Psychological Medicine (2016), **46**, 2133–2144. © Cambridge University Press 2016
doi:10.1017/S0033291716000659

ORIGINAL ARTICLE

Cognition and psychopathology in first-episode psychosis: are they related to inflammation?

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Background. Cognitive deficits are present from the onset of psychosis and are considered a core feature of the disorder. Increasing evidence suggests that cognitive function is associated with inflammatory processes. This study evaluated the association between cognition and inflammatory biomarkers in first-episode psychosis (FEP), in order to identify cognitive phenotypes from inflammatory expression profiles.

Method. A case-control study of 92 FEP patients and 80 matched controls was used. Neurocognitive assessment, including verbal ability, sustained attention, verbal memory, working memory and executive function, was performed. The expression of pro- and anti-inflammatory mediators of the main intracellular inflammatory pathway was measured in peripheral blood mononuclear cells and plasma.

Results. FEP patients performed worse in all cognitive domains compared to controls and had higher expression of pro-inflammatory mediators and lower expression of anti-inflammatory mediators. In the FEP group, cognition and psychopathology were associated with inflammation. Hierarchical regression analysis showed that association between the anti-inflammatory prostaglandin 15d-PGJ_2 and sustained attention on one hand, and COX-2 expression and executive function on the other, were statistically significant.

Conclusions. Our study provides evidence for an association between anti-inflammatory biomarkers and cognition in FEP. The identification of a subgroup of patients based on these measures could be useful to guide treatment programmes by providing tools to select a personalized treatment approach, but longitudinal studies are needed before. In the future, establishment of biomarkers linked to cognition would be useful to monitor the course of cognitive impairment, but substantially more data will be required. Determination of IκBα, the inhibitory protein of the pro-inflammatory transcription factor NFκB, could be useful in early phases to assess clinical severity.

Received 23 October 2015; Revised 3 March 2016; Accepted 3 March 2016; First published online 8 April 2016

Key words: Biomarkers, cognition, first-episode psychosis (FEP), inflammation, prostaglandin, schizophrenia.

Introduction

Schizophrenia is a complex and multifactorial disorder characterized by a wide phenotypic variation and with evolutionary patterns ranging from a devastating chronic disease to multistage forms. Typically, the onset of the disorder is in late adolescence or early adulthood and includes positive, negative, affective and cognitive symptoms (Van Os & Kapur, 2009; Farreras & Rozman, 2012).

The traditional concept of schizophrenia has been reformulated in the last decade, considered not only as a mental disease but as a heterogeneous disorder with multisystemic impact in addition to its psychiatric expression (Kirkpatrick, 2009). The current literature, both in basic and clinical research, suggests that the search of diagnostic and therapeutic response markers, objective and easily replicable, may lead to an earlier diagnosis, improving the prognosis. The term 'biomarker' refers to a broad subcategory of medical signs – analytical or image data – which can be accurately and reproducibly measured (Strimbu & Tavel, 2010),

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quantify the state of the disease or response to treatment and are useful as indicators of severity. In psychiatry, biomarkers may improve diagnostic accuracy when added to clinical instruments and may help the transition to a more precise medicine by providing tools to select a personalized treatment approach; however, few of these biomarkers have led to tests with clinical utility due to the clinical heterogeneity of the samples and the variability in research designs (Kapur *et al.* 2012). First-episode psychosis (FEP) patients are an exceptional group in which to study the risk factors and markers associated with the development of schizophrenia and related disorders. Furthermore, the FEP samples allow clinicians to minimize the potential impact of confounds, such as illness duration or prolonged antipsychotic treatment (Kapur *et al.* 2012; Bernardo *et al.* 2013; Bernardo & Bioque, 2014).

Disturbances in cognition are present from the onset of psychosis and are a core feature of the disorder (Heinrichs & Zakzanis, 1998; Harvey, 2009). They are closely related to functioning from the earliest stages of the disease (Green, 1996) and may be important predictors of poor functional outcome (Green *et al.* 2004*a*; Keefe & Fenton, 2007). The literature reports multiple cognitive and heterogeneous deficits in FEP patients compared to controls (Lewandowski *et al.* 2014), particularly in attention, verbal memory, executive function, working memory and processing speed (Bilder *et al.* 2000; Nuechterlein *et al.* 2004; Cuesta *et al.* 2015). These deficits have been observed even before the onset of the characteristic positive symptoms of the illness, both in children at risk (Cornblatt & Erlenmeyer-Kimling, 1985) and in adolescents who later develop schizophrenia (Davidson *et al.* 1999). The evidence supports that delayed treatment for FEP is associated with poorer cognitive and clinical outcomes (Chang *et al.* 2013). Patients with schizophrenia have benefited in cognitive performance through cognitive rehabilitation techniques; however, there is no effective pharmacological treatment aimed at improving these difficulties. The development of therapeutic strategies to improve cognition in schizophrenia could benefit from the identification of biomarkers determining whether a specific treatment produces the desired cognitive effects. In this sense, the identification of biomarkers for cognition state could be useful in the creation of new treatment programmes to improve prognosis and functioning of these patients.

Increasing evidence suggests that severe mental disorders are associated with inflammatory processes (Felger & Lotrich, 2013), mainly in schizophrenia and related disorders (Zajkowska & Mondelli, 2014; Leza *et al.* 2015). Numerous studies have reported an activation of the inflammatory response in peripheral and central systems in schizophrenia, with an increase of cytokines involved in the regulation of inflammatory response (Miller *et al.* 2011). One of the main pro-inflammatory pathways is that triggered by activation of the nuclear factor κB (NFκB), which activates specific DNA sequences that codify the pro-inflammatory enzymes, inducible nitric oxide synthase (iNOS) and isoform 2 of the enzyme cyclooxygenase-2 (COX-2). This overactivation can produce cell damage by lipid peroxidation of cell membranes. Endogenous counterbalancing mechanisms take place when an inflammatory or immune stimulus appears, as the activation of peroxisome proliferator-activated receptors (PPARγ) by prostaglandin 15-deoxy-PGJ_2 (15d-PGJ_2), a COX-derived product. Garcia-Bueno *et al.* (2013) found a dysregulation of the pro-/anti-inflammatory pathways in peripheral blood mononuclear cells (PBMCs) in FEP patients. At the 1-year follow-up study (Garcia-Bueno *et al.* 2014) they suggested a more severe pro-/anti-inflammatory deregulation than in earlier pathological stages in FEP. A notable finding was that the anti-inflammatory mediator 15d-PGJ2 might be used as a soluble plasmatic biomarker for FEP and could be a potential protective factor for FEP, whereas COX-2 and NO^-_2, the soluble, stable metabolites of nitric oxide, seemed to be reliable potential risk factors.

Recent studies link inflammatory markers with cognitive function in severe mental disorders (Gimeno *et al.* 2009) and schizophrenia (Penades *et al.* 2015), suggesting that the presence of inflammation is associated with worse cognitive performance (Ribeiro-Santos *et al.* 2014). It has been suggested that cytokines play a central role in complex functions of the central nervous system such as cognition (Meyer *et al.* 2011). It has been shown that chemokine monocyte chemoattractant protein-1 (MCP-1) levels are negatively associated with learning and memory (verbal and working), nitrite levels were negatively associated with executive function, and glutathione levels were positively associated with executive function in a FEP group (Martinez-Cengotitabengoa *et al.* 2012). In a recent study, an association between a weak antioxidant capacity and cognitive functioning was found at baseline and at 2 years follow-up in a sample of early-onset FEP (Martinez-Cengotitabengoa *et al.* 2014).

The present study investigated the association between cognition and inflammatory biomarkers in a FEP sample in order to identify differential cognitive phenotypes from inflammatory expression profiles, which could be useful in stratifying a subgroup of patients. We studied the main pro-inflammatory pathway triggered by the activation of NFκB, which is crucial in the counterbalancing mechanisms between inflammatory and anti-inflammatory pathways. The identification of a specific subgroup of patients could

https://doi.org/10.1017/S0033291716000659 Published online by Cambridge University Press

be useful in the creation of new treatment programmes by providing tools to select a personalized treatment approach.

Method

Subjects

The population of the study came from a multicentre, naturalistic and longitudinal project designed to evaluate clinical, neuropsychological, neuroimaging, biochemical and genetic variables in FEP (the PEPs Project; Bernardo *et al.* 2013).

From the cohort of Flamm-PEPs, a multicentre project developed at the Spanish National Network for Mental Health Research (Centro de Investigación Biomédica en Red de Salud Mental), our study included 92 patients with a FEP and 80 matched controls recruited in five clinical centres. The inclusion criteria for patients were (*a*) age between 7 and 35 years; (*b*) presence of positive/negative/disorganized symptoms not exceeding 1 year's duration prior to inclusion; (*c*) fluency in Spanish language; (*d*) signed informed consent. Exclusion criteria for patients were (*a*) the presence of organic diseases with mental repercussions; (*b*) history of head trauma with loss of consciousness; (*c*) mental retardation according to DSM-IV (APA, 1994) criteria. The patients were matched with controls by age (±10%), gender and parental socioeconomic status, measured with the Hollingshead–Redlich Scale (±1 level) (Hollingshead & Redlich, 1958). Inclusion criteria for controls were (*a*) age between 7 and 35 years; (*b*) absence of psychotic symptoms, or current or past major depression; (*c*) no history of psychotic disorder among first-degree relatives; (*d*) fluency in Spanish language; (*e*) signed informed consent. Exclusion criteria for controls were the same as for patients.

None of the subjects, FEP or controls, was receiving immunosuppressive drugs or vaccinations for at least 6 months prior to inclusion in the study or anti-inflammatory analgesics the 2 days prior to drawing of blood sample, nor had they ongoing infections, fever, allergies, or other serious medical conditions.

The study was approved by the ethics committees of all the participating hospitals and all subjects participated after providing a written, informed consent.

Clinical assessment

The Structured Clinical Interview (SCID-I-II; First *et al.* 1994, 1997) was used in adults to establish the diagnosis according to DSM-IV criteria, and the Kiddie-Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version (K-SADS-PL; Kaufman *et al.* 1997) for the under-age population. The severity of psychotic symptoms was evaluated by the Positive and Negative Syndrome Scale (PANSS; Kay *et al.* 1987; Peralta & Cuesta, 1994). The Global Assessment of Functioning Scale (GAF; Endicott *et al.* 1976) and the Children's Global Assessment Scale (C-GAS; Shaffer *et al.* 1983) were used to assess the severity of symptoms and the level of functioning. To assess depressive symptoms we used the Montgomery–Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979) and the Young Mania Rating Scale (YMRS; Young *et al.* 1978) for mania symptoms. To determine the duration of untreated psychosis, the number of days elapsed between the onset of psychotic symptoms and the first treatment for psychosis was registered. We collected data on drug misuse habits by adapting the European Adaptation of a Multidimensional Assessment Instrument for Drug and Alcohol Dependence scale (Kokkevi & Hartgers, 1995). Following international consensus (Gardner *et al.* 2010), the potency equivalents to chlorpromazine of every antipsychotic dosage were calculated. The diagnosis and treatment were determined at 6-month visits to ensure greater reliability. The complete clinical protocol used in the PEPs project has been published elsewhere (Bernardo *et al.* 2013).

Neuropsychological assessment

Neuropsychological assessment was performed according to the National Institute of Mental Health MATRICS consensus (Green *et al.* 2004*b*; Carter *et al.* 2008). It was conducted at the 2-month visit to ensure clinical stability (Cuesta *et al.* 2015). As included subjects had a wide age range, adapted tests by age and educational level were used, corrected with normative data. Seven scales grouped into four cognitive domains in addition to verbal ability using the Vocabulary subtest of the WISC-IV (Wechsler, 2003) for child and WAIS-III (Wechsler, 1997) for adults were performed. Sustained attention was assessed by the Continuous Performance Test (CPT-II; Conners, 2004) corrected by age and educational level. Working memory was evaluated using the Digit and Letters and Numbers subtest of WAIS-III for adults and WISC-IV for children. To assess verbal memory, the Verbal Learning Test Spain Complutense for adults (TAVEC; Benedet, 1998*a*) and children (TAVECi; Benedet, 1998*b*) were used, and the Wisconsin Card Sorting Test (WCST; Heaton, 1993) to assess executive function, corrected by age and educational level. Lower scores in these tests are regarded as an indication of poor cognitive performance except in attention, in which higher scores indicated lower cognitive performance.

Biological sample

Venous blood samples (10 ml) were collected between 08:00 and 10:00 hours after overnight fast. Samples

https://doi.org/10.1017/S0033291716000659 Published online by Cambridge University Press

were maintained at 4 °C until preparation after approximately 1 h. The sample collection and protocol for extracting cells (PBMCs) were as published previously (Garcia-Bueno *et al.* 2013, 2014).

Briefly, prostaglandin levels in plasma (PGE_2 and 15d-PGJ_2) were measured by enzyme immunoassay. Nitrites (NO^-_2), the final and stable product of nitric oxide (NO), were measured using the Griess method. Lipid peroxidation was determined by thiobarbituric acid reactive substances (TBARS) assay (Cayman Chemicals, Estonia) in plasma. Determination of pro-inflammatory p65 NFκB subunit and anti-inflammatory PPARγ respective transcriptional activities were carried out in nuclear extracts from PBMC. NFκB activity occurs after proteasomal degradation of it inhibitory protein (IκBα), allowing movement from cytoplasm to the nucleus where they bind to consensus κB sequences in DNA. PPARγ transcription factor activity was determined using ELISA-based kits (Cayman Chemicals, Estonia). Protein levels of IκBα, COX-2 and iNOS were quantified by Western blot in cytosolic extracts from PBMCs.

Since this was a naturalistic study, there were no guidelines for the treatment administered (drugs and/or psychosocial interventions).

Statistical analysis

Differences in sociodemographic and clinical characteristics between patients and controls were assessed using two-tailed χ^2 tests on categorical data and *t* test for continuous variables. A two-tailed non-parametric Mann–Whitney *U* test was performed when continuous variables did not meet the assumption of normality in the Kolmogorov–Smirnov test.

All neuropsychological variables were transformed into standard equivalents, *T* scores (mean = 50, standard deviation = 10) except verbal ability, showing IQ scores (mean = 100, standard deviation = 15). Principal component analysis was performed with all neuropsychological variables and they were grouped into four cognitive domains (verbal memory, sustained attention, executive function, working memory; see Supplementary material). To test neurocognitive performance and inflammatory expression differences between patients and control groups, MANCOVA was performed, controlling for years of education and tobacco use in neurocognition and controlling for tobacco use and body mass index (BMI) in biological markers.

Correlation and correction for multiple comparisons using the Holm–Sidak method was performed to assess the association between cognition and inflammation in FEP patients and controls. Hierarchical regression analysis was performed in the FEP group for each of the inflammatory variables that obtained statistical correlation after multiple comparisons with cognitive domains.

A partial correlation controlling for plausible confounding factors was used to calculate the association between clinical characteristics and inflammatory markers in the FEP group.

All statistical analyses were performed using SPSS Statistics v. 20 for Windows (IBM Corp., USA).

Results

Demographic and clinical characteristics

Baseline demographic and clinical data of patients and controls are shown in Table 1.

We did not find any differences between patient and control groups in demographic and clinical data except in percentage of tobacco smokers, higher in FEP group, and in educational background, lower in FEP group.

Neurocognitive differences between FEP group and controls

Patients showed worse cognitive performance in all cognitive domains studied compared to controls (see Table 2).

No differences between FEP adults ($\geqslant$18 years) and FEP young children (9–17 years) were found in cognitive performance, either in patients who were under treatment or in patients who were not.

Pro-/anti-inflammatory comparisons between FEP group and controls

In nuclear extracts from PBMCs, the expression of the inflammatory transcription factor NFκB was increased in the FEP group, but did not reach statistical significance, while its inhibitory protein IκBα was significantly decreased compared to controls. The expression of the two main enzymatic sources of inflammatory and oxido-nitrosative (I&ON) soluble mediators, iNOS and COX-2, was higher in the FEP group than in controls, with significant differences between groups. The main pro-inflammatory product of COX-2, PGE_2, and the index of oxido-nitrosative stress cellular damage, TBARS, appeared significantly increased. The mean plasma levels of the oxido-nitrosative stress markers NO^-_2 were increased in FEP patients, but they did not reach statistical significance.

By contrast, the plasma levels of the COX-2-derived, anti-inflammatory prostaglandin 15d-PGJ_2, and the transcriptional activity of PPARγ were lower in FEP patients than in controls, with significant differences in 15d-PGJ_2 levels (see Table 3).

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Table 1. *Baseline demographic and clinical characteristics*

Characteristic	Patients ($N = 92$)	Controls ($N = 80$)	p values
Age, years	23.93 ± 5.87	25.31 ± 6.87	0.158
Adults (age range 18–35), *n* (%)	77 (83.7)	71 (88.8)	0.384
Children (age range 9–17), *n* (%)	15 (16.3)	9 (11.2)	
Gender, *n* (%)			
Male	62 (67.4)	52 (65.0)	0.749
Female	30 (32.6)	28 (35.0)	
Years of education	12.85 ± 3.58	14.85 ± 3.94	0.001
Socioeconomic status, *n* (%)			
High	19 (20.6)	12 (15.0)	0.263
Medium-high	12 (13.0)	17 (21.2)	
Medium	29 (31.5)	30 (37.5)	
Medium-low	25 (27.2)	19 (23.8)	
Low	7 (7.6)	2 (2.5)	
Duration of untreated psychosis, days	91.37 ± 95.31	–	
Diagnosis, *n* (%)			
Affective psychosis	19 (20.7)	–	–
Non-affective psychosis	73 (79.3)	–	–
PANSS			
Total	51.51 ± 19.55	–	–
Positive	10.63 ± 5.83	–	–
Negative	14.29 ± 5.86	–	–
General	26.59 ± 10.39	–	–
Young Mania Rating Scale	1.77 ± 3.89	–	–
MADRS	6.25 ± 5.89	–	–
Overall functioning score (GAF/C-GAS)	68.04 ± 14.03	–	–
Baseline antipsychotic medication, *n* (%)			
Risperidone	30 (32.6)	–	–
Aripiprazole	11 (11.9)	–	
Olanzapine	10 (10.9)	–	
Paliperidone	8 (8.7)	–	
Quetiapine	6 (6.5)	–	
Clozapine	5 (5.4)	–	
Ziprasidone	2 (2.2)	–	
None	20 (21.7)	–	
Lithium use, *n* (%)	10 (10.9)	–	–
Chlorpromazine equivalent treatment	280.93 ± 255.39	–	–
Body mass index	24.86 ± 4.19	23.44 ± 3.18	0.053
Cannabis use, *n* (%)	17 (18.48)	12 (15.19)	0.684
Tobacco use, *n* (%)	54 (58.69)	19 (23.75)	<0.001

MADRS, Montgomery–Asberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; GAF/C-GAS, Global Assessment of Functioning Scale/Children's Global Assessment Scale.

No differences were found between FEP adults (⩾18 years) and FEP young children (9–17 years) in pro-/anti-inflammatory biomarkers, even when comparing patients who were under or without treatment.

Cognitive markers and inflammation

In the FEP group, verbal ability obtained a statistically significant correlation with plasma levels of the anti-inflammatory mediator 15d-PGJ_2 ($r = 0.222$, $p = 0.042$) and pro-inflammatory mediators iNOS ($r = 0.263$, $p = 0.028$) and PGE_2 ($r = -0.273$, $p = 0.011$). Higher scores in verbal ability were correlated with higher levels of 15d-PGJ_2 and iNOS and lower levels of PGE_2, but did not pass the correction for multiple comparisons with the Holm–Sidak method. Sustained attention was negatively associated with plasma levels of 15d-PGJ_2 ($r = -0.373$, $p = 0.001$) and NO^{-}_{2} ($r = -0.300$, $p = 0.048$). Considering that sustained attention has been encoded conversely, the results show an association between lower plasma

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Table 2. *MANCOVA results comparing the neuropsychological domain scores between patients and controls*

Neuropsychological tests	Cognitive domain	Patients ($N = 92$)	Controls ($N = 80$)	F	df	p value
Vocabulary WAIS/WISC-IV	Verbal ability	95.43 ± 15.701	109.19 ± 12.23	19.53	1	<0.001
TAVEC/TAVECi Short-term	Verbal memory	108.52 ± 33.10	143.66 ± 22.04	41.32	1	<0.001
TAVEC/TAVECi Long-term						
TAVEC (total)						
CPT-II comissions	Sustained attention	133.93 ± 14.83	120.47 ± 14.88	29.86	1	<0.001
CPT-II (*d'*)						
CPT-II (hit reaction time)						
Digits	Working memory	79.51 ± 15.95	95.95 ± 15.13	26.05	1	<0.001
Letter and number						
WAIS/WISC-IV						
WCST perseverations	Executive function	81.45 ± 26.73	96.34 ± 20.34	20.30	1	<0.001
WCST errors						

WAIS, Wechsler Adult Intelligence Scale; WISC-IV, Wechsler Intelligence Scale for Children – IV; TAVEC, Verbal Learning Test Spain Complutense for adults; TAVECi, Verbal Learning Test Spain Complutense for children; CPT-II, Continuous Performance Test – II; WCST, Wisconsin Card Sorting Test.

Years of education and tobacco use as covariates. Lower scores in these tests are regarded as indication of poor cognitive performance except in attention, in which higher scores indicated lower cognitive performance.

Table 3. *MANCOVA results comparing the inflammatory biomarkers scores between patients and controls*

	Patients ($N = 92$)	Controls ($N = 80$)	F	df	p value
15d-PGJ_2[a] (pg/ml plasma)	583.05 ± 149.38	645.91 ± 158.28	6,76	1	0.010
$PPAR\gamma$[a] (arbitrary units)	1.37 ± 0.81	1.60 ± 0.96	2,16	1	0.143
$I\kappa B\alpha$[a] (% from control)	85.70 ± 42.18	103.70 ± 44.78	12,32	1	0.001
$NF\kappa B$[b] (arbitrary units)	7.82 ± 7.08	5.82 ± 2.49	2,73	1	0.100
iNOS[b] (% from control)	127.64 ± 46.34	94.62 ± 28.74	27,19	1	<0.001
COX-2[b] (% from control)	126.87 ± 48.17	106.72 ± 58.23	5,45	1	0.021
PGE_2[b] (pg/ml plasma)	474.77 ± 503.56	309.72 ± 239.47	4,69	1	0.032
NO^-_2[b] (pg/ml plasma)	14.06 ± 4.26	13.10 ± 3.52	1,54	1	0.216
TBARS[b] (μM plasma)	3.40 ± 3.50	2.21 ± 2.38	6,24	1	0.013

Tobacco and body mass index used as covariates.

[a] Anti-inflammatory biomarker.

[b] Pro-inflammatory biomarker.

levels of the anti-inflammatory mediator 15d-PGJ_2 and poor cognitive performance and between higher plasma levels of NO^-_2 and better performance in this cognitive domain. After correction for multiple comparisons with the Holm–Sidak approach, the association between sustained attention and 15d-PGJ_2 remained statistically significant. Regarding executive function, the results showed a positive association with COX-2 ($r = 0.361$, $p = 0.003$), that is, better performance in this cognitive domain was linked with higher protein expression of COX-2. This association remained statistically significant after correction for multiple comparisons. A positive association between working memory and the protein expression of the pro-inflammatory agent iNOS ($r = 0.265$, $p = 0.029$) was found, but did not pass the Holm–Sidak approach for multiple comparisons. Verbal memory was not associated with any of the inflammatory biomarkers.

No correlation between any cognitive function and inflammatory expression levels was found in the control group.

A hierarchical multiple regression analysis was performed within the FEP group to assess the ability of two inflammatory mediator (15d-PGJ_2 and COX-2) to predict performance on cognition (sustained attention and executive function) after controlling for potential confounders (age, gender, total antipsychotic chlorpromazine equivalent dose, BMI, tobacco and cannabis

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Table 4. *Hierarchical regression models of cognitive and biological markers*

Cognitive domain	Variables in the model	β	t	R^2	p
Model 1:	Age	−0.143	−1.285	0.190	0.203
Sustained attention	Gender	−0.252	−2.355		0.021
	Body mass index	−0.107	−0.965		0.338
	Tobacco use	−0.160	−1.444		0.153
	Cannabis use	−0.087	0.805		0.423
	Chlorpromazine equivalent antipsychotic treatment	0.147	1.333		0.18
Model 2:	Age	−0.101	−0.943	0.278	0.349
Sustained attention	Gender	−0.178	−1.697		0.094
	Body mass index	−0.086	−0.810		0.420
	Tobacco use	−0.151	−1.434		0.156
	Cannabis use	0.070	0.676		0.501
	Chlorpromazine equivalent antipsychotic treatment	0.186	1.758		0.083
	15d-PGJ_2	−0.312	−2.950		0.004
Model 1:	Age	−0.104	−0.766	0.046	0.447
Executive function	Gender	0.054	0.416		0.679
	Body mass index	−0.069	−0.510		0.612
	Tobacco use	0.082	0.606		0.547
	Cannabis use	−0.154	−1.168		0.248
	Chlorpromazine equivalent antipsychotic treatment	−0.027	−0.198		0.844
Model 2:	Age	−0.089	−0.693	0.163	0.491
Executive function	Gender	0.007	0.058		0.954
	Body mass index	−0.017	−0.135		0.893
	Tobacco use	0.072	0.569		0.571
	Cannabis use	−0.157	−1.265		0.211
	Chlorpromazine equivalent antipsychotic treatment	−0.007	−0.059		0.953
	COX-2	0.350	2.824		0.007

use). It was conducted for those inflammatory biomarkers that were correlated with cognitive domains, after correction for multiple comparisons. Preliminary analyses were conducted to ensure no violation of the assumptions of normality, linearity, multicollinearity and homoscedasticity. Including in the first step confounding variables, the model explained 19% of the variance in sustained attention and was statistically significant ($p = 0.015$). After entry 15d-PGJ_2 at second step the total variance explained by the model as a whole was 28% ($F_{7,72} = 3.95$, $p = 0.001$). 15d-PGJ_2 plasma levels explained an additional 9% of the variance in sustained attention, after controlling for confounders (change for $R^2 = 0.09$, change for $F_{1,72} = 8.703$, $p = 0.004$). In the final model, only 15d-PGJ_2 levels were statistically significant ($\beta = -0.312$, $p = 0.004$) (see Table 4). Regarding the association between COX-2 and executive function, including in the first step confounding variables, the model explained 5% of the variance in executive function but was not statistically significant ($p = 0.829$). After entry of COX-2 at second step the total variance explained by the model as a whole was 16% ($F_{7,57} = 1.589$, $p = 0.157$). COX-2 expression explained an additional 12% of the variance in executive function, after controlling for confounders (change for $R^2 = 0.117$, change for $F_{1,57} = 7.976$, $p = 0.007$). In the final model, only COX-2 expression was statistically significant ($\beta = 0.350$, $p = 0.007$) (see Table 4). The hierarchical regression analysis between verbal ability, working memory and verbal memory was not performed because they were not correlated with any of the inflammatory biomarkers after correction for multiple comparisons.

Clinical status and inflammation

A partial correlation was used to assess the association between inflammatory biomarkers and psychopathology. As shown in Table 5, there was significant correlation between IκBα and all PANSS subtests and total PANSS score after controlling for possible confounding factors. No associations were found between any of the other biological measurements and psychopathology (see Table 5).

Discussion

Our results show that pro-/anti-inflammatory biomarkers were associated with cognitive functioning in FEP, identifying differential cognitive phenotypes from inflammatory expression profiles. The FEP

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Table 5. *Partial correlation between inflammatory expression and psychopathology*

Pro-/anti-inflammatory biomarkers	PANSS positive	PANSS negative	PANSS general	PANSS total
15d-PGJ_2	−0.132	−0.175	−0.179	−0.193
PPARγ	−0.153	0.024	−0.083	−0.080
IκBα	0.452**	0.331*	0.370*	0.444**
PGE_2	−0.173	−0.013	−0.102	−0.113
NFκB	0.212	−0.242	−0.036	−0.041
TBARS	0.177	0.240	0.136	0.205
NO^-_2	0.043	0.023	−0.016	0.010
iNOS	0.140	−0.019	0.103	0.090
COX-2	0.180	0.050	−0.008	0.067

PANSS, Positive and Negative Syndrome Scale.

Values are partial correlation coefficients adjusted for age, gender, total antipsychotic chlorpromazine equivalent dose, body mass index, and tobacco and cannabis use.

**$p \leqslant 0.001$, *$p < 0.05$.

group performed worse in all cognitive domains assessed in comparison to control subjects matched for age, gender and socio-economic level. The FEP patients also showed significant higher levels of all the pro-inflammatory mediators compared to controls, with significant differences between groups in PGE_2, TBARS, iNOS and COX-2. Furthermore, patients showed lower expression of all anti-inflammatory markers, with significant differences in 15d-PGJ_2 and IκBα expression between groups. The most important finding of this study is that in the FEP group, after controlling for the possible effects of confounding factors, 15d-PGJ_2 levels predicted sustained attention and COX-2 expression predicted executive function.

It has been previously demonstrated that FEP patients perform worse in cognitive tasks (Mohamed *et al.* 1999) compared to controls, and exhibit an altered anti-inflammatory activity that influences progressive inflammatory processes (Martinez-Gras *et al.* 2011; Meyer *et al.* 2011; Garcia-Bueno *et al.* 2013), which agrees with our results. Recent studies link cognitive function with inflammatory markers in schizophrenia, suggesting that the presence of inflammation is associated with worse cognitive performance (Ribeiro-Santos *et al.* 2014). Our finding of an inflammatory expression levels in relation with cognitive function among the patients, but not among normal controls, may have several aetiologies. Comparatively, the association of inflammatory expression levels with cognitive impairment in schizophrenia needs to be viewed in the context of higher expression of pro-inflammatory levels and lower expression of anti-inflammatory ones compared to controls. FEP patients appear to reflect an imbalance between pro- and anti-inflammatory markers. Consequently, this dysregulation may reflect cognitive impairment. This speculative mechanism needs to be explored in future longitudinal investigations about how pro-/anti-inflammatory dysregulation might cause cognitive impairment in schizophrenia.

We found a positive association between executive function and COX-2 protein expression levels. A study by Muller *et al.* (2005) found a positive effect of the celecoxib add-on therapy on the total PANSS score and a positive effect with a tendency to significance on two cognitive factors (conceptual and abstract thinking). These results suggest that COX-2 expression (and its pro- and anti-inflammatory derived products) probably influences different aspects of cognition, specifically those related to prefrontal cortex. Martinez-Cengotitabengoa *et al.* (2012) reported a negative association between executive functioning and oxidative stress markers (nitrite levels). We did not find such association, instead we found a relation between sustained attention and the NO^-_2 expression, and between working memory and verbal ability and iNOS levels. The differences among the studies may be due to methodological differences or to the patients' clinical status. They included small samples ($N = 28$) and antipsychotic-naive patients, whereas we included a large sample of patients ($N = 92$) with antipsychotic treatment, which has been shown to modulate inflammatory markers.

After controlling for the known confounding variables, no associations between cognitive domains and inflammation mediators were found in our study except in sustained attention and executive function. In studies by Dickerson *et al.* (2007) and Zhang *et al.* (2013) no association was found between attention and inflammation that may be due to the heterogeneity of patient sample or study methodology. Dickerson *et al.* included schizophrenia patients with a mean duration of illness of 19.1 years whereas our sample

https://doi.org/10.1017/S0033291716000659 Published online by Cambridge University Press

included FEP patients with presence of symptoms not exceeding 1 year. Neither of these studies evaluated the executive function nor took into account other factors that may be affecting cognitive performance or the measured biological parameters, such as tobacco or alcohol consumption.

Our study provides evidence for an association between anti-inflammatory biomarkers and cognition in FEP. The identification of a subgroup of patients based on these measures could be useful to guide treatment programmes by providing tools to select a personalized treatment approach, but longitudinal studies are needed before. In the future, establishment of biomarkers linked to cognition would be useful to monitor the course of cognitive impairment and therapeutic response, but substantially more data will be required. Some studies show that sustained attention deficit remains stable during FEP (Becker *et al.* 2010) and over the course of the disease (Erlenmeyer-Kimling *et al.* 2000; Liu *et al.* 2002), and the Garcia-Bueno *et al.* (2014) 1-year longitudinal study suggests the expression of 15d-PGJ_2 and COX-2 as a trait markers for psychosis. The association we found between 15d-PGJ_2 levels and sustained attention and between executive function and COX-2 expression suggests that these biomarkers may also be useful as biomarkers of cognitive status, but substantially more data is required. Longitudinal studies examining the association between cognitive phenotypes and inflammatory mediators are necessary to elucidate if these biomarkers would be state or trait markers for cognition. Previous studies suggested 15d-PGJ_2 plasma levels as a potential protection factor for FEP (Garcia-Bueno *et al.* 2014). According to our data, better performance on tasks of sustained attention are associated with higher levels of anti-inflammatory expression (15d-PGJ_2), which might suggest that this is also a protective factor for cognition. 15d-PGJ_2 lower levels in FEP patients might have a detrimental effect on sustained attention, so pharmacological treatment directed towards an increase in 15d-PGJ_2/PPARγ signalling would be beneficial for enhancement of cognitive impairment. Animal models suggest that prostaglandins play a neuroprotective role by increasing neuronal glucose metabolism, restoring brain ATP levels and preventing the impairment in glutamate uptake mechanisms induced by exposure to stress (Garcia-Bueno *et al.* 2007).

In relation to psychopathology, our results showed an association between the expression of the anti-inflammatory subunit IκBα and clinical status. Contrary to what was expected, elevated levels of IκBα were associated with severity of psychiatric symptoms as measured by PANSS rating. A meta-analysis by Miller *et al.* (2011) suggests that cytokine alterations in schizophrenia may vary with clinical status. Some cytokines appear to be state-related markers, as they were increased during acute exacerbations and normalized with antipsychotic treatment, whereas others may be trait markers. In the Flamm-PEPs study, the results show potential risk (COX-2)/protective (15d-PGJ_2) factors common both to baseline and follow-up visits (Garcia-Bueno *et al.* 2014). However, IκBα lost its validity in the 1-year follow-up visit, which in accord with this study suggests that this biomarker could be useful in early phases of the disease for assessing clinical severity.

There are some potential limitations in the study that should be considered. There is evidence in the literature of a potential anti-inflammatory effect of antipsychotics (Miller *et al.* 2011; MacDowell *et al.* 2013), mainly atypical antipsychotics, and 78% of the patients included in our study were under atypical antipsychotic treatment. To remove this potential limitation hierarchical regression analysis controlling for equivalent doses of chlorpromazine (Gardner *et al.* 2010) was performed. To control the possible effects of tobacco and cannabis on cognition (Moss *et al.* 2009; DeRosse *et al.* 2010) they were also included as covariates. Other limitation of the study is that other external factors that could explain the relationship between cognitive deficits and inflammatory markers, such as leading a sedentary lifestyle (Singh *et al.* 2012; Stubbs *et al.* 2015) have not been taken into account, since these data have not been recorded in our study. Due to the cross-sectional rather than longitudinal design of the study, we cannot support a causative or longitudinally evolving process as the underlying mechanism for this association between cognition and anti-inflammatory expression. Longitudinal studies to confirm the prognostic value of inflammatory mediation in cognitive function and studies to replicate our findings including confounding factors discussed above are needed.

The strength of this study is that it includes patients with FEP over a wide range of ages, which represents an excellent group in which to study the risk and protective factors associated with the development of the disease, allowing control of confounding variables such as chronicity or medical treatment (Bernardo *et al.* 2013). Studies such as the PEPs, with a homogeneous representative sample of real life and with a complete and extensive neuropsychological and clinical assessment, allow us to move into clinical benefits. Another key feature of this study is that it includes multiple cognitive domains and biological markers and we evaluated their association controlling for potential confounding factors, allowing us to establish multiple associations between these factors.

In conclusion, our study provides evidence for an association between anti-inflammatory biomarkers and

https://doi.org/10.1017/S0033291716000659 Published online by Cambridge University Press

cognition in FEP. The identification of a subgroup of patients based on these measures could be useful to guide treatment programmes by providing tools to select a personalized treatment approach, but longitudinal studies are needed before. In the future, the establishment of biomarkers linked to cognition would be useful to monitor the course of cognitive impairment and therapeutic response, but substantially more data is necessary. Better performance on tasks of sustained attention are associated with higher levels of anti-inflammatory prostaglandin (15d-PGJ_2), which might suggest that this biomarker would be a protective factor for cognition. Our data can generate knowledge about the physiology associated with cognition and provide a better understanding of the neuropsychological correlates associated with inflammatory phenotypes.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291716000659.

Acknowledgements

This work was supported by: Ministerio de Economía y Competitividad, Instituto de Salud Carlos III (ISCIII) 2009–2011: PEPs study PI 080208; Centro de investigación Biomédica en Red en Salud Mental (CIBERSAM) Intramural Projects 2010: Flamm-PEPs study; Instituto de Salud Carlos III; Fondo Europeo de Desarrollo Regional, Unión Europea, 'Un manera de hacer Europa' and Government of Catalonia, Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2014SGR441). This work was developed (in part) at the Centro Esther Koplowitz (Barcelona).

The authors thank Ferran Torres (Platform for Medical Statistics, Institut d'Investigacions Biomèdiques August Pi i Sunyer -IDIBAPS-, Hospital Clinic, Barcelona) and Cristina V. Oliveira (Barcelona Clínic Schizophrenia Unit, Hospital Clínic, Barcelona) for their methodological support.

All authors are from Flamm-PEPs, a Spanish multicentric, collaborative, and translational group inside Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM) aimed to study inflammatory pathways in psychosis both as possible biomarkers and as possible new therapeutical targets incorporated in the PEPs study, a research project in first-episode psychosis.

Declaration of Interest

None.

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