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Association between baseline pro-inflammatory cytokines and brain activation during social exclusion in patients with vulnerability to suicide and depressive disorder

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ABSTRACT

Background: Neuroimaging studies suggest that social distress and suicidal vulnerability share common cerebral bases. Moreover, increased peripheral inflammatory activity is involved in both social distress and suicidal behavior.

Objective: To evaluate, in suicidal and non-suicidal individuals, the association between the activation of specific cerebral regions (anterior cingulate, insula and orbitofrontal cortex) during experimental social exclusion and the baseline blood levels of the pro-inflammatory cytokines interleukin-6 (IL-6), interleukin-1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α) and of the anti-inflammatory cytokine interleukin-2 (IL-2).

Methods: In total, 101 euthymic women were recruited: 42 suicide attempters (SA), 40 affective controls (AC), and 19 healthy controls (HC). During functional MRI (fMRI), they performed the Cyberball game, a validated social exclusion task. Blood levels of IL-1β, IL-6, TNF-α and IL-2 were measured prior to fMRI. The activation of insula, orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) during the explicit social exclusion (ESE) vs social inclusion (INC) conditions of the Cyberball game was analyzed in function of the baseline cytokine levels.

Results: IL-1β was negatively associated with right OFC activation ($p = 0.01$) in ESE vs. INC, whereas IL-2 was positively associated with activation of the right ACC ($p = 0.02$), insula ($p = 0.002$) and OFC ($p = 0.004$) in ESE vs. INC. These associations remained significant after controlling for group, indicating that they were independent of the suicidal status.

Conclusion: Baseline IL-1β and IL-2 blood levels are differentially associated with cerebral activation involved in the perception of social exclusion, independently of suicidal behavior. Our results may help to better understand the role of basal inflammation in social distress and its link with mood disorder pathophysiology.

1. Introduction

Inflammation and hypersensitivity to social rejection are both putative pathophysiological mechanisms in psychiatric illness. Growing evidences suggest the involvement of inflammation in mood disorders, and suicidal behaviors/vulnerability (Courtet et al., 2016). Two meta-analyses showed that basal blood inflammatory markers are increased during depressive episodes. Specifically, Dowlati et al. found that TNF-

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α and IL-6 are higher in depressed patients compared with healthy individuals (n = 24 studies included) (Dowlati et al., 2010). Howren et al. (2009) reported a positive association between blood levels of C-reactive protein (CRP), IL-1β and IL-6 and depression in clinical and community populations, even after adjustment for body mass index (Howren et al., 2009). Moreover, patients with a personal history of suicide attempt have higher baseline blood levels of inflammatory cytokines and CRP than depressed non-attempters, independently of the time interval between suicidal behavior and cytokine quantification (Courtet et al., 2015). CRP level has been positively associated with the number of past suicide attempts. Two meta-analyses reported that the blood levels of the pro-inflammatory cytokines IL-1β and IL-6 are significantly increased and those of the anti-inflammatory IL-2 are decreased in suicidal patients compared with non-suicidal patients and healthy controls (Black and Miller, 2015; Ducasse et al., 2015).

Most suicidal acts are preceded by environmental stress, particularly interpersonal stressors (Foster, 2011). Such stressful conditions have been associated with increased levels of the pro-inflammatory cytokines IL-1β, IL-6 and TNF-α (Eisenberger et al., 2017; Moieni and Eisenberger, 2018; Haapakoski et al., 2015; Stieglitz et al., 2015; Gimeno et al., 2009; Wium-Andersen et al., 2013). Several studies have found that negative social events in daily life, particularly interpersonal loss, social rejection and negative social feedback, increase inflammatory activity (Schultze-Florey et al., 2012), including the levels of CRP, IL-6, and TNF-α, in healthy subjects (Chiang et al., 2012; Marin et al., 2009; Muscatell et al., 2016a). High basal CRP level increases depression symptoms in conditions of psychosocial stress, especially among women (Das, 2016). Moreover, inflammatory processes and higher blood levels of TNF-α and IL-6 have been linked to greater feelings of social disconnection in women (Moieni and Eisenberger, 2018).

Functional imaging studies have shown that social exclusion activates insula, orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) (Cacioppo et al., 2013), which are considered to be key regions in suicidal vulnerability (Holmes et al., 2018; Chase et al., 2017; Olié et al., 2015, 2017). Interestingly, the inflammatory and neural responses to social rejection are associated in healthy individuals. Indeed, TNF-α blood level increases in healthy individuals after experimental social stress, based on the Trial Social Stress Task. This increase is associated with greater activity in the dorsal ACC and anterior insula during experimental social exclusion (Slavich et al., 2010); Eisenberger et al., 2017). According to Eisenberger et al. (2017), inflammation could strengthen the neural sensitivity to social exclusion (Eisenberger et al., 2017). However, the association between inflammation markers and neural response to social rejection has never been studied in patients with history of mood disorder and suicidal acts.

