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REGULAR RESEARCH ARTICLE

The Influence of Oxytocin and Prolactin During a First Episode of Psychosis: The Implication of Sex Differences, Clinical Features, and Cognitive Performance

María Hidalgo-Figueroa,Alejandro Salazar, Cristina Romero-López-Alberca, Karina S. MacDowell, Borja García-Bueno, Miquel Bioque, Miquel Bernardo, Mara Parellada, Ana González-Pinto, María Paz García Portilla, Antonio Lobo, Roberto Rodriguez-Jimenez, Esther Berrocoso, Juan C. Leza; From the FLAMM-PEPs study*, CIBERSAM

Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), ISCIII, Madrid, Spain (Drs Hidalgo-Figueroa, Romero-López-Alberca, MacDowell, García-Bueno, Bioque, Bernardo, Parellada, González-Pinto, García Portilla, Lobo, Rodriguez-Jimenez, Berrocoso, and Leza); Biomedical Research and Innovation Institute of Cadiz (INiBICA), Research Unit, Puerta del Mar University Hospital, Cádiz, Spain (Drs Hidalgo-Figueroa, Salazar, Romero-López-Alberca, and Berrocoso); Neuropsychopharmacology and Psychobiology Research Group, Psychobiology Area, Department of Psychology (Drs Hidalgo-Figueroa and Berrocoso), and Department of Statistics and Operational Research (Dr Salazar), University of Cádiz, Puerto Real (Cádiz), Spain; The Observatory of Pain, University of Cádiz, Cádiz, Spain (Dr Salazar); Personality, Evaluation and Psychological Treatment Area, Department of Psychology, Universidad de Cádiz, Puerto Real (Cádiz), Spain (Dr Romero-López-Alberca); Departamento de Farmacología y Toxicología, Facultad de Medicina, Univ. Complutense de Madrid, Instituto de Investigación Sanitaria Hospital 12 de Octubre (i+12), IUINQ, Madrid, Spain (Drs MacDowell, García-Bueno, Leza); Institut d'investigacions Biomèdiques August Pi i Sunyer (IDIBAPs), Barcelona Clínic Schizophrenia Unit (BCSU), Neuroscience Institute, Hospital Clínic de Barcelona, Department of Medicine, University of Barcelona, Barcelona, Spain (Drs Bioque and Bernardo); Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, IiSGM, School of Medicine, Universidad Complutense, Madrid, Spain (Dr Parellada); Department of Psychiatry, Hospital Universitario de Alava, BIOARABA, EHU, Vitoria-Gasteiz, Spain (Dr González-Pinto); Department of Psychiatry, Universidad de Oviedo, Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Instituto de Neurociencias del Principado de Asturias (INEUROPA), Servicio de Salud del Principado de Asturias (SESPA), Oviedo, Spain (Dr García Portilla); Department of Medicine and Psychiatry, Universidad de Zaragoza, Instituto de Investigación Sanitaria Aragón (IIS Aragón), Zaragoza, Spain (Dr Lobo); Department of Psychiatry, Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12)/Universidad Complutense de Madrid (UCM), Madrid, Spain (Dr Rodriguez-Jimenez).

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Significance Statement

This study examines the plasma oxytocin and prolactin levels during a first episode of psychosis (FEP) and their relationship to the severity of clinical and cognitive symptoms. Previous studies, mainly on schizophrenia, found some correlations between the level of these hormones and illness severity, although how they influence a FEP is not well understood. We found that low oxytocin, high prolactin, a poor premorbid IQ, and sustained attention were all factors associated with a FEP. We observed sexual dimorphism in the relationship between these molecules and the attention domain. Low oxytocin was correlated with poor sustained attention in women, while low oxytocin and high prolactin in men was correlated with better performance in this domain. These biological and cognitive characteristics could be considered as potential therapeutic targets in cases of FEP, where sex should be taken into consideration.

Correspondence: Esther Berrocoso, PhD, Neuropsychopharmacology Psychobiology Research Group, Psychobiology Area, Department of Psychology, University of Cádiz, 11510 Cádiz, Spain (esther.berrocoso@uca.es).

*FLAMM-PEPs is a multicenter, collaborative, and translational research group within CIBERSAM, the aim of which is to study inflammatory pathways in psychosis both as possible biomarkers and as possible new therapeutic targets. FLAMM-PEPs is now part of the PEPs study, a Spanish research project into first episode psychosis.

M.H-F. and A.S. contributed equally to this work.

Abstract

Background: Approximately 3% of the population suffers a first episode of psychosis (FEP), and a high percentage of these patients subsequently relapse. Because the clinical course following a FEP is hard to predict, it is of interest to identify cognitive and biological markers that will help improve the diagnosis, treatment, and outcome of such events and to define new therapeutic targets. Here we analyzed the plasma oxytocin and prolactin levels during an FEP, assessing their correlation with clinical and cognitive features.
Methods: The oxytocin and prolactin in plasma was measured in 120 FEP patients and 106 healthy controls, all of whom were subjected to a clinical and neuropsychological assessment. Most patients were under antipsychotics. Statistical analyses aimed to identify factors associated with the FEP and to search for associations between the variables. This study is preliminary and exploratory because the P-values were not corrected for multiple comparisons.
Results: FEP patients had less oxytocin, more prolactin, and a poor premorbid IQ, and they performed worse in sustained attention. Male patients with higher prolactin levels experienced more severe psychotic symptoms and required higher doses of antipsychotics. Low oxytocin was associated with poor sustained attention in women, whereas low oxytocin and high prolactin in men correlated with better performance in sustained attention.
Conclusion: Low oxytocin, high prolactin, and poor premorbid IQ and sustained attention are factors associated with an FEP, representing potential therapeutic targets in these patients. These biological factors and cognitive domains might play an important role during a FEP, which could help us to develop new strategies that improve the outcomes of this disorder and that should perhaps be gender specific.

