Exploring Vascular Endothelial Growth Factor and Other Blood-Brain Barrier Biomarkers in Cognition of First-Episode Psychosis:

An Observational Study

Alejandro Ballesteros, MD; María Flores-Lopez, MSc; Ana M. Sánchez-Torres, PhD; Gustavo J. Gil-Berrozpe, MSc; Lucía Moreno-Izco, MSc; Ana Gavito, MSc; Antonia Serrano, MSc; Fernando Rodríguez de Fonseca, MD, PhD; and Manuel J. Cuesta, MD, PhD

Abstract

Background: Cognitive deficits are a core feature of early stages of schizophrenia. However, according to neurodevelopmental models, the extent to which chemokines and growth factors are involved in cognitive function remains debatable. We aimed to investigate whether homeostatic/inflammatory chemokines and growth factors are associated with cognitive impairment in patients with first-episode psychosis (FEP) in remission.

Methods: Fifty patients, 21 healthy siblings, and 24 controls participated in the study. The primary outcomes were associations between cognition and growth factors (brain-derived neurotrophic factor [BDNF] and vascular endothelial growth factor [VEGF]), homeostatic markers (CXCL12), and inflammatory chemokines (CCL2, CCL3, CX3CL1, and CCL11) using a whole-blood immunoassay procedure. Differences between the FEP group, siblings, and controls were also examined to understand distinct group profiles.

Results: The VEGF levels were significantly higher in the FEP group than in the control group. High VEGF levels are significantly associated with lower social cognition scores. Moreover, a post hoc hierarchical regression model explained 34.5% of the variance in social cognition ($F_{11, 32} = 1.533$, $P = .168$), with inflammatory variables explaining 13.5% and VEGF showing statistical significance ($\beta = -1.936$, $P = .022$). No additional significant results were found for the other inflammatory biomarkers.

Conclusions: Our preliminary results suggest that an increase in VEGF might help preserve social cognition after first-episode psychosis. These findings might suggest that a compensatory mechanism could outweigh other VEGF-related hypotheses, such as blood-brain barrier opening and chronic neuroinflammation. However, this hypothesis requires further investigation to address the methodological challenges of determining chemokine levels and controlling for confounding variables.

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Author affiliations are listed at the end of this article.

Psychotic disorders encompass various syndromes with different cognitive alterations.[1] These deficits negatively affect functional outcomes and, unlike clinical symptoms, do not respond well to antipsychotics.[2] Pathogenetic mechanisms involving neurodevelopmental alterations or neurotoxic environmental effects are facilitated by disruption of the blood-brain barrier (BBB).[3] A meta-analysis of the duration of untreated psychosis and cognition suggests that neurodevelopmental factors are prominent in first-episode psychosis (FEP), occurring before its onset, and remaining stable over time.[4] Understanding the factors that potentially influence BBB permeability is crucial for the development of better treatments.

Immune abnormalities during neurodevelopment, particularly in microglial cells, are central to the pathophysiology of schizophrenia.[5] In particular, low-grade inflammation is associated with illness onset.[6,7] Environmental factors, such as maternal immune activation and early-life adversity, are linked to schizophrenia,[8] and the underlying immune mechanistic frameworks related to BBB anomalies.[9,10] Moreover, BBB

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Clinical Points

- Proangiogenic VEGF actions may predominate over blood-brain barrier effects.
- Chemokines may be associated with early neurodevelopmental disturbances.
- A VEGF increase in first-episode psychosis might be a reactive mechanism to preserve social cognition.

opening contributes to FEP by facilitating disruption of glutamate homeostasis, brain permeability of bacterial and other proinflammatory mediators, and induced synaptic dysfunction.[11] Over the course of the illness, a proinflammatory state affects FEP; it is present in drug-naïve FEP, partially normalizes with antipsychotics, and may influence clinical severity.[12]

Chemokines are involved in BBB opening and play important roles in neurodevelopment and signaling. Some are homeostatic and control cell migration, while others are proinflammatory.[13,14] Elevated chemokine levels are found in FEP and ultra-high-risk (UHR) individuals, possibly as a response to pathological processes.[15] Certain chemokine levels (MIP-3α) predict remission of positive symptoms in FEP,[16] while others, such as CCL2, represent trait markers[17] and correlate with cognitive deficits in schizophrenia, particularly verbal and working memory.[18] A recent mild cognitive impairment study suggested that an imbalance in inflammatory chemokines (IC) may predict cognitive deficits beyond FEP or schizophrenia evidence.[19] Literature regarding the differences in chemokine levels between patients with FEP and their siblings is scarce. Interestingly, a psychosis twin study found no differences in CCL2 cerebrospinal levels but did find variations in other biomarkers related to microglial activation.[20]

Growth factors also influence BBB permeability in the schizophrenia via several mechanisms involving reduced cerebral perfusion and impaired homeostatic processes in the cerebral microenvironment.[21] Brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) influence neuronal growth and plasticity as notable candidates for the early detection of schizophrenia.[22] VEGF also modulates BBB permeability, facilitating the entry of proinflammatory products.[23–25] BDNF is linked to cognitive impairment across various stages of schizophrenia and bidirectional results for FEP,[26] whereas VEGF levels are directly related to cognitive impairment severity in FEP[27] and inversely related to chronic schizophrenia[28,29] and naïve FEP.[30] However, literature on sibling studies is limited. Notably, an increased ratio of proBDNF (synaptic pruning-related) to mature BDNF (neuronal growth and plasticity-related) in FEP patients and their unaffected siblings compared to controls suggests an enhanced apoptotic phenomena.[31]

Both biomarker groups may play roles in a previously conceived schizophrenia pathogenetic model, indicating that cellular-level alterations in the BBB could increase permeability, deposit neurotoxic proteins, and impact cognition.[32] Providing additional molecular evidence and overcoming previous methodological issues are advisable, as previous studies focused on proinflammatory cytokines require replication.[33] Assessing both inflammatory and noninflammatory chemokine could offer a broader view of their roles in the pathophysiology of FEP. This study aimed to examine the differences in the levels of the following biomarkers between patients, siblings, and controls, defined in 3 groups: the first is IC (CCL2, CCL3, CX3CL1, and CCL11[18,34–36]); second, noninflammatory and homeostatic chemokine (NIC) CXCL12[37]; and third, proteins involved in trophic homeostasis and BBB regulation, BDNF and VEGF.[38] Our second aim was to test the influence of these biomarkers on cognitive function in patients, siblings, and healthy controls.

METHODS

The Study Population

Patients aged 17–45 years who were admitted with FEP to our psychiatry department were included after signing an informed consent form. Exclusion criteria were significant medical/neurological conditions, head injury with cognitive consequences, intellectual disability, and symptoms due to substance effects per the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*) criteria.[39] Healthy siblings and age- and sex-matched controls were included. Siblings and controls were assessed for affective and psychotic disorders using the abbreviated version of the Comprehensive Assessment Symptoms and History (CASH).[40] The exclusion criteria for siblings included intellectual disability and psychiatric, neurological, or medical illness, including substance use disorders. Controls were excluded if they had first-degree relatives with psychosis. Controls were recruited mainly through public advertising and hospital staff.

Ethics

This study was approved by the Ethics Committee of the Health Navarre System. All participants provided written informed consent in accordance with local Institutional Review Board guidelines. Informed consent allows the curator to sign if the patient cannot.

