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Influence of Menstrual Cycle Length and Age at Menarche on Symptoms, Cognition, Social Cognition, and Metacognition in Patients with First-Episode Psychosis

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Abstract: A protective effect has traditionally been attributed to estrogen in psychotic disorders. The aim of this study was to investigate cumulative lifetime estrogen by assessing the menstrual cycle length, age at menarche, and years of difference between the onset of psychotic symptoms and the age of menarche, measuring their effects on symptoms, cognition, social cognition, and metacognition. As it was not possible to directly measure cumulative estrogen levels over the lifetime of a patient, the study sample was composed of 42 women with first-episode psychosis; estrogen levels were inferred by the menstrual cycle length, age at menarche, and years of difference between the onset of psychotic symptoms and menarche. All patients were assessed with a battery of questionnaires using the BDI, PSYRATS, PANSS, STROOP, TAVEC, WSCT, IPSAQ, and BCIS questionnaires. The results

related to menstrual cycle length showed a relationship with memory; specifically, shorter cycles with semantic strategies (p = 0.046) and longer cycles with serial strategies in the short term (p = 0.005) as well as in the long term (p = 0.031). The results also showed a relationship with perseverative errors (p = 0.035) and self-certainty (p = 0.049). Only personalized bias (p = 0.030) was found to be significant in relation to the age at menarche. When analyzing the differences in years of difference between the age at menarche and the onset of psychotic symptoms, the results indicated lower scores in women with a smaller difference between both events in memory (short-term (p = 0.050), long-term (p = 0.024), intrusions (p = 0.013), and recognition (p = 0.043)) and non-perseverative errors (p = 0.024). No relationship was found between symptoms and menstrual characteristics. The investigatory outcomes seem to indicate a relationship between estrogen cumulative effects and the memory domain. More in-depth investigations in the field are necessary in order to improve personalized treatment in women with psychosis.

Keywords: schizophrenia; first psychotic episode; hormonal cycle; reproductive cycle; estrogen; memory

1. Introduction

The course of schizophrenia, its expression, and the response to treatment varies widely among patients [1], although it is commonly a highly incapacitating disease that entails a considerable societal burden [2].

Nonetheless, the prognosis of psychotic disorders is still partially unknown [3,4]; first-episode psychosis (FEP) is a five-year critical period in which social development deteriorates. At present, the course of the illness can be determined based on cognitive and social cognition functioning [5–7]. Additionally, substance misuse and abuse in women with FEP is being discussed as a possible oxidative factor that can cause further cognitive deficits and negative symptomatology [8,9].

Cumulative evidence has established that cognition, social cognition, and metacognition are among the best predictors of functional outcomes in psychosis [7,10–13]. People with psychosis often present important deficits in these three constructs, which are stable and appear prior to the onset of the disorder [10,14,15]. However, a growing body of literature suggests that psychological interventions aiming to improve cognition, social cognition, and metacognition have potential for promoting recovery [7,16].

A body of research has focused on understanding the sex differences in psychosis. Commonly, studies have found a lower prevalence and better recovery in females [17], which has led to the estrogenic hypothesis. This hypothesis suggests a protective effect of estrogen [18–21]. Estrogen plays several roles in females, from the development of secondary sexual characteristics to the regulation of the menstrual cycle. However, this effect is not exclusive to females as estrogen has recently been linked to anti-inflammatory, neuroprotective, and cognitive effects in males [22,23].

The duration of the menstrual cycle is associated with the length of the follicular phase, meaning that shorter follicular phases indicate shorter cycles [24]. Additionally, shorter menstrual cycles are usually associated with lower estradiol levels per cycle, but with a larger cumulative concentration over time [25]. On the other hand, shorter and longer cycles have been related to an increased probability of chronic anovulation and, consequently, a lower exposure to estrogen [25,26].

A delayed age at menarche has also been associated with negative and positive events in adulthood such as worse psychosocial functioning and a greater cardiovascular risk. Conversely, it has a protective effect against breast and endometrial cancer [25,27].