Keywords: First-episode psychosis, oxytocin, prolactin, cognition, sexual dimorphism.

Introduction

Approximately 3% of the general population suffers a first episode of psychosis (FEP), the clinical evolution of which is hard to predict. Following an FEP, patients may enter total remission or may relapse, even entering a chronic disease state (Perälä et al., 2007; Peralta et al., 2021). Remission is observed in only one-third of patients after an FEP, whereas a high percentage of patients suffer a relapse over the ensuing 5 years (Robinson et al., 1999). One possible diagnoses after an FEP is that of schizophrenia, which has a prevalence of 1% in the general population (Lichtermann et al., 2000; Perälä et al., 2007). Schizophrenia spectrum disorders are considered to be multifactorial diseases for which genes and environment are essential risk factors (Lichtermann et al., 2000). At present, no biological markers (biomarkers) are available for an FEP, tools that would be very valuable to better diagnose and obtain a prognosis following such events and to more adequately establish pharmacological treatments at the onset of such disorders (Galletly et al., 2016; Peralta et al., 2021). Indeed, appropriate diagnosis and early intervention are likely to improve the prognosis of the disease (García-Bueno et al., 2014). As such, there is considerable interest in studying what factors are associated with an FEP because these patients are at the onset of the disease, a point at which the effect of possible confounding factors is minimal, such as the duration of the illness or prolonged antipsychotic treatment (Bernardo and Bioque, 2014).

Previous studies of patients who experienced an FEP described cognitive deficits from the onset of psychosis, specifically in the domains of attention, verbal memory, executive function, working memory, and processing speed (Aas et al., 2014; Cuesta et al., 2015; Cabrera et al., 2016). However, there is a need for pharmacological treatments designed to improve cognitive performance in these patients. Accordingly, identifying biomarkers of the individual's cognitive state would be useful to

develop new therapeutic strategies to improve the outcome of an FEP (Cabrera et al., 2016; Labad, 2019).

Altered plasma oxytocin and prolactin levels have been described in patients suffering psychiatric disorders (Beckmann et al., 1985; Goldman et al., 2008; Cochran et al., 2013; Petrikis et al., 2016; Delgado-Alvarado et al., 2019; Strauss et al., 2019; Studerus et al., 2021), although the association of these alterations with the neuropsychiatric and clinical characteristics of an FEP are not well understood. Oxytocin is a hormone mainly synthesized in the supraoptic and paraventricular nuclei of the hypothalamus, nuclei with projections to other brain areas where this hormone acts as a neurotransmitter (Jurek and Neumann, 2018). Oxytocin is involved in social behavior, emotion, and learning (Kania et al., 2020), and as such, it has been implicated in neuropsychiatric behavior (Cochran et al., 2013). In fact, alterations to oxytocin plasma levels have been described in patients with autism, schizophrenia, mood anxiety disorders or other pathologies in which social behaviors deteriorate (Cochran et al., 2013; Kirsch, 2015; Carrasco et al., 2020), although it also fulfils crucial functions during childbirth, lactation, and mating (Jurek and Neumann, 2018). Indeed, oxytocin is released into the bloodstream from the posterior pituitary gland to act in different tissues, and because the plasma and serum levels of oxytocin are usually correlated with the brain levels, it can be considered a peripheral biomarker (Carrasco et al., 2020). For example, lower levels of peripheral oxytocin have been associated with the severity of symptoms in schizophrenia (Feifel et al., 2016), and its potential role in social behavior and cognition has led the oxytocinergic system to be considered as a potential therapeutic target to treat psychotic disorders (Feifel et al., 2016; Schmidt et al., 2020). Both preclinical and clinical studies have demonstrated that exogenous oxytocin is a potential treatment for schizophrenia (Feifel et al., 2016; Shilling and Feifel, 2016). However, a recent meta-analysis found no robust evidence of alterations to oxytocin in cases of psychosis, possibly reflecting the heterogeneity of these studies and indicating that more analyses are needed to define oxytocin as a biomarker for a FEP (Rutigliano et al., 2016).

Alterations to prolactin levels have also been described in psychiatric patients (Riecher-Rössler, 2017). Prolactin is a hormone mainly synthesized in the anterior pituitary gland, with a notable role in lactation (Delgado-Alvarado et al., 2019). In addition, prolactin is involved in several central nervous system functions, such as the regulation of stress, energy balance, anxiety, neurogenesis, food intake, and maternal behavior (Patil et al., 2014). Patients with schizophrenia frequently have elevated levels of prolactin as a consequence of pharmacological treatment, although an increase in prolactin has also been demonstrated in untreated psychiatric patients (Garcia-Rizo et al., 2012; Riecher-Rössler et al., 2013; Petrikis et al., 2016; Delgado-Alvarado et al., 2019; Pisk et al., 2019; Studerus et al., 2021). The elevation of prolactin is lower when second-generation antipsychotics, such as ziprasidone, clozapine, olanzapine, aripiprazole, or quetiapine, are used (Kane et al., 1981; Beasley et al., 1996; Daniel and Copeland, 2000; Crespo-Facorro et al., 2017; Wadoo et al., 2017); however, other antipsychotics, such as paliperidone or risperidone, do increase prolactin levels (Berwaerts et al., 2010). High levels of prolactin in antipsychotic-naïve patients could be explained by stress (Riecher-Rössler et al., 2013; Ittig et al., 2017), a phenomenon that induces prolactin production and dopamine release through a feedback loop (Riecher-Rössler et al., 2013; Riecher-Rössler, 2017). FEP is frequently linked to stressful situations, which could be related to the increased dopamine neurotransmission described during psychotic episodes (Howes and Kapur, 2009; Riecher-Rössler, 2017). However, the exact mechanisms by which prolactin is increased, even in antipsychotic-naïve patients, is not clear (Labad, 2019).

Although oxytocin and prolactin plasma levels have already been studied in psychiatric patients, due to the heterogeneity of these studies and their findings (Penadés et al., 2015; Rutigliano et al., 2016), more analyses are needed to define the association of these molecules with an FEP. Moreover, the correlation between these molecules and clinical or neuropsychological variables in this population of patients has yet to been fully evaluated. As such, in this study we aimed to examine the prolactin and oxytocin plasma levels in patients who experience an FEP, comparing them with matched control participants. Furthermore, we will examine the relationship between the levels of these hormones with clinical and neuropsychological symptoms, comparing them between sexes.

METHODS

Participants

The participants of this study came from Flamm-PEPs, a multicentre project carried out by the Spanish Network for Mental Health Research, and they included a total of 120 FEP patients and 106 sex- and age-matched healthy controls (HCs). The detailed inclusion/exclusion criteria and clinical protocol have been published elsewhere (Bernardo et al., 2013; García-Bueno et al., 2014, 2015), but in essence, the inclusion criteria for FEP patients were (1) age 9–35 years, (2) onset and duration of psychotic symptoms <1 year, and (3) speak Spanish correctly. The exclusion criteria were (1) IQ < 70 together with impaired functioning, (2) history of traumatic head injury with a loss of consciousness, and (3) history of organic disease with mental repercussions. The patients were matched with HC participants by gender, age, and parental socioeconomic status. These exclusion criteria were also applied to the HCs, and as well as having past or present psychiatric disorder (DMS-IV-TR criteria), a history of psychotic disorder among first-degree relatives was also considered. This study was approved by the ethics committees at all the participating centers, and all participants provided a written, informed consent (García-Bueno et al., 2014, 2015).

Clinical Assessment

Diagnosis was established according to DSM-IV-TR criteria for adults and the Kiddie-Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version (Kaufman et al., 1997) for the participants younger than 18 years of age. The Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987; Peralta and Cuesta, 1994) was used to evaluate the severity of the psychotic symptoms, whereas the severity of symptoms and the level of functioning were assessed with the Global Assessment of Functioning Scale (Endicott et al., 1976) and the Children's Global Assessment Scale (Shaffer et al., 1983). The potency equivalents of the daily antipsychotic dosage of chlorpromazine were calculated following international consensus criteria (Gardner et al., 2010).

Neuropsychological Assessment

A neuropsychological battery was delivered and assessed by trained neuropsychologists following the National Institute of Mental Health MATRICS consensus (Green et al., 2004; Carter et al., 2008). The neuropsychological tests evaluated premorbid IQ through the verbal ability scores of the Vocabulary sub-test

of wechsler intelligence scale for children (WISC)-IV for children (Wechsler, 2003) and wechsler adult intelligence scale (WAIS)-III for adults (Wechsler, 1955); working memory with the Digit and Letters and Numbers sub-test of WAIS-III for adults, and WISC-IV for children; processing speed with the Trail Making Test Form A (Reitan and Wolfson, 1993); executive function with the Trail Making Test Form B (Reitan and Wolfson, 1993); and sustained attention through the Continuous Performance Test-II (Conners and Staff, 2004), corrected for age and educational level. Higher scores in verbal ability and working memory tests indicate better performance in these domains, whereas higher scores in the processing speed, executive function, and attention tests are indicative of worse performance in these cognitive domains.

Blood Sample Collection

Venous blood samples (10 mL) were collected between 8:00 AM and 10:00 AM after overnight fasting. Blood tubes were centrifuged at 641 g for 10 minutes at 4°C, and the resulting plasma samples were stored at –80°C until use.

Biochemical Determinations in Plasma

Oxytocin levels were determined with a commercial competitive ELISA kit (ref. 500440, Cayman Chemical, Tallinn, Estonia) following the manufacturer's instructions and measuring absorbance at 405 nm (Synergy 2, Biotek, Winooski, VT). The intra- and inter-assay coefficients of variation were 7.2% and 7.0%, respectively. To obtain valid assay results, plasma samples were previously purified on C18 Sep-Pak columns (Waters, The Netherlands, UK) to remove molecules that could interfere with the assay (Szeto et al., 2011; Carrasco et al., 2020).

Prolactin levels were evaluated using a commercial ELISA kit (ref. 500730, Cayman Chemical) following the manufacturer's instructions and measuring absorbance at 450 nm (Synergy 2, Biotek). The intra- and inter-assay coefficients of variation were 3.7% and 4.6%, respectively. Levels of prolactin >20 ng/mL in men and 25 ng/mL in women were considered hyperprolactinemia (Halbreich et al., 2003).

Statistical Analysis

A descriptive analysis was carried out, showing the absolute and relative (%) frequencies for the qualitative variables, and the central tendency measures (mean) with measures of dispersion (SD). The normality in the distribution of the quantitative variables was verified with the Kolmogorov-Smirnov test. The differences between controls and patients were analyzed using Student *t* tests (checking for equality of variance with Levene's test) or a Mann-Whitney's U test. In the case of the biological markers, the differences between HCs and FEP patients were presented in a plot, showing the mean differences and SEM. The potential relationships between the biological markers and neuropsychological/clinical variables were assessed with correlation coefficients, Pearson's correlation coefficient in the case of normality, and Spearman's rank correlation coefficient otherwise.

The factors associated with the occurrence of an FEP were assessed using a Binary Logistic Regression Model, where the dependent variable was the occurrence of the aforementioned episode. The co-variables tested were hormone levels, demographic factors (body mass index [BMI], age, and sex), clinical features (PANSS, Global Assessment of Functioning Scale/Children's Global Assessment Scale, and antipsychotic treatment), and neuropsychological test scores of both HC and FEP patient groups. A stepwise regression method was used to select the final set of co-variates in the model, and the goodness of fit was assessed with the Hosmer-Lemeshow test. We present the odds ratios (ORs) with 95% confidence interval (CI) as well as the statistical significance of each variable in the model according to the Wald test.

In all cases, the statistical significance was set at $P<\alpha=.05$. Corrections were not made for multiple comparisons, because we present exploratory analyses without a global null hypothesis, which needs all individual null hypotheses to be true simultaneously. The analyses were carried out with IBM SPSS v.24, Armonk, NY, StatGraphics XVIII and GraphPad Prism 9, San Diego, CA.

RESULTS

Demographic and Clinical Characteristics

The demographic and clinical characteristics of the 120 individuals that had suffered an FEP and 106 HCs in the study were recorded (Table 1). There was a significant difference in the BMI between HCs and FEP patients, the latter displaying a higher BMI than the HCs ($P=.001$; Table 1). When these data were analyzed according to sex, the difference in BMI between HCs and FEP patients was significant only in men ($P=.013$): the mean of BMI of HC men was 23.68 (3.16), and the mean BMI of male FEP patients was 25.29 (±3.76). Most of the patients were under psychotic medication, and they showed higher severity in the symptomatology compared with antipsychotic-naïve patients ($P<.01$; supplementary Table 1). Moreover, a positive correlation was found between daily dose of antipsychotics and the symptom severity ($P<.01$; supplementary Table 1).

Neuropsychological Assessment in Healthy Participants and FEP Patients

When compared with the HCs, FEP patients showed significant lower scores in verbal ability ($P<.001$) and 2 indices of working memory, digit ($P<.001$) and letter and number ($P<.001$) subtests of the Weschler scales, indicating that these patients presented worse performance in verbal ability and working memory (Table 2). The FEP patients also obtained higher scores in the Form A ($P<.001$) and Form B ($P<.001$) trail-making tests, indicating worse performance in processing speed and executive function (Table 2). FEP patients obtained worse scores in the sustained attention domain ($P<.001$), except for some CTP-II tests included in the evaluation in which no significant differences were observed between the 2 groups (Table 2): hit reaction time (Hit-RT, $P=.291$), hit reaction time by block (Hit-RT-BC, $P=.143$), standard error of hit reaction time by block (Hit-RT-BC-SE, $P=.109$), and standard error of hit reaction time by interstimulus interval (Hit-RT-ISI-SE, $P=.741$).

When the data were examined separately by sex, both female and male FEP patients performed worse in verbal ability, working memory, processing speed, executive function, and attention. However, they performed distinctly in some measures of the attention domain (Table 2: *significant *P* values in men only; #significant *P* values in women only). Male FEP patients scored worse in omission errors (mean score in male HCs, 46.6±15.49; in male FEP patients, 60.1±29.13, $P<.001$). Detectability (mean score in male HCs, 42.46±10.25; in male FEP patients, 50.38±9.18, $P<.001$) and Hit-RT-ISI (mean score in male HCs, 48.55±8.61; in male FEP patients, 52.83±11.79, $P<.037$). Female FEP patients scored worse in the Hit-RT-BC-SE test (mean score in female, HCs 53.55±9.15; in female FEP patients, 59.91±0.86, $P=.031$).

Table 1. Demographic and Clinical Characteristics of the Study Population

Characteristic	Control (n = 106)	Patients baseline (n = 120)
Age, y (mean ± SD)	25.43 ± 6.41	23.9 ± 5.8
Sex, n (%)		
Male	70 (66)	82 (68.3)
Female	36 (34)	38 (31.7)
Ethnic group, n (%)		
Caucasian	96 (90.6)	113 (94.2)
Hispanic	6 (5.7)	3 (2.5)
Others	4 (4)	4 (3.3)
Body mass index (mean ± SD)	23.14 ± 3.16	24.89** ± 4.04
Psychiatric history		
Duration of untreated psychosis, d	—	96.95 (113.79)
Diagnosis, n (%)		
Affective psychosis	—	22 (18.3)
Non-affective psychosis	—	98 (81.7)
Psychopathology score (mean ± SD)		
PANSS		
Total	—	53.76 ± 19.78
Positive	—	11.38 ± 6.16
Negative	—	14.44 ± 6.05
General	—	27.94 ± 10.17
Overall functioning score (GAF)	—	67.31 ± 14.35
Antipsychotic medication, n (%); DDD of CPZ eq., mg, mean ± (SD)		
Risperidone	—	43 (35.8); 434.5 (338.38)
Aripiprazole	—	12 (10.0); 370.83 (213.69)
Olanzapine	—	15 (12.5); 285 (130.52)
Quetiapine	—	7 (5.8); 331.43 (181.42)
Clozapine	—	8 (6.7); 403.13 (192)
Ziprasidone	—	2 (1.7); 450 (0)
Paliperidone	—	10(8.3); 440.1 (324.13)
None	—	23 (19.2)
DDD of CPZ eq., mg	—	394.44 (275.04)

Abbreviations: DDD of CPZ eq., defined daily dose of chlorpromazine equivalent; GAF, Global Assessment of Functioning Scale; PANSS, Positive and Negative Syndrome Scale. Comparisons between the controls and first episode of psychosis patients assessed using: a *t* test (age, body mass index), a chi-squared test (gender), a likelihood ratio (ethnic group) or Kruskal-Wallis (antipsychotic medication): **$P < .01$.