Clinical Assessments

Demographic and premorbid data were collected, including age, sex, education, occupation, and living arrangements. The CASH is a semistructured interview designed to provide a comprehensive assessment of

current and past symptoms and episodes and include the Scale for the Assessment of Positive Symptoms and the Scale for the Assessment of Negative Symptoms. Reality–distortion and negative and disorganization dimensions were obtained as described elsewhere.[40] It has been used extensively in longitudinal FEP studies to investigate psychotic disease progression and treatment effectiveness. It aids in diagnosing and monitoring psychotic disorders and adapts to changing diagnostic criteria for comparative studies.[41] A final *DSM-5* diagnosis was established by consensus after assessment and using all available information 6 months after inclusion in the study by 2 senior psychiatrists. Positive, negative, and disorganization scores were obtained from the CASH interviews.

The antipsychotic dosage was measured by converting the doses at the time of the psychopathological assessment and the total exposure during the episode to chlorpromazine equivalents (CPZ-eq[42]).

Cognitive Assessments

Cognitive functioning was assessed using a comprehensive battery of 10 standardized neuropsychological tests validated in a Spanish population. This battery of tests was designed to obtain a global cognition score, and the 7 cognitive dimensions proposed in the MATRICS Consensus Cognitive Battery[43,44]: attention, processing speed, working memory, verbal memory, visual memory, executive functioning, and social cognition. The premorbid intelligence quotient was also assessed, and the total cognition score was obtained by averaging the 7 cognitive functions. The battery of tests for cognitive examination has been detailed in our previous work.[45] The tests were administered at 2 months by 2 experienced neuropsychologists in 2 sessions of 1–1.5 hours in length, and they were conducted sequentially in the same order from the lowest to the highest level of difficulty in order to both reduce the effect of fatigue and to facilitate cooperation. Both neuropsychologists achieved good inter-rater reliability and were blinded to the psychopathological examinations.

Laboratory Investigations

Venous blood samples were extracted after 2 months of treatment in 12-hour-fasted conditions from 8:30 to 11:00 AM. We used 10 mL K2 EDTA tubes (BD Vacutainer, New Jersey). To monitor the blood concentrations of chemokines and growth factors, we used a whole-blood procedure that facilitates the measurement of chemokines and growth factors without the interference of red blood sequestration or centrifugation (to obtain plasma) or coagulation (to obtain serum).[46] To this end, tubes containing whole blood were frozen and stored at −80°C until assayed. On the day of the assay, the blood samples were thawed and homogenized for 30 s at 4°C. A 1 mL sample of the homogenate was then diluted 1/3 with Milli-Q water and centrifuged at 16,000 × g for 20 min at 4°C. The supernatants were then used for chemokine/growth factor measurements using a Bio-Plex Suspension Array System 200 (Bio-Rad Laboratories, California, US) with Procarta Immunoassay Kits using polystyrene beads and a Plasma Standard Diluent Kit (Affymetrix-Panomics; California, US). This type of analysis is based on the Luminex technology. At the same time, a human chemokine 7-plex panel was used to detect CCL2 (MCP-1), CCL3 (MIP-1a), CCL11 (eotaxin), CXCL12 (SDF-1a), CX3CL1 (fractalkine), BDNF, and VEGF levels. Characterization was performed according to the manufacturer's instructions. Raw data were analyzed using the Bio-Plex Manager software version 4.1 (Bio-Rad Laboratories, California). Data are expressed as picograms of protein per milliliter of plasma. For a more detailed description of the blood sample preparation and analysis protocol, please refer to Araos et al.[47]

Statistical Analysis

Before commencing statistical processing and analysis, the data were visually inspected for outliers. Normality of the data distribution was checked using the Shapiro-Wilk test. Continuous data were expressed as mean ± standard deviation, whereas categorical variables were expressed as percentages, where appropriate. Student *t* test for unpaired samples and the χ^2 test were used to compare cases with controls.

For normally distributed variables, 1-way analysis of variance (ANOVA) was used to compare the three groups. Pearson coefficients were used to assess correlations between cognitive variables and serum chemokines/growth factors, with *r* values interpreted as follows: >0.90 (very high), 0.70–0.90 (high), 0.50–0.70 (moderate), 0.30–0.50 (low), and <0.30 (little to no correlation).

For cases only and as a post hoc analysis when applicable, multivariate regression analyses were performed for each serum chemokine/growth factor concentration, correcting for confounding variables. Inflammatory biomarkers and confounding variables were included in 4 blocks: premorbid adjustment and sociodemographic (age, sex, and civil status), immune (including one of the three groups defined in "aims of study"), exogenous (antipsychotics and presence/absence of F10-19 substance disorder), and clinical block (positive, negative, and disorganized score).

Significance was set at $P < .05$, unless Bonferroni correction was applied, adjusting *P* values by the number of comparisons. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS version 21.0, IBM, Illinois, US). Figures were created using JASP 0.19 and Microsoft PowerPoint (Office 2021).

Table 1.

Sociodemographic and Clinical Characteristics and Inflammatory Levels of Participants

Variables	Patients (FEP) (n = 50)	Siblings (S) (n = 21)	Controls (HC) (n = 24)	Statistic	
				FEP/S	FEP/HC
Age, mean ± SD, y	25.54 ± 5.722	24.9 ± 6.64	23.29 ± 5.76	$t = 0.41$, $P = .69$	$T = 1.58$, $P = .12$
Male/female, n (%)	35/15 (70%/30%)	9/12 (42.9%/57.1%)	18/6 (75%/25%)	$\chi^2 = 3.54$, $P = .06$	$\chi^2 = 0.2$, $P = .66$
Education, mean ± SD, y	13.37 ± 3.251	14.19 ± 2.80	14.04 ± 2.84	$t = -1.07$, $P = .29$	$t = -0.87$, $P = .39$
Married/unmarried, n (%)	15/33 (30%/66%)	5/1 6 (23.8%/76.2%)	4 / 20 (16.7 %/83.3 %)	$\chi^2 = 3.66$, $P = .16$	$\chi^2 = 1.69$, $P = .43$
Low/high maternal level of education, n (%)[a]	23/27 (46%/54%)	13/8 (61.9%/38.1%)	14/10 (58.3%/41.7 %)	$\chi^2 = 1.497$, $P = .221$	$\chi^2 = 0.987$, $P = .321$
Low/high paternal level of education, n (%)[b]	25/25 (50%/50 %)	10/11 (47.6%/52.47 %)	14/10 (58.3%/41.7 %)	$\chi^2 = 0.034$, $P = .855$	$\chi^2 = 0.452$, $P = .501$
Premorbid adjustment in adolescence, mean ± SD	12.18 ± 4.62	10.10 ± 3.51	NA	$t = -1.81$, $P = .07$	NA
Duration of illness, mean ± SD, mo	4.505 ± 3.945	NA	NA	NA	NA
Positive symptoms, mean ± SD[c]	0.480 ± 0.647	NA	NA	NA	NA
Negative symptoms, mean ± SD[d]	0.680 ± 0.836	NA	NA	NA	NA
Disorganized symptoms, mean ± SD[e]	0.393 ± 0.578	NA	NA	NA	NA
CPZeq, mean ± SD[f]	428.15 ± 299.98	NA	NA	NA	NA

[a]Basic education or lower level of studies vs vocational training or higher education completed.
[b]Basic education or lower level of studies vs vocational training or higher education completed.
[c]Measured by CASH.
[d]Measured by CASH.
[e]Measured by CASH.
[f]CPZeq is the conversion of antipsychotic daily dose to chlorpromazine equivalents and represents the average daily dose.
Abbreviations: CASH = Comprehensive Assessment of Symptoms and History, CPZeq = chlorpromazine equivalents, NA = not applicable.

RESULTS

Descriptive Data of the Sample

Our sample comprised 50 patients with FEP, 21 siblings, and 24 healthy controls, all of whom provided informed consent. Clinical severity and descriptive variables are presented in Table 1. No group differences were found in terms of age, sex, years of education, or civil status.

As shown in previous publications by our group using the same sample and data, Cronbach α coefficients for the neuropsychological test composite scores in the FEP sample ranged from 0.62 (attention) to 0.75 (working memory).[45]

Bivariate Analysis

One-way ANOVA was conducted to compare inflammatory biomarkers and cognitive performance among patients, siblings, and controls. Patients showed significantly lower scores than their siblings in terms of attention, processing speed, working memory, executive functioning, and global cognition. Compared to the controls, patients also had significantly lower scores for all cognitive variables. Among the inflammatory biomarkers, only VEGF analysis showed $F = 3.763$, $P = .027$, indicating that VEGF was the only biomarker that showed a statistically significant association within the model, which includes the 3 intragroup comparisons (patients, siblings, and controls). Specifically, the P value for the comparison between patients and controls was less than .025. The remaining analyses of inflammatory biomarkers did not show significant associations, with F values ranging from 3.782 to 0.416 and P values ranging from .661 to .026. However, the P values for intragroup comparisons did not survive the Bonferroni correction (Table 2; Figure 1).

Correlation analysis revealed no significant differences in inflammatory variables between siblings and controls. In patients, a significant negative correlation was found between VEGF and social cognition (n = 46, $r = -0.435$, $P = .002$) according to Cohen criteria.[48] Further details are provided in Table 3 and Figure 2. Supplementary Tables 1 and 2 are in the online data supplement for more details related to the siblings and control groups. We applied Bonferroni correction for multiple comparisons in all correlation analyses, covering 8 cognitive results across the 3 inflammation groups defined in the objectives.

Post Hoc Social Cognition Multivariate Analysis in FEP Sample: HMR Controlling Premorbid Adjustment, Sociodemographic, Inflammatory, and Clinical Variables

Hierarchical multivariate regression (HMR) was performed to assess the impact of several factors on the social cognition scores in the FEP sample. The model contained 11 independent variables grouped into 4 blocks: premorbid adjustment and sociodemographic, inflammatory, exogenous, and clinical blocks of variables.

After the entry of all factors, the total variance explained by the model as a whole was 34.5% ($F_{11,\ 32} = 1.533$, $P = .168$). Inflammatory variables

Table 2.

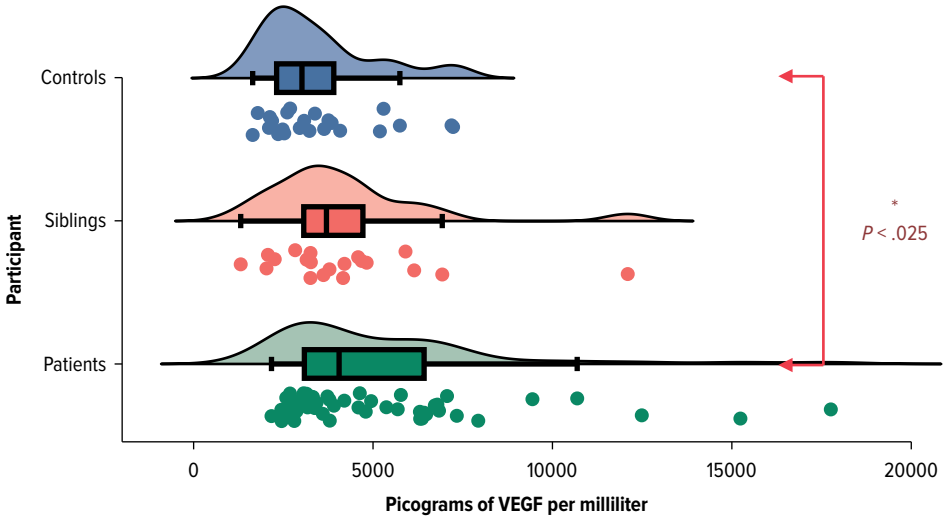
Comparison of Neurocognition and Inflammatory Biomarkers Among 3 Groups

Variables	Patients (FEP) (n = 50)	Siblings (S) (n = 21)	Controls (HC) (n = 24)	Statistic		Post hoc *P* values		
				F	*P*	FEP-HC	FEP-S	S-HC
Cognitive variables								
Attention	−2.618 ± 1.536	−1.158 ± 1.552	0.003 ± 1.629	22.309	**<.001**	**<0.001**	**.002**	0.048
Speed processing	−1.514 ± 0.873	−0.129 ± 0.715	0.001 ± 0.693	36.559	**<.001**	**<0.001**	**<.001**	0.86
Verbal memory	−1.029 ± 1.199	−0.219 ± 0.884	−0.001 ± 0.686	9.211	**<.001**	**0.001**	.011	0.772
Visual memory	−1.733 ± 2.373	−0.724 ± 1.682	−0.001 ± 1.002	6.186	**.003**	**0.003**	.14	0.462
Working memory	−1.122 ± 0.878	−0.164 ± 0.84	−0.001 ± 0.751	17.136	**<.001**	**<0.001**	**<.001**	0.805
Executive functioning	−1.234 ± 0.218	1.168 ± 0.754	0.001 ± 0.763	14.29	**<.001**	**<0.001**	**.001**	0.758
Social cognition	−1.353 ± 1.058	−0.669 ± 0.846	0.001 ± 1.000	14.452	**<.001**	**<0.001**	**.033**	0.079
Cognition total score	−1.498 ± 0.781	−0.422 ± 0.582	0.038 ± 0.546	40.512	**<.001**	**<0.001**	**<.001**	0.094
IC								
CCL2	472.592 ± 310.891	410.613 ± 208.387	338.088 ± 146.536	2.244	.112	0.096	.637	0.624
CCL3	7.874 ± 9.575	7.923 ± 8.612	5.745 ± 6.412	0.416	.661	0.656	1.000	0.753
CX3CL1	28.480 ± 25.132	23.813 ± 14.579	14.962 ± 5.432	3.782	.026	0.02	.647	0.307
CCL11	87.695 ± 39.503	76.724 ± 26.713	69.875 ± 26.025	2.402	.096	0.094	.446	0.785
NIC								
CXCL12	442.541 ± 254.152	446.733 ± 152.825	388.874 ± 105.063	0.637	.531	0.548	.997	0.624
HP-BBB								
BDNF	834.023 ± 382.004	1,021.548 ± 643.535	923.548 ± 437.090	1.232	.297	0.716	.28	0.764
VEGF	5,271.579 ± 3,235.1745	4,221.834 ± 2,349.858	3,472.397 ± 1,592.4385	3.763	.027	**<0.025**	.317	0.637

Bold values indicate significant differences after Bonferroni correction (*P* < .0036 for cognitive variables, *P* < .006 for inflammatory chemokines, *P* < .05 for noninflammatory chemokines and *P* < .025 for homeostatic processes and blood-brain barrier regulation biomarkers). Cognitive parameters are expressed as *Z*-scores. Inflammatory variables are measured in picograms per milliliter. Abbreviations: BDNF = brain-derived neurotrophic factor, FEP = first-episode psychosis, HP-BBB = homeostatic processes and blood-brain barrier regulation biomarkers, IC = inflammatory chemokines, NIC = noninflammatory and homeostatic chemokines, VEGF = vascular endothelial growth factor.

Figure 1.

Distribution of VEGF Levels Across FEP, Siblings, and Controls



*Significant at *P* < .05 for patients vs controls comparison.
Abbreviations: FEP = first-episode psychosis, VEGF = vascular endothelial growth factor.

Table 3.

Correlations of Neurocognition and Inflammatory Biomarkers in FEP group

Cognitive domain	Statistic	CCL2 (IC)	CCL3 (IC)	CX3CL1 (IC)	CCL11 (IC)	CXCL12 (NIC)	BDNF (HP-BBB)	VEGF (HP-BBB)
Attention	*r* value	0.092	0.070	−0.081	0.27	−0.020	−0.064	−0.064
	P value	.537	.643	.587	.856	.895	.670	.667
Speed processing	*r* value	0.057	0.052	−0.103	−0.111	−0.156	−0.071	−0.108
	P value	.707	.733	.494	.461	.301	.638	.476
Verbal memory	*r* value	−0.068	−0.198	−0.218	−0.133	−0.125	−0.097	0.061
	P value	.651	.186	.141	.373	.404	.516	.681
Visual memory	*r* value	−0.056	0.150	−0.008	0.040	0.016	0.016	0.162
	P value	.713	.324	.956	.790	.917	.917	.281
Working memory	*r* value	0.054	−0.065	−0.110	−0.011	−0.058	−0.236	−0.212
	P value	.722	.672	.467	.944	.700	.114	.158
Executive functioning	*r* value	−0.060	−0.033	.008	−0.039	<0.001	−0.108	−0.251
	P value	.697	.830	.959	0.801	.999	.480	.096
Social cognition	*r* value	0.009	0.056	0.071	−0.024	0.042	−0.295	**−0.435***
	P value	.951	.713	.640	.876	.784	.046	**.002**
Cognition total score	*r* value	−0.052	0.010	−0.070	−0.082	−0.077	−0.221	−0.135
	P value	.737	.950	.652	0.599	.618	.150	.383

Correlations for *P* values under .05 are in bold. **P* values under .0015 for IC, .07 for NIC, and .003 for HP-BBB group of biomarkers (significant after Bonferroni correction). Cognitive parameters are expressed as *Z*-scores. Inflammatory variables are measured in picograms per milliliter. Abbreviations: BDNF = brain-derived neurotrophic factor, FEP = first-episode psychosis, HP-BBB = homeostatic processes and blood brain barrier regulation biomarkers, IC = inflammatory chemokines, NIC = noninflammatory and homeostatic chemokines, VEGF = vascular endothelial growth factor.

were entered in Block 2, explaining 13.5% of the variance in social cognition in the FEP sample. In the final model, VEGF was statistically significant, resulting in the following: $\beta = -1.936$, $P = .022$ (Tables 4 and 5).

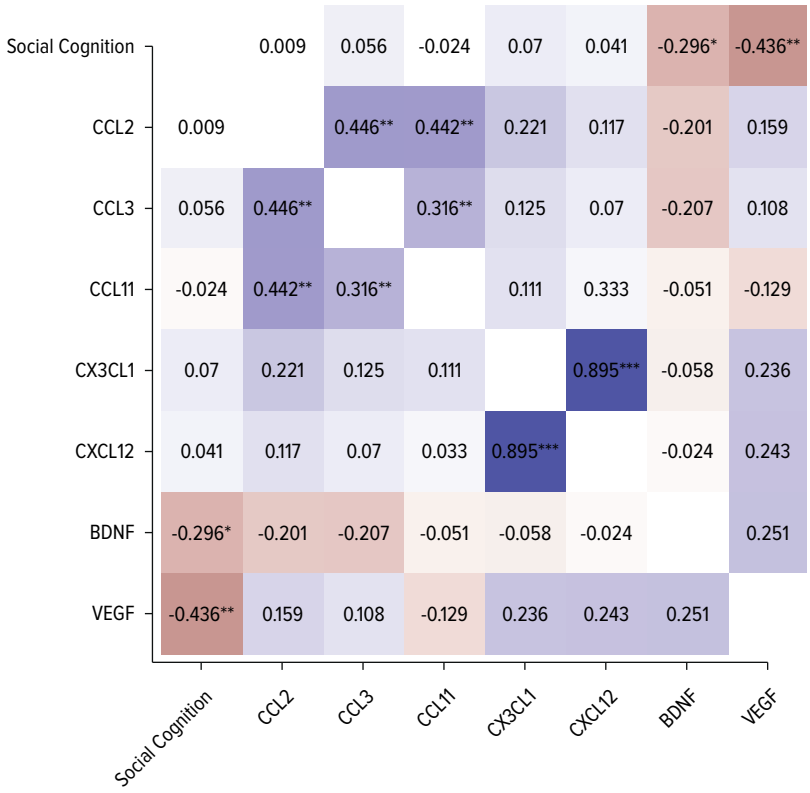
DISCUSSION

Our main findings included significant group differences in blood VEGF concentrations, with other chemokines distributed equally between the groups. VEGF levels were higher in patients than in controls but not in siblings. No significant associations were found between homeostatic or inflammatory chemokines and cognitive domains in any of the groups. However, a significant inverse association between VEGF and social cognition was found in FEP patients, who had lower social scores and higher VEGF levels than the other groups. This association persisted after the multivariate analysis.

We will first address our primary findings regarding group differences in blood VEGF concentrations. Although we did not find significant differences in other inflammatory biomarkers, it is worth noting that we observed a potential association between CX3CL1, which did not survive the Bonferroni correction. To interpret our results, it is interesting to consider that low-grade inflammation during the second hit may induce schizophrenia symptoms from a kindling perspective.[6] Under this narrative, the hypothesis that second-hit environmental factors may have triggered only certain inflammatory biomarkers in a sensitized FEP sample due to early-life factors seems plausible. Notably, chemokine receptor abnormalities occur during the "first hit" affect parvalbumin neuron migration and cause prefrontal cortex deficits in schizophrenia.[49] Furthermore, our findings align with those of other FEP studies related to selective low-grade inflammation. These studies also reported a lack of association between inflammatory biomarkers and widespread cognitive domain functioning.[50] Overall, VEGF may act as a state marker in FEP independent of the normalizing effect of antipsychotics on inflammation.[51] Our finding is also not attributable to prior substance abuse exposure, as both factors were controlled as covariates, and our sample was in remission regarding addiction, which is a documented factor that may affect VEGF.[52] Nevertheless, further research is needed to determine if VEGF is a reliable state marker and if it is sensitive to other documented environmental factors of the second hit, particularly in naive samples.

Figure 2.

Correlation Matrix of and Inflammatory Variables and Social Cognition in Patients



Significant at *$P < .05$, **$P < .01$, and ***$P < .001$ in the correlogram.
Abbreviations: BDNF = brain-derived neurotrophic factor; VEGF = vascular endothelial growth factor.

Table 4.

Model Summary of HMR Analyses of Social Cognition, After Controlling for Premorbid Adjustment, Sociodemographic, Inflammatory, Exogenous and Clinical Variables

Cognitive domain	Statistic	Step 1: premorbid adjustment and sociodemographic block	Step 2: inflammatory block (BDNF and VEGF)	Step 3: exogenous block	Step 4: Clinical block	Global *R* of the model
Social cognition	R^2 change	0.147	0.135	0.013	0.05	0.345
	F change	1.678	3.482	0.322	0.817	
	P value	.175	.041	.727	.494	

Abbreviations: BDNF = brain-derived neurotrophic factor, HMR = hierarchical multiple regression, VEGF = vascular endothelial growth factor.