Emerging research indicates that early menarche correlates with higher estrogen levels [28]. In the case of women with psychosis, there seems to be an association between early puberty and a later onset of symptoms, which is consistent with the estrogenic hypothesis [29,30]. Furthermore, symptoms seem to fluctuate throughout the menstrual cycle and are heightened during the late luteal and early follicular phases. Interestingly,

this association is also present in patients with mood disorders [26,30–32]. In addition, postpartum and menopause psychosis have been related to the abrupt decrease in estrogen after these events [26,30,33].

Compared with healthy populations, women with psychosis have lower estrogen levels [33]. Recent studies have suggested that selective estrogen receptor modulators (SERMs) can improve cognitive symptoms in men and women with psychosis [34,35].

However, how estrogen cumulative effects influence symptoms, cognition, social cognition, and metacognition is still unknown, although a pharmacological treatment with SERMs seems to provide results. Therefore, the present study intended to obtain preliminary data on how pubertal and menstrual characteristics influence the expression of the illness and whether the protective effect of estrogen can be detected. The length of the cycle, age at menarche, and time elapsed since the age at menarche as well as the onset of symptoms could be variables that help us to indirectly deduce the level of estrogen.

The aim of this work was to conduct an exploratory analysis of the clinical, cognitive, social cognitive, and metacognitive differences according to the length of the menstrual cycle, age at menarche, and years of difference between the onset of psychosis and age at menarche in women with FEP. We hypothesized that these indicators could be related to clinical, cognitive, social cognitive, and metacognitive variables with a positive relationship between them and the inferred estrogen levels. An exploratory analysis was performed based on these data because these were the only data that were available as we did not count hormone levels.

2. Method and Materials

The sample of this study was composed of 42 women recruited through the following Spanish outpatient mental health centers between the years 2012 and 2017: The Health Assistance Institute of Girona; Sant Pau Hospital (Barcelona); Andalusian Service of Jaén; Andalusian Service of Málaga Pere Mata's Institute (Reus); Jiménez Díaz Foundation (Madrid); Mental Health Hygiene Centre of Les Corts (Barcelona); Mental Health Centre of Healthcare and University Corporation of Parc Taulí (Sabadell); Clínic Hospital of València; and Parc Sanitari Sant Joan de Déu (PSSJD).

The inclusion criteria were women between the age of 18 and 45 years with FEP having a diagnosis of schizophrenia, an unspecified psychotic disorder, a schizoaffective disorder, a delusional disorder, a brief psychotic disorder, or a schizophreniform disorder based on DSM-V criteria in addition to psychopathological stability over the previous 3 months (meaning no changes in medication) and having obtained 3 or above on the delusion, grandiosity, or suspicion items on The Positive and Negative Syndrome Scale (PANSS). The exclusion criteria established were an intellectual disability (premorbid IQ inferior or equal to 70), the presence of a cranioencephalic traumatism, a substance abuse disorder, amenorrhea, or the use of hormonal contraceptives, having obtained 5 or above on the hostility and absence of cooperation items and a score of 6 on the suspiciousness item on the PANSS in order to facilitate adherence and collaboration during the evaluation.

Three variables were used to conduct the analysis. To start with, the cycle duration was defined as the average number of days that the menstrual cycle lasted. This variable was subjectively reported by participants, who had to choose which of the three groups they belonged to: short menstrual cycle (<28 days); mean (28–30 days); or long (>30 days). This classification was previously defined in the research protocols used in other studies. The second variable, age at menarche, was defined as the age of first menstruation and was asked of participants or reported based on their clinical history. The age at menarche was divided into three groups: early menarche (aged 9–12); mean (aged 13); or late menarche (aged 14–16). These groups were organized considering the distribution of the sample using the mean and conceptual information. In this case, the age of most women (50%) at menarche was at 13 years; therefore, we used this as the middle group. Those above and below the median formed the other two groups. For the last variable, if 0–5.99, 6–19.99, or >20 years passed between the age at menarche and illness onset, it was defined as the

time when symptoms were reported for the first time. This group was divided considering the proximity to hormonal changes; below 5 years between the onset and menarche age was considered to be close to developmental changes and more than 20 years was considered to be hormonal maturation changes.

Regarding the assessment, the data were gathered during the inclusion of the study and through clinical histories; clinical, cognitive, social cognition, and metacognition evaluations were based on a clinical interview and the questionnaires from Table 1.

Table 1. Questionnaires.

Symptom Evaluation
• The **Beck Depression Inventory (BDI)** was used to evaluate depressive symptoms as it has a high internal consistency and content validity. Higher scores indicate worse symptomatology [36–38]; • The **Psychotic Symptom Rating Scales (PSYRATS)** was used to assess the severity of hallucinations and delusions in psychotic patients as it has demonstrated its validity as a complement in order to evaluate these dimensions. Higher scores indicate a greater presence of hallucinations and delusions [39]; • The **Positive and Negative Syndrome Scale (PANSS)** is a semi-structured interview that allows for differentiating between positive, negative, and general symptoms. Higher scores mean a greater symptom severity [40,41].
Cognitive Evaluation
• The **Stroop Test** was used for its reliability in evaluating executive functioning, measuring cognitive inhibition, and flexibility [42–44]; • The **Test de Aprendizaje Verbal España-Complutense (TAVEC)**, the Spanish version of the California Verbal Learning Test, assesses learning capacity, memory domains, and strategies used in addition to counting with reliability and validity. Higher scores indicate a better performance [45–47]; • The **Wisconsin Card Sorting Test (WSCT)** is an executive functioning test used to evaluate problem solving and the ability to change tasks and response maintenance, and it measures these constructs well. A good development on this test is reflected by high scores [48].
Social Cognition Evaluation
• The **Hinting Task**, used to evaluate the theory of mind, was chosen because of its strong psychometric properties. In our study, we used the abbreviated version; the higher the punctuation, the higher this ability [49,50]; • The **Emotion Recognition Face Test** consists of a set of different pictures that represent different emotions and the patient must choose between two options. We selected this test because of its reliability in detecting deficits, even though it reaches ceiling performance scores [51,52]; • The **Internal, Situational, and Personal Attributions Questionnaire (IPSAQ)**, which has supported internal reliability [53], is used to describe the causal locus of the thinking of a person. High results reflect the attributional style they tend to use and whether it is a personalizing or externalizing bias style [54].
Metacognitive Evaluation
• The **Beck Cognitive Insight Scale (BCIS)** is a self-assessed scale that evaluates the capacity of the patient to think about their own behavior and includes two scales: self-certainty and self-reflectivity. The higher the punctuations obtained on each scale, the more developed their capacity. This scale was chosen because its assessment is based on good psychometric properties [55].

2.1. Ethical Aspects

The present study was approved by the Ethical Committee of Sant Joan de Déu (coordinator center) (protocol code: PIC-73-11; date of approval: 22 November 2011) and the ethical committee of each of the participant centers, following the guidelines of the Declaration of Helsinki. In addition, each participant was provided with an informative sheet and signed an informed consent form.

2.2. Statistical Analysis

The data analysis was performed using the ANOVA descriptive test and partial eta squared (η^2) to calculate the effect size. We considered a *p*-value equal to or less than 0.05 to be statistically significant. Regarding the effect size, the following criteria were used: less than 0.1 indicated a small effect; between 0.1 and 0.15, a medium one; and larger than 0.15, a high effect size [56]. Multiple analysis corrections were not applied based on the effect size because we were performing an exploratory analysis [57]. We also performed a multimodal regression analysis that compared the three categories of each of the three main variables with the significant variables in the bivariate analysis. Moreover, we included age as a covariant. The reference category of menstrual cycle length was the middle group; in menarche age, the reference group was also the middle group. However, in the difference between the age at menarche and the onset of the illness, the reference group was the first one.

3. Results

Table 2 contains a description of the sociodemographic variables of the sample. The mean age of the patients was 31 years with a standard deviation of 8.06. As can be seen, 76.2% of our sample were single and 69.1% were not working (i.e., 28.6% unemployed; 21.4% inactive; 14.3% permanently or temporarily sick leave and 4.8% pensioners).

Table 2. Sociodemographic characteristics of the sample.

Variables	Categories		*N*	%
Marital status	Single		32	76.2
	Married or living with a partner		4	9.5
	Separated		4	9.5
	Divorced		1	2.4
	Widowed		1	2.4
Study level	Primary	Incomplete	1	2.4
		Complete	6	14.3
	Secondary	Incomplete	7	16.7
		Complete	11	26.2
	University	Incomplete	6	14.3
		Complete	11	26.2
Working situation	Active occupied		5	11.9
	Active unemployed		12	28.6
	Student		6	14.3
	Housework		2	4.8
	Pensioner		2	4.8
	Permanent or temporary sick leave		6	14.3
	Inactive		9	21.4
Principal diagnostic	Schizophrenia		9	21.4
	Unspecified psychotic disorder		11	26.2
	Schizoaffective disorder		8	19.0
	Delusional disorder		4	9.5
	Brief psychotic disorder		5	11.9
	Schizophreniform disorder		5	11.9
Menstrual cycle description	<28 days		15	35.7
	28–30 days		20	47.6
	>30 days		5	11.9
Age at menarche	9–12 years		12	28.6
	13 years		21	50.0
	14–16 years		9	21.4
Difference in age at menarche and age of symptom onset	0–5.99 years		8	19.0
	6–19.99 years		20	47.6
	>20 years		14	33.3

Regarding the variables studied, most patients had a 28–30 day menstrual cycle (47.6%). On the other hand, 35.7% had shorter ones (<28 days); only 11.9% were longer (>30 days). The mean menarche age was 12.31 with a standard deviation of 1.62 and the mean difference in years between the menarche age and the age of symptom onset was 15.14 with a standard deviation of 7.71.

We found no relationship between the age at menarche and the age of illness onset ($r = 0.137$; $p = 0.388$).

When analyzing the cycle length (Table 3), we found statistically significant differences with high effect sizes between the groups primarily in relation to memory and specifically in terms of semantic strategies ($p = 0.046$) and serial strategies with short-term ($p = 0.005$) and long-term ($p = 0.031$) memory. We also found a relationship between the cycle length and perseverative errors ($p = 0.035$) and self-certainty ($p = 0.049$).

Table 3. Relationship between cycle length and symptoms, cognition, social cognition, and metacognition.

			<28 Days		28–30 Days		>30 Days		*p*-Value	Partial Eta Squared
			M	SD	M	SD	M	SD		
Symptoms	PSYRATS	BDI	14.87	7.43	15.00	11.20	13.40	8.17	0.944	0.003
		Hallucinations	1.62	5.82	5.00	9.44	5.20	11.63	0.523	0.037
		Delusions	9.00	7.20	4.45	5.66	4.20	4.92	0.107	0.120
		PANSS: positive	13.73	7.35	13.40	4.16	12.00	5.24	0.839	0.009
		PANSS: negative	13.80	4.51	13.85	6.43	15.00	5.05	0.909	0.005
		PANSS: general	29.27	7.24	28.75	9.75	28.20	9.58	0.969	0.002
Cognition	STROOP	Word	44.87	11.82	42.00	9.52	39.80	8.26	0.577	0.031
		Color	40.93	8.65	34.89	7.54	35.40	7.47	0.096	0.125
		Word–color	49.93	13.80	40.11	10.73	40.40	8.65	0.059	0.149
		Interference	56.67	10.53	50.72	6.37	50.40	6.43	0.106	0.120
	TAVEC	Short-term free recall	44.64	11.90	38.13	11.56	36.54	16.21	0.245	0.075
		Short-term recall with keys	43.71	11.56	37.83	15.02	33.22	14.25	0.266	0.071
		Long-term free recall	43.73	10.76	39.42	16.09	35.59	16.42	0.488	0.039
		Long-term recall with keys	41.77	12.67	36.20	15.50	32.75	15.89	0.386	0.052
		Semantic strategy on short-term recall with keys	50.39	10.50	42.73	6.94	43.81	9.22	**0.046**	0.158
		Semantic strategy on long-term recall with keys	48.48	10.10	42.26	8.22	43.96	9.82	0.156	0.098
		Serial strategy on short-term recall with keys	44.19	0.52	50.04	6.51	47.46	4.07	**0.005**	0.256
		Serial strategy on long-term recall with keys	45.60	4.12	53.34	10.83	47.46	5.73	**0.031**	0.176
		Perseverations	44.48	7.82	49.32	9.03	56.57	11.24	**0.035**	0.110
		Total intrusions on recall with keys	52.65	13.17	49.11	10.70	54.91	21.33	0.598	0.028
		Total intrusions on free recall	49.57	8.28	45.59	4.85	47.49	9.52	0.268	0.071
		Hits on recognition	48.93	11.89	43.76	16.04	41.52	20.27	0.511	0.037
	WSCT	Hits	75.00	11.70	70.39	8.28	75.75	15.71	0.406	0.053
		Total errors	45.43	7.50	40.61	6.00	44.00	6.22	0.135	0.100
		Perseverative errors	46.29	9.19	40.44	8.26	46.75	5.32	0.122	0.120
		Non-perseverative errors	44.57	7.47	41.22	5.97	40.50	8.39	0.336	0.064
		Hinting task	1.68	0.36	1.70	0.24	1.73	0.28	0.930	0.004
Social cognition	Emotion recognition facial test		18.33	1.11	17.65	1.42	17.20	1.64	0.183	0.088
Metacognition	IPSAQ	Externalization bias	2.47	3.83	1.00	3.88	3.00	3.16	0.404	0.048
		Personalizing bias	0.89	0.50	1.26	0.68	1.45	0.88	0.149	0.100
	BCIS	Self-reflectivity	13.14	4.19	14.50	6.91	16.00	6.25	0.629	0.025
		Self-certainty	7.64	3.54	6.90	3.23	11.40	4.56	**0.049**	0.155

The results for the menarche age can be found in Table 4. The only statistically significant result found was for personalizing bias ($p = 0.030$) with a high effect size ($\eta^2 = 0.168$). The group with a later menarche was the one that obtained worse scores.

Regarding the years of difference between the onset of psychotic symptoms and menarche age (Table 5), the results indicated lower scores in women with the smallest difference between both events in memory (short-term ($p = 0.050$), long-term ($p = 0.024$), intrusions ($p = 0.013$), and recognition ($p = 0.043$)) and non-perseverative errors ($p = 0.024$); all of them had a high effect size.

Table 4. Relationship between the age at menarche and symptoms, cognition, social cognition, and metacognition.

			9–12 Years		13 Years		14–16 Years		*p*-Value	Partial Eta Squared
			M	SD	M	SD	M	SD		
Symptoms	PSYRATS	BDI	12.00	8.07	20.40	12.26	15.56	8.53	0.072	0.130
		Hallucinations	3.37	7.08	8.91	12.67	0.00	0.00	0.063	0.142
		Delusions	4.80	5.84	9.27	7.73	4.89	5.27	0.152	0.097
		PANSS: positive	11.95	3.32	16.27	8.73	13.00	3.12	0.094	0.114
		PANSS: negative	13.55	5.81	16.18	6.87	14.56	4.39	0.481	0.037
		PANSS: general	28.41	6.15	32.37	13.98	27.89	5.69	0.431	0.042
Cognition	STROOP	Word	40.82	7.80	43.25	12.26	45.89	7.67	0.648	0.023
		Color	37.36	8.41	37.00	9.68	38.33	5.48	0.934	0.004
		Word–color	43.75	13.17	43.45	13.37	43.44	10.27	0.997	0.000
		Interference	53.35	10.56	54.00	7.48	48.67	4.82	0.341	0.056
	TAVEC	Short-term free recall	39.60	14.27	42.22	8.56	39.10	11.65	0.816	0.011
		Short-term recall with keys	37.97	15.44	39.75	12.36	38.05	15.01	0.943	0.003
		Long-term free recall	38.62	15.25	42.62	12.42	39.76	14.54	0.757	0.015
		Long-term recall with keys	35.93	15.47	37.54	15.14	37.62	15.93	0.944	0.003
		Semantic strategy on short-term recall with keys	45.24	10.70	46.08	7.42	45.31	8.24	0.970	0.002
		Semantic strategy on long-term recall with keys	42.84	10.89	45.36	8.58	45.98	8.10	0.654	0.022
		Serial strategy on short-term recall with keys	46.99	5.21	49.80	6.85	46.83	3.63	0.335	0.056
		Serial strategy on long-term recall with keys	50.74	11.06	50.22	7.25	48.12	4.59	0.768	0.014
		Perseverations	48.15	8.10	50.18	12.20	46.11	8.60	0.634	0.027
		Total intrusions on recall with keys	51.96	12.47	44.17	1.63	56.97	17.92	0.071	0.130
		Total intrusions on free recall	48.59	7.63	43.97	4.68	48.37	6.48	0.171	0.089
		Hits on recognition	42.35	15.95	48.83	8.62	44.51	19.79	0.532	0.033
	WSCT	Hits	77.27	9.28	71.26	9.57	70.25	13.08	0.747	0.017
		Total errors	42.75	5.82	45.20	8.36	41.13	7.40	0.569	0.032
		Perseverative errors	43.05	8.16	45.30	9.65	42.63	9.47	0.763	0.015
		Non-perseverative errors	42.25	5.34	45.20	8.35	40.50	8.14	0.335	0.061
		Hinting task	1.70	0.28	1.68	0.28	1.70	0.36	0.988	0.001
Social cognition		Emotion recognition facial test	17.91	1.31	17.45	1.44	17.78	1.64	0.687	0.019
	IPSAQ	Externalization bias	1.95	4.02	2.00	2.93	0.33	4.21	0.527	0.032
		Personalizing bias	1.01	0.54	1.07	0.61	1.68	0.82	**0.030**	0.168
Metacognition	BCIS	Self-reflectivity	14.14	6.66	14.27	5.83	14.75	4.27	0.970	0.002
		Self-certainty	8.50	3.80	7.55	3.56	6.63	4.00	0.465	0.039

Table 5. Relationship between the difference in age at menarche and age of onset of psychosis and symptoms, cognition, social cognition, and metacognition.

			0–5.99 Years		6–19.99 Years		>20 Years		*p*-Value	Partial Eta Squared
			M	SD	M	SD	M	SD		
Symptoms	PSYRATS	BDI	16.00	8.50	15.45	10.91	13.15	8.98	0.757	0.015
		Hallucinations	5.71	10.36	4.80	10.05	2.17	5.13	0.635	0.025
		Delusions	3.88	6.15	5.85	6.78	7.83	6.12	0.408	0.047
		PANSS: positive	13.75	3.66	13.95	6.83	12.14	3.92	0.625	0.024
		PANSS: negative	14.50	4.54	15.75	6.97	12.57	4.27	0.299	0.060
		PANSS: general	29.63	6.57	30.85	11.39	26.93	4.34	0.445	0.041
Cognition	STROOP	Word	36.57	7.66	46.37	8.66	42.14	11.91	0.082	0.127
		Color	35.00	4.80	37.89	8.37	37.93	9.97	0.717	0.018
		Word–color	42.57	8.72	43.16	10.76	44.71	16.07	0.915	0.005
		Interference	54.00	7.09	49.47	6.55	55.79	11.17	0.111	0.112
	TAVEC	Short-term free recall	32.98	17.01	39.62	10.82	44.63	10.18	0.112	0.109
		Short-term recall with keys	28.73	16.94	37.66	13.96	44.49	10.80	0.050	0.146
		Long-term free recall	28.74	18.60	39.49	12.89	46.19	10.15	**0.024**	0.179
		Long-term recall with keys	26.64	16.41	36.10	15.59	42.68	11.38	0.066	0.133
		Semantic strategy on short-term recall with keys	42.72	9.74	45.55	8.90	46.76	9.76	0.648	0.023
		Semantic strategy on long-term recall with keys	39.57	10.60	45.33	9.59	44.92	9.24	0.382	0.049
		Serial strategy on short-term recall with keys	46.74	3.34	47.80	4.17	48.06	7.70	0.872	0.007

Table 5. *Cont.*

			0–5.99 Years		6–19.99 Years		>20 Years		*p*-Value	Partial Eta Squared
			M	SD	M	SD	M	SD		
Cognition	TAVEC	Serial strategy on long-term recall with keys	50.18	7.99	48.78	5.18	51.74	13.06	0.645	0.023
		Perseverations	50.05	9.99	49.89	9.66	45.00	8.23	0.282	0.073
		Total intrusions on recall with keys	63.34	20.58	47.48	8.58	49.77	9.93	**0.013**	0.204
		Total intrusions on free recall	52.05	10.50	45.98	4.88	46.83	6.66	0.124	0.104
		Hits on recognition	31.83	25.32	48.16	9.78	45.79	12.99	**0.043**	0.153
	WSCT	Hits	72.33	12.72	71.84	9.40	74.38	11.44	0.799	0.013
		Total errors	39.67	6.02	44.00	7.40	43.23	6.33	0.499	0.039
		Perseverative errors	43.33	8.82	43.58	9.13	43.62	8.58	0.998	0.000
		Non-perseverative errors	36.17	6.08	44.74	6.30	42.62	6.49	**0.024**	0.193
		Hinting task	1.81	0.24	1.62	0.28	1.73	0.33	0.276	0.065
Social cognition	Emotion recognition facial test		17.38	1.41	17.75	1.59	18.00	1.11	0.610	0.025
	IPSAQ	Externalization bias	0.88	4.64	1.25	3.43	2.57	3.84	0.511	0.034
		Personalizing bias	1.39	0.88	1.22	0.71	0.98	0.38	0.370	0.051
Metacognition	BCIS	Self-reflectivity	16.25	6.78	14.68	4.75	12.64	6.81	0.369	0.051
		Self-certainty	8.88	4.61	7.58	3.49	7.71	3.79	0.711	0.018

When performing the multimodal regression analysis concerning the menstrual cycle length, age ($p = 0.009$), serial strategy on short-term recall with keys ($p = 0.002$), and self-certainty ($p = 0.023$) were included in the model. However, in the analysis of each subgroup, we only found a tendency toward a significance regarding the lowest cycle and middle cycle in the serial strategy on short-term recall with keys (B = 0.118; $p = 0.088$).

Considering the results of the age at menarche, hallucinations measured by the PSYRATS ($p = 0.013$), a positive PANSS ($p = 0.048$), and personalized bias ($p < 0.001$) were included in the model. In this case, personalized bias had a tendency to differ between subgroups 1 and 2 (B = 0.074; $p = 0.061$). A positive PANSS (B = 1.769; $p = 0.098$) and personalized bias (B = 38.845; $p = 0.051$) had a tendency to differ between subgroups 2 and 3.

Finally, regarding the difference between the age at menarche and the age of onset, the only variable included in the model was hits on recognition ($p = 0.032$), which was significant between subgroups 1 and 2 (B = 0.902; $p = 0.046$).

4. Discussion

In the present study, we have suggested differences based on the length of the cycle, the time elapsed since the age at menarche and the onset of symptoms, and the age at menarche following the expected protective estrogen hypothesis, indicating that these could be relevant indicators.

Our first finding was that the duration of the menstrual cycle was significantly associated with the different domains of memory. We observed that the semantic strategy was the least used in women with an average cycle length whereas the serial strategy was used more often. Patients with psychosis often present deficits in semantic processing; thus, they tend to rely more on serial memory. According to our results, patients with shorter and longer cycles performed better on semantic processing, indicating a better performance on memory; other authors have suggested that this is related to less severe symptoms [58,59]. Our results were in line with the estrogen levels associated with cycle length reported by Mumford et al. [25], and were also consistent with those in previous studies that reported an association between memory and processes of encoding and recalling [60–62]. They are also in line with the estrogen synthesis of the brain, which takes place mostly in the hippocampus and temporal regions [63,64].

Another significant result was that we found that women with shorter menstrual cycles appeared to have more cognitive flexibility and a greater inhibition capacity. These results were consistent with previous studies that reported that the interaction between estrogen and the dopaminergic system modulates executive functions [22,60]. Furthermore, an association between total estradiol and cognitive function in women has been observed [65].

The women with mean menstrual cycles showed less self-certainty, which was also consistent with a reported association between estrogen levels and cycle length [25]. Self-certainty is a metacognitive construct that has been associated with the emergence and maintenance of delusions [66,67] as well as neurocognitive performance [13]

The age at menarche was associated with personalized bias, a cognitive bias directly implicated in the emergence and maintenance of delusions [68,69]. This suggested that women with lower estrogen levels may attribute others with the consequences of negative events. This result followed our expectations although it was the only significant variable.

Similar to previous studies, we did not find a relationship between the age at menarche and the onset of illness [29]. Nonetheless, a more complex relationship between these factors has already been proposed in a previous study [70] and it is possible that there is a critical period in which estrogen exerts its effects [22,60]. Moreover, an early age at menarche has been associated with an increased risk of suffering a mental illness post-menarche [71]. An early age at menarche has also been associated with various factors during prenatal and childhood development such as body weight, trauma, or exposure to certain chemicals [71,72].

Based on the time elapsed since the age at menarche and the onset of symptoms, we also observed important differences in cognition. More precisely, short-term recall with keys and free long-term recall exhibited a larger period of time between both successes and an improved performance. This fact could indicate a better conservation of memory strategies [22,62,73,74], which may be due to the neuroprotective effects of estrogen [60].

We observed significant differences in intrusions, recognition, and non-perseverative errors; unexpectedly, the best performance was seen in the middle group. The worst performance was seen in the shortest period group, indicating that the shorter this time was, the worse the development was, thereby suggesting that a lack of estrogen implies a poorer performance [26,61].

The results obtained indicated a possible association between a few pubertal and menstrual characteristics on account of the protective influence of estrogen. However, the results of our study must be interpreted in the light of several limitations. First, we had a limited sample size, which should be larger in prospective research. Moreover, we based our groups on predefined characteristics and the distribution of the sample and conceptual knowledge. We did not have access to the blood measures of the hormonal parameters. Finally, the fact that correction analyses for multiple testing were not included should also be noted as a limitation. Notwithstanding these limitations, our results highlighted a possible relationship between menarche age, the menstrual cycle, and social cognitive, metacognitive, and neurocognitive performance in women with FEP. In the absence of research on the menstrual and pubertal characteristics of women with FEP, we only intended to conduct an exploratory analysis to guide future investigations on this subject.

Therefore, our findings suggest a relationship between the length of the cycle, the age at menarche, and the time elapsed since the age at menarche and the onset of symptoms with cognitive and metacognitive performance in women with FEP. In the future, it may be worth monitoring menstrual cycle characteristics and hormone blood levels as they are easy indicators to compile and could be useful tools to modulate medication and offer more individualized and personalized treatment. Further studies need to be performed with bigger sample sizes, continuous menstrual monitoring, and blood test analytics to corroborate this relationship.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data are not available upon request due to restrictions (e.g., privacy or ethical). The data presented in this study are available upon request from the corresponding author. Our institution is working on a repository of data.

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