.71, 15.90)	12.43 (11.10, 13.77)	—	3.12	0.08 (0.09)	[1] = [2] (ns)	—	—
IDS-C_{30}	13.01 (11.31, 14.71)	14.26 (12.66, 15.86)	4.74 (2.26, 7.22)	165.91	**< 0.001 (0.001)**	[1] = [2] (ns)	**[2] > [3]****	**[1] > [3]****
YMRS	2.04 (1.36, 2.72)	3.96 (3.42, 4.50)	0.47 (−0.19, 1.23)	66.34	**< 0.001 (0.001)**	**[1] < [2]****	**[2] > [3]****	**[1] > [3]***

(Continues)

TABLE 2 | (Continued)

Females						Post hoc analysis		
Mean (confidence interval)	**SZ (*N* = 181) [1]**	**BD (*N* = 273) [2]**	**HC (*N* = 268) [3]**	**Statistic**	***p* (FDR)**	**[1] vs. [2]**	**[2] vs. [3]**	**[1] vs. [3]**
BDI	13.83 (12.17, 15.49)	14.58 (13.30, 15.87)	2.63 (1.30, 3.95)	188.24	**< 0.001 (0.001)**	[1] = [2] (ns)	**[2] > [3]****	**[1] > [3]****
CGI	4.22 (4.07, 4.37)	3.84 (3.72, 3.96)	—	15.14	**< 0.001 (0.001)**	**[1] > [2]***	—	—
PANSS positive	13.65 (13.08, 14.23)	9.24 (8.77, 9.71)	7.07 (6.50, 7.63)	266.86	**< 0.001 (0.001)**	**[1] > [2]****	**[2] > [3]****	**[1] > [3]****
PANSS negative	15.98 (15.32, 16.63)	9.94 (9.41, 10.47)	7.08 (6.44, 7.73)	378.88	**< 0.001 (0.001)**	**[1] > [2]****	**[2] > [3]****	**[1] > [3]****
PANSS general	30.57 (29.51, 31.63)	23.38 (22.51, 24.25)	16.47 (15.41, 17.52)	340.16	**< 0.001 (0.001)**	**[1] > [2]****	**[2] > [3]****	**[1] > [3]****
PANSS total	60.17 (58.14, 62.20)	42.32 (40.66, 43.98)	30.61 (28.60, 32.62)	417.62	**< 0.001 (0.001)**	**[1] > [2]****	**[2] > [3]****	**[1] > [3]****
Substance use								
Ever smoked cigarettes, yes (%)	85 (46.96%)	132 (48.35%)	44 (16.42%)	55.58	**< 0.001 (0.001)**	[1] = [2] (ns)	**[2] > [3]****	**[1] > [3]****
Lifetime alcohol abuse, yes (%)	8 (4.42%)	22 (8.06%)	2 (0.75%)	11.18	**0.004 (0.005)**	[1] = [2] (ns)	**[2] > [3]****	[1] = [3] (ns)
Ever take illicit drugs. yes (%)	50 (27.62%)	91 (33.33%)	87 (32.46%)	2.43	0.30 (0.31)	—	—	—
Pharmacological treatment								
Number of antidepressants	0.32 (0.23, 0.40)	0.56 (0.49, 0.63)	—	17.77	**< 0.001 (0.001)**	**[1] < [2]****	—	—
Number of antipsychotics	1.76 (1.62, 1.89)	0.99 (0.88, 1.10)	—	71.63	**< 0.001 (0.001)**	**[1] > [2]****	—	—
Number of mood stabilizers	0.06 (−0.17, 0.13)	0.75 (0.70, 0.81)	—	208.77	**< 0.001 (0.001)**	**[1] < [2]****	—	—
Number of tranquilizers	0.29 (0.22, 0.36)	0.18 (0.13, 0.24)	—	5.77	**< 0.001 (0.001)**	**[1] > [2]***	—	—
Lithium	0.06 (−0.01, 0.14)	0.56 (0.50, 0.62)	—	104.26	**< 0.001 (0.001)**	**[1] < [2]****	—	—
Somatic disease								
Hypertension, yes (%)	24 (13.26%)	51 (18.68%)	14 (5.22%)	16.65	**< 0.001 (0.001)**	[1] = [2] (ns)	**[2] > [3]****	**[1] > [3]***
Diabetes, yes (%)	16 (8.84%)	17 (6.23%)	8 (2.99%)	6.03	0.05 (0.06)	—	—	—

(Continues)

TABLE 2 | (Continued)

Females						Post hoc analysis		
Mean (confidence interval)	**SZ (*N* = 181) [1]**	**BD (*N* = 273) [2]**	**HC (*N* = 268) [3]**	**Statistic**	***p* (FDR)**	**[1] vs. [2]**	**[2] vs. [3]**	**[1] vs. [3]**
Hyper-hypothyroidism, yes (%)	30 (16.57%)	77 (28.20%)	46 (17.16%)	8.66	**0.01 (0.01)**	**[1] < [2]***	**[2] > [3]***	[1] = [3]
Cancer, yes (%)	7 (3.87%)	24 (8.79%)	12 (4.48%)	4.56	0.10 (0.11)	—	—	—
Migraine, yes (%)	16 (8.84%)	34 (12.45%)	24 (8.96%)	1.01	0.60 (0.60)	—	—	—
Functioning and quality of life								
GAF	53.69 (51.94, 55.44)	61.07 (59.64, 62.50)	88.49 (86.74, 90.24)	867.22	**< 0.001 (0.001)**	**[1] < [2]****	**[2] < [3]****	**[1] < [3]****
Global quality of life (WHOQoL-BREF)	12.59 (12.05, 13.13)	12.89 (12.49, 13.30)	17.24 (16.84, 17.63)	292.30	**< 0.001 (0.001)**	[1] = [2] (ns)	**[2] < [3]****	**[1] < [3]****
Physical health (WHOQoL-BREF)	13.60 (13.20, 14.00)	13.58 (13.28, 13.89)	18.02 (17.73, 18.32)	523.39	**< 0.001 (0.001)**	[1] = [2] (ns)	**[2] < [3]****	**[1] < [3]****
Psychological health (WHOQoL-BREF)	12.91 (12.43, 13.39)	12.84 (12.48, 13.19)	16.72 (16.38, 17.06)	288.04	**< 0.001 (0.001)**	[1] = [2] (ns)	**[2] < [3]****	**[1] < [3]****
Social relationships (WHOQoL-BREF)	13.17 (12.67, 13.68)	13.58 (13.21, 13.96)	16.61 (16.24, 16.98)	171.73	**< 0.001 (0.001)**	[1] = [2] (ns)	**[2] < [3]****	**[1] < [3]****
Environment (WHOQoL-BREF)	14.41 (14.01, 14.81)	15.45 (15.16, 15.75)	17.67 (17.38, 17.96)	200.51	**< 0.001 (0.001)**	**[1] < [2]****	**[2] < [3]****	**[1] < [3]****

Abbreviations: BDI, Beck Depression Inventory; CGI, Clinical Global Impression Scale; DST, Digit Symbol Test; FDR, false discovery rate; GAF, global assessment of functioning; IDS-C30, Inventory of Depressive Symptomatology; MWT-B, Vocabulary Intelligence Test; ns, not significant; PANSS, Positive and Negative Symptom Scale; TMT, Trail Making Test; VDS, Verbal Digit Span; VLMT, Verbal Learning Memory Test; WHOQoL-BREF, World Health Organization Quality of Life Questionnaire, brief version; YMRS, Young Mania Rating Scale. Significant differences ($p < 0.05$) are marked in bold.

*$p < 0.05$.

**$p < 0.001$.

TABLE 3 | Group differences among males.

Males						Post hoc analysis		
Mean (confidence interval)	**SZ (*N* = 336) [1]**	**BD (*N* = 270) [2]**	**HC (*N* = 188) [3]**	**Statistic**	***p* (FDR)**	**[1] vs. [2]**	**[2] vs. [3]**	**[1] vs. [3]**
Sociodemographic variables								
Age	40.49 (37.65, 43.33)	47.84 (45.00, 50.67)	40.82 (37.40, 44.24)	68.39	**< 0.001 (0.001)**	**[1] < [2]****	**[2] > [3]****	[1] = [3] (ns)
Living alone, yes (%)	154 (45.83%)	101 (37.41%)	51 (27.13%)	18.11	**< 0.001 (0.001)**	[1] = [2] (ns)	**[2] > [3]***	**[1] > [3]****
Family history of psychiatric illness, yes (%)	174 (51.79%)	191 (70.74%)	85 (45.21%)	35.80	**< 0.001 (0.001)**	**[1] < [2]***	**[2] > [3]****	**[1] > [3]***
Currently paid employment, yes (%)	95 (28.27%)	118 (43.70%)	103 (54.79%)	42.08	**< 0.001 (0.001)**	**[1] < [2]***	**[2] < [3]****	**[1] < [3]****
Neurocognitive variables								
Verbal intelligence (MWT-B)	27.13 (26.53, 27.74)	28.29 (27.68, 28.90)	29.84 (29.08, 30.59)	31.03	**< 0.001 (0.001)**	**[1] < [2]***	**[2] < [3]***	**[1] < [3]****
TMT-A	39.96 (38.35, 41.58)	34.09 (32.25, 35.94)	28.13 (26.01, 30.26)	130.41	**< 0.001 (0.001)**	**[1] > [2]****	**[2] > [3]****	**[1] > [3]****
TMT-B	99.11 (91.78, 100.45)	82.27 (77.31, 87.22)	63.43 (57.85, 69.01)	129.82	**< 0.001 (0.001)**	[1] = [2] (ns)	**[2] > [3]****	**[1] > [3]****
VDS forward digit span	8.67 (8.43, 8.91)	9.46 (9.19, 9.74)	10.70 (10.39, 11.02)	91.62	**< 0.001 (0.001)**	**[1] < [2]****	**[2] < [3]****	**[1] < [3]****
VDS backward digit span	5.42 (5.18, 5.66)	6.35 (6.07, 6.63)	7.77 (7.45, 8.09)	113.57	**< 0.001 (0.001)**	**[1] < [2]****	**[2] < [3]****	**[1] < [3]****
DST	50.35 (48.65, 52.06)	61.70 (59.75, 63.65)	76.10 (73.86, 78.33)	265.15	**< 0.001 (0.001)**	**[1] < [2]****	**[2] < [3]****	**[1] < [3]****
VLMT correctly recalled words	42.24 (40.61, 43.86)	47.39 (45.81, 48.96)	52.88 (50.99, 54.76)	63.87	**< 0.001 (0.001)**	**[1] < [2]****	**[2] < [3]****	**[1] < [3]****
VLMT recognition	10.19 (9.56, 10.82)	11.12 (10.50, 11.74)	12.26 (11.53, 12.98)	16.11	**< 0.001 (0.001)**	[1] = [2] (ns)	**[2] < [3]***	**[1] < [3]****
Clinical features								
Age at first outpatient treatment	25.66 (24.49, 26.84)	30.99 (29.71, 32.28)	—	36.01	**< 0.001 (0.001)**	**[1] < [2]****	—	—
Duration of illness	11.44 (10.28, 12.60)	12.63 (11.26, 14.00)	—	1.68	0.20 (0.21)	[1] = [2] (ns)	—	—
IDS-C_{30}	12.73 (11.69, 13.78)	12.63 (11.46, 13.80)	2.59 (0.87, 4.32)	109.47	**< 0.001 (0.001)**	[1] = [2] (ns)	**[2] > [3]****	**[1] > [3]****
YMRS	2.47 (1.93, 3.02)	3.63 (3.06, 4.19)	0.61 (−0.26, 1.48)	32.93	**< 0.001 (0.001)**	**[1] < [2]***	**[2] > [3]****	**[1] > [3]***
BDI	12.49 (8.44, 12.54)	12.70 (0.63, 11.46)	2.81 (1.22, 4.41)	113.48	**< 0.001 (0.001)**	[1] = [2] (ns)	**[2] > [3]****	**[1] > [3]****

(Continues)

TABLE 3 | (Continued)

Males						Post hoc analysis		
Mean (confidence interval)	**SZ (*N* = 336) [1]**	**BD (*N* = 270) [2]**	**HC (*N* = 188) [3]**	**Statistic**	***p* (FDR)**	**[1] vs. [2]**	**[2] vs. [3]**	**[1] vs. [3]**
CGI	4.38 (4.28, 4.49)	3.86 (3.74, 3.98)	—	40.29	**< 0.001 (0.001)**	**[1] > [2]****	—	—
PANSS positive	14.46 (14.00, 14.93)	9.25 (8.73, 9.78)	7.12 (6.32, 7.92)	341.10	**< 0.001 (0.001)**	**[1] > [2]****	**[2] > [3]****	**[1] > [3]****
PANSS negative	16.27 (15.71, 16.83)	10.33 (9.70, 10.95)	7.37 (6.42, 8.33)	331.88	**< 0.001 (0.001)**	**[1] > [2]****	**[2] > [3]****	**[1] > [3]****
PANSS general	29.96 (29.15, 30.77)	23.30 (22.39, 24.22)	16.32 (14.94, 17.71)	305.28	**< 0.001 (0.001)**	**[1] > [2]****	**[2] > [3]****	**[1] > [3]****
PANSS total	60.76 (59.16, 62.37)	43.00 (41.19, 44.82)	30.75 (27.99, 33.52)	415.54	**< 0.001 (0.001)**	**[1] > [2]****	**[2] > [3]****	**[1] > [3]****
Substance use								
Ever smoked cigarettes. yes (%)	212 (63.10%)	142 (52.59%)	46 (24.47%)	47.64	**< 0.001 (0.001)**	**[1] > [2]***	**[2] > [3]****	**[1] > [3]****
Lifetime alcohol abuse. yes (%)	34 (10.12%)	32 (11.85%)	1 (0.53%)	9.49	**0.009 (0.01)**	[1] = [2] (ns)	**[2] > [3]****	**[1] > [3]****
Ever take illicit drugs. yes (%)	155 (46.13%)	108 (40%)	83 (44.15%)	10.99	**0.004 (0.005)**	**[1] > [2]***	**[2] < [3]***	[1] = [3] (ns)
Pharmacological treatment								
Number of antidepressants	0.25 (0.19, 0.32)	0.59 (0.52, 0.67)	—	48.07	**0.004 (0.005)**	**[1] < [2]****	—	—
Number of antipsychotics	1.77 (1.68, 1.86)	0.93 (0.82, 1.03)	—	146.49	**< 0.001 (0.001)**	**[1] > [2]****	—	—
Number of mood stabilizers	0.08 (0.04, 0.13)	0.79 (0.73, 0.84)	—	355.72	**< 0.001 (0.001)**	**[1] < [2]****	—	—
Number of tranquilizers	0.29 (0.24, 0.34)	0.13 (0.07, 0.18)	—	19.23	**< 0.001 (0.001)**	**[1] > [2]****	—	—
Lithium	0.04 (−0.01, 0.09)	0.59 (0.53, 0.64)	—	210.61	**< 0.001 (0.001)**	**[1] < [2]****	—	—
Somatic disease								
Hypertension. yes (%)	55 (16.37%)	69 (25.56%)	26 (13.83%)	5.68	0.06 (0.06)	—	—	—
Diabetes. yes (%)	24 (7.14%)	21 (7.78%)	11 (5.85%)	0.07	0.97 (0.97)	—	—	—
Hyper-hypothyroidism. yes (%)	18 (5.36%)	39 (14.44%)	11 (5.85%)	12.22	**0.002 (0.002)**	**[1] < [2]***	**[2] > [3]***	[1] = [3] (ns)

(Continues)

TABLE 3 | (Continued)