Our study's second objective was to examine chemokines and growth factor levels, as well as cognitive aspects, with a particular focus on social cognition. Unlike other cognitive domains, social cognition is consistently impaired in UHR individuals, influenced by clinical symptoms, and correlates with overall functioning.[53] Recent literature suggests that persistent low-grade inflammation also plays a pivotal role in clinical symptoms and social functioning in FEP, possibly mediating poor outcomes such as prolonged untreated psychosis and hippocampal abnormalities.[54] Additionally, chemokines and growth factors are involved in microglial sensitization[55] and clinical symptoms.[6] Contrary to the neurodevelopmental first hit, VEGF may be increased in FEP and is significantly and inversely associated with VEGF and social cognition, as discussed and illustrated in Figure 3, inspired by Rampino.[56]

In a vascular model of schizophrenia, decreased VEGF gene expression suggests angiogenesis defects

Table 5.

Summary of HMR Coefficients Analyses Summarizing Individual Variable Results in FEP Participants

Statistic	B	SE	β	*P*
Step 1: premorbid and sociodemographic block				
Premorbid adjustment	−0.084	0.04	0.323	.044
Age	0.002	0.046	0.01	.969
Gender	−0.454	0.39	−0.19	.252
Civil status	0.351	0.596	0.121	.56
Step 2: inflammatory block				
BDNF	−0.293	0.929	−0.053	.755
VEGF	−1.936	0.802	−0.368	**.022**
Step 3: exogenous block				
CPZeq	0.000	0.000	0.13	.484
Addiction disorder[a]	0.087	0.42	0.034	.836
Step 4: clinical block				
Positive score	0.055	0.345	0.031	.873
Negative score	0.144	0.289	0.106	.621
Disorganized score	−0.652	0.444	−0.33	.151

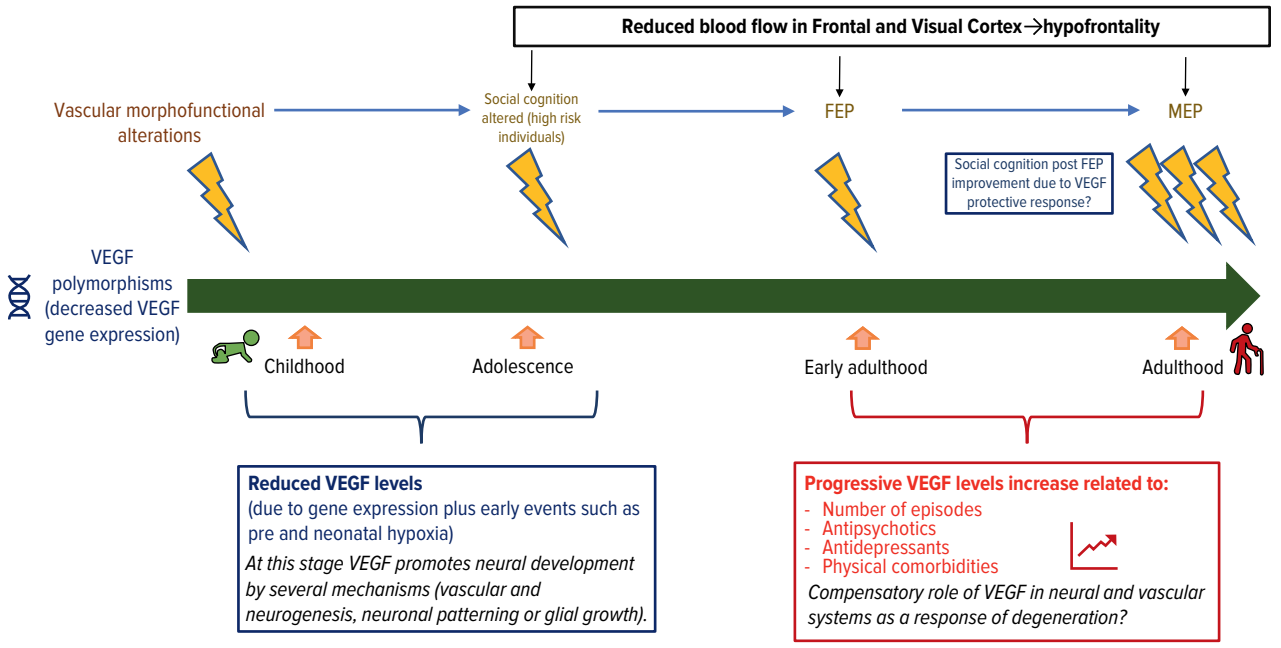
[a]Presence or absence of F10–19 substance use disorder.
Bold values indicate significant results ($P < .05$). Please refer to the abbreviations and footnotes of Table 2 and 3 for a detailed explanation. Abbreviations: BDNF = brain-derived neurotrophic factor; CPZeq = chlorpromazine equivalents; FEP = first-episode psychosis; HMR = hierarchical multiple regression; VEGF = vascular endothelial growth factor.

during early brain development, leading to reduced blood flow and hypofrontality.[56] The role of vascular changes in the course of the illness is debated, with mixed results from postonset studies indicating that VEGF may have mechanistic or protective roles.

In FEP, the literature shows mixed results: a meta-analysis found no significant VEGF changes,[57] and another study reported decreased VEGF levels,[27] but not cognitive domain associations. Later-stage schizophrenia studies showed no significant results in chronic schizophrenia[58] and increased VEGF levels in patients with multiple episodes of schizophrenia.[57] We found a moderate inverse association between VEGF and social cognition, which allowed us to theorize that VEGF may contribute to improvements in social cognition over time post-FEP. This potential link could be related to VEGF regulation and systemic inflammation, similar to that observed in affective disorders.[59] We hypothesized that this phenomenon was related to systemic inflammatory disorders. Thus, animal models show that increased VEGF levels can benefit cognition in systemic inflammatory illnesses like diabetes[60] and play a protective role in neurodegenerative illnesses.[61] Conversely, VEGF's potential to promote neuroinflammation raises concerns as it modulates BBB opening and facilitates chronic neuroinflammation in FEP, even at normal blood concentrations. While this has been

Figure 3.

Theoretical Model of VEGF in Schizophrenia



Abbreviations: BDNF = brain-derived neurotrophic factor; FEP = first episode of psychosis; MEP = multi episode psychosis; VEGF = vascular endothelial growth factor.

extensively described in chronic neurodegenerative/addiction disorders[23] rather than in FEP, the evolving nature of BBB permeability in other brain illnesses[62] suggests that this explanation is plausible. Further research at various stages of psychosis is required.

Several factors could explain the differences between our study and previous studies. First, VEGF measurement methods vary; while plasma ELISA determination is commonly used,[58] whole blood testing might provide different estimates due to dynamic compartments, including red blood cells.[46] Whole blood testing may be a suitable approach for evaluating peripheral chemokine levels despite the risk of subtle hemolysis. This may be undetectable through macroscopic examination,[63] but it can be managed by monitoring plasma or serum hemoglobin levels and optimizing the sample processing time.[46] As our study did not address the first factor, further investigation is recommended. Furthermore, simultaneous assessment of positive symptoms, blood extraction, and cognitive evaluation would be suitable for enhancing the understanding of VEGF determination value, given the association of hypoperfusion with psychotic symptoms.[64]

In addition, one may argue that these results could be explained by antipsychotic dose size,[56,65] antidepressant use,[58] duration of illness,[65] or physical comorbidities.[57] Despite not controlling for all of them, we included the antipsychotic dose and substance misuse disorders in the multivariate analyses. Notably, elevated serum levels of VEGF-A have been linked to alcohol dependence severity[52] and delta-9-tetrahydrocannabinol (THC) exposure in animal models.[66] Therefore, we controlled for the presence or absence of a history of *DSM-5* substance abuse disorders. However, detailed control of substance addiction, including severity and duration of consumption, may be necessary. Finally, unlike previous VEGF FEP studies, we conducted post hoc analyses to control for positive symptoms.

CONCLUSIONS

On speculative grounds, we could tentatively draw parallel with research on animal models of systemic illnesses[60] when interpreting this initial evidence. Thus, the association between VEGF and social cognition may represent a reactive protective mechanism that preserves social cognition following the onset of FEP. If confirmed, this would suggest that VEGF's proangiogenic and antihypoperfusion actions of VEGF outweigh its effects on BBB permeability. Persistent nonsignificant chemokine results might reflect their roles in other stages. However, these preliminary results should be interpreted with caution. First, our cross-sectional study design prevents the establishment of causality between VEGF levels and social cognition. Second, the complexity of chemokine signaling suggests that a simple biomarker approach using only whole blood, plasma, or serum may be inadequate. Research on UHR indicates reduced VEGF levels,[67] and we hypothesized that VEGF level shifts at illness onset may serve as an adaptive mechanism. The long-term effectiveness of this mechanism remains unclear. Future longitudinal studies are needed to fully understand this relationship and control for confounding variables.

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Author Affiliations: Bioaraba, Nuevas Terapias en Salud Mental, Osakidetza Basque Health Service, Araba Mental Health Network, Vitoria-Gasteiz, Spain (Ballesteros); Grupo de Neuropsicofarmacología, Unidad de Gestión Clínica de Salud Mental, Instituto IBIMA, Hospital Regional Universitario de Málaga, Malaga, Spain (Flores-Lopez, Gavito, Serrano, Rodríguez de Fonseca); Servicio de Psiquiatría, Hospital Universitario de Navarra, Pamplona, Spain (Moreno-Izco, Sánchez-Torres, Gil-Berrozpe, Cuesta); Instituto de Investigación Sanitaria de Navarra, Pamplona, Spain, IdiSNA (Sánchez-Torres, Gil-Berrozpe, Cuesta); Instituto de Investigación Biomédica de Málaga—Plataforma en Nanomedicina (IBIMA Plataforma BIONAND), Málaga, Spain (Serrano); Unidad Clínica de Neurología-Alianza NEURORECA, Instituto IBIMA, Hospital Regional Universitario de Málaga, Malaga, Spain (Rodríguez de Fonseca).

Corresponding Author: Manuel J. Cuesta, MD, PhD, Department of Psychiatry, Complejo Hospitalario de Navarra, c/Irunlarrea 4.31008 Pamplona, Navarra, Spain (mcuestaz@cfnavarra.es).

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References

1. Insel TR. Rethinking schizophrenia. *Nature*. 2010;468(7321):187–193.
2. Galderisi S, Bucci P, Mucci A, et al. Categorical and dimensional approaches to negative symptoms of schizophrenia: focus on long-term stability and functional outcome. *Schizophr Res*. 2013;147(1):157–162
3. Pollak TA, Drndarski S, Stone JM, et al. The blood–brain barrier in psychosis. *Lancet Psychiatry*. 2018;5(1):79–92.
4. Bora E, Yalincetin B, Akdede BB, et al. Duration of untreated psychosis and neurocognition in first-episode psychosis: a meta-analysis. *Schizophr Res*. 2018; 193:3–10.

5. Parellada E, Gassó P. Glutamate and microglia activation as a driver of dendritic apoptosis: a core pathophysiological mechanism to understand schizophrenia. *Transl Psychiatry*. 2021;11(1):271.
6. Müller N. Inflammation in schizophrenia: pathogenetic aspects and therapeutic considerations. *Schizophr Bull*. 2018;44(5):973–982.
7. Upthegrove R, Khandaker GM. Cytokines, oxidative stress and cellular markers of inflammation in schizophrenia. *Curr Top Behav Neurosci*. 2020; 44:49–66.
8. Ramsay H, Surcel HM, Björnholm L, et al. Associations between maternal prenatal C-reactive protein and risk factors for psychosis in adolescent offspring: findings from the Northern Finland Birth Cohort 1986. *Schizophr Bull*. 2021;47(3):766–775.
9. Rasile M, Lauranzano E, Faggiani E, et al. Maternal immune activation leads to defective brain-blood vessels and intracerebral hemorrhages in male offspring. *EMBO J*. 2022;41(23):e111192.
10. Nettis MA, Pariante CM, Mondelli V. Early-life adversity, systemic inflammation and comorbid physical and psychiatric illnesses of adult life. *Curr Top Behav Neurosci*. 2020;44:207–225.
11. Pollak TA, Drndarski S, Stone JM, et al. The blood-brain barrier in psychosis. *Lancet Psychiatry*. 2018;5(1):79–92.
12. Suvisaari J, Mantere O. Inflammation theories in psychotic disorders: a critical review. *Infect Disord: Drug Targets*. 2013;13(1):59–70.
13. Ragozzino D. CXC chemokine receptors in the central nervous system: role in cerebellar neuromodulation and development. *J Neurovirol*. 2002;8(6):559–572.
14. Raman D, Sobolik-Delmaire T, Richmond A. Chemokines in health and disease. *Exp Cell Res*. 2011;317(5):575–589.
15. Kelsven S, de la Fuente-Sandoval C, Achim CL, et al. Immuno-inflammatory changes across phases of early psychosis: the impact of antipsychotic medication and stage of illness. *Schizophr Res*. 2020;226:13–23.
16. Pardo-de-Santayana G, Juncal-Ruiz M, Vázquez-Bourgon J, et al. Active psychosis and pro-inflammatory cytokines in first-episode of psychosis. *J Psychiatr Res*. 2021;134:150–157.
17. Frydecka D, Krzystek-Korpacka M, Lubeiro A, et al. Profiling inflammatory signatures of schizophrenia: a cross-sectional and meta-analysis study. *Brain Behav Immun*. 2018;71:28–36.
18. Martínez-Cengotitabengoa M, Mac-Dowell KS, Leza JC, et al. Cognitive impairment is related to oxidative stress and chemokine levels in first psychotic episodes. *Schizophr Res*. 2012;137(1–3):66–72.
19. Tran-Chi VL, Maes M, Nantachai G, et al. Cytokine dysregulation in amnestic mild cognitive impairment. *Sci Rep*. 2024;14(1):22486.
20. Johansson V, Jakobsson J, Fortgang RG, et al. Cerebrospinal fluid microglia and neurodegenerative markers in twins concordant and discordant for psychotic disorders. *Eur Arch Psychiatry Clin Neurosci*. 2017;267(5):391–402.
21. Najjar S, Pahlajani S, De Sanctis V, et al. Neurovascular unit dysfunction and blood-brain barrier hyperpermeability contribute to schizophrenia neurobiology: a theoretical integration of clinical and experimental evidence. *Front Psychiatry*. 2017;8:83.
22. Mohammadi A, Rashidi E, Amooeian VG. Brain, blood, cerebrospinal fluid, and serum biomarkers in schizophrenia. *Psychiatry Res*. 2018;265:25–38.
23. Requena-Ocaña N, Flores-Lopez M, Papaseit E, et al. Vascular endothelial growth factor as a potential biomarker of neuroinflammation and frontal cognitive impairment in patients with alcohol use disorder. *Biomedicines*. 2022;10(5):947.
24. Argaw AT, Asp L, Zhang J, et al. Astrocyte-derived VEGF-A drives blood-brain barrier disruption in CNS inflammatory disease. *J Clin Investig*. 2012;122(7): 2454–2468.
25. Chapouly C, Tadesse Argaw A, Horng S, et al. Astrocytic TYMP and VEGFA drive blood-brain barrier opening in inflammatory central nervous system lesions. *Brain*. 2015;138(Pt 6):1548–1567.
26. Nieto RR, Carrasco A, Corral S, et al. BDNF as a biomarker of cognition in schizophrenia/psychosis: an updated review. *Front Psychiatry*. 2021;12: 662407.
27. Zhao Y, Xiao W, Chen K, et al. Neurocognition and social cognition in remitted first-episode schizophrenia: correlation with VEGF serum levels. *BMC Psychiatry*. 2019;19(1):403.
28. Chukaew P, Bunmak N, Auampradit N, et al. Correlation of BDNF, VEGF, TNF-α, and S100B with cognitive impairments in chronic, medicated schizophrenia patients. *Neuropsychopharmacol Rep*. 2022;42(3):281–287.
29. Chen P, Chen W, Xu L, et al. Decreased serum VEGF and NRG1β1 levels in male patients with chronic schizophrenia: VEGF correlation with clinical symptoms and cognitive deficits. *J Psychiatr Res*. 2024;176:85–92.
30. Su Q, Xuekelaiti Z, Ma H, et al. The associations between duration of untreated psychosis, growth factors, and neurocognition in patients with drug-naïve schizophrenia. *Schizophr Res*. 2024;274:113–120.
31. Yesilkaya UH, Gica S, Menekseoglu PO, et al. Can the imbalance between neurotrophic and apoptotic proteins Be the "Beware the ides of March" for unaffected relatives of schizophrenia patients? *Mol Neurobiol*. 2022;59(12): 7413–7422.
32. Stanca S, Rossetti M, Bokulic Panichi L, et al. The cellular dysfunction of the brain-blood barrier from endothelial cells to astrocytes: the pathway towards neurotransmitter impairment in schizophrenia. *Int J Mol Sci*. 2024;25(2):1250.
33. Stuart MJ, Baune BT. Chemokines and chemokine receptors in mood disorders, schizophrenia, and cognitive impairment: a systematic review of biomarker studies. *Neurosci Biobehav Rev*. 2014;42:93–115.
34. Chamera K, Trojan E, Szuster-Głuszczak M, et al. The potential role of dysfunctions in neuron-microglia communication in the pathogenesis of brain disorders. *Curr Neuropharmacol*. 2020;18(5):408–430.
35. Noto C, Maes M, Ota VK, et al. High predictive value of immune-inflammatory biomarkers for schizophrenia diagnosis and association with treatment resistance. *World J Biol Psychiatry*. 2015;16(6):422–429.
36. Roomruangwong C, Noto C, Kanchanatawan B, et al. The role of aberrations in the immune-inflammatory response system (IRS) and the compensatory immune-regulatory reflex system (CIRS) in different phenotypes of schizophrenia: the IRS-CIRS theory of schizophrenia. *Mol Neurobiol*. 2020;57(2):778–797.
37. Toritsuka M, Kimoto S, Muraki K, et al. Deficits in microRNA-mediated Cxcr4/Cxcl12 signaling in neurodevelopmental deficits in a 22q11 deletion syndrome mouse model. *Proc Natl Acad Sci U S A*. 2013;110(43): 17552–17557.
38. Murphy BP, Pang TY, Hannan AJ, et al. Vascular endothelial growth factor and brain-derived neurotrophic factor in quetiapine treated first-episode psychosis. *Schizophr Res Treat*. 2014;2014:719395.
39. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*. 5th ed. American Psychiatric Publishing; 2013.
40. Andreasen NC, Flaum M, Arndt S. The Comprehensive Assessment of Symptoms and History (CASH): an instrument for assessing diagnosis and psychopathology. *Arch Gen Psychiatry*. 1992;49(8):615–623.
41. Cuesta MJ, Sánchez-Torres AM, Moreno-Izco L, et al. Neurocognitive correlates of the varied domains of outcomes at 20 year follow-up of first-episode psychosis. *Psychiatry Res*. 2022;318:114933.
42. Ho BC, Andreasen NC, Ziebell S, et al. Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. *Arch Gen Psychiatry*. 2011;68(2):128–137.
43. Green MF, Nuechterlein KH, Gold JM, et al. Approaching a consensus cognitive battery for clinical trials in schizophrenia: the NIMH-MATRICS conference to select cognitive domains and test criteria. *Biol Psychiatry*. 2004;56(5):301–307.
44. Green MF, Nuechterlein KH. The MATRICS initiative: developing a consensus cognitive battery for clinical trials. *Schizophr Res*. 2004;72(1):1–3.
45. Cuesta MJ, Moreno-Izco L, Ribeiro M, et al. Motor abnormalities and cognitive impairment in first-episode psychosis patients, their unaffected siblings and healthy controls. *Schizophr Res*. 2018;200:50–55.
46. Karsten E, Breen E, Herbert BR. Red blood cells are dynamic reservoirs of cytokines. *Sci Rep*. 2018;8(1):3101.
47. Araos P, Pedraz M, Serrano A, et al. Plasma profile of pro-inflammatory cytokines and chemokines in cocaine users under outpatient treatment: influence of cocaine symptom severity and psychiatric co-morbidity. *Addict Biol*. 2015;20(4): 756–772.
48. Grice JW, Barrett PT. A note on Cohen's overlapping proportions of normal distributions. *Psychol Rep*. 2014;115(3):741–747.
49. Volk DW, Lewis DA. Early developmental disturbances of cortical inhibitory neurons: contribution to cognitive deficits in schizophrenia. *Schizophr Bull*. 2014; 40(5):952–957.
50. Malmqvist A, Schwieler L, Orhan F, et al. Increased peripheral levels of TARC/CCL17 in first episode psychosis patients. *Schizophr Res*. 2019;210:221–227.
51. Capuzzi E, Bartoli F, Crocamo C, et al. Acute variations of cytokine levels after antipsychotic treatment in drug-naïve subjects with a first-episode psychosis: a meta-analysis. *Neurosci Biobehav Rev*. 2017;77:122–128.
52. Heberlein A, Muschler M, Lenz B, et al. Serum levels of vascular endothelial growth factor A increase during alcohol withdrawal. *Addict Biol*. 2010;15(3): 362–364.
53. Mondragón-Maya A, Ramos-Mastache D, Román PD, et al. Social cognition in schizophrenia, unaffected relatives and ultra- high risk for psychosis: what do we currently know? *Actas Esp Psiquiatr*. 2017;45(5):218–226.
54. Goff DC, Zeng B, Ardekani BA, et al. Association of hippocampal atrophy with duration of untreated psychosis and molecular biomarkers during initial antipsychotic treatment of first-episode psychosis. *JAMA Psychiatry*. 2018;75(4): 370–378.
55. Wolf SA, Boddeke HWGM, Kettenmann H. Microglia in physiology and disease. *Annu Rev Physiol*. 2017;79(1):619–643.
56. Rampino A, Annese T, Torretta S, et al. Involvement of vascular endothelial growth factor in schizophrenia. *Neurosci Lett*. 2021;760:136093.
57. Misiak B, Stramecki F, Stańczykiewicz B, et al. Vascular endothelial growth factor in patients with schizophrenia: a systematic review and meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018;86:24–29.
58. Pu J, Liu Y, Gui S, et al. Vascular endothelial growth factor in major depressive disorder, schizophrenia, and bipolar disorder: a network meta-analysis. *Psychiatry Res*. 2020;292:113319.

59. Ho KKY, Lui SSY, Wang Y, et al. Theory of mind performances in first-episode schizophrenia patients: an 18-month follow-up study. *Psychiatry Res*. 2018;261:357–360.
60. Taylor SL, Trudeau D, Arnold B, et al. VEGF can protect against blood brain barrier dysfunction, dendritic spine loss and spatial memory impairment in an experimental model of diabetes. *Neurobiol Dis*. 2015;78:1–11.
61. Elahi FM, Casaletto KB, La Joie R, et al. Plasma biomarkers of astrocytic and neuronal dysfunction in early- and late-onset Alzheimer's disease. *Alzheimers Dement*. 2020;16(4):681–695.
62. Han L, Jiang C. Evolution of blood-brain barrier in brain diseases and related systemic nanoscale brain-targeting drug delivery strategies. *Acta Pharm Sin B*. 2021;11(8):2306–2325.
63. Kirschner MB, Kao SC, Edelman JJ, et al. Haemolysis during sample preparation alters microRNA content of plasma. *PLoS One*. 2011;6(9):e24145.
64. Katsel P, Roussos P, Pletnikov M, et al. Microvascular anomaly conditions in psychiatric disease. Schizophrenia–angiogenesis connection. *Neurosci Biobehav Rev*. 2017;77:327–339.
65. Ye F, Zhan Q, Xiao W, et al. Altered serum levels of vascular endothelial growth factor in first-episode drug-naïve and chronic medicated schizophrenia. *Psychiatry Res*. 2018;264:361–365.
66. Martínez-Peña AA, Petrik JJ, Hardy DB, et al. Delta-9-tetrahydrocannabinol increases vascular endothelial growth factor (VEGF) secretion through a cyclooxygenase-dependent mechanism in rat granulosa cells. *Reprod Toxicol*. 2022;111:59–67.
67. Ye J, Wei Y, Zeng J, et al. Serum levels of tumor necrosis factor-α and vascular endothelial growth factor in the subtypes of clinical high risk individuals: a prospective cohort study. *Neuropsychiatr Dis Treat*. 2023;19:1711–1723.

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Supplementary Material

Article Title: Exploring Vascular Endothelial Growth Factor and Other Blood-Brain Barrier Biomarkers in Cognition of First-Episode Psychosis: An Observational Study

Authors: Alejandro Ballesteros, MD; María Flores-Lopez, MSc; Ana M. Sánchez-Torres, PhD; Gustavo J. Gil-Berrozpe, MSc; Lucía Moreno-Izco, MSc; Ana Gavito, MSc; Antonia Serrano, MSc; Fernando Rodríguez de Fonseca, MD, PhD; Manuel J. Cuesta, MD, PhD

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

1. **Table 1** Correlations of Neurocognition and Inflammatory Biomarkers in Control Group

2. **Table 2** Correlations of Neurocognition and Inflammatory Biomarkers in Control Group

DISCLAIMER

This Supplementary Material has been provided by the authors as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Table 1. Correlations of neurocognition and inflammatory biomarkers in control group

Cognitive domain	Statistic	CCL2	CCL3	CX3CL1	CCL11	CXCL12	BDNF	VEGF
Attention	r value	-0.034	-0.071	0.028	**-0.538**	0.168	-0.162	-0.142
	p value	0.879	0.788	0.902	**0.010**	0.456	0.472	0.529
Speed processing	r value	0.029	-0.002	-0.140	-0.355	0.085	-0.245	**-0.448**
	p value	0.898	0.993	0.534	0.105	0.707	0.271	**0.037**
Verbal memory	r value	0.218	-0.095	-0.117	0.005	-0.250	0.080	-0.151
	p value	0.330	0.716	0.603	0.983	0.262	0.724	0.503
Visual memory	r value	0.266	0.180	0.018	-0.171	-0.006	0.125	-0.219
	p value	0.231	0.489	0.937	0.447	0.981	0.578	0.328
Working memory	r value	0.074	-0.142	-0.348	-0.354	-0.094	-0.084	-0.268
	p value	0.743	0.587	0.113	0.106	0.677	0.711	0.228
Executive functioning	r value	-0.050	-0.025	-0.104	-0.173	-0.329	-0.284	-0.240
	p value	0.826	0.925	0.644	0.443	0.135	0.201	0.283
Social cognition	r value	0.072	-0.186	-0.031	-0.284	-0.125	-0.315	0.097
	p value	0.744	0.475	0.887	0.189	0.571	0.144	0.660
Cognition total score	r value	0.202	-0.140	-0.163	**-0.466**	-0.103	-0.203	-0.256
	p value	0.380	0.605	0.480	**0.033**	0.657	0.378	0.262

Correlations for p values under 0.05 are typed in bold. *p values under 0.006 (significant after Bonferroni correction). Please refer to the abbreviations and footnotes of Tables 1 and 2 for a detailed explanation.

Supplementary Table 2. Correlations of neurocognition and inflammatory biomarkers in control group

Cognitive domain	Statistic	CCL2	CCL3	CX3CL1	CCL11	CXCL12	BDNF	VEGF
Attention	r value	-0.175	-0.022	0.061	0.206	-0.017	-0.211	-0.400
	p value	0.473	0.938	0.803	0.398	0.944	0.385	0.090
Speed processing	r value	0.249	0.117	0.357	0.139	0.233	-0.455	-0.074
	p value	0.304	0.677	0.133	0.571	0.336	0.050	0.763
Verbal memory	r value	0.128	0.056	-0.133	0.051	-0.375	0.244	-0.187
	p value	0.601	0.843	0.588	0.834	0.114	0.315	0.443
Visual memory	r value	0.366	0.202	-0.303	0.392	-0.402	0.156	-0.131
	p value	0.124	0.471	0.207	0.097	0.088	0.524	0.594
Working memory	r value	-0.314	-0.068	0.207	-0.008	0.249	-0.121	-0.454
	p value	0.191	0.810	0.396	0.973	0.304	0.622	0.051
Executive functioning	r value	0.000	-0.135	0.244	0.058	0.257	0.120	0.011
	p value	0.999	0.631	0.315	0.815	0.288	0.625	0.963
Social cognition	r value	-0.194	0.192	-0.209	0.308	0.044	-0.006	-0.117
	p value	0.426	0.493	0.390	0.200	0.857	0.981	0.632
Cognition total score	r value	-0.013	-0.077	-0.082	0.300	-0.187	-0.160	**-0.481**
	p value	0.960	0.795	0.747	0.227	0.457	0.525	**0.043**

Correlations for p values under 0.05 are typed in bold. *p values under 0.006 (significant after Bonferroni correction). Please refer to the abbreviations and footnotes of Tables 1 and 2 for a detailed explanation.