Therefore, the aim of this study was to evaluate the association between baseline cytokine levels and brain activation in response to experimental social exclusion in women with history of major depressive episode, with and without suicide attempts. We hypothesized i) a positive association between changes in the activity of cerebral regions (ACC, insula and OFC) during experimental social exclusion (versus inclusion) and baseline blood levels of pro-inflammatory cytokines (IL-6, IL-1β, TNF-α); ii) a negative association between changes in the activity of cerebral regions (ACC, insula and OFC) during experimental social exclusion (versus inclusion) and baseline blood levels of an anti-inflammatory cytokine (IL-2); iii) an effect of history of suicidal acts on this relationship.

To test our hypothesis, we included the sample of euthymic female individuals primarily recruited for the study conducted by Olié et al. (2017) and addressed this additional research question.

2. Materials and methods

2.1. Participants

The study sample included three groups of euthymic women: 1) suicide attempters (SA; n = 42): individuals with a history of major depressive episode and at least one suicide attempt during their lifetime. Suicide attempt was defined as any act carried out with some intent to die; 2) affective controls (AC; n = 40): women with history of major depressive episode without suicidal acts; 3) healthy controls (HC; n = 19): individuals with no history of any major DSM-IV axis I disorder and of suicidal behavior/acts. Participants were included in a previous functional magnetic resonance imaging (fMRI) study on brain processing of social rejection in SA (Olié et al., 2017). The selection process was precisely described in this article.

HC were recruited through advertisement and from a list of volunteers from the Montpellier Academic Hospital database. Patients (SA and AC) were recruited among the outpatients of the Department of Emergency Psychiatry and Post-Acute Care, Montpellier Academic Hospital. All participants were Caucasian, right-handed (assessed using the Edinburgh scale (Oldfield, 1971)). Only women were included in this study to avoid any sex effect and to ensure a sufficient statistical power.

Patients needed to be euthymic at the time of inclusion for fMRI (Hamilton Depression Rating Scale score < 7 and Young Mania Rating Scale score < 7). Exclusion criteria were: lifetime history of severe head trauma, central nervous system disorder, chronic instable organic disorder, and history of alcohol or drug abuse or dependence within the 12 last months.

The local Ethics Committee (CPP Sud Mediterranee IV, CHU Montpellier) approved the study protocol. All participants provided a written informed consent before entering the study.

2.2. Clinical assessment

Participants underwent a standardized interview led by a psychiatrist to determine the depression score and to assess the absence of manic or psychotic symptoms, according to the DSM-IV criteria using the Mini-International Neuropsychiatric Interview, version 5.0.0. During the standardized interview, a psychiatrist administered the French version of the National Adult Reading Test (NART) (Mackinnon et al., 1999) to provide an estimate of the verbal IQ, the Beck Depression Inventory (BDI) for a subjective measure of the depressive state, and the Hamilton depression scale (HAMD) to score depression (Hamilton, 1960). History of childhood maltreatment was assessed with the Childhood Trauma Questionnaire (CTQ) (Scher et al., 2004) and the level of anxiety with the State-Trait Anxiety Inventory (STAI) scale (Julian, 2011). All psychotropic treatments during the last 24 h before MRI were recorded. The severity of the most severe suicide attempt was evaluated with the Risk Rescue Rating Scale (RRRS) (Weisman and Worden, 1972) and the Suicide Intent Scale (SIS). The RRRS measures the medical danger of the attempt (risk factors) and the probability of being rescued (rescue factors). The SIS is a 19-item ordinal scale to evaluate the intent to die (Beck et al., 1979).