Males						Post hoc analysis		
Mean (confidence interval)	**SZ (*N* = 336) [1]**	**BD (*N* = 270) [2]**	**HC (*N* = 188) [3]**	**Statistic**	***p* (FDR)**	**[1] vs. [2]**	**[2] vs. [3]**	**[1] vs. [3]**
Cancer. yes (%)	4 (1.19%)	14 (5.19%)	6 (3.19%)	5.84	0.05 (0.06)	—	—	—
Migraine. yes (%)	11 (3.27%)	17 (6.30%)	7 (3.72%)	1.96	0.38 (0.39)	—	—	—
Functioning and quality of life								
GAF	51.65 (50.38, 52.92)	61.81 (60.40, 63.23)	88.03 (85.85, 90.21)	801.02	**< 0.001 (0.001)**	**[1] < [2]****	**[2] < [3]****	**[1] < [3]****
Global quality of life (WHOQoL-BREF)	12.70 (12.27, 13.13)	12.83 (12.38, 13.27)	16.81 (16.31, 17.31)	180.06	**< 0.001 (0.001)**	[1] = [2] (ns)	**[2] < [3]****	**[1] < [3]****
Physical health (WHOQoL-BREF)	13.75 (13.43, 14.07)	14.19 (13.86, 14.52)	17.75 (17.38, 18.11)	301.65	**< 0.001 (0.001)**	[1] = [2] (ns)	**[2] < [3]****	**[1] < [3]****
Psychological health (WHOQoL-BREF)	13.26 (12.89, 13.62)	13.37 (12.99, 13.75)	16.71 (16.29, 17.13)	182.49	**< 0.001 (0.001)**	[1] = [2] (ns)	**[2] < [3]****	**[1] < [3]****
Social relationships (WHOQoL-BREF)	12.49 (12.06, 12.91)	12.88 (12.44, 13.31)	15.93 (15.45, 16.42)	126.64	**< 0.001 (0.001)**	[1] = [2] (ns)	**[2] < [3]****	**[1] < [3]****
Environment (WHOQoL-BREF)	14.04 (13.73, 14.35)	15.35 (15.03, 15.67)	17.31 (16.95, 17.67)	185.78	**< 0.001 (0.001)**	**[1] < [2]****	**[2] < [3]****	**[1] < [3]****

Abbreviations: BDI, Beck Depression Inventory; CGI, Clinical Global Impression Scale; DST, Digit Symbol Test; FDR, false discovery rate; GAF, Global Assessment of Functioning; IDS-C_{30}, Inventory of Depressive Symptomatology; MWT-B, Vocabulary Intelligence Test; ns, not significant; PANSS, Positive and Negative Symptom Scale; TMT, Trail Making Test; VDS, Verbal Digit Span; VLMT, Verbal Learning Memory Test; WHOQoL-BREF, World Health Organization Quality of Life Questionnaire, brief version; YMRS, Young Mania Rating Scale. Significant differences ($p < 0.05$) are marked in bold.

*$p < 0.05$.

**$p < 0.001$.

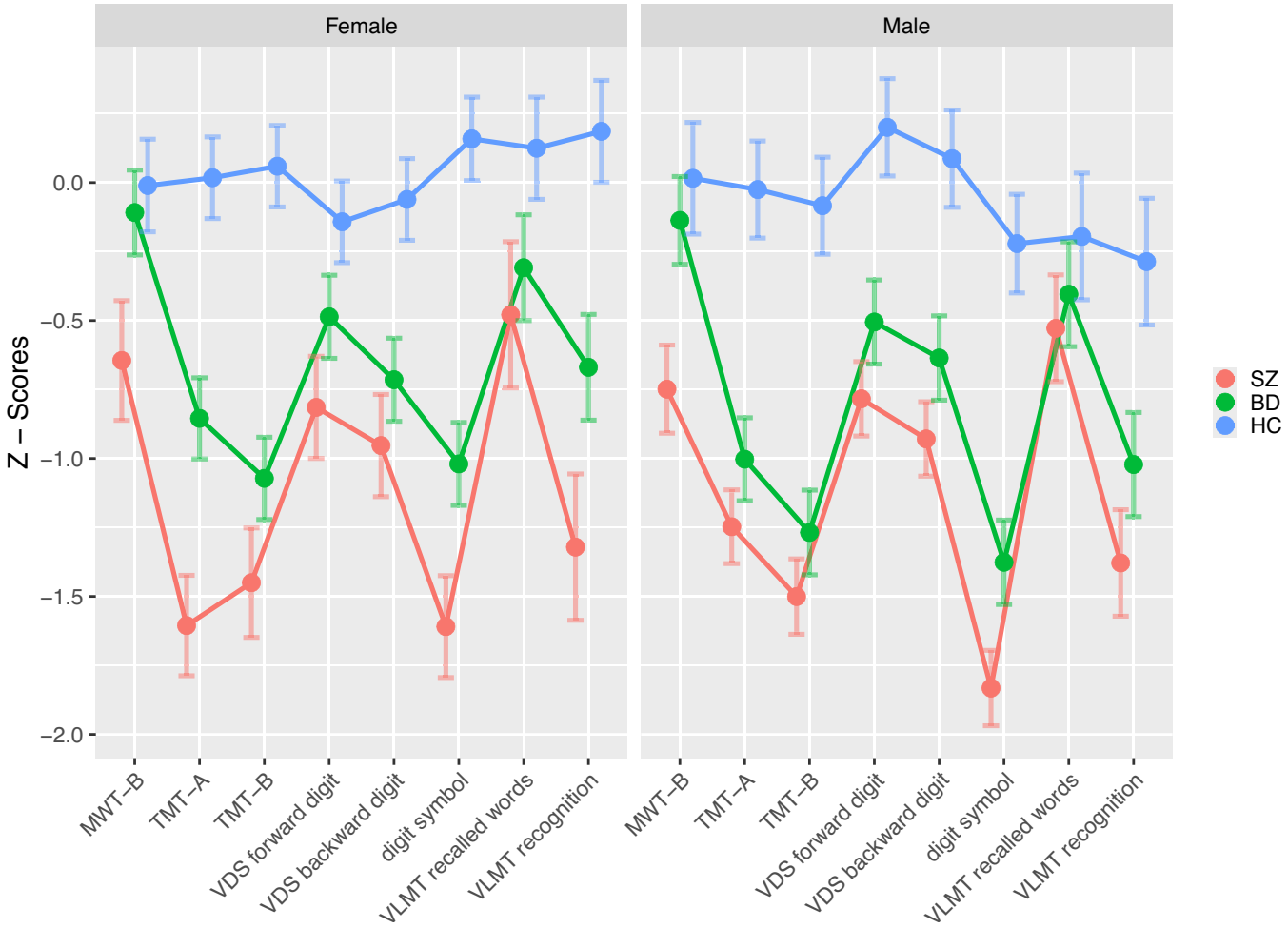

FIGURE 1 | Z-scores of neurocognitive performance across different tasks for female (left panel) and male (right panel) groups. The lines represent three groups: SZ (red), BD (green), and HC (blue).

et al. [9] reported a higher rate of consumption in women, while Diflorio and Jones [13] found a greater tendency in men. These results underscore the impact of both sex and diagnosis on substance use patterns. However, further research is needed to determine whether this gender disparity persists across various types of substance use.

Consumption habits, along with the effects of psychotropic agents, are often associated with physical comorbidities. Specifically, in our sample, and in line with the literature, females with SMI presented a higher prevalence of thyroid alterations [10, 13]. These alterations noted in individuals with BD receiving lithium therapy may be indeed a direct consequence of the medication, given the established association between lithium and thyroid dysfunction as a known adverse effect [13]. Notably, females have a significantly higher risk of hypothyroidism in both diagnostic groups, but with a small-to-moderate effect size [13, 35]. Furthermore, Bendayan et al. [31] reported a higher risk of hypertension and diabetes in individuals with SMI. However, our data only replicated this pattern in females with SMI and hypertension. Regarding QoL, differences were found between diagnoses in the environmental subdomain. This variation may be influenced by country-specific policies, which can directly influence access to environmental resources. More research exploring QoL in SZ and BD should be conducted to better address sex-specific needs.

To the best of our knowledge, this is the first multicentric study to explore sex differences in severe mental disorders in a variety of outcomes using a large sample. Conversely, the findings of the present study should be interpreted considering some limitations. First, the total sample may not have sufficient statistical power to detect interactions between diagnosis and sex. Second, given the multiple interaction tests performed, we acknowledge that some of these results may be false positives. Nonetheless, the present study should be considered exploratory. Additionally, data on female reproductive life events and gender were not collected, which may significantly influence the clinical presentation and disease course of SZ and BD. Another limitation is the lack of ethnic diversity in the sample, given that participants were drawn exclusively from German and Austrian populations. Finally, medical comorbidity data were collected though self-reports, assuming a potential subjective bias. However, participants were specifically asked whether a medical doctor had ever provided the diagnosis, which may help mitigate this concern.

Our data highlight the importance of considering sex differences in BD and SZ, as sex may significantly impact their

pathogenesis and course. Treatment plans should be sex-sensitive to improve clinical outcomes, while promoting healthy lifestyle habits and monitoring physical comorbidities. Future research should explore the role of sex, gender, and hormones in disease presentation, course, and treatment response.

Author Contributions

T.G.S. and P.F. designed the PsyCourse Study. C.T., S.A., and M.S.N. wrote the manuscript. R.B. and M.S.N. performed the statistical analysis. M.H., M.B., U.H., S.P., E.V., A.M.A., and B.S. revised the manuscript draft at different stages. M.H., M.B., U.H., S.P., K.A., P.F., A.N.F., M.O.K., D.R.E., E.C.S., T.G.S., F.S., I.G.A., V.A., B.T.B., U.D., D.E.D., A.J.F., C.F., M.J., G.J., C.K., J.R., E.Z.R., M.S., A.S., C.S., J.W., and J.Z. contributed to acquisition and/or processing and/or managing of data. All authors approved the final version of the manuscript.

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Acknowledgments

E. Vieta thanks the support of the Spanish Ministry of Science, Innovation and Universities (PI15/00283; PI18/00805; PI21/00787; PI24/00432) integrated into the Plan Nacional de I+D+I and co-financed by the ISCIII-Subdirección General de Evaluación y el Fondo Europeo de Desarrollo Regional (FEDER); CIBERSAM; and the Comissionat per a Universitats i Recerca del DIUE de la Generalitat de Catalunya to the Bipolar Disorders Group (2021 SGR 1358) and the project SLT006/17/00357, from PERIS 2016–2020 (Departament de Salut). CERCA Programme/Generalitat de Catalunya.

C. Torrent has been supported through a "Miguel Servet" postdoctoral contract (CPI14/00175) and a Miguel Servet II contract (CPII19/00018) and thanks the support of the Spanish Ministry of Innovation and Science (PI17/01066, PI20/00344, and PI24/00407), funded by the Instituto de Salud Carlos III and cofinanced by the European Union (FEDER) "Una manera de hacer Europa."

S. Amoretti has been supported by Sara Borrell doctoral program (CD20/00177) and M-AES mobility fellowship (MV22/00002), from the Instituto de Salud Carlos III (ISCIII), and co-funded by European Social Fund "Investing in your future," and thanks the support of the Spanish Ministry of Innovation and Science (PI24/00671), funded by the Instituto de Salud Carlos III and cofinanced by the European Union (FEDER) "Una manera de hacer Europa" and La Marató-TV3 Foundation grants (202234-32).

I.-G. Anghelescu was endorsed by the Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung [BMBF]) within the initial phase of the German Center for Mental Health (DZPG) (grant: 01EE2303A, 01EE2303F to P.F., T.G.S.).

U. Dannlowski was funded by the German Research Foundation (DFG, grant FOR2107 DA1151/5-1, DA1151/5-2, DA1151/9-1, DA1151/10-1, DA1151/11-1 to U.D.; SFB/TRR 393, project grant no 521379614) and the Interdisciplinary Center for Clinical Research (IZKF) of the medical faculty of Münster (grant Dan3/022/22 to UD).

U. Heilbronner was supported by the European Union's Horizon 2020 Research and Innovation Programme (PSY-PGx, grant agreement No 945151) and the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation, project number 514201724).

T.G. Schulze was supported by the European Union Horizon 2020 Research and Innovation Program (PSY-PGx, grant agreement No 945151), and also by the Deutsche Forschungsgemeinschaft within the framework of the projects www.kfo241.de and www.PsyCourse.de [SCHU 1603/4–1, 5–1, 7–1]. T.G. Schulze was further supported by the Dr. Lisa Oehler Foundation (Kassel, Germany), the Bundesministerium für Bildung und Forschung (BMBF, Federal Ministry of Education and Research; projects: IntegraMent [01ZX1614K], BipoLife [01EE1404H],

e:Med Program [01ZX1614K]) and the European Union's Horizon 2020 Research and Innovation Programme (ERA-NET Neuron Projects GEPI-BIOPSY [BMBF No 01EW2005] and MulioBio [BMBF No 01EW2009]).

Conflicts of Interest

E. Vieta has received grants and served as a consultant, advisor, or CME speaker for the following entities (unrelated to the present work): AB-Biotics, Abbott, Allergan, Angelini, Dainippon Sumitomo Pharma, Ferrer, Gedeon Richter, Janssen, Lundbeck, Otsuka, Sage, Sanofi-Aventis, and Takeda. I.-G. Anghelescu served as a consultant or speaker (unrelated to the present work) for Aristo, Idorsia, Johnson & Johnson, Merck, Recordati, and Schwabe. The other authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Peer Review

The peer review history of this article is available from the corresponding author upon reasonable request.

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