Peripheral Inflammation is Associated with brain SPECT Perfusion Changes in Schizophrenia

Guillaume FOND
AP-HM: Assistance Publique Hopitaux de Marseille
Alexandra GAROSI
AP-HM: Assistance Publique Hopitaux de Marseille
Mélanie Faugere
AP-HM: Assistance Publique Hopitaux de Marseille
Jacques-Yves Campion
AMU: Aix-Marseille Universite
Christophe LANCON
AMU: Aix-Marseille Universite
Laurent Boyer
AMU: Aix-Marseille Universite
Raphaelle RICHIERI
AMU: Aix-Marseille Universite
Eric Guedj (eric.guedj@ap-hm.fr)
CHU Timone https://orcid.org/0000-0003-1912-6132

Short Report

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Abstract

Purpose. Peripheral inflammation is frequent in schizophrenia, and plays a major role in pathophysiology, prognosis, and persistence of psychotic symptomatology under treatment.

Aim. To determine the correlation between peripheral inflammation and brain SPECT perfusion in stabilized antipsychotic-treated outpatients with schizophrenia, and to determine whether such perfusion changes are correlated to 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 3mg/L). The identified clusters were secondarily correlated with clinical symptoms.

Results. After adjustment for age, sex, educational level, illness duration, antidepressant, 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). An increased perfusion of the left amygdala was found in patients with hs-CRP ≥ 3 mg/L compared to those with hs-CRP level < 3mg/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.

Introduction

Elucidating the underlying pathophysiology of schizophrenia may aid in better selection and development of treatments. In the 1970s, monoaminergic theory was the leading nosological theory, hypothesizing that schizophrenia was due to dopamine dysfunctions. This approach has shown its limits as first-line anti-dopaminergic antipsychotics are effective in only 34% of the patients[1] and as clozapine, the most effective antipsychotic, has the lower antidopaminergic potency with an efficiency of only 60% in patients not responding to previous antipsychotic[2]. Current biological hypotheses on persistent psychotic symptoms under treatment focus on differences in the functioning of dopaminergic pathways or changes in glutamate or other neurotransmitter pathways. These views are not mutually 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 have now more than two decades of data highlighting the role of immune-inflammatory processes in schizophrenia. Among them, 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 expression of proinflammatory genes has been found on transcript and protein level in schizophrenia brain postmortem histology[4]. Schizophrenia patients have multiple sources of inflammation including Toxoplasma infection and overweight[5]. All these results have boosted the immune-inflammatory hypothesis in schizophrenia[6]. While microglial activation induced by peripheral inflammation has been well documented in the post-mortem brain studies of schizophrenia[4, 7], little is known on 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[8]. 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 is 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 persistence of psychotic symptomatology under antipsychotic treatment.

Methods

Study design

All outpatients were 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, from April 2011. The patients were referred from the whole Provence-Alpes Cotes d'Azur region (South of 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*) having had a 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.

Sociodemographic, clinical, and treatment variables

The clinical evaluation included diagnostic confirmation by two trained psychiatrists of the Schizophrenia Expert Centres using a structured clinical interview [9] 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), obesity (yes/no defined by a body mass index ≥ 30). Chlorpromazine equivalent doses (CPZ100eq) were calculated according to the minimum effective dose method [10]. Schizophrenic symptomatology was assessed using the Positive And Negative Syndrome Scale (PANSS) [11]. Current depressive symptoms were evaluated using the Calgary Depression Rating Scale for Schizophrenia (CDSS) [12].

Biological measurements

Hs-CRP was measured by routine blood samples using sensitive regular immunoassays (ELISA). The results were expressed as milligram per litre, and the detection limit was 0.08 µg/ml. A cut-off of 3 mg/L was used to classify patients has "low-grade peripheral inflammation" (≥ 3mg/L) vs. "no peripheral inflammation" (< 3mg/L), using a threshold previously reported [13].

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 ± 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 minutes in quiet surroundings with their eyes closed. The acquisition was performed 20 minutes 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 fan-beam collimator to improve sensitivity. The total scan time was 25 minutes with sixty projections per head of 25 s collected in 128 x 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 using SPM8 (Wellcome 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/rorden/mricro/mricro.html) and transferred to Statistical parametric mapping (SPM). Data were standardized with the Montreal Neurological Institute (MNI) atlas based on the ^{99m}Tc-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), and highly sensitive C reactive protein (hs-CRP) (mg/L). On the hypothesis of possible non-linear relationship between peripheral inflammation and brain perfusion, a second analysis was performed between groups according to a 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/). MNI coordinates were converted into Talairach coordinates, and brain structures were identified using the Talairach Daemon database (http://ric.uthscsa.edu/projects/talairachdaemon.html).

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 are presented in Table 1.

Table 1
Socio-demographic and clinical variables of the 137 patients with schizophrenia. CDSS Calgary Depression Rating Scale.

Socio-demographic characteristics	
Sex (female) (N, %)	39 (28.5)
Age (years), (mean, SD)	36.02 (11.82)
Academic level (education level > 12 years) (N, %)	78 (56.9)
Illness characteristics	
Illness duration (years) (mean, SD)	13.40 (10.09)
Current illness severity (PANSS total score mean, SD)	76.31 (21.07)
Current major depressive disorder (CDSS score ≥ 6) (N, %)	37 (27.0)
Treatment variables	
Antidepressant treatment (N, %)	39 (28.5)
Daily antipsychotic dose (CPZ100eq) (mean, SD)	902.61 (693.48)
Metabolic variables	
Current daily tobacco smoking (N, %)	69 (50.4)
Body Mass Index (mean, SD)	26.47 (5.57)
Obesity (Body Mass Index ≥ 30)	34 (24.8)
C-reactive protein blood level (mg/L) (mean, SD)	3.74 (5.38)
C-reactive protein blood level ≥ 3mg/L	52 (38.0)

All significant SPECT results were found using p-voxel < 0.001, uncorrected, and a cluster size of at least 80 voxels (Fig. 1). The 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. An 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 level inferior to 3. No other significant cluster was found on SPM analysis.

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

	Cluster	voxel	Talairach coordinates			Localization
	k	T-score	x	y	z	
Negative correlation between hs-CRP level and perfusion	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
Increased perfusion in patients with hs-CRP level ≥ 3mg/L	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.

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), positive (PANSS positive factor), negative (PANSS negative factor) and excitement (PANSS excitement score) symptoms.

Table 3
Correlations of brain perfusion with psychotic and depressive symptomatology and highly sensitive C-reactive-protein (hs-CRP) blood levels.

	Right Inferior Frontal Gyrus BA47		**Right middle/superior temporal gyrus BA13 & BA19**		**Left superior parietal lobe BA7**		**Right postcentral and transverse temporal gyrus BA43**		**Left amygdala**	
	Pearson	**(p)**	**Pearson**	**(p)**	**Pearson**	**(p)**	**Pearson**	**(p)**	**Pearson**	**(p)**
Illness severity (total PANSS score)	**-0.231**	**0.007**	0.022	0.800	0.012	0.890	-0.075	0.387	0.019	0.823
PANSS Positive factor	**-0.209**	**0.014**	0.134	0.119	-0.022	0.799	0.021	0.810	0.055	0.520
PANSS Negative factor	**-0.172**	**0.044**	0.002	0.982	0.017	0.842	-0.163	0.057	0.015	0.866
PANSS Excited factor	**-0.180**	**0.036**	-0.083	0.334	0.035	0.688	0.016	0.848	-0.068	0.427
PANSS Cognitive factor	-0.132	0.125	0.053	0.536	0.030	0.730	0.001	0.988	-0.078	0.366
PANSS Depressive factor	-0.080	0.351	-0.075	0.386	0.002	0.979	-0.037	0.667	0.101	0.241
CDSS depressive score	0.030	0.729	0.035	0.685	0.022	0.796	-0.032	0.709	0.136	0.114
Hs-CRP	**-0.371**	**< 0.001**	**-0.215**	**0.011**	**-0.260**	**0.002**	**-0.293**	**0.001**	**0.221**	**0.009**

PANSS Positive and Negative Syndrome Scale for Schizophrenia. CDSS Calgary Depression Rating Scale. Hs-CRP: highly sensitive C-Reactive Protein. Significant correlations are in bold.

Discussion

In stabilized outpatients with schizophrenia, peripheral inflammation was associated with brain perfusion changes of 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 fronto-temporal and bilateral parietal areas. Brain perfusion is a biomarker of global brain functioning through global synaptic activity. Peripheral inflammation induces microglial activation in the brain (the so-called neuroinflammation) [14], which has been extensively explored in schizophrenia in the last decade. In schizophrenia patients, peripheral inflammation can alter the blood-brain barrier, increasing its permeability and the impact on brain perfusion, supporting the “mild encephalitis” hypothesis of schizophrenia [15]. Neuroinflammation has been suggested to accelerate brain

neuroprogression and ageing (the so-called “inflammaging” process) [16]. This neuro-progression may induce an increase in the microglia density reported in post-mortem schizophrenia brain studies [17]. Based on our results, one could hypothesize that inflammation-associated brain perfusion changes may be the long-term consequence of the ongoing “brainflammaging” process. 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 the participants were probably exposed to chronic low-grade inflammation for several years.

The right inferior frontal gyrus was the only area which perfusion was correlated to both peripheral inflammation and persistence of positive symptoms under treatment. The frontal cortex is the richest brain area in dopaminergic neurons and is responsible for language processing and speech production, which has been recently demonstrated as a reliable marker 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 to negative emotions, has been found as a useful predictor of schizophrenia risk[21]. This lobe is connected to prefrontal cortex that 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 by antipsychotics, which suggests that frontal perfusion changes correlated to inflammation were also correlated to persistence of psychotic symptoms under treatment. The association of inflammation with 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 the higher hs-CRP levels (those $\geq$ 3mg/L) were associated with increased perfusion of the left amygdala. This cut-off was used as previously shown to qualify “low-grade peripheral inflammation” [13], on the complementary hypothesis of non-linear 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]. Amygdala is classically associated with anxiety, which is poorly investigated in the 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 the perfusion of amygdala 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 perfusion changes in amygdala perfusion of patients with schizophrenia may help predicting their risk of cardiovascular events, as this is the second cause of death in this population after 35 years[27].

While peripheral inflammation has been associated with depressive symptoms in schizophrenia[28], we found no significant association between brain perfusion of our 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 aera to limit the selection bias. Our results were adjusted for important confounding factors including age, sex, educational level, illness duration, antidepressant, 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 the 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 understanding the illness trajectory associated with inflammatory processes in schizophrenia. It is well known that long-term inflammation is associated with cognitive impairment in schizophrenia[29], 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 to the observed brain perfusion abnormalities. Inflammatory disturbances are often associated with oxidative stress, however no marker of oxidative stress and mitochondrial dysfunction was available in daily practice. The question of the definition of low-grade peripheral inflammation remains open, other pro-inflammatory markers like IL-6, TNF and IL-1 would be potentially more prone to capture low-grade inflammation. However, these markers are not available in daily clinical practice.

Conclusion

Peripheral inflammation is associated with changes of 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 biomarker.

Declarations

Funding

None

Conflicts of interest/Competing interests

The authors declare that they have no conflicts of interest

Ethics approval

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

Consent to participate

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

Consent for publication

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

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

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Figures

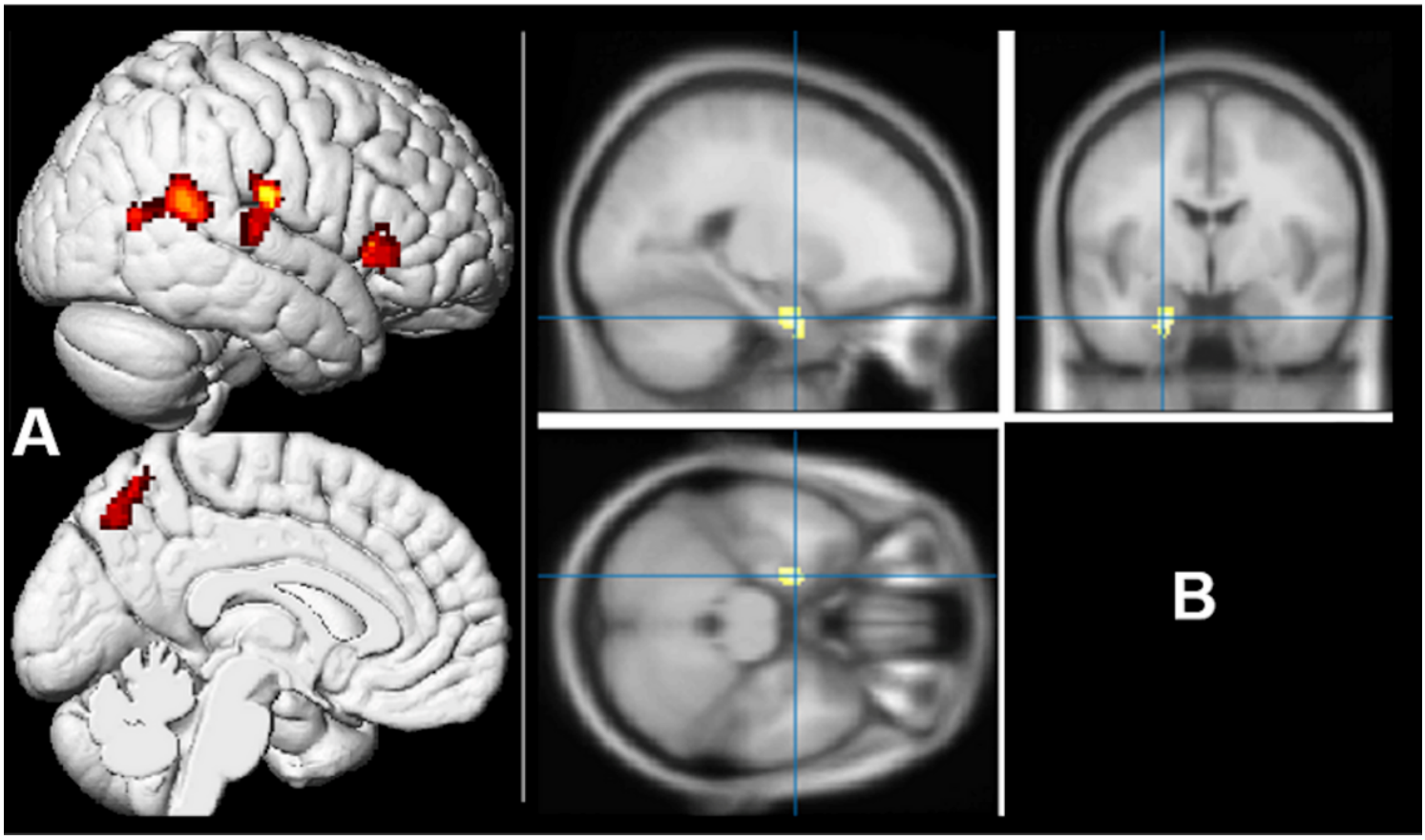

Figure 1

SPECT perfusion findings (p-voxel < 0.001, p-cluster < 0.05, k > 80; uncorrected). Hs-CRP: highly sensitive C-Reactive Protein. A. Negative correlation between hs-CRP level and perfusion: Right Inferior Frontal Gyrus BA47, Right middle/superior temporal gyrus BA13 & BA19, Left superior parietal lobe BA7, Right postcentral and transverse temporal gyrus BA43 B. Increased perfusion in patients with hs-CRP level ≥ 3mg/L: Left amygdala