2.3. Cyberball game

The Cyberball game, a virtual ball-tossing game (Williams et al., 2000), is a validated paradigm to study social exclusion and has been widely used in fMRI studies. Participants were instructed that they would play with two other players during fMRI. In reality, participants were playing with a preset computer program and were given a cover story to ensure that they believed the other players were real. The Cyberball game comprises three successive conditions. In the first condition (Implicit Social Exclusion, ISE), the participant watches the other “players” play the Cyberball game. Participants were told that,

because of technical difficulties, the link to the other two scanners was not yet functional and thus, at first, they would only watch, but not play with the other two players. This story was intended to allow participants to view a scene visually identical to the exclusion condition but without experiencing exclusion. In the second condition (inclusion, INC), participants played with the other two players and received the ball as many times as the two virtual players. In the final condition (Explicit Social Exclusion, ESE), participants were progressively excluded by the two other players who did not throw the ball to the participant. Each session consisted of 60 ball tosses per condition (i.e., 180 ball tosses in total). The computer players waited 0.5–3.0 seconds before making a throw to heighten the sense that the participant was actually playing with other individuals. The ESE condition included eight ball tosses to the participant during the initial transition phase towards total exclusion.

2.4. Image acquisition

For fMRI, a 1.5 T whole-body MRI system (MAGNETON AVANTO, Siemens, Erlangen, Germany) equipped with a standard 12-channel receive-only head coil was used, at the neuroradiology department - I2FH (Montpellier Academic Hospital). Sixty volumes of BOLD echo planar images (EPI) were obtained during the Cyberball Game. The features of gradient-Echo EPI images were as follows: TR = 2 s, TE = 40 ms, FOV = 220 mm, 25 axial slices (5 mm slice thickness), slice gap = 0.5 mm, voxel size = 3.43 × 3.43 × 5 mm, flip angle 90°. Slices covered a region extending from the vertex to the lower parts of the cerebellum.

A 3D magnetization-prepared, rapid acquisition gradient echo (MP-RAGE) sequence was also obtained for each participant with the following parameters: TR = 2100 ms, TE = 4.1 ms, IR = 1100 ms, 15° flip angle, PAT = 2, aligned with the corpus callosum, voxel-size 0.98 × 0.98 × 1 mm, 160 transversal slices.

2.5. fMRI data analysis

Data were analyzed using SPM12 (Wellcome Department of Imaging Neuroscience, London, UK) implemented in Matlab 2015 (Mathworks, Inc., Natick, MA) using a block-designed model. The five first volumes of each fMRI run were discarded due to the time needed to launch of the Cyberball game synchronized with fMRI acquisition. The remaining 55 volumes were retained for functional analysis. EG-EPI data were re-oriented to the anterior commissure, slice-time corrected, realigned to the first volume, co-registered, normalized to the T1 template (provided by the Montreal Neurological Institute), and smoothed with an 8-mm FWHM Gaussian filter. Contrast images were estimated for the ESE and INC conditions for every participant using a first-level general linear model. Realignment parameters were added in the regressor to correct for head movements, and a 128-second high-pass filter was used to remove non-physiological slow signal shifts. Regions of interest (ROIs) were selected on the basis of *a priori* hypotheses concerning the specific anatomical brain regions that could be associated with inflammatory responses to acute social distress. Anatomical ROIs were created for brain regions known to be involved in processing rejection-related distress and suicidal vulnerability (ACC, insula and OFC). The ROIs were constructed in Pickatlas (Maldjian et al., 2003) using templates from the atlas by Tzourio-Mazoyer et al. (2002). The MarsBaR toolbox (http://marsbar.sourceforge.net) was then used to extract the mean parameter estimates (modeling the amplitude of the BOLD response during ESE vs. INC), averaged across all voxels in the ROI.

2.6. Baseline dosage of the cytokine blood level

Blood samples were collected in 5 ml dry tubes (BD Vacutainer, Franklin Lakes, NJ), centrifuged, and serum was stored at −80 °C. IL-1β, IL-2, IL6 and TNF-α were measured by using high sensitivity sandwich enzyme-linked immunoassay assay (ELISA) kits (Quantikine HS ELISA, R&D Systems n.d., and IL-2 Human ELISA Kit, High Sensitivity, Thermo Fisher Scientific, n.d.). Reagents and calibrators were used according to the manufacturers' guidelines with a minimum detection threshold of 0.023 pg/ml for IL-1β, 0.94 pg/ml for IL-2, 0.016 pg/ml for IL-6, and 0.038 pg/ml for TNF-α.

2.7. Statistical analyses

Data were described using percentages for categorical variables, and mean and standard deviation (SD) for quantitative variables. The three groups (SA, AC and HC) were compared using the Student's *t*-test or analysis of variance (ANOVA) for continuous independent variables, and the Chi-square or Fisher's tests for categorical variables. When comparisons in the three groups were statistically significant, two-by-two comparisons were carried out using the Bonferroni correction for multiple comparisons. As three hypotheses were tested for each variable, the new critical p-value was $\alpha/3 = 0.017$.

The relationships between cytokine values and cerebral activation data in the three groