Peripheral inflammation is associated with brain SPECT perfusion changes in schizophrenia

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Abstract

Purpose Peripheral inflammation is frequent in schizophrenia and could play a role in the pathophysiology, prognosis, and persistence of psychotic symptomatology under treatment. We seek to determine the relationship between peripheral inflammation and brain SPECT perfusion in stabilized antipsychotic-treated outpatients with schizophrenia, and to determine whether such perfusion changes are correlated with persistent symptoms.

Methods Highly sensitive C-reactive protein blood level (hs-CRP) and brain SPECT perfusion were assessed in 137 stabilized outpatients with schizophrenia. Whole-brain voxel-based associations were searched with SPM between SPECT perfusion and hs-CRP (correlation analysis to quantitative levels and between-group analysis according to a threshold of 3 mg/L). The identified clusters were secondarily correlated with clinical symptoms.

Results After adjustment for age, sex, educational level, illness duration, antidepressant use, chlorpromazine equivalent dose, tobacco smoking and obesity, a negative correlation was found between hs-CRP level and the perfusion of 4 brain areas: the right inferior frontal gyrus, the right middle/superior temporal gyrus, the left superior parietal lobe, and the right postcentral/transverse temporal gyrus (p-voxel < 0.001, k > 80, uncorrected). Increased perfusion of the left amygdala was found in patients with hs-CRP ≥ 3 mg/L compared to those with hs-CRP levels < 3 mg/L. A negative correlation was found between perfusion of the right inferior frontal gyrus and the persistence of positive, negative, and excitement symptoms under antipsychotic treatment.

Conclusion In stabilized patients with schizophrenia, peripheral inflammation is associated with brain perfusion changes that are correlated with the persistence of psychotic symptomatology.

Keywords Psychiatry · Schizophrenia · Mental health · SPECT · Brain perfusion · Neuroimaging

Introduction

Elucidating the underlying pathophysiology of schizophrenia may help in better selection and development of treatments. Current antipsychotic treatments have limits, as first-line antipsychotics are effective in only 34% of patients [1]. Clozapine, the most effective antipsychotic, is effective in only 60% of patients not responding to previous antipsychotics [2]. Biological hypotheses on treatment resistance still focus on neurotransmitter pathways, including dopaminergic or glutamatergic pathways. These views are not exclusive, with several pathways converging and possibly contributing to the neurobiology of persistence of psychotic symptoms under treatment.

In addition to these possible explanations, we now have more than two decades of data highlighting the role of immune-inflammatory processes in schizophrenia. Among salient findings, genome-wide studies have shown that the
mutation of the human leukocyte antigen was the most consistent pattern of schizophrenia [3]. An overall increase in the expression of proinflammatory genes has been found in schizophrenia post-mortem brains [4], which may be due to multiple sources of inflammation, including Toxoplasma infection and overweight [5]. However, neuroinflammation studies in schizophrenia have shown inconsistencies, probably due to the heterogeneity of included patients and used biomarkers. Little is known about the consequences of inflammation on living brain perfusion. Our hypothesis is that inflammation may induce alterations of the neurovascular unit (including astrocytes, endothelial cells and neurons), which could lead to brain perfusion changes [6]. We also hypothesized that these functional changes would be an indirect marker of persistent psychotic symptoms under antipsychotic treatment.

The main objective of this study was to determine the impact of peripheral inflammation on brain SPECT (single-photon emission computed tomography) perfusion in patients with schizophrenia. The secondary objective is to determine whether these perfusion changes are associated with the persistence of psychotic symptomatology under antipsychotic treatment.

Methods

Study design

All outpatients have been recruited in the regional psychiatric academic hospital from Assistance Publique des Hôpitaux de Marseille (AP-HM) academic hospital (http://fr.ap-hm.fr), Marseille, France, since April 2011. The patients were referred from the whole Provence-Alpes-Côte-d’Azur region (South France) by their general practitioner or psychiatrist, who subsequently received a detailed evaluation report with suggestions for personalized interventions.

Study population

Inclusion criteria

All stabilized outpatients (defined by stable background treatment, i.e., antipsychotic and/or antidepressant for at least 8 weeks without change or dose modification) with an ICD-10 diagnosis of schizophrenia/schizoaffective disorder (F20*, F25*) who had brain SPECT perfusion with $^{99m}$Tc-HMPAo and measurement of highly sensitive C-reactive protein (hs-CRP) were consecutively included.

Exclusion criteria

Patients with a history of neurological disorders (including stroke, epilepsy and head injury) or any non-psychiatric concurrent illnesses affecting the central nervous system (such as lupus, rheumatoid arthritis, multiple sclerosis or acute infectious disorder) and patients not speaking French were excluded. These exclusion criteria are consistent with previous studies carried out in the field of immune inflammation and schizophrenia (reviewed in [7]).

Sociodemographic, clinical, and treatment variables

The clinical evaluation included diagnostic confirmation by two trained psychiatrists of the schizophrenia expert center using a structured clinical interview [8] and data on age, sex, educational level (university level defined by > 12 years of education: yes/no), illness duration (years), antidepressant (yes/no), current daily tobacco smoking status (yes/no), and obesity (yes/no defined by a body mass index $\geq 30$ kg/m$^2$). Chlorpromazine equivalent doses (CPZ100eq) were calculated according to the minimum effective dose method [9]. Psychotic symptomatology was assessed using the Positive And Negative Syndrome Scale (PANSS) [10]. Current depressive symptoms were evaluated using the Calgary Depression Rating Scale for Schizophrenia (CDSS) (major depressive disorder was defined by a CDSS score $\geq 6$) [11], and comorbid generalized anxiety disorder was defined according to the structured clinical interview for DSM-IV-TR axis I disorders [12].

Biological measurements

Fasting glucose (mM) and hs-CRP (mg/L) were measured by routine blood samples using sensitive regular immunoassays (ELISA) for hs-CRP (with a detection limit of 0.08 µg/ml). A cut-off of 3 mg/L was used to classify patients with “low-grade peripheral inflammation” ($\geq 3$ mg/L) vs. “no peripheral inflammation” (< 3 mg/L) using a threshold previously reported [7]. Hypertension and diabetes were defined according to the World Health Organization standards ($\geq 140$ mmHg for systolic pressure and/or $\geq 90$ mmHg for diastolic pressure and fasting glucose $\geq 7$ nM, respectively) [13, 14].

Brain SPECT perfusion procedure

All SPECT perfusion exams were carried out at AP-HM, France, under the same conditions for all patients included in this study, with a mean delay of 16.1 days $\pm 27.5$ with the clinical/biological evaluation. The patients received an intravenous injection of 740 MBq of $^{99m}$Tc-HMPAo after a rest period of 15 min in quiet surroundings with their eyes closed. The acquisition was performed 20 min later after an additional period of sensorial rest.
SPECT acquisition was performed using the same double-headed rotating gamma camera (E.cam, Siemens, Erlangen, Germany) equipped with a fan-beam collimator to improve sensitivity. The total scan time was 25 min with 60 projections per head of 25 s collected in a 128×128 format. Tomographic 3D reconstruction was performed using a filtered back-projection algorithm.

**Brain SPECT perfusion analyses**

A whole-brain voxel-based analysis was performed, without a priori hypothesis of selected regions, using SPM8 (Welcome Trust Centre for Neuroimaging) running on MATLAB (Mathworks Inc.). Images were initially converted from DICOM to NifTi format using MRicro (https://people.cas.sc.edu/orden/mricro/mricro.html) and transferred to statistical parametric mapping (SPM). Data were standardized with the Montreal Neurological Institute (MNI) atlas based on the 99mTc-HMPAO SPECT template of SPM using a 12-parameter affine transformation followed by nonlinear transformations and trilinear interpolation. The dimensions of the resulting voxels were 2×2×2 mm. Standardized data were smoothed with a Gaussian filter (full width at half maximum of 8 mm) to blur individual variations in gyral anatomy and to increase the signal-to-noise ratio. Multiple regression analysis was performed on the whole group of patients including the following variables: age, sex, educational level (university level defined by >12 years of education: yes/no), illness duration (years), antidepressant (yes/no), chlorpromazine equivalent dose (mg/d), current daily tobacco smoking status (yes/no), obesity (yes/no according to a body mass index of 30 kg/m²), and highly sensitive C-reactive protein (hs-CRP) (mg/L).

On the hypothesis of a possible nonlinear relationship between peripheral inflammation and brain perfusion, a complementary analysis was secondarily performed between groups according to an hs-CRP threshold < or ≥ 3 mg/L, including all other mentioned covariables. These two analyses were two-sided exploring positive/negative correlations and increase/decrease in perfusion.

We used the “proportional scaling” routine to check for individual variations in global brain perfusion. Positive and negative correlations/associations were searched for each variable using SPM (T) maps at a height threshold voxel-level significance of p < 0.001, uncorrected, with a cluster extent of at least 80 voxels determined by SPM after Monte Carlo simulations. The perfusion values of each cluster were extracted at the individual level using MARSBAR (http://marsbar.sourceforge.net/), and correlations were searched with PANSS scores. MNI coordinates were converted into Talairach coordinates, and brain structures were identified using the Talairach Daemon database (http://ric.uthscsa.edu/projects/talairachdaemon.html).

Finally, to explore the possible role of psychiatric and metabolic comorbidities, we compared perfusion means of found SPECT clusters in the following groups: comorbid major depressive disorder (y/n), general anxiety disorders (y/n), tobacco smokers (y/n), hypertension (y/n), and diabetes (y/n), with Bonferroni correction for multiple testing.

**Ethical concerns**

The data collection was approved by the Commission Nationale de l’Informatique et des Libertés (CNIL number 1223715). The study was designed in accordance with the Declaration of Helsinki and French good clinical practice. All patients were informed of the study and gave written informed consent.

**Results**

A total of 137 stabilized outpatients with schizophrenia were included in the study. The sample characteristics and those of the two hs-CRP groups are presented in Table 1. Patients with hs-CRP levels ≥ 3 mg/L were older (38.6 (SD 10.6) vs. 34.4 (12.2) years, p = 0.045) and had more psychiatric (major depressive disorders 40.0% vs. 21.0%, p = 0.019, generalized anxiety disorders 25.0% vs. 10.6%, p = 0.026) and physical health comorbidities (obesity 46.2% vs. 11.8%, p < 0.001) and hypertension (34.6% vs. 17.6%, p = 0.024).

All significant SPECT results were found using p-voxel < 0.001, uncorrected, and a cluster size of at least 80 voxels (Fig. 1). Table 2 lists the most significant voxels. A negative correlation was found between hs-CRP level and perfusion of 4 clusters: the right inferior frontal gyrus, the right middle/superior temporal gyrus, the left superior parietal lobe, and the right postcentral/transverse temporal gyrus. Increased perfusion of the left amygdala was found in patients with hs-CRP at least higher than 3 mg/L in comparison to patients with hs-CRP levels less than 3 mg/L. No other significant cluster was found on SPM analysis.

The correlations of brain perfusion with psychotic and depressive symptomatology and hs-CRP blood levels are presented in Table 3. The perfusion of the right inferior frontal cluster was negatively correlated with global illness severity (PANSS total score) and positive (PANSS positive factor), negative (PANSS negative factor), and excitement (PANSS excitement score) symptoms.

We found no significant association between the SPECT clusters of perfusion and comorbid major depressive disorder, general anxiety disorder, tobacco smoking, hypertension, and diabetes mellitus (all p > 0.20).
Discussion

In stabilized outpatients with schizophrenia, peripheral inflammation was associated with brain perfusion changes in the frontal, temporal, and parietal regions. A negative correlation was found between perfusion of the right inferior frontal gyrus and persistence of psychotic symptoms under antipsychotic treatment, more specifically of positive, negative, and excitement symptoms.

Peripheral inflammation was first negatively correlated with perfusion of the right frontotemporal and bilateral parietal areas. Brain perfusion is a biomarker of global brain functioning through global synaptic activity. How peripheral inflammation can impact brain functioning and its role in schizophrenia is a timely and complex question. A recent review of the use of TSPO in schizophrenia concluded that schizophrenia was associated with lower levels of TSPO brain concentrations, which may suggest altered function or lower density of brain immune cells [15]. Other inflammatory mechanisms of brain inflammation independent of TSPO are also not excluded [15]. Recent post-mortem schizophrenia studies suggest that astrocytes and parvalbumin interneurons are altered in the brains of schizophrenia patients, but not microglial cells involved in neuroinflammation [16]. In schizophrenia patients, peripheral inflammation can alter the blood–brain barrier, increasing its permeability and impacting brain perfusion. Blood–brain barrier dysfunction could relate to glutamergic and inflammatory abnormalities, which are increasingly understood to play a part in the pathogenesis of psychosis [17]. Currently, the heterogeneity of both schizophrenia subtypes and neuroinflammation biomarkers prevents clear conclusions about the mechanisms involved and the markers for detecting them. Based on our results, one could hypothesize that inflammation-associated brain perfusion changes may be the long-term consequence of an ongoing process in some of these patients. This assumption is consistent with a mean illness duration of 13 years in our sample, while inflammation is often identified in the early phases of these illnesses [18], suggesting that the brains of some participants were probably exposed to chronic low-grade inflammation for several years.

The right inferior frontal gyrus was the only area in which perfusion was correlated with both peripheral inflammation and persistence of positive symptoms under treatment. The frontal cortex is the brain area richest in dopaminergic neurons and is responsible for language processing and speech production, which recently have been demonstrated as reliable markers of schizophrenia [19]. The right inferior frontal gyrus is also involved in the recognition of emotions of fear,
disgust, and anger [20]. Emotion recognition deficits, particularly negative emotions, have been found to be a useful predictor of schizophrenia risk [21]. This lobe is connected to the prefrontal cortex, which is involved in social interactions, which may explain the correlation between decreased perfusion of this area and increased emotional and social withdrawal [21]. Our patients were treated with antipsychotics, which suggests that frontal perfusion changes correlated with inflammation were also correlated with the persistence of psychotic symptoms under treatment. The association of inflammation with the persistence of psychotic symptoms under treatment has been well established elsewhere [22], and anti-inflammatory strategies have shown effectiveness in improving schizophrenia symptomatology [23].

In addition, we found that higher hs-CRP levels (those $\geq 3$ mg/L) were associated with increased perfusion

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**Table 2** SPECT perfusion findings ($p$-voxel $< 0.001$, $p$-cluster $< 0.05$, $k > 80$; uncorrected)

| Cluster | Voxel | $T$-score | Talairach coordinates | Localization |
|---------|-------|-----------|-----------------------|-------------|
| 276     | 4.90  | 36 27 0   | Right inferior frontal gyrus, BA47 |
| 324     | 4.70  | 53 $-42$ 19 | Right superior temporal gyrus, BA13 |
| 3.59    | 53 $-60$ 14 | Right middle temporal gyrus, BA19 |
| 228     | 4.07  | $-24$ $-64$ 46 | Left superior parietal lobule, BA7 |
| 238     | 4.05  | 57 $-15$ 19 | Right postcentral gyrus, BA43 |
| 107     | 4.02  | $-22$ $-5$ $-23$ | Left amygdala |

The $k$-value represents the number of voxels inside a particular cluster. Talairach coordinates are expressed in mm. BA Brodmann area.
of the left amygdala. This cut-off was used as previously shown to qualify “low-grade peripheral inflammation” [7] on the complementary hypothesis of a nonlinear relationship between hs-CRP levels and brain perfusion. This dose effect may be the result of a synergistic reaction of glutamate and quinolinic acid, a product of neuroinflammation [24]. The amygdala is classically associated with anxiety, which is poorly investigated on schizophrenia scales. This may explain the absence of correlation between amygdala perfusion and psychotic symptomatology in our results. However, this result is consistent with amygdala alterations consistently found in patients with schizophrenia [25]. Changes in amygdala perfusion have been associated with increased bone marrow activity, arterial inflammation, and risk of later cardiovascular events in middle-aged men without identified disease [26]. Future studies should determine whether changes in amygdala perfusion of patients with schizophrenia may help predict their risk of cardiovascular events, as this is the second cause of death in this population after age 35 years [27].

The associations of peripheral inflammation with older age, psychiatric anxiety/mood comorbidities, obesity, and hypertension were expected and consistent with previous studies [28–30]. While peripheral inflammation has been associated with depressive symptoms in schizophrenia [31], we found no significant association between brain perfusion of the 5 areas and depressive symptomatology. This suggests that other mechanisms may mediate the association between inflammation and depression in schizophrenia, e.g., diet, physical activity, physical illness, or social isolation.

### Strengths

Although the role of peripheral inflammation has been extensively explored in schizophrenia in the last two decades, its correlation with brain perfusion is reported for the first time in this study. All patients were assessed using the same protocol to limit heterogeneity. They were recruited through a large regional geographical area to limit selection bias. Our results were adjusted for important confounding factors, including age, sex, educational level, illness duration, antidepressant use, chlorpromazine equivalent dose, tobacco smoking, and obesity.

### Limits and perspectives

Although our sample was large, enabling adjustment for multiple confounding factors, our results should be replicated in other populations, including schizophrenia patients with different sociodemographic and illness characteristics. Our sample consisted of middle-aged patients with a mean illness duration that was quite long (approximately 13 years), suggesting that the brain perfusion changes in our results are probably biomarkers of mid- to long-term inflammatory processes. Further explorations of earlier stages of the illness (such as early illness and the prodromic phase) may help understand the illness trajectory associated with inflammatory processes in schizophrenia. It is well known that long-term inflammation is associated with cognitive impairment in schizophrenia [32]; however, we did not carry out a cognitive test battery in the present study to explore the associations with cognitive impairment. Mitochondrial dysfunctions and oxidative stress could also participate in the observed brain perfusion abnormalities. Inflammatory disturbances are often associated with oxidative stress;
however, no marker of oxidative stress or mitochondrial dysfunction is available in daily practice. The question of the definition of low-grade peripheral inflammation remains open, and other proinflammatory markers, such as IL-6, TNF, and IL-1, would potentially be more prone to capture low-grade inflammation. However, these markers are not available in daily clinical practice. All the participants of the present study were treated with antipsychotics that may also modulate brain perfusion and inflammatory status [33]. We have included antipsychotic daily doses and antidepressants in the statistical model; however, we cannot exclude that they may also play a role in the observed results. Future studies should explore the role of antipsychotic drugs with more homogeneous treatments.

**Conclusion**

Peripheral inflammation is associated with changes in frontal, temporal, and parietal regions in stabilized patients with schizophrenia. The perfusion of the right inferior frontal gyrus was negatively correlated with the persistence of positive, negative, and excitement symptoms under antipsychotic treatment. As anti-inflammatory strategies have shown possible effectiveness in schizophrenia, future studies should determine whether such therapeutic intervention is mediated by brain perfusion changes and consequently whether brain SPECT could be used as a biomarker.

**Availability of data and material** The SPECT data that support the findings are available from the corresponding author upon reasonable request.

**Code availability** Not applicable.

**Declarations**

**Ethics approval** The retrospective observations required no ethical approval requirement other than informed consent.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

**Conflict of interest** The authors declare no competing interests.

**References**

1. Lally J, Ajnakina O, Di Forti M, Trotta A, Demjaha A, Kolliakou A, et al. Two distinct patterns of treatment resistance: clinical predictors of treatment resistance in first-episode schizophrenia spectrum psychoses. Psychol Med. 2016;46:3231–40.

2. Siskind D, Siskind V, Kisely S. Clozapine response rates among people with treatment-resistant schizophrenia: data from a systematic review and meta-analysis. Can J Psychiatry. 2017;62:772–7.

3. Schizophrenia Working Group of the Psychiatric Genomics Consortium. Insights from 108 schizophrenia-associated genetic loci. Nature. 2014;511:421–7.

4. van Kesteren CFMG, Gremmels H, de Witte LD, Hol EM, Van Gool AR, Falkai PG, et al. Immune involvement in the pathogenesis of schizophrenia: a meta-analysis on postmortem brain studies. Transl Psychiatry. 2017;7:e1075.

5. Sutterland AL, Fond G, Kuin A, Koeter MWJ, Lutter R, van Gool T, et al. Beyond the association. Toxoplasma gondii in schizophrenia, bipolar disorder, and addiction: systematic review and meta-analysis. Acta Psychiatr Scand. 2015;132:161–79.

6. Sukumar N, Sabesan P, Anazodo U, Palaniyappan L. Neurovascular uncoupling in schizophrenia: a bimodal meta-analysis of brain perfusion and glucose metabolism. Front Psychiatry. 2020;11:754.

7. Fond G, Lançon C, Asquier P, Boyer L. C-reactive protein as a peripheral biomarker in schizophrenia. An Updated Systematic Review. Front Psychiatry. 2018;9:392.

8. First M. Structured Clinical interview for the DSM-IV Axis I Disorders. American Psychiatric association. 1996.

9. Leucht S, Samara M, Heres S, Patel MX, Woods SW, Davis JM. Dose equivalents for second-generation antipsychotics: the minimim effective dose method. Schizophr Bull. 2014;40:314–26.

10. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13:261–76.

11. Addington D, Addington J, Matica-Tyndale E, Joyce J. Reliability and validity of a depression rating scale for schizophrenics. Schizophr Res. 1992;6:201–8.

12. First MB, et al. Structured clinical interview for DSM-IV-TR axis I disorders, research version, patient edition. (SCID-I/P). New York: Biometrics Research, New York State Psychiatric Institute. 2002.

13. Mediterranean WHORO for the E. Clinical guidelines for the management of hypertension. 2005 [cited 2021 Jul 19]. Available from: https://apps.who.int/iris/handle/10665/119738

14. World Health Organization, International Diabetes Federation. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: report of a WHO/IDF consultation. 2006 [cited 2021 Jul 19]. Available from: http://www.who.int/diabetes/publications/diagnosis_diabetes2006/en/

15. Meyer JH, Cervenka S, Kim M-J, Kreisl WC, Henter ID, Innis RB. Neuroinflammation in psychiatric disorders: PET imaging and promising new targets. Lancet Psychiatry. 2020;7:1064–74.

16. Marques TR, Ashok AH, Pilling T, Veronese M, Turkheimer FE, Dazzan P, et al. Neuroinflammation in schizophrenia: meta-analysis of in vivo microglial imaging studies. Psychol Med. 2019;49:2186–96.

17. Pollak TA, Drndarski S, Stone JM, David AS, McGuire P, Abbott NJ. The blood-brain barrier in psychosis. Lancet Psychiatry. 2018;5:79–92.

18. Fraguas D, Díaz-Caneja CM, Ayora M, Hernández-Álvarez F, Rodríguez-Quiroga A, Recio S, et al. Oxidative stress and inflammation in first-episode psychosis: a systematic review and meta-analysis. Schizophr Bull. 2019;45:742–51.

19. Corcoran CM, Carrillo F, Fernández-Slezak D, Bedi G, Klim C, Javitt DC, et al. Prediction of psychosis across protocols and risk cohorts using automated language analysis. World Psychiatry. 2018;17:67–75.
20. Sprengelmeyer R, Rausch M, Eysel UT, Przuntek H. Neural structures associated with recognition of facial expressions of basic emotions. Proc Biol Sci. 1998;265:1927–31.

21. Martin D, Croft J, Pitt A, Strelchuk D, Sullivan S, Zammit S. Systematic review and meta-analysis of the relationship between genetic risk for schizophrenia and facial emotion recognition. Schizophr Res. 2020;218:7–13.

22. Potkin SG, Kane JM, Correll CU, Lindenmayer J-P, Agid O, Marder SR, et al. The neurobiology of treatment-resistant schizophrenia: paths to antipsychotic resistance and a roadmap for future research. NPJ Schizophr. 2020;6:1.

23. Çakici N, van Beveren NJM, Judge-Hundal G, Koola MM, Sommer IEC. An update on the efficacy of anti-inflammatory agents for patients with schizophrenia: a meta-analysis. Psychol Med. 2019;49:2307–19.

24. Dantzer R, Walker AK. Is there a role for glutamate-mediated excitotoxicity in inflammation-induced depression? J Neural Transm. 2014;121:925–32.

25. Ho NF, Li Hui Chong P, Lee DR, Chew QH, Chen G, Sim K. The amygdala in schizophrenia and bipolar disorder: a synthesis of structural MRI, diffusion tensor imaging, and resting-state functional connectivity findings. Harv Rev Psychiatry. 2019;27:150–64.

26. Tawkol A, Ishai A, Takx RA, Figueroa AL, Ali A, Kaiser Y, et al. Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study. Lancet. 2017;389:834–45.

27. Samaras K, Correll CU, Curtis J. Premature mortality and schizophrenia: the need to heal right from the start. JAMA Psychiatry. 2016;73:535–6.

28. Lee EE, Hong S, Martin AS, Eyler LT, Jeste DV. Inflammation in schizophrenia: cytokine levels and their relationships to demographic and clinical variables. Am J Geriatr Psychiatry. 2017;25:50–61.

29. North HF, Bruggemann J, Cropley V, Swaminathan V, Sundram S, Lenroot R, et al. Increased peripheral inflammation in schizophrenia is associated with worse cognitive performance and related cortical thickness reductions. Eur Arch Psychiatry Clin Neurosci. 2021;271:595–607.

30. Tsai S-Y, Sajatovic M, Hsu J-L, Chung K-H, Chen P-H, Huang Y-J. Body mass index, residual psychotic symptoms, and inflammation associated with brain volume reduction in older patients with schizophrenia. Int J Geriatr Psychiatry. 2020;35:728–36.

31. Fond G, Faugere M, Richieri R, Cermolacce M, Korchia T, Micoulaud-Franchi JA, et al. Depressive symptoms and chronic peripheral inflammation are associated with impaired functional remission in schizophrenia independently of psychotic remission. J Affect Disord. 2021;280:267–71.

32. Bora E. Peripheral inflammatory and neurotrophic biomarkers of cognitive impairment in schizophrenia: a meta-analysis. Psychol Med. 2019;49:1971–9.

33. Fond G, Resseguer N, Schürhoff F, Godin O, Andrianarisoa M, Brunel L, et al. Relationships between low-grade peripheral inflammation and psychotrophic drugs in schizophrenia: results from the national FACE-SZ cohort. Eur Arch Psychiatry Clin Neurosci. 2017;268:541–53.

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