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Research paper

Sex matters: Differences in prodromes, clinical and neuropsychological features in individuals with a first episode mania or psychosis☆

Roberto Palacios-Garran [a,b,c,1], Silvia Amoretti [a,b,d,e,f,1], Maria Serra-Navarro [a,b], Carla Torrent [a,b], Marina Garriga [a,b], Natalia E. Fares-Otero [a,b], Maria Sagué-Vilavella [a,b], Santiago Madero [b,d], M. Florencia Forte [a,b], Laura Montejo [a,b], Pilar Salgado-Pineda [g], Irene Montoro [h], Vanessa Sánchez-Gistau [h], Edith Pomarol-Clotet [g], Giulia Menculini [i], Alfonso Tortorella [i], Isabella Pacchiarotti [a,b], Clemente Garcia-Rizo [b,d], Josep Antoni Ramos-Quiroga [e,f], Anabel Martínez-Arán [a,b,*], Eduard Vieta [a,b,*], Norma Verdolini [a,b,j]

[a] Bipolar and Depressive Disorders Unit, Hospital Clinic, Institute of Neuroscience (UB Neuro), Department of Medicine, Facultat de Medicina i Ciències de la Salut, University of Barcelona, Fundació Clínic per la Recerca Biomèdica-Institut d'Investigacions Biomèdiques August Pi I Sunyer (FCRB-IDIBAPS), CIBERSAM-ISCIII, Barcelona, Catalonia, Spain

[b] Departament de Medicina, Facultat de Medicina i Ciències de la Salut, Universitat de Barcelona (UB), Barcelona, Spain

[c] Hospital Universitario Jerez de la Frontera, University of Cádiz, Cádiz, Spain

[d] Barcelona Clinic Schizophrenia Unit, Hospital Clinic de Barcelona, Departament de Medicina, Institut de Neurociències (UBNeuro), Universitat de Barcelona (UB), FCRB-IDIBAPS), CIBERSAM-ISCIII, Barcelona, Spain

[e] Psychiatric Genetics Unit, Vall d'Hebron Research Institute (VHIR), CIBERSAM-ISCIII, Barcelona, Catalonia, Spain

[f] Department of Psychiatry, Hospital Universitari Vall d'Hebron, Barcelona, Catalonia, Spain

[g] FIDMAG Germanes Hospitalàries Research Foundation, CIBERSAM-ISCIII, Sant Boi de Llobregat, Barcelona, Spain

[h] Hospital Universitari Institut Pere Mata, Institut d'Investigació Sanitària Pere Virgili (IISPV), Universitat Rovira i Virgili, CIBERSAM-ISCIII, Reus, Tarragona, Spain

[i] Department of Psychiatry, University of Perugia, Perugia, Italy

[j] Local Health Unit Umbria 1, Department of Mental Health, Mental Health Center of Perugia, Perugia, Italy

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ABSTRACT

Objective: This study was aimed at identifying sex differences in patients presenting a first episode mania (FEM) or psychosis (FEP) to help shaping early treatment strategies focused on sex differences.

Methods: Patients with a FEM or FEP underwent a clinical, neuropsychological (neurocognitive functions and emotional intelligence) and functional assessment. Performance on those variables was compared between groups through general linear model, with sex and group (FEM vs FEP) as main effects and group by sex interactions.

Results: The total sample included 113 patients: FEM = 72 (45.83 % females) and FEP = 41 (46.34 % females). There were significant main effects for group (not for sex) for most of the clinical features (depressive, negative and positive symptoms) and psychosocial functioning ($\chi^2 = 8.815$, $p = 0.003$). As for neuropsychological performance, there were significant main effects for sex and group. Females performed better than males in verbal memory ($\chi^2 = 9.038$, p = 0.003) and obtained a higher emotional intelligence quotient ($\chi^2 = 13.20$, $p < 0.001$). On the contrary, males obtained better results in working memory ($\chi^2 = 7.627$, $p = 0.006$). FEP patients significantly underperformed FEM patients in most cognitive domains. There were significant group by sex interactions for few neuropsychological variables, namely processing speed ($\chi^2 = 4.559$, $p = 0.033$) and verbal fluency ($\chi^2 = 8.913$, $p = 0.003$).

☆ Location of work and address for reprints: Bipolar and Depressive Disorders Unit, Hospital Clínic, University of Barcelona, Institute of Neuroscience, IDIBAPS, CIBERSAM-ISCIII, 170 Villarroel st, 12-0, 08036, Barcelona, Catalonia, Spain.

* Corresponding authors at: Bipolar and Depressive Disorders Unit, Hospital Clinic, University of Barcelona, Institute of Neuroscience, IDIBAPS, CIBERSAM-ISCIII, 170 Villarroel st, 12-0, 08036 Barcelona, Catalonia, Spain.

E-mail addresses: AMARTIAR@clinic.cat (A. Martínez-Arán), EVIETA@clinic.cat (E. Vieta).

[1] The first two authors contributed equally to this work.

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Limitations: Differences between sexes were evaluated, but the influence of gender was not considered. Retrospective evaluation of prodromes and substance use. No healthy control group comparator.
Conclusion: The main finding is the presence of significant sex effect and group by sex interaction on specific neurocognitive cognition and emotional intelligence measures. Tailored sex-based early treatment strategies might be implemented.

1. Introduction

Sex can make a difference in the characteristics of many psychiatric disorders. It can affect incidence and prevalence but also other clinical features such as age of onset, severity, and clinical course or treatment response (Pinares-Garcia et al., 2018). Sex differences are based on genetics, anatomy, and physiology, representing a biological construct. This may be linked with sex hormones (Gogos et al., 2019) and dysregulations in the hypothalamic-pituitary-adrenal axis (Bangasser and Valentino, 2014), and appear in various psychiatric disorders (Pinares-Garcia et al., 2018).

As for schizophrenia (SCZ), previous studies highlighted a slightly more frequent prevalence in males than in females, with a 1.4-fold increase (Kahn et al., 2015). The age of onset of the first episode psychosis (FEP) is lower in males, with a peak of incidence at around 20–24 years old, meanwhile in females it occurs 5 or more years later (Kahn et al., 2015). Sex differences in the clinical presentation have been described, with higher prevalence of affective symptoms in females(Ochoa et al., 2012). On the contrary, negative symptoms, disorganization and substance abuse were found to be more prevalent in males (Køster et al., 2008; Ochoa et al., 2012). In general, SCZ symptoms seem to be more severe in males, and sex differences impact also on disease progression and prognosis (Murray and Castle, 1991). In particular, males present longer and more frequent hospitalizations and less responsiveness to antipsychotics (Gogos et al., 2019; Szymanski et al., 1995; Usall et al., 2003). Conversely, rates of remission and recovery are higher in females (Carpiniello et al., 2012).

As for bipolar disorder (BD) type I, the prevalence is similar in males and females (Vieta et al., 2018). The age of onset is around 20 years across both sexes (Vieta et al., 2018), although some studies have reported that females may be faintly older than males (Diflorio and Jones, 2010; Gogos et al., 2019; Kawa et al., 2005). In general, females have a higher predisposition to present a depressive onset (Viguera et al., 2001), more depressive episodes (Altshuler et al., 2010; Bräunig et al., 2009) and to present refractory depression (Nivoli et al., 2011). Few studies also reported increased rates of rapid cycling (Baldassano et al., 2005; Robb et al., 1998) and mixed symptoms (Gogos et al., 2019; Suppes et al., 2005) whilst males would be more prone to mania, present more frequently mania as their first episode and report higher rates of unipolar mania (Diflorio and Jones, 2010). Similarly to SCZ, males with BD present more comorbid substance use disorders than females whilst females with BD had more lifetime comorbid eating disorders, post-traumatic stress disorder (Baldassano et al., 2005; Suominen et al., 2009).

Sex differences in neurocognition and psychosocial functioning have been studied in both SCZ and BD. In SCZ, findings are controversial. Several studies indicate higher levels of cognitive functioning in females, especially in language, executive function, and memory domains (Goldstein et al., 1998; Goldstein et al., 1994) whilst males tend to have more cognitive impairment (Mendrek and Mancini-Marïe, 2016; Zhang et al., 2017). These differences were found even at FEP(Pu et al., 2019). Nevertheless, other studies have exposed worse cognitive functioning in females than in males (Brébion et al., 2018; Leger and Neill, 2016; Lewine et al., 1996). Other studies found no sex differences in the assessment of cognitive impairment (Bozikas et al., 2010) in chronic SCZ patients or in patients with a FEP (Zhang et al., 2012).

In BD, a significant sex effect on specific neurocognitive measures related to working and verbal memory domains has been found (Baldassano et al., 2005). Specifically, males performed better than females in working memory tasks, whereas females outperformed males in verbal learning and memory recognition tasks (Solé et al., 2022).

Sex differences have been assessed also in emotional intelligence. As for patients presenting a first episode mania (FEM), the Emotional Intelligence Quotient (EIQ) was positively associated with female sex and verbal memory performance (Varo et al., 2022). On the contrary, no significant differences in emotional intelligence between males and females were found in patients presenting a FEP (Casado-Ortega et al., 2021). Interestingly, while the EIQ did not differed in FEM in comparison with healthy controls (HC) and BD (Solé et al., 2022), emotional intelligence (EI) was found to be already impaired in FEP patients at onset, representing this impairment a stable pattern and a relevant feature of SCZ (Green et al., 2012).

Both SCZ and BD are frequently preceded by the emergence of prodromal symptoms that can typically last months or years (Barajas et al., 2017; Conroy et al., 2018; Kahn et al., 2015). Sex differences in SCZ are present in prodromes too, with males displaying poorer premorbid functioning than females, including greater social withdrawal, isolation, and poor self-care before the FEP (Mendrek and Mancini-Marïe, 2016). There is less information about sex differences during the BD prodrome, particularly during the prodrome to a FEM. Characterizing the particular features of each sex prodrome for both BD and SCZ might help recognizing patients with a higher risk of developing a first episode. Similarly, identifying the clinical variables, psychosocial functioning and neurocognitive characteristics that differed in males and females might help shaping specific tailored early treatment strategies. Our main aim is to identify sex differences in patients that experienced their first FEM (or FEP), with onset in late adolescence or adulthood, and to compare the specific features that characterized males (or females) with a FEM (or a FEP). We selected participants aged 18 and above to focus on the adult onset of the disorder, which presents distinct clinical characteristics from the earlier presentation. Finally, the specific effect exerted by the combination of sex (female vs male) and type of first episode (FEP vs FEM) has been explored to understand their potential interaction on clinical and neuropsychological variables.

2. Material and methods

2.1. Participants

The cohort of the present cross-sectional study has been drawn from the "Prodromes and Predictors in First Episode Mania and Psychosis" – ProPreF project, a two year-study focused on prodromes, predictors and longitudinal outcomes in patients presenting a FEM/FEP, described elsewhere (Verdolini et al., 2022). This multicentric study included the Bipolar and Depressive Disorders Unit of IDIBAPS-Hospital Clínic in Barcelona, FIDMAG Research Foundation and the Institut Pere Mata. All centers are members of the Spanish Network Center for Biomedical Research in Mental Health (CIBERSAM) (Salagre et al., 2019).

Subjects in the early stages of the disease that presented a FEP or FEM were recruited. The inclusion criteria for patients were: (I) age between 18 and 45 years at the time of first evaluation; (II) having experienced their FEP/FEM along the previous four years; (III) had their FEP/FEM at 18 years old or later (IV) being in full or partial clinical remission (i.e., after discharge from the hospital) (Verdolini et al., 2022).

Exclusion criteria were the presence of (I) intellectual disability

(defined as intelligence quotient [IQ] <70); (II) any medical condition affecting neuropsychological performance; (III) alcohol/substance dependence in the 12 months previously study inclusion (excluding caffeine and tobacco); (IV) having received electroconvulsive therapy in the year before participation.

The study was carried out following the latest version of the Declaration of Helsinki and it was reviewed by the ethical committee of the three recruiting centers. Participants gave written informed consent prior to study enrollment.

2.2. Procedures

At the time of evaluation, a trained researcher assessed clinical diagnosis of the patients with the semi-structured interview based on the Structured Clinical Interview for DSM Disorders (SCID-I-II) (First and Gibbon, 2004) and diagnoses were confirmed according to DSM-5 criteria (American Psychiatric Association, 2013). Patients meeting the DSM-5 A-D criteria for a manic episode, were categorized as a FEM. Patients presenting at least two of the five symptoms of criterion A for a DSM-5 psychotic disorder and not experienced the DSM-5 A-D criteria for a manic episode, were categorized as a FEP.

The presence of a full FEP or FEM was evaluated by at least two investigators and an agreement was reached on the diagnosis. The diagnosis was based on the summaries of the patients' files, the life charts of psychotic and mood episodes and the assessment of the clinical presentation at first inpatient hospitalization or mental health service presentation.

All assessments were performed by a trained psychiatrist or psychologist. At baseline, all patients underwent a clinical and neuropsychological assessment when they were stable or in partial remission.

2.3. Socio-demographic information

Socio-demographic data (i.e., age, educational level, working status) were collected and stored in an electronic data repository.

2.4. Clinical assessment

Clinical symptoms at the time of evaluation were assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), the Young Mania Rating Scale (YMRS) (Young et al., 1978) and the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). A total score was obtained from each scale. Higher scores correspond to greater severity.

Psychosocial functioning was assessed through the Functional Assessment Short Test (FAST) (Rosa et al., 2007). The FAST assessment refers to the last 15 days and comprises 24 items, which are divided in 6 specific areas of functioning: 1) Autonomy; 2) Occupational functioning; 3) Cognitive functioning; 4) Financial issues; 5) Interpersonal relationships; and 6) Leisure Time. Items can be rated using a 4-point scale, from 0 = no difficulty to 3 = severe difficulty. The global score is calculated by summing up all the scores of each item, ranging from 0 to 72, resulting in a measure of disability where higher scores refer to more serious difficulties.

2.5. Prodromal symptoms

Patients and their caregivers, if they were available, were inquired to retrospectively report prodromal symptoms' duration and type. First, we explained psychosis in clear language. We then provided the patient with the date of their first hospitalization or first contact with the mental health service in order to set a time point for diagnosis. Following this, patients were asked when they first experienced changes in behavior or other prodromal symptoms. During the interview, we used a timeline and asked for important dates in the life of the patients' lives to help with the recall process. Trained evaluators conducted a semi-structured interview with the Bipolar Prodrome Symptom Scale-Retrospective (BPSS-R) (Correll et al., 2007), focusing mainly on prodromic symptoms' type, frequency, and duration. Prodromal symptoms' severity and frequency were rated on an ordinal scale from 0 (absent) to 4 (static lifetime or character trait) (Correll et al., 2014; Correll et al., 2007). Any prodromal symptom independent of severity, frequency, and any episode occurring before the FEM/FEP in the lifetime of the patient, was assessed in the interview. Only those symptoms occurring within 3 years and 1 month before the first full episode displaying at least moderate severity were considered in the analyses (Correll et al., 2014; Correll et al., 2007; Kafali et al., 2019). In addition, symptoms with a frequency score of 4 (static lifetime or character trait) were not included as they are not considered part of the proximal prodrome (Correll et al., 2014, Correll et al., 2007).

Furthermore, information on the use of cannabis and alcohol during the prodromal phase was obtained. The Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982) was used to assess the achievement of developmental goals during the childhood and adolescent periods in the participant's lives (Cannon-Spoor et al., 1982).

2.6. Neurocognitive functioning

The neuropsychological battery measured the following neurocognitive domains: 1. Estimated intelligence quotient (IQ), assessed with the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 1955) vocabulary subtest; 2. Working memory index of the WAIS-III, calculated by the performance on the Digit Span, Arithmetic and Letter-Number Sequencing subtests; 3. Processing speed index of the WAIS-III calculated by the Digit Symbol and Symbol Search subtests); 4. Verbal learning and memory, assessed with the California Verbal Learning Test (CVLT) (Delis et al., 1993); 5. Logical memory, evaluated using the Wechsler Memory Scale, 3rd edition (WMS-III) (Wechsled, 1997); 6. measures of executive functions, evaluated using the Wisconsin Card Sorting Test (WCST) (Berg, 1948). Sustained attention, tested with the Continuous Performance Test–II (CPT-II), version 5 (Conners, 2005); 8. Visual memory: the total score of the immediate recall of Rey-Osterrieth Complex Figure (ROCF) test (Osterrieth, 1944); and 9. Verbal fluency (phonemic and semantic), assessed with the Controlled Oral Word Association Test (COWAT) (Benton, 1967).

Higher scores correspond to better performance in all cognitive domains except for sustained attention.

2.7. Emotional intelligence assessment

Emotional Intelligence (EI) was evaluated using the Spanish version of the Mayer-Salovey-Caruso Intelligence Test (MSCEIT), V2.0 (Mayer et al., 2003). This instrument consists of 141 items and provides eight task scores that measure the four branches of EI: 1. Perceiving Emotions: to recognize and to appraise emotions accurately; 2.Facilitating Emotions: to access or generate feelings when they facilitate thoughts; 3. Understanding Emotions: to understand complex emotions and how emotions transition from one stage to another, to recognize the causes of emotions, and to understand relationships among emotions; 4. Managing Emotions: to stay aware of one's emotions, and to solve emotion-laden problems. The Perceiving Emotions and Facilitating Emotions branches are assigned to the Experiential Area, while the Understanding Emotions and Managing Emotions branches are assigned to the Strategic Area. The test provides an overall score, the EIQ, and also scores in the two areas, in the four branches and in each of the specific tasks. Lower scores indicate poorer performance in EI. The average range of EIQ is 100, with a standard deviation (SD) of 15.

All cognitive end emotional scores were standardized with respect to the subject's age, sex and/or educational level according to standardized normative data found in the test manual.

Table 1
Sex differences in FEM.

Prodromal phase	Groups		Statistics
	F-FEM($n = 33$)	**M-FEM($n = 39$)**	***t* or *χ2*, *p*-value**
Alcohol use (n, %)			8.003, **0.045**
No	15, 53.1	10, 40	
<1 unit/week	5, 16.1	3, 8.1	
1–5 units/week	9, 29	13, 35.1	
>5 units/week	2, 6.5	11, 29.8	
Cannabis use (n, %)			13.698, **0.02**
No	17, 53.1	8, 32	
<1 cig/week	0	3, 8.1	
1–5 cig/week	9, 28.1	6, 16.2	
>5 cig/week	6, 18.8	20, 54.1	
Prodromal symptoms			
Concentration difficulties, yes (n, %)	7, 21.2	18, 46.2	4.906, **0.046**
Irritability, yes (n, %)	18, 54.5	10, 25.6	6.284, **0.016**
Clinical variables			
MADRS (mean ± SD)	6.28 ± 6.065	5.97 ± 5.325	0.223, 0.824
YMRS (mean ± SD)	1.39 ± 1.694	2.13 ± 2.931	−1.27, 0.208
PANSS Total Score (mean ± SD)	40.55 ± 9.504	41.18 ± 11.461	−0.257, 0.208
PANSS positive symptoms (mean ± SD)	7.48 ± 1.121	8.21 ± 2.549	−1.512, 0.135
PANSS negative symptoms(mean ± SD)	10.39 ± 4.387	10.37 ± 5.17	0.022, 0.982
PANSS general psychopathology (mean ± SD)	22.67 ± 6.06	22.61 ± 5.833	0.043, 0.966
FAST Total Score (mean ± SD)	15.36 ± 11.48	20.41 ± 14.649	−1.611, 0.112
FAST autonomy (mean ± SD)	1.82 ± 2.007	2.72 ± 3.095	−1.425, 0.159
FAST working functioning (mean ± SD)	5.64 ± 5.6	7.95 ± 6.018	−1.663, 0.101
FAST cognitive functioning (mean ± SD)	2.85 ± 2.347	3.51 ± 2.978	−1.043, 0.301
FAST finances (mean ± SD)	0.18 ± 0.584	0.54 ± 1.282	−1.476, 0.145
FAST relationships (mean ± SD)	2.82 ± 3.147	3.89 ± 3.985	−1.257, 0.213
FAST leisure (mean ± SD)	2.06 ± 2.061	1.86 ± 1.858	0.415, 0.679
PAS (mean ± SD)	11.12 ± 8.069	12.49 ± 7.301	−0.747, 0.457
Neuropsychological variables			
Intellectual quotient (mean ± SD)	100.41 ± 10.762	108.29 ± 13.612	−2.494, **0.016**
Working memory (mean ± SD)	86.52 ± 11.956	100.27 ± 14.786	−3.876, **<0.001**
Processing speed (mean ± SD)	99.15 ± 16.868	101.71 ± 16.939	−0.576, 0.567
Verbal memory (mean ± SD)	234.765 ± 43.559	220.272 ± 53.606	1.096, 0.278
Logical memory (mean ± SD)	209.778 ± 36.982	205.538 ± 47.662	0.362, 0.719
Executive function (mean ± SD)	134.876 ± 23.947	137.818 ± 22.345	−0.476, 0.636
Sustained attention (mean ± SD)	133.298 ± 15.611	127.277 ± 10.95	1.593, 0.119
Visual memory (mean ± SD)	56.95 ± 12.536	56.28 ± 6.654	0.249, 0.815
Verbal fluency (mean ± SD)	77.305 ± 14.45	86.047 ± 16.356	−1.980, 0.053
Emotional intelligence variables			
MSCEIT EIQ (mean ± SD)	120.09 ± 13.918	107.46 ± 17.363	2.733, **0.009**
MSCEIT Experiential - CIEX (mean ± SD)	113.74 ± 12.832	101.65 ± 14.819	2.957, **0.005**
MSCEIT Strategic - CIES (mean ± SD)	106.43 ± 12.116	101.57 ± 15.337	1.193, 0.240
MSCEIT Perceiving emotions - CIEP (mean ± SD)	113.61 ± 13.079	101.25 ± 15.264	2.985, **0.005**
MSCEIT Facilitating Emotions - CIEF (mean ± SD)	108.77 ± 12.216	100.74 ± 13.525	2.093, **0.042**
MSCEIT Understanding emotions - CIEC (mean ± SD)	104.22 ± 13.253	101.83 ± 12.253	0.633, 0.530
MSCEIT Managing emotions - CIEM (mean ± SD)	101.96 ± 22.542	100.71 ± 17.026	0.214, 0.832

Abbreviations: EIQ = Emotional Intelligence Quotient; FAST = Functional Assessment Staging; FEM = First Episode Mania; F=Females; M = Males; MADRS = Montgomery-Asberg Depression Rating Scale; MSCEIT = Mayer-Salovey-Caruso Emotional Intelligence Test; PANSS=Positive and Negative Syndrome Scale; PAS=Premorbid Adjustment Scale; SD=Standard Deviation; YMRS=Young Mania Rating Scale. Bold for statistically significant *p* values.

2.8. Statistical analysis

Descriptive statistics were used to define sample characteristics. Continuous variables were given as mean value ± SD and were compared using Student *t*-test. Categorical variables were expressed as total number and percentages and differences among groups were assessed through Chi-square ($\chi 2$) or Fisher's exact test as appropriate.

Principal Component Analysis (PCA) was used for neuropsychological variables, to reduce measures to a few principal domains and avoid repetitive information of separate test cognitive variables (for example, semantic cued recall (Short and Long Delay) of CVLT and free recall). The neuropsychological assessment was represented by five factor scores (verbal memory, logical memory, executive functions, sustained attention, and verbal fluency) (Supporting Table 1).

First, clinical and neuropsychological variables were compared between sexes (males and females) and diagnostic groups (FEM and FEP). Next, performance on clinical and socio-demographic, neuropsychological variables and psychosocial functioning was also compared between diagnostic groups through general linear models (GLM), with sex and group as main effects and the group by sex interactions. In case of significant interactions between sex and group, post-hoc Bonferroni pairwise comparisons were applied. In all GLM, Estimated Marginal Means or adjusted prevalence and the 95 % Interval of confidence (IC) were reported for each variable of interest. All analyses were performed with the IBM Statistical Package for Social Sciences version 23. Statistical significance was set at $p < 0.05$.

3. Results

The total sample consisted of 113 subjects with a mean age of 27.1 years ($SD = 6.58$, range 18–43). The sample included 72 (66.7 %) patients with a FEM (females: 33, 45.83 %), and 41 (36.28 %) patients with a FEP (females: 19, 46.34 %). No differences between diagnostic groups were identified in socio-demographic variables.

3.1. Sex differences in FEM

Differences were found in cannabis and alcohol use during the

Table 2
Sex differences in FEP

Prodromal phase	Groups		Statistics
	F-FEP($n = 19$)	M-FEP($n = 22$)	*t or χ2,* p-value
Alcohol use (n, %)			7.553,
No	10, 52.6	11, 50	**0.035**
<1 unit/week	1, 5.3	0	
1–5 units/week	8, 42.1	5, 22.7	
>5 units/week	0	6, 27.3	
Cannabis use (n, %)			0.46,
No	10, 52.6	13, 59.09	1
<1 cig/week	1, 5.3	1, 4.55	
1–5 cig/week	4, 21.1	4, 18.18	
>5 cig/sem	4, 21.1	4, 18.18	
Prodromal symptoms			
Communication difficulty, yes (n, %)	1, 5.3	7, 31.8	5.115, **0.05**
Clinical variables			
MADRS (mean ± SD)	9.50 ± 8.009	8.86 ± 6.374	0.274, 0.786
YMRS (mean ± SD)	1.33 ± 2	1.90 ± 2.300	0.830, 0.412
PANSS Total Score (mean ± SD)	52.50 ± 11.346	52.86 ± 20.043	0.417, 0.679
PANSS positive symptoms (mean ± SD)	10.33 ± 4.665	10.05 ± 4.260	0.198, 0.844
PANSS negative symptoms(mean ± SD)	14.11 ± 4.351	15.81 ± 8.524	0.763, 0.450
PANSS general psychopathology (mean ± SD)	28.06 ± 5.589	27 ± 9.386	0.417, 0.679
FAST Total Score (mean ± SD)	23.00 ± 8.725	27.64 ± 14.114	1.272, 0.212
FAST autonomy (mean ± SD)	2.67 ± 2	4.38 ± 2.872	2.186, **0.04**
FAST working functioning (mean ± SD)	8.61 ± 4.960	9.09 ± 5.631	0.286, 0.776
FAST cognitive functioning (mean ± SD)	4.50 ± 2.595	5.91 ± 4.034	1.335, 0.190
FAST finances (mean ± SD)	1.11 ± 1.568	0.64 ± 1.049	1.099, 0.281
FAST relationships (mean ± SD)	3.78 ± 3.209	5.77 ± 3.491	1.880, 0.068
FAST leisure (mean ± SD)	2.33 ± 2.029	2.05 ± 1.588	0.491, 0.627
PAS (mean ± SD)	14.94 ± 8.781	16.90 ± 9.049	0.685, 0.498
Neuropsychological variables			
Intellectual quotient (mean ± SD)	100.63 ± 13.769	102.05 ± 12.250	−0.321, 0.750
Working memory (mean ± SD)	85.08 ± 10.452	88.29 ± 16.885	−0.641, 0.527
Processing speed (mean ± SD)	97.67 ± 11.331	85.95 ± 14.939	2.601, **0.014**
Verbal memory (mean ± SD)	224.632 ± 39.975	175.584 ± 57.593	2.961, **0.006**
Logical memory (mean ± SD)	188.091 ± 44.78	178.905 ± 41.921	0.579, 0.568
Executive function (mean ± SD)	143.483 ± 9.379	134.393 ± 20.287	1.684, 0.105
Sustained attention (mean ± SD)	134.66 ± 16.544	137.935 ± 16.02	−0.581, 0.566
Visual memory (mean ± SD)	55.64 ± 6.812	54.42 ± 7.191	0.493, 0.526
Verbal fluency (mean ± SD)	78.573 ± 10.268	67.762 ± 16.412	2.328, **0.027**
Emotional intelligence variables			
MSCEIT EIQ (mean ± SD)	119.10 ± 17.032	101.67 ± 18.112	2.322, **0.031**
MSCEIT Experiential - CIEX (mean ± SD)	108.8 ± 13.045	95 ± 14.715	2.331, **0.03**
MSCEIT Strategic - CIES (mean ± SD)	104.40 ± 11.207	97.42 ± 11.912	1.414, 0.173
MSCEIT Perceiving emotions - CIEP (mean ± SD)	106.00 ± 14.119	96.58 ± 13.166	1.606, 0.125
MSCEIT Facilitating Emotions - CIEF (mean ± SD)	111.5 ± 15.707	96.91 ± 13.166	2.122, **0.047**
MSCEIT Understanding emotions - CIEC (mean ± SD)	101.70 ± 11.186	103.27 ± 12.571	0.303, 0.765
MSCEIT Managing emotions - CIEM (mean ± SD)	105.20 ± 11.094	93.33 ± 13.819	2.234, **0.037**

Abbreviations: EIQ = Emotional Intelligence Quotient; FAST = Functional Assessment Staging; FEP=First Episode Psychosis; F=Females; M = Males; MADRS = Montgomery-Asberg Depression Rating Scale; MSCEIT = Mayer-Salovey-Caruso Emotional Intelligence Test; PANSS=Positive and Negative Syndrome Scale; PAS=Premorbid Adjustment Scale; SD=Standard Deviation; YMRS=Young Mania Rating Scale. Bold for statistically significant p values.

prodromal phase (Table 1).

The prodrome *Concentration Difficulties* was predominant among males ($p = 0.046$). However, *Irritability* was more frequent among females ($p = 0.016$).

No differences were found as for clinical variables (Table 1). Significantly higher IQ scores were found in FEM males in comparison with females ($p = 0.016$) and performed better at working memory evaluation ($p < 0.001$).

FEM females obtained better results than males at EIQ ($p = 0.009$), in the Experiential Area (CIEX; $p = 0.005$) and in the specific EIQ branches: Perceiving emotion (CIEP; $p = 0.005$) and Facilitating Emotions (CIEF; $p = 0.042$).

3.2. Sex differences in FEP

During the prodromal phase, there were no significant differences between males and females in the use of cannabis (Table 2). Nevertheless, there were significant differences in alcohol use ($p = 0.035$).

As for prodromal symptoms, *Communication difficulties* were predominant among males ($p = 0.05$).

No differences were reported in terms of clinical variables (Table 2). The two groups differed in the autonomy FAST subdomain, with worse autonomy for males ($p = 0.04$).

FEP females attained higher scores than FEP males at processing speed estimation ($p = 0.014$), performed better at verbal memory evaluation ($p = 0.006$) and verbal fluency assessment ($p = 0.027$).

Females obtained better results in EIQ than males ($p = 0.031$), showing differences in the Experiential area (CIEX; $p = 0.03$) and in the Facilitating Emotions (CIEF; $p = 0.047$) and Managing emotions (CIEM; $p = 0.037$) branches.

3.3. Differences in FEM and FEP females

No difference was reported in cannabis and alcohol use (Table 3).

The prodromes *Speech pressure* ($p = 0.014$), *Sleep decrease* ($p = 0.004$), *Increased creativity* ($p = 0.06$) and *Lability* ($p = 0.007$) were significantly more common in FEM females. On the contrary, *Decreased energy* ($p = 0.014$) was more frequent in the group of FEP females.

Table 3
Differences in females with a FEM or a FEP.

Prodromal phase	Groups		Statistics
	F-FEM(n = 33)	**F-FEP(n = 19)**	***t or χ2,* p-value**
Alcohol use (n, %)			2.509,
No	15, 48.4	10, 52.6	0.509
<1 unit/week	5, 16.1	1, 5.3	
1–5 units/week	9, 29	8, 42.1	
>5 units/week	2, 6.5	0	
Cannabis use (n, %)			1.904,
No	17, 53.1	10, 52.6	0.68
<1	0	1, 5.3	
cig/week	9, 28.1	4, 21.1	
1–5 cig/week	6, 18.8	4, 21.1	
>5 cig/sem			
Prodromal symptoms			
Decreased energy, yes (n, %)	0	4, 21.1	8.647, **0.014**
Lability, yes (n, %)	16, 48.5	2, 10.5	8.579, **0.007**
Speech pressure, yes (n, %)	7, 21.2	0	6.981, **0.029**
Sleep decrease, yes (n, %)	11, 33.3	0	11.653, **0.004**
Increased creativity, yes (n, %)	10, 30.3	0	10.428, **0.006**
Clinical variables			
MADRS (mean ± SD)	6.28 ± 6.065	9.50 ± 8.009	−1.483, 0.149
YMRS (mean ± SD)	1.39 ± 1.694	1.33 ± 2.000	0.109, 0.914
PANSS Total Score (mean ± SD)	40.55 ± 9.504	52.50 ± 11.346	−3.802, **0.001**
PANSS positive symptoms (mean ± SD)	7.48 ± 1.121	10.33 ± 4.665	−2.551, **0.020**
PANSS negative symptoms(mean ± SD)	10.39 ± 4.387	14.11 ± 4.351	−2.907, **0.006**
PANSS general psychopathology (mean ± SD)	22.67 ± 6.06	28.06 ± 5.589	−3.193, **0.003**
FAST Total Score (mean ± SD)	15.36 ± 11.48	23 ± 8.725	−2.663, **0.011**
FAST autonomy (mean ± SD)	1.82 ± 2.007	2.67 ± 2.000	−1.446, 0.157
FAST working functioning (mean ± SD)	5.64 ± 5.6	8.61 ± 4.960	−1.954, 0.058
FAST cognitive functioning (mean ± SD)	2.85 ± 2.347	4.50 ± 2.595	−2.245, **0.032**
FAST finances (mean ± SD)	0.18 ± 0.584	1.11 ± 1.568	−2.425, **0.025**
FAST relationships (mean ± SD)	2.82 ± 3.147	3.78 ± 3.209	−1.027, 0.311
FAST leisure (mean ± SD)	2.06 ± 2.061	2.33 ± 2.029	−0.456, 0.651
PAS (mean ± SD)	11.12 ± 8.069	14.94 ± 8.781	−1.528, 0.136
Neuropsychological variables			
Intellectual quotient (mean ± SD)	100.41 ± 10.762	100.63 ± 13.769	−0.053, 0.958
Working memory (mean ± SD)	86.52 ± 11.956	85.08 ± 10.452	0.390, 0.700
Processing speed (mean ± SD)	99.15 ± 16.868	97.67 ± 11.331	0.736, 1.481
Verbal memory (mean ± SD)	234.765 ± 43.559	224.632 ± 39.975	0.764, 0.450
Logical memory (mean ± SD)	209.778 ± 36.982	188.091 ± 44.780	1.492, 0.151
Executive function (mean ± SD)	134.876 ± 23.947	143.483 ± 9.379	−1.617, 0.115
Sustained attention (mean ± SD)	133.298 ± 15.661	134.66 ± 16.544	−0.256, 0.800
Visual Memory (mean ± SD)	56.95 ± 12.536	55.64 ± 6.812	−0.418, 0.679
Verbal fluency (mean ± SD)	77.305 ± 14.45	78.573 ± 10.268	−0.312, 0.757
Emotional intelligence variables			
MSCEIT EIQ (mean ± SD)	120.09 ± 13.918	119.10 ± 17.032	0.161, 0.874
MSCEIT Experiential - CIEX (mean ± SD)	113.74 ± 12.832	108.8 ± 13.045	1.005, 0.329
MSCEIT Strategic - CIES (mean ± SD)	106.43 ± 12.116	104.40 ± 11.207	0.468, 0.646
MSCEIT Perceiving emotions - CIEP (mean ± SD)	113.61 ± 13.079	106.00 ± 14.119	1.454, 0.165
MSCEIT Facilitating Emotions - CIEF (mean ± SD)	108.77 ± 12.216	111.5 ± 15.707	−0.486, 0.634
MSCEIT Understanding emotions - CIEC (mean ± SD)	104.22 ± 13.253	101.70 ± 11.186	0.561, 0.581
MSCEIT Managing emotions - CIEM (mean ± SD)	101.96 ± 22.542	105.20 ± 11.094	−0.553, 0.584

Abbreviations: EIQ = Emotional Intelligence Quotient; FAST = Functional Assessment Staging; FEM = First Episode Mania; FEP=First Episode Psychosis; F=Females; M = Males; MADRS = Montgomery-Asberg Depression Rating Scale; MSCEIT = Mayer-Salovey-Caruso Emotional Intelligence Test; PANSS=Positive and Negative Syndrome Scale; PAS=Premorbid Adjustment Scale; SD=Standard Deviation; YMRS=Young Mania Rating Scale. Bold for statistically significant p values.

PANSS total scores were significantly higher in FEP females (p = 0.001) plus all PANSS subscales punctuations. FEP Females also obtained higher FAST total score and consequently worse psychosocial functioning (p = 0.011), particularly in the FAST cognitive functioning (p = 0.032) and FAST finances (p = 0.025) subdomains.

No differences on neuropsychological variables or EI were observed (Table 3).

3.4. Differences in FEM and FEP males

There were no significant differences between males with a FEM or a FEP as for the use of alcohol (Table 4). Nonetheless, there were significant differences as for the use of cannabis (p = 0.023).

FEP males reported more frequently than FEM males the prodromal symptoms *Isolation* (p = 0.047) and *Depression* (p = 0.007). The prodromal symptoms more frequently reported by FEM males were *Agitation* (p = 0.018), *Mood elevation* (p = 0.001), *Speech pressure* (p = 0.02), *Racing thoughts* (p = 0.018), *Increased energy* (p < 0.001), *Decreased need for sleep* (p = 0.018), *Increased self-esteem* (p = 0.002) and *Increase creativity* (p = 0.002).

Differences were found for clinical variables: PANSS total score (p = 0.006), PANSS positive symptoms (p = 0.042) and PANSS negative symptoms (p = 0.003) were higher in FEP than FEM males.

The FAST domains of autonomy and cognitive functioning were significantly worse in the FEP group (p = 0.047 and p = 0.021, respectively).

Significant differences were reported in several neuropsychological variables with better results in males with a FEM than a FEP in working memory (p = 0.021), processing speed (p = 0.001), verbal memory (p = 0.01) and verbal fluency (p = 0.001). FEP males accomplished a better

Table 4
Differences in males with a FEM or a FEP.

Prodromal phase	Groups		Statistics
	M-FEM(n = 39)	**M-FEP(n = 22)**	***t or χ2,* p-value**
Alcohol use (n, %)			4.015,
No	10, 40	11, 50	0.244
<1 unit/week	3, 8.1	0	
1–5 units/week	13, 35.1	5, 22.7	
>5 units/week	11, 29.76	6, 27.3	
Cannabis use (n, %)			9.075,
No	8, 32	13, 59.09	**0.027**
<1 cig/week	3, 8.1	1, 4.55	
1–5 cig/week	6, 16.2	4, 18.18	
>5 cig/sem	20, 54.1	4, 18.18	
Prodromal symptoms			
Isolation, yes (n, %)	9, 23.1	11, 50	4.627, **0.047**
Depression, yes (n, %)	1, 2.6	6, 27.3	8.453, **0.007**
Agitation, yes (n, %)	16, 41	2, 9.1	6.896, **0.018**
Mood elevation, yes (n, %)	17, 43.6	1, 4.5	10,380, **0.001**
Speech pressure, yes (n, %)	16, 41	1, 4.5	9.312, **0.02**
Racing thoughts, yes (n, %)	15, 38.5	2, 9.1	6.036, **0.018**
Increased energy, yes (n, %)	22, 56.4	1. 4.5	16.108, **<0.001**
Decreased need for sleep, yes (n, %)	16, 41	2, 9.1	6.896, **0.018**
Increased self-esteem, yes (n, %)	16, 41	1, 4.5	9.312, **0.002**
Increased creativity, yes (n, %)	13, 33.3	0	9.319, **0.002**
Clinical variables			
MADRS (mean ± SD)	5.97 ± 5.325	8.86 ± 6.374	−1.761, 0.087
YMRS (mean ± SD)	2.13 ± 2.931	1.90 ± 2.300	0.325, 0.746
PANSS Total Score (mean ± SD)	41.18 ± 11.461	52.86 ± 20.043	−2.854, **0.006**
PANSS positive symptoms (mean ± SD)	8.21 ± 2.549	10.05 ± 4.260	−2.077, **0.042**
PANSS negative symptoms(mean ± SD)	10.37 ± 5.17	15.81 ± 8.524	−3.057, **0.003**
PANSS general psychopathology (mean ± SD)	22.61 ± 5.833	27 ± 9.386	−1.948, 0.061
FAST Total Score (mean ± SD)	20.41 ± 14.649	27.64 ± 14.114	−1.876, 0.067
FAST autonomy (mean ± SD)	2.72 ± 3.095	4.38 ± 2.872	−2.044, **0.047**
FAST working functioning (mean ± SD)	7.95 ± 6.018	9.09 ± 5.631	−0.736, 0.465
FAST cognitive working (mean ± SD)	3.51 ± 2.978	5.91 ± 4.034	−2.420, **0.021**
FAST finances (mean ± SD)	0.54 ± 1.282	0.64 ± 1.049	−0.312, 0.756
FAST relationships (mean ± SD)	3.89 ± 3.985	5.77 ± 3.491	−1.897, 0.064
FAST leisure (mean ± SD)	1.86 ± 1.858	2.05 ± 1.588	−0.396, 0.694
PAS (mean ± SD)	12.49 ± 7.301	16.90 ± 9.049	−1.925, 0.063
Neuropsychological variables			
Intellectual quotient (mean ± SD)	108.29 ± 13.612	102.05 ± 12.250	1.675, 0.102
Working memory (mean ± SD)	100.27 ± 14.786	88.29 ± 16.885	2.441, **0.021**
Processing speed (mean ± SD)	101.71 ± 16.939	85.95 ± 14.939	3.439, **0.001**
Verbal memory (mean ± SD)	220.272 ± 53.606	175.584 ± 57.593	2.701, **0.010**
Logical memory (mean ± SD)	205.538 ± 47.662	178.905 ± 41.921	1.929, 0.061
Executive function (mean ± SD)	137.818 ± 22.345	134.393 ± 20.287	0.548, 0.587
Sustained attention (mean ± SD)	127.227 ± 10.95	137.935 ± 16.02	−2.537, **0.017**
Visual memory (mean ± SD)	56.28 ± 6.654	54.42 ± 7.191	0.89, 0.38
Verbal fluency (mean ± SD)	86.047 ± 16.356	67.762 ± 16.412	3.693, **0.001**
Emotional intelligence variables			
MSCEIT EIQ (mean ± SD)	107.46 ± 17.363	101.67 ± 18.112	0.917, 0.369
MSCEIT Experiential - CIEX (mean ± SD)	101.65 ± 14.819	95 ± 14.715	1.266, 0.218
MSCEIT Strategic - CIES (mean ± SD)	101.57 ± 15.337	97.42 ± 11.912	0.882, 0.385
MSCEIT Perceiving emotions - CIEP (mean ± SD)	101.25 ± 15.264	96.58 ± 13.166	0.950, 0.351
MSCEIT Facilitating Emotions - CIEF (mean ± SD)	100.74 ± 13.525	96.91 ± 13.166	−0.315, 0.755
MSCEIT Understanding emotions - CIEC (mean ± SD)	101.83 ± 12.253	103.27 ± 12.571	−0.315, 0.756
MSCEIT Managing emotions - CIEM (mean ± SD)	100.71 ± 17.026	93.33 ± 13.819	1.394, 0.175

Abbreviations: EIQ = Emotional Intelligence Quotient; FAST = Functional Assessment Staging; FEM = First Episode Mania; FEP=First Episode Psychosis; F=Females; M = Males; MADRS = Montgomery-Asberg Depression Rating Scale; MSCEIT = Mayer-Salovey-Caruso Emotional Intelligence Test; PANSS=Positive and Negative Syndrome Scale; PAS=Premorbid Adjustment Scale; SD=Standard Deviation; YMRS=Young Mania Rating Scale. Bold for statistically significant p values.

perform at sustained attention evaluation ($p = 0.017$). No differences on emotional intelligence scores were observed.

3.5. General linear model analysis

There were significant main effects for sex for neuropsychological variables, namely working memory and verbal memory (Table 5). While females performed better in verbal memory ($\chi^2 = 9.038$, $p = 0.003$), males obtained better results in working memory ($\chi^2 = 7.627$, $p = 0.006$). Furthermore, main effects for sex were reported for the MSCEIT task. In particular, females obtained a higher EIQ ($\chi^2 = 13.20$, $p < 0.001$) and performed better than males in the Experiential Area ($\chi^2 = 13.63$, $p < 0.001$), and in the MSCEIT branches Perceiving emotions ($\chi^2 = 9.504$, $p < 0.001$) and Facilitating emotions ($\chi^2 = 10.17$, $p < 0.001$).

There were significant main effects for group for most of the clinical features. Higher MADRS ($\chi^2 = 6.170$, $p = 0.013$) and PANSS scores (PANSS positive symptoms: $\chi^2 = 14.912$, $p < 0.001$; PANSS negative symptoms: $\chi^2 = 17.084$, $p < 0.001$; PANSS general psychopathology $\chi^2 = 13.938$, $p < 0.001$; and PANSS total scores $\chi^2 = 21.382$, $p < 0.001$) were reported for FEP than FEM patients. In terms of functioning, FEP patients also reported higher FAST scores ($\chi^2 = 8.815$, $p = 0.003$) in comparison with FEM patients, indicating worse psychosocial functioning.

As for neuropsychological performance, there were significant main

Table 5
Main effects and interactions for clinical and neurocognitive variables.

	FEM (n = 72)		FEP (n = 41)		Effect					
(mean ± SD)	Male (n = 39)	Female (n = 33)	Male (n = 22)	Female (n = 19)	Group		Sex		GroupXSex	
	Mean (IC 95 %)	Mean (IC 95 %)	Mean (IC 95 %)	Mean (IC 95 %)	X^2	p	X^2	p	X^2	p
Socio-demographic variables										
Age	27.64 (25.60–29.69)	26.39 (24.17–28.62)	26.41 (23.69–29.13)	28 (25.07–30.93)	0.021	0.884	0.018	0.893	1.231	0.267
Clinical variables										
MADRS	5.97 (4.03–7.92)	6.28 (4.16–8.40)	8.86 (6.24–11.48)	9.50 (6.67–12.33)	6.170	**0.013**	0.150	0.699	0.019	0.891
YMRS	2.13 (1.40–2.85)	1.39 (0.61–2.18)	1.90 (0.92–2.89)	1.33 (0.27–2.40)	0.095	0.758	2.009	0.156	0.031	0.860
PANSS positive symptoms	8.21 (7.25–9.18)	7.48 (6.45–8.52)	10.05 (8.75–11.35)	10.33 (8.93–11.74)	14.912	**<0.001**	0.131	0.717	0.695	0.405
PANSS negative symptoms	10.37 (8.61–12.13)	10.39 (8.50–12.29)	15.81 (13.44–18.18)	14.11 (11.55–16.67)	17.084	**<0.001**	0.570	0.450	0.605	0.437
PANSS general psychopathology	22.61 (20.52–24.69)	22.67 (20.43–24.90)	27 (24.20–29.80)	28.06 (25.03–31.08)	13.938	**<0.001**	0.182	0.670	0.144	0.704
PANSS total	41.18 (37.12–45.25)	40.55 (36.18–44.91)	52.86 (47.39–58.32)	52.50 (46.59–58.41)	21.382	**<0.001**	0.038	0.845	0.003	0.956
FAST total	20.41 (16.35–24.46)	15.36 (11.07–19.66)	27.64 (22.38–32.89)	23 (17.19–28.81)	8.815	**0.003**	3.735	0.053	0.007	0.935
PAS total	12.49 (9.98–14.99)	11.12 (8.40–13.84)	16.90 (13.49–20.32)	14.94 (11.36–18.63)	6.712	**0.010**	1.094	0.296	0.035	0.852
Neuropsychological variables										
Intellectual quotient	108.29 (103.96–112.62)	100.41 (95.94–104.89)	102.05 (96.53–107.58)	100.63 (94.60–106.65)	1.322	0.250	3.152	0.076	1.514	0.218
Working memory	100.27 (95.42–105.11)	86.52 (81.41–91.62)	88.29 (81.86–94.73)	85.08 (77.72–92.43)	4.768	**0.029**	7.627	**0.006**	2.939	0.086
Processing speed	101.71 (96.29–107.13)	99.15 (93.34–104.96)	85.95 (79.02–92.87)	97.67 (89.87–105.46)	6.648	**0.010**	1.875	0.171	4.559	**0.033**
Verbal memory	220.272 (202.606–237.937)	234.765 (215.738–253.791)	175.584 (153.759–197.409)	224.633 (200–85-248.415)	6.727	**0.009**	9.038	**0.003**	2.673	0.102
Logical memory	205.383 (188.989–221.776)	209.779 (193.048–226.510)	178.905 (159.585–198.225)	188.091 (165.358–210.825)	6.194	**0.013**	0.493	0.483	0.061	0.805
Executive function	137.818 (130.597–145.039)	134.876 (126.991–142.761)	134.394 (124.917–143.870)	143.483 (132.738–154.229)	0.323	0.570	0.454	0.500	1.740	0.187
Sustained attention	127.277 (122.128–132.427)	133.298 (127.638–138.959)	137.935 (131.573–144.297)	134.66 (127.501–141.82)	3.693	0.055	0.193	0.661	2.209	0.137
Visual memory	56.28 (53.14–59.43)	56.95 (53.50–60.41)	54.42 (50.43–58.41)	55.64 (51.12–60.17)	0.667	0.414	0.238	0.626	0.020	0.887
Verbal fluency	86.05 (80.56–91.53)	77.30 (71.38–83.23)	67.76 (60.92–74.61)	78.57 (71.31–85.83)	6.752	**0.009**	0.100	0.752	8.913	**0.003**
Social cognition variables										
MSCEIT EIQ	107.46 (101.09–113.83)	120.09 (113.44–126.74)	101.67 (92.66–110.67)	119.10 (109.24–128.96)	0.672	0.412	13.20	**<0.001**	0.336	0.562
MSCEIT Experiential - CIEX	101.65 (96.14–107.16)	113.74 (108.23–119.25)	95 (87.37–102.63)	108.80 (100.44–117.16)	2.733	0.098	13.63	**<0.001**	0.060	0.807
MSCEIT Strategic - CIES	101.57 (96.34–106.79)	106.43 (101.21–111.66)	97.42 (90.18–104.65)	104.40 (76.47–112.33)	0.865	0.352	3.178	0.075	0.101	0.751
MSCEIT Perceiving emotions - CIEP	101.25 (95.80–106.70)	113.61 (108.04–119.18)	96.58 (88.87–104.30)	106 (97.55–114.45)	3.020	0.082	9.504	**<0.001**	0.173	0.677
MSCEIT Facilitating Emotions - CIEF	100.74 (95.26–106.22)	108.77 (103.17–114.38)	96.91 (88.98–104.83)	11.5 (103.19–119-81)	0.024	0.876	10.17	**<0.001**	0.855	0.355
MSCEIT Understanding emotions - CIEC	101.83 (96.94–106.73)	104.22 (99.22–109.22)	103.27 (96.04–110.51)	101.70 (94.11–109.29)	0.028	0.867	0.016	0.900	0.379	0.538
MSCEIT Managing emotions - CIEM	100.71 (93.72–107.70)	101.96 (94.82–109.10)	93.33 (83.45–103.22)	105.20 (94.37–116.03)	0.208	0.648	2.100	0.147	1.376	0.241

Abbreviations: EIQ = Emotional Intelligence Quotient; FAST = Functional Assessment Staging; FEM = First Episode Mania; FEP=First Episode Psychosis; IC = Lower–Upper values within Wald Confidence Interval of 95 %; MADRS = Montgomery-Asberg Depression Rating Scale; MSCEIT = Mayer-Salovey-Caruso Emotional Intelligence Test; PANSS=Positive and Negative Syndrome Scale; PAS=Premorbid Adjustment Scale; SD=Standard Deviation; YMRS=Young Mania Rating Scale. Bold for statistically significant p values.

effects for group for working memory ($\chi^2 = 4.768$, $p = 0.029$), processing speed ($\chi^2 = 6.648$, $p = 0.010$), verbal memory ($\chi^2 = 6.727$, $p = 0.009$), logical memory ($\chi^2 = 6.194$, $p = 0.013$) and verbal fluency ($\chi^2 = 6.752$, $p = 0.009$), with lower scores for FEP patients than FEM ones. Also, premorbid adjustment was significantly poorer for FEP than FEM patients ($\chi^2 = 6.712$, $p = 0.010$).

In addition, there were significant group by sex interactions for few neuropsychological variables, namely processing speed ($\chi^2 = 4.559$, $p = 0.033$) and verbal fluency ($\chi^2 = 8.913$, $p = 0.003$). Post-hoc Bonferroni revealed that FEP males performed worse than FEM males in processing speed (Mean Difference-MD = 15.76, Confidence Interval-CI = 3.92–27.60, $p = 0.003$). Similarly, FEP males performed worse than FEM males (MD = 18.28, CI = 30.09–6.48, $p < 0.001$) in verbal fluency (see Fig. 1). Moreover, FEM females performed better than FEP males patients in processing speed (MD = 13.20, 95 % CI = -11.60–14.57, $p = 0.025$).

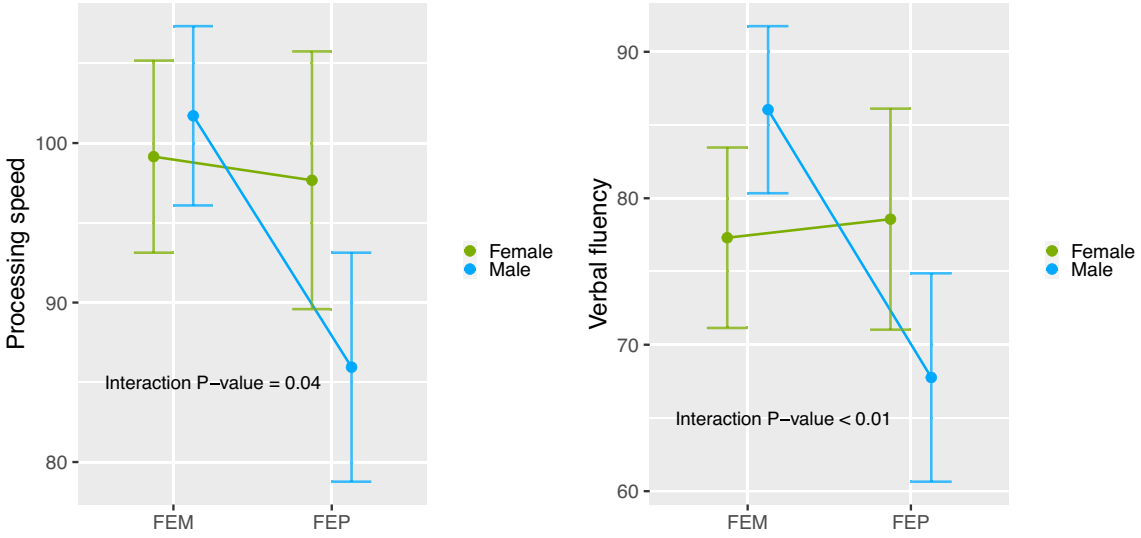

Fig. 1. Significant group by sex interac3on in neuropsychological variables. Abbreviations: FEM = First Episode Mania; FEP=First Episode Psychosis.

4. Discussion

The present study explored the differences between females and males in prodromal symptoms, clinical variables, functioning and neuropsychological characteristics of individuals with a FEM or a FEP. The main finding emerging from our analyses is the presence of significant sex effect and group by sex interaction on specific neurocognitive cognition and emotional intelligence measures.

Females performed better than males in verbal memory and obtained a higher EIQ and higher scores in specific EI branches (i.e. Perceiving emotions and Facilitating emotions). Conversely, males obtained better results in working memory. In a study assessing whether male FEP patients have greater neurocognitive impairment than females at illness onset, FEP females outperformed males on verbal memory whilst males presented a better cognitive performance on reaction time, visual memory, and a planning task (Ayesa-Arriola et al., 2014). In a previous study comparing sex differences in neurocognition in BD patients, males also obtained better results than females in working memory (Solé et al., 2022). In the present study, these differences seem to be already present at the early stages of the disease, in FEM or FEP taken together.

As for EI, females outperformed males in EIQ and Perceiving emotions and Facilitating emotions branches. In the general population, a female advantage in the recognition of other people's emotions and in the ability to understand others' feelings has been identified (Di Tella et al., 2020). Regarding EI as a construct, most studies find that women perform better than men (Brackett et al., 2004; Day and Carroll, 2004; Fischer et al., 2018; Joseph and Newman, 2010), while one study found no differences (Pardeller et al., 2017). Regarding psychiatric populations, the results are not conclusive in early episodes of non-affective psychosis: while Labad et al. (Labad et al., 2016) found significant differences between the sexes, Casado Ortega(Casado-Ortega et al., 2021) did not. However, it is worth noting that both studies focused only on the Managing emotions´ branch. In chronic stages, the results seem to be more conclusive, and in SCZ patients, females showed better results than males (DeTore et al., 2018; Eack et al., 2010; Ferrer-Quintero et al., 2021). As for BD, differences have been found both at early(Varo et al., 2022) and chronic (Varo et al., 2020) stages, with females outperforming males.

As expected, significant group effect was obtained for most of the clinical features, and FEP patients presented higher depressive and psychotic symptoms as well as worse psychosocial functioning and premorbid adjustment. Group effect was also reported for neuropsychological variables, particularly in processing speed, working memory, verbal memory, logical memory, and verbal fluency, with lower scores for FEP patients than FEM ones. In a meta-analysis assessing neurocognitive impairment in FEM patients in comparison with FEP and HCs, Bora and Pantelis (Bora and Pantelis, 2015) identified that FEP patients significantly underperformed FEM patients in most cognitive domains, namely processing speed, working memory, verbal memory, and fluency, and on individual tasks, particularly in digit symbol and category fluency. Despite this, the authors identified that the deficits were significant but moderate. They concluded that cognitive differences between FEP and FEM might be quantitative rather than qualitative(Bora and Pantelis, 2015). Even though neuropsychological impairment was already evident in FEM patients, cognitive performance in FEM patients lied in a continuum of cognitive impairment, between FEP patients and HCs (Bora and Pantelis, 2015). Predictors of BD versus SCZ diagnosis were evaluated in a previous longitudinal multicentric study and patients with a final diagnosis of BD had a better baseline premorbid adjustment and psychosocial functioning, lesser negative symptoms and lower number of perseverative errors on the WCST (Monchi et al., 2001), a neuropsychological test assessing the ability to display flexibility in the face of changing schedules of reinforcement (Salagre et al., 2020). Another study found that FEM patients performed better in verbal memory, reasoning and flexibility compared to FEP (Montalvo et al., 2018).

Interestingly, a significant group by sex interaction was found for few neuropsychological variables in the present study. Not only FEM males outperformed FEP males patients in processing speed and verbal fluency but also FEM females performed better than FEP males in processing speed. In the present study, we identified that the processing speed performance not only depended on being a FEP or a FEM patient, but also on the effect exerted by sex. Sex showed an effect on the performance, resulting in FEM females outperforming FEP males. Previous findings on the sex effect on processing speed performance are conflicting. While few studies (Kestens et al., 2021) did not found a clear sex effect, other studies identified that females outperformed males in processing speed (Roivainen et al., 2021). Biological factors have been studied to explain this effect. In particular, hyperprolactinaemia was found to have a negative impact on cognitive function in people with early psychosis (Montalvo et al., 2014). In particular, increased prolactin levels were associated with impaired processing speed in males but not in females, and this association was independent of cortisol and testosterone (Montalvo et al., 2018).

Classically, the prevalence of drug use is higher in males than females (McHugh et al., 2018). The consumption of cannabis is more common among males than in females in all age groups (McHugh et al., 2018). We observed that there was a significant difference in the use of alcohol and cannabis among females and males with a FEM in the prodromal phase. These findings are congruent with the latest report by the Spanish Ministry of Health about alcohol, tobacco and illegal drugs, reporting that in all age groups, alcohol and cannabis consumption is higher among men (Ministerio de Sanidad. Delegación del Gobierno para el Plan Nacional sobre Drogas, 2022). However, the prevalence of cannabis use in our sample is much higher than in general population. Since the use of cannabis and other drugs in adolescents and young adults can lead to early onset FEM or FEP and is associated with comorbidities and worse clinical outcomes (Kahn et al., 2015; Vieta et al., 2018), these findings might have implications for including substance use targeted interventions in current early treatment programs.

In terms of prodromal symptoms, there is growing interest in identifying early manifestations. As for sex differences in mania prodromal symptoms, *Irritability* was more frequently reported in females patients whilst *Concentration difficulties* in males. Psychosis prodromal symptoms were similar in both sexes, despite *Communication difficulties* was more frequently included in the males FEP prodrome. In the comparison of prodromal symptoms in females with a FEM or a FEP, *Decreased energy* was more prevalent in FEP females while *Lability, Speech pressure, Sleep decrease* and *Increased creativity* in FEM females. In contrast, *Social isolation* and *Depression*, were the specific prodromal symptoms in FEP males whereas *Physical agitation, Mood elevation, Speech pressure, Racing thoughts, Increased energy, Decreased need for sleep, Increased self-esteem* and *Increased creativity* in FEM males. Although *Social isolation* is considered in literature as one of the most prevalent prodromal symptoms of a FEP (Cornblatt et al., 2003; Jackson et al., 1995; Mäki et al., 2014) and an essential component of the initial prodrome in SCZ (Häfner et al., 1999), it only revealed as a noteworthy prodromal symptom of a FEP in the comparison with a FEM in males but not in females. A similar trend was seen for the specific prodromal symptoms of a FEM, such as *Physical agitation* and *Increased energy* (Correll et al., 2007), among others. Therefore, exploring sex differences in prodromal characteristics would make the diagnostic process easier, earlier, and more accurate.

4.1. Limitations

The present study has several limitations. First, we assessed differences between sexes, but we did not assess the influence that gender might exert (Tannenbaum et al., 2016). Second, the retrospective assessment of the prodromes and substance use with possible recall bias should be acknowledged. Third, prodromal symptoms were assessed with the BPSS-R scale, which was not developed to evaluate prodromal symptoms in SCZ (Correll et al., 2007). Nonetheless, the development of the BPSS-R was also based on interviews for the assessment of the psychotic and SCZ prodrome. The BPSS-R was used to assess both FEM and FEP patients to limit this bias. Fourth, the overall sample size is limited, especially for psychosis, with <30 participants between the two sex groups. Indeed, the group of FEP patients was smaller, which might have influenced the valuation of differences between groups. While sample size may be an issue for certain variables (De Prisco and Vieta, 2024), the study power was able to prove the presence of significant sex effect and group by sex interaction on specific neurocognitive cognition and emotional intelligence measures. In addition, the multiple comparisons conducted in our analyses may represent another limitation, raising the concerns for chance findings due to type I errors. However, as the outcomes of our analyses are inter-correlated, it may be not appropriate to adjust *p*-values for multiple comparisons (Barnett et al., 2022). Nonetheless, the present study should be considered as exploratory due to the limitations in sample size, particularly within the psychosis group, and thus the findings should be interpreted with caution. To strengthen the validity and generalizability of the results, replication in future studies, with larger sample sizes, is essential. Fifth, patients have been included in the study if they experienced their FEP/FEM along the previous four years. Thus, we recruited patients in the early stages of the disease. Sixth, differences in medication might account for some of the differences between males and females and between FEM and FEP (Ilzarbe and Vieta, 2023; Vidal et al., 2023). Finally, we did not count with of a HC group that would allow a comparison with general population.

Despite these limitations, the present study assessed sex differences in FEP and FEM patients, whose comparison was not reported in previous literature. Furthermore, we can rely on clinical, cognitive, and psychosocial outcomes that were assessed using standardized measures.

5. Conclusions

In conclusion, it seems undeniable that sex matters in mental health. The branch of research focused on sex differences should be improved in order to tailor personalised early treatment strategies focused on sex differences. Taking sex into consideration could improve the efficacy of psychological and pharmacological treatments strategies. Indeed, males patients would benefit from treatment strategies aimed at recognizing emotions and accessing feelings. Similarly, neuropsychological-focused improving strategies would consider the variation of cognitive performance between males and females.

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Author statement

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We understand that Corresponding Authors are the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). They are responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided current, correct email addresses, which are accessible by the Corresponding Authors and have been configured to accept emails from (EVIETA@clinic.cat & AMARTIAR@clinic.cat).

Role of the funding sources

The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Authors' contributions

RPG, NV and SA designed the study, managed the literature searches, undertook the statistical analysis, and wrote the first draft of the manuscript. EV, AMA designed the study and supervised the realization of the study. MSN, MG, MSV, SM, LM, PSP, IM, IP and CGR helped in the recruitment of the patients and in the realization of the study procedures, revised the first draft and added critical comments to guide the redaction of the final manuscript. CT, VSG, EPC, AT, GM, NF and JARQ revised the first draft and added critical comments to guide the redaction of the final manuscript. All the authors revise the second draft of the article and provided critical comments to guide the redaction of the final

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CRediT authorship contribution statement

Roberto Palacios-Garran: Writing – original draft, Data curation, Conceptualization. **Silvia Amoretti:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Maria Serra-Navarro:** Writing – review & editing, Data curation. **Carla Torrent:** Writing – review & editing, Funding acquisition, Data curation. **Marina Garriga:** Writing – review & editing, Data curation. **Natalia E. Fares-Otero:** Writing – review & editing. **Maria Sagué-Vilavella:** Writing – review & editing, Data curation. **Santiago Madero:** Writing – review & editing, Data curation. **M. Florencia Forte:** Writing – review & editing, Data curation. **Laura Montejo:** Writing – review & editing, Data curation. **Pilar Salgado-Pineda:** Writing – review & editing, Data curation. **Irene Montoro:** Writing – review & editing, Data curation. **Vanessa Sánchez-Gistau:** Writing – review & editing, Supervision. **Edith Pomarol-Clotet:** Writing – review & editing, Supervision. **Giulia Menculini:** Writing – review & editing, Supervision. **Alfonso Tortorella:** Writing – review & editing, Supervision. **Isabella Pacchiarotti:** Writing – review & editing, Supervision, Data curation. **Clemente Garcia-Rizo:** Writing – review & editing, Data curation. **Josep Antoni Ramos-Quiroga:** Writing – review & editing, Supervision. **Anabel Martínez-Arán:** Writing – review & editing, Supervision, Conceptualization. **Eduard Vieta:** Writing – review & editing, Conceptualization. **Norma Verdolini:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

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SA has been a consultant to and/or has received honoraria/grants from Otsuka-Lundbeck, with no financial or other relationship relevant to the subject of this article.

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JARQ was on the speakers' bureau and/or acted as consultant for Eli-Lilly,Janssen-Cilag, Novartis, Shire, Takeda, Bial, Shionogui, Lundbeck, Almirall, Braingaze, Sincrolab, Medice, Rubió and Raffo in the last 5 years. He also received travel awards (air tickets + hotel) for taking part in psychiatric meetings from Janssen-Cilag, Rubió, Shire, Takeda, Shionogui, Bial, Medice and Eli-Lilly. The Department of Psychiatry chaired by him received unrestricted educational and research support from the following companies in the last 5 years: Eli-Lilly, Lundbeck, Janssen-Cilag, Actelion, Shire, Ferrer, Oryzon, Roche, Psious and Rubió.

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Data availability statement

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

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