Table 2. Neuropsychological Evaluation: T-Scores (Means ± SD) Obtained for the Controls and FEP Patients

Cognitive domain	Neuropsychological test	Control (n = 106)	FEP patients (n = 120)	*P*
Verbal ability	Vocabulary subtest (WISC-IV/WAIS-III)	109.19 ± 12.23	94.26 ± 18.34	<.001
Working memory	Digit subtests (WISC-IV/WAIS-III)	52.66 ± 9.31	45.27 ± 8.74	<.001
	Letter and number subtests (WISC-IV/WAIS-III)	55.05 ± 9.24	43.53 ± 12.22	<.001
Processing speed	Trail making test (Form A)	24.48 ± 9.98	37.42 ± 20.81	<.001
Executive function	Trail making test (Form B)	57.33 ± 26.81	87.69 ± 41.42	<.001
Sustained attention	Omission errors	52.25 ± 26.30	59.86 ± 25.94	<.001 (*)
	Commission errors	44.71 ± 8.65	52.21 ± 11.42	<.001
	Hit-RT	51.46 ± 8.99	53.16 ± 10.85	.291
	Hit-RT-SE	47.53 ± 10.51	58.01 ± 13.53	<.001
	Variability	47.53 ± 9.83	57.18 ± 13.34	<.001
	Detectability	45.2 ± 10.77	51.80 ± 9.68	<.001 (*)
	Perseveration	48.05 ± 8.43	63.79 ± 31.46	.001
	Hit-RT-BC	48.16 ± 9.31	50.61 ± 11.26	.143
	Hit-RT-BC-SE	52.38 ± 8.99	55.01 ± 11.08	.109 (#0.031)
	Hit-RT-ISI	47.87 ± 10.43	52.02 ± 12.87	.030 (*0.037)
	Hit-RT-ISI-SE	50.63 ± 10.92	51.33 ± 14.59	.741

Abbreviations: FEP, first episode of psychosis; Hit-RT, hit reaction time; Hit-RT-BC, hit reaction time by block; Hit-RT-BC-SE, standard error of hit reaction time by block; Hit-RT-ISI, hit reaction time by interstimulus interval; Hit-RT-ISI-SE, standard error of hit reaction time by interstimulus interval; WAIS, wechsler adult intelligence scale; WISC, wechsler intelligence scale for children. A *t* test or Mann-Whitney's U test was used to compare the controls and FEP patients. The analysis of the complete groups or the sex-disaggregated data produced the same results, except for those *P* values marked with asterisks: *$P < .05$ only in men or #$P < .05$ in women.

Plasma Oxytocin and Prolactin Levels in Healthy Participants and FEP Patients

Oxytocin and prolactin were quantified in plasma (Figure 1), and oxytocin levels were decreased in FEP patients relative to HCs ($P < .001$; Figure 1A). By contrast, higher prolactin levels were detected in FEP patients (Figure 1B). No correlation was found between plasma oxytocin and prolactin levels ($r = 0.15$, $P = .193$).

When the data were sex disaggregated, the same results were observed for both women (HCs vs FEP patients, oxytocin and prolactin, $P = .005$) and men (HCs vs FEP patients, oxytocin $P = .002$, prolactin $P < .001$: Figure 1C–F). Except for 1 sample from a male patient with 24 ng/mL of prolactin, all the plasma samples contained prolactin levels <20 ng/mL in men and 25 ng/mL in women (Figure 1D, F). Therefore, the increased prolactin levels in FEP patients were not considered to be hyperprolactinemia.

Patients treated with antipsychotics showed higher levels of prolactin compared with those antipsychotic-naïve patients or HCs ($P < .001$: supplementary Table 2). Patients treated with risperidone or paliperidone showed even higher levels of prolactin than those treated with other antipsychotics ($P = .039$; supplementary Table 2).

Correlation Between Biological Markers and Clinical Characteristics

Although the plasma oxytocin levels were not significantly correlated with any clinical variable, several significant correlations were found with the plasma prolactin levels (Table 3). Pharmacological treatment was positively correlated with prolactin levels in patients (rho = 0.259, $P = .014$), indicating that higher prolactin levels were related to higher daily doses of antipsychotics. However, significant correlations were not found between daily doses of antipsychotics and prolactin levels in patients treated with risperidone or paliperidone (rho = –0.010, $P = .951$; supplementary Table) or in patients treated with other antipsychotics ($r = 0.020$, $P = .916$; supplementary Table 2). Regarding the association between plasma prolactin levels and PANSS scores, no correlation was found in either antipsychotic-naïve patients, patients with risperidone/paliperidone, or in patients with other antipsychotics (supplementary Table 2). The sex-disaggregated data showed that the correlation between plasma prolactin and antipsychotic doses was evident only in men (rho = 0.298, $P = .017$). There was also a positive correlation between the plasma prolactin levels and the PANSS score in men (rho = 0.257, $P = .041$), indicating that men with more prolactin suffered more severe positive symptoms. Moreover, higher levels of prolactin were also related to a higher general PANSS score in men ($r = 0.312$, $P = .012$; Table 3).

Correlation Between Biological Markers and Neuropsychological Assessment of FEP Patients

Lower plasma levels of oxytocin were significantly correlated with better cognitive performance in the executive function domain, as reflected by the lower scores in the trail-making test (Form B: rho = 0.276, $P = .04$; Table 4). After analyzing the sex-disaggregated data, some correlations were observed between

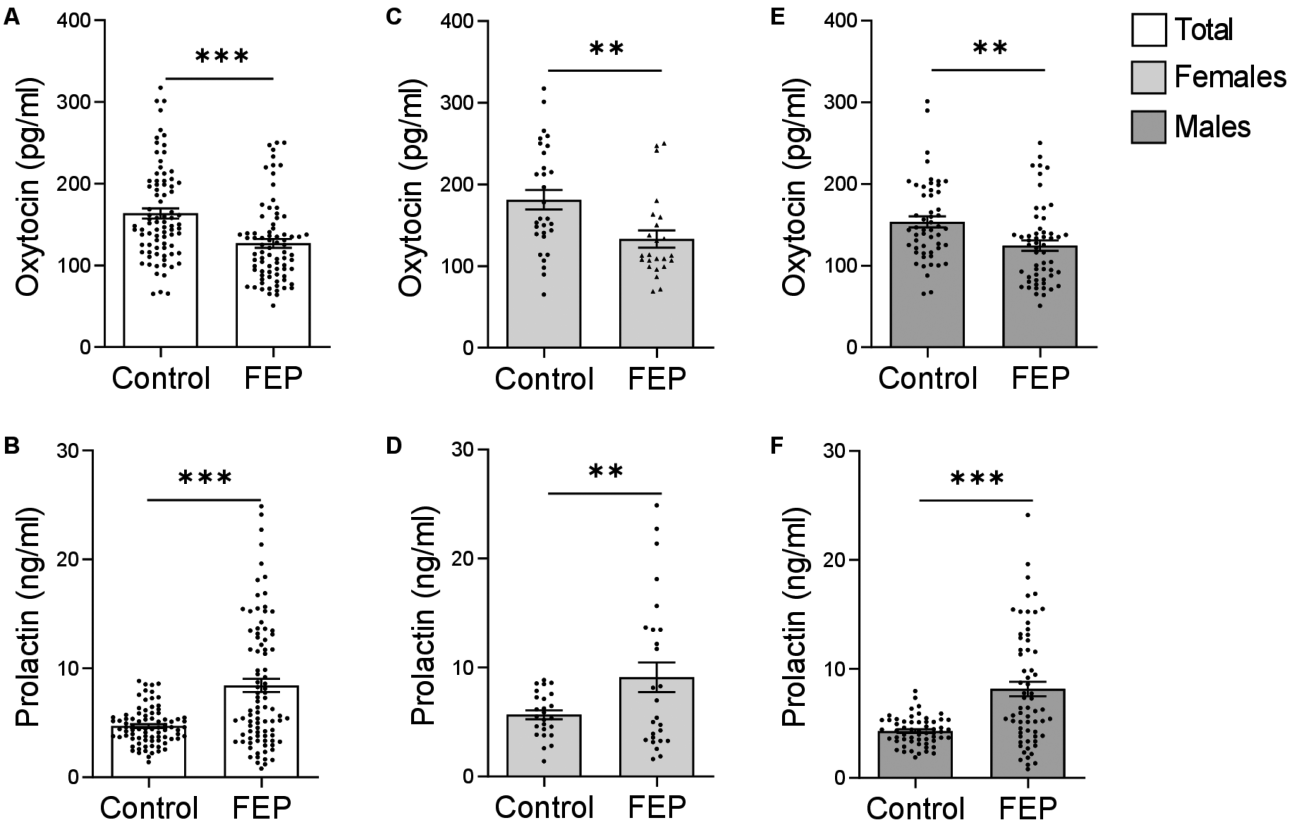

Figure 1. Mean differences ± SEM of the biological markers in plasma from controls and first episode of psychosis (FEP) patients. (A–B) Plasma levels of oxytocin (control, n = 83; FEP, n = 80) and prolactin (control, n = 83; FEP, n = 90) in the complete groups, including both women and men. (C–D) Plasma levels of oxytocin (control, n = 30; FEP, n = 24) and prolactin (control, n = 25; FEP, n = 26) in women. (E–F) Plasma levels of oxytocin (control, n = 53; FEP, n = 56) and prolactin (control, n = 58; FEP, n = 64) in men; *t* tests were used to compare the data between the groups: **P < .01; ***P < .001.

Table 3. Correlations Between Biological Markers and Clinical Features

	Coefficient of correlation					
	Oxytocin			Prolactin		
	Total	Women	Men	Total	Women	Men
PANSS Positive	0.098	−0.131	0.184	0.159	−0.010	0.257
PANSS Negative	−0.028	0.060	−0.049	0.056	0.024	0.042
PANSS General	0.080	−0.129	0.186	0.139	−0.152	0.312
PANSS Total	0.073	−0.056	0.166	0.137	−0.093	0.239
GAF	−0.183	−0.187	−0.179	−0.005	−0.091	0.045
DDD of CPZ eq., mg	0.023	0.087	0.156	0.259	0.133	0.298

Abbreviations: DDD of CPZ eq., defined daily dose of chlorpromazine equivalent; GAF, Global Assessment of Functioning Scale; PANSS, Positive and Negative Syndrome Scale. Bolded values: statistically significant correlation (Spearman or Pearson correlations, *P < .05).

Table 4. Significant Correlations (Spearman or Pearson, P < .05) Between Biological Markers and Neuropsychological Variables

			Coefficient of correlation		
Biological marker	Cognitive domain	Test	Total	Women	Men
Oxytocin	Executive function	Trail making test (Form B)	0.276*	−0.189	0.207
	Sustained attention	Omission errors	0.249	−0.318	0.348*
		Perseveration	−0.016	−0.583*	−0.011
Prolactin	Working memory	Digits	−0.232	−0.524*	−0.083
		Letter and number	−0.405**	−0.484	−0.384*
	Sustained attention	Hit-RT	−0.226	0.028	−0.336*

Abbreviations: Hit-RT, hit reaction time. Bolded values are statistically significant correlation (Spearman or Pearson correlations): *P < .05; **P < .01.

oxytocin levels and the scores in tests evaluating sustained attention. Women showed a negative correlation between plasma oxytocin and their scores in the perseveration test (rho = −0.583, P = .018), indicating that low oxytocin levels were related to worse cognitive performance in this aspect of the attention domain. By contrast, men showed a positive correlation with scores in the omission test (rho = 0.348, P = .028), suggesting that lower oxytocin levels were related to better cognitive performance in this aspect of attention domain (Table 4).

On the other hand, higher plasma prolactin levels were correlated with worse working memory performance (rho = −0.405, P = .002), a correlation that was maintained in both women and men yet with certain differences. Specifically, this correlation between plasma prolactin and working memory in men was significant in the letter and number test (rho = −0.384, P = .012), whereas in women this was the case in the digit test (r = −0.524, P = .045). In terms of attention, men showed a negative correlation between the Hit-RT test results and plasma prolactin levels (r = −0.336, P = .026), with more prolactin associated with lower score in this test and thus, better cognitive performance (Table 4).

Binary Logistic Regression Analysis

In the binary logistic regression model, the factors associated with an FEP were lower levels of oxytocin (OR = 0.981), higher levels of prolactin (OR = 1.039), a lower premorbid IQ (OR = 0.938), and higher score in the Hit-RT-BC test (OR = 1.088). Lower premorbid IQ scores were related to a worse verbal ability, and a higher score in the Hit-RT-BC test was associated with an attention deficit. The other co-variables tested did not have any effect in the model. The highest OR observed between these hormones was evident for prolactin, indicating that for each unit increase in this hormone, the risk of suffering a FEP increased by 3.9% (Table 5).

Table 5. Factors Associated with a FEP (Binary Logistic Regression Model)

Variables	OR	95% CI (OR)	P
Oxytocin level	0.981	(0.970; 0.993)	.001
Prolactin level	1.039	(1.020; 1.058)	<.001
Premorbid IQ	0.938	(0.900; 0.978)	.003
Hit-RT-BC	1.088	(1.023; 1.158)	.008

Abbreviations: CI, confidence interval; FEP, first episode of psychosis; -RT-BC, hit reaction time by block; OR, odds ratio. Hosmer and Lemeshow test: chi-squared = 9.445; degrees of freedom, 8; P = .306; R^2 (Nagelkerke) = 0.578.

Discussion

The objective of the present work was to study the plasma levels of oxytocin and prolactin during an FEP and to determine whether they might be correlated with the clinical characteristics or neurocognitive performance of these individuals. We found that patients suffering an FEP had lower plasma oxytocin levels than controls. Although little is known about how oxytocin specifically affects an FEP, a previous study described no differences in plasma oxytocin from unmedicated FEP patients (Rubin et al., 2013). However, several studies have analyzed oxytocin in the plasma of patients with schizophrenia, producing results from no changes in oxytocin to lower or even higher levels (Beckmann et al., 1985; Glovinsky et al., 1994; Goldman et al., 2008; Strauss et al., 2019). These apparent inconsistencies between studies could be related to the stage of the episode or to differences in patient's characteristics, such as sex or

symptomatology (Rubin et al., 2010, 2011). Indeed, high oxytocin levels have previously been associated with positive symptoms, whereas low levels have been related to a negative symptomatology (Rubin et al., 2013; Kirsch, 2015). Moreover, medication can also influence oxytocin levels, because a negative correlation has been described between second-generation antipsychotics and oxytocin levels in the cerebrospinal fluid of schizophrenia patients (Sasayama et al., 2012). However, at an initial stage of FEP, we did not find any association between the daily equivalent dose of chlorpromazine and oxytocin in our participants. Differences in types of samples in which oxytocin is measured, for example, plasma, serum, or cerebrospinal fluid, may also explain some of the inconsistencies observed (Kirsch, 2015).

Regarding the association between clinical characteristics and oxytocin, low levels of this hormone were previously related to the severity of symptoms in schizophrenia, especially to negative and cognitive symptoms (Shilling and Feifel, 2016). Indeed, oxytocin administration was studied as a supplementary treatment in patients with schizophrenia to specifically manage negative and cognitive symptoms (Kirsch, 2015; Shilling and Feifel, 2016). However, we did not observe any correlation between oxytocin and the PANSS or GAF scores, in accordance with a previous study of the plasma oxytocin levels and clinical symptoms in FEP (Rubin et al., 2013). These contradictory results between schizophrenia and FEP suggest that the relationship between oxytocin and psychotic symptoms may change from the initial and later stages of psychosis. Regarding cognitive performance, we did observe a notable correlation between low levels of oxytocin and better executive function performance (evaluated by the trail-making test, form B) and sustained attention in men (evaluated by omission errors). By contrast, there was a correlation between low levels of oxytocin and worse sustained attention in women (as evaluated by the perseveration test). These results contrast with those from a previous study where no connection between oxytocin levels and cognitive performance was found in FEP patients (Rubin et al., 2013), and another in which low levels of oxytocin were related to impaired cognitive performance in patients with schizophrenia, a group of predominantly male patients (Strauss et al., 2019). It is interesting to highlight this opposite relationship between low levels of endogenous oxytocin and cognitive performance in women as opposed to men, because it could have important implications for understanding this association and may help improve clinical trials based on exogenous oxytocin therapy (Bradley and Woolley, 2017). To our knowledge, this is the first study showing significant associations between oxytocin in FEP patients and performance in different cognitive domains. However, more studies are needed to better understand these associations and to confirm that oxytocin could serve as a biomarker of cognitive performance, with opposite orientations in male and female patients.

In contrast to oxytocin, we found that prolactin levels increased in FEP patients. Previous reports described increases in prolactin due to antipsychotic treatment (Berwaerts et al., 2010; Wadoo et al., 2017), and indeed, we found a positive correlation between the dose of antipsychotic medication and the baseline prolactin levels in patients. Interestingly, an increase in prolactin levels in patients was even described recently in the absence of medication (Garcia-Rizo et al., 2012; Riecher-Rössler et al., 2013; Petrikis et al., 2016; Delgado-Alvarado et al., 2019; Pisk et al., 2019; Studerus et al., 2021). Although it is unclear why prolactin increases in these unmedicated patients, prolactin release is known to augment under stressful situations and this may be one reason for the increase in prolactin in FEP patients (Delgado-Alvarado et al., 2019; Labad, 2019). We observed that unmedicated patients presented regular levels of prolactin, but they also showed less severe symptoms. Some second-generation antipsychotics, such as paliperidone or risperidone, can produce a high increase in prolactin levels even at low doses (Berwaerts et al., 2010; Peuskens et al., 2014), whereas others, including ziprasidone, clozapine, olanzapine, aripiprazole, or quetiapine, do not induce such an increase (Kane et al., 1981; Beasley et al., 1996; Daniel and Copeland, 2000; Peuskens et al., 2014; Crespo-Facorro et al., 2017; Wadoo et al., 2017). We observed that patients with higher severity of symptoms presented higher levels of prolactin, independently of the type of antipsychotic, although those patients treated with risperidone or paliperidone showed even higher levels. Therefore, we cannot rule out that the increased prolactin level during an FEP is a side effect of the antipsychotics or that it occurs specifically in patients with more severe episodes. Consistent with previous studies (Delgado-Alvarado et al., 2019; Pisk et al., 2019), we also found correlations between prolactin levels and psychotic symptomatology. Specifically, men with higher levels of prolactin showed more positive and general symptoms of a psychopathology. Hence, high prolactin may have an impact on the severity of the FEP in male but not female patients. Accordingly, previous studies suggested that prolactin may even have a protective role in FEP female patients (González-Blanco et al., 2016; Delgado-Alvarado et al., 2019; Labad, 2019). Oxytocin has been proposed as one of the factors that regulates prolactin release in physiological conditions (Grattan, 2015), but in our study we did not observe any correlation between plasma oxytocin and prolactin levels.

We found that FEP male and female patients with higher prolactin performed worse in working memory. Considering that male patients with increased prolactin developed a more severe illness, we might expect greater cognitive impairments. Indeed, increased prolactin was previously related to impaired cognitive performance at early stages of psychosis, specifically in terms of processing speed (Montalvo et al., 2014). Subsequent studies indicated that this domain was exclusively affected in FEP male patients (Montalvo et al., 2018), although contrary to expectation, male patients performed better, specifically in the Hit-RT attention task. Although we found an association between high prolactin levels and higher antipsychotic dosage, it is worth mentioning that antipsychotic treatment should not influence cognitive profiles (Zabala et al., 2010), suggesting that prolactin may affect cognitive performance independently of such medication, at least in FEP patients at baseline. However, it is described that D_2 receptor blockage by chronic antipsychotic treatment induces a downregulation of D_1 receptors in the prefrontal cortex that may produce cognitive impairments (Castner et al., 2000). Further analyses are needed to better understand the relation between prolactin, antipsychotics, and cognitive performance.

In addition to the results discussed above, using a binary logistic regression model we found that an increase in prolactin or a decrease in oxytocin was associated with the onset of an FEP. In addition, the binary logistic regression model also showed that a lower premorbid IQ and worse performance in the Hit-RT-BC test (sustained attention domain) were factors associated with an FEP. These results help to clarify the controversy in the literature regarding changes in oxytocin levels in psychosis (Kirsch, 2015), and they offer further support to the hypothesis that high prolactin and low premorbid IQ are factors associated with psychosis (Labad et al., 2015; Ayesa-Arriola et al., 2018).

Conclusion

As seen elsewhere (Cuesta et al., 2015; Bioque et al., 2016), FEP patients performed worse than HCs in terms of verbal ability,

working memory, processing speed, executive function, and attention. Although male patients suffer more significant functional impairment than females (Häfner and an der Heiden, 1997), sexual dimorphism with respect to cognitive impairment is clearly understudied. In our sample, most cognitive deficits were apparently similar in males and females, although both males and females did display some specific deficits (i.e., worse performance by males in omission, detectability, and the Hit-RT-IS tests; and worse performance by females in the Hit-RT-BC-SE test). Although these are minor differences, it would be interesting to carry out further studies to clarify the influence of sex on the different cognitive domains and to design more precise therapeutic approaches for these patients (Danaher et al., 2018).

Some limitations to this study must also be borne in mind. First, we included FEP patients with both affective and non-affective psychosis, and we did not consider the final diagnosis in the follow-up, which may change in some patients. Second, measurement of the variables during the follow-up would be useful to evaluate whether the factors we identified here at baseline are useful biomarkers of the outcome after an FEP. Third, and with regards to the sex differences, it should be noted that 68% of the patients included in the analyses were males and only 32% were females. Thus, our results may be influenced by the higher number of men in the cohort. Fourth, we obtained a small size effect in our preliminary and exploratory results that should be further corroborated. Finally, the lack of a different-from-psychosis patient group precludes conclusions about the specificity of the results with respect to psychosis. Indeed, other disease-related conditions could also show similar results.

The strengths of our study are the broad neuropsychological battery used to assess different domains of cognitive performance and the valuable population of patients that participated. In addition, studying FEP patients at baseline allows us to search for alterations and associated factors, avoiding possible confounding factors such as the impact of the duration of the disorder or the long-term pharmacological treatments. Lastly, to better understand the influence of sex, we included a sex-disaggregated analysis in our study.

Taken together, our findings suggest that oxytocin, prolactin, premorbid IQ, and sustained attention (as reflected by the score in the Hit-RT-BC test) could be biological and cognitive factors associated with an FEP and potential therapeutic targets. Moreover, low oxytocin and high prolactin specifically in the plasma of women were indicative of worse performance in sustained attention (evaluated with the perseveration test) and poor working memory, respectively. Conversely, low oxytocin and high prolactin in the plasma of men indicated better performance in sustained attention (evaluated by omissions errors and the Hit-RT tests, respectively) and poor working memory. However, future studies will be required to describe vulnerable domains in more detail and to determine whether changes in these variables help predict the outcome in these patients.

Supplementary Materials

Supplementary data are available at *International Journal of Neuropsychopharmacology (IJNPPY)* online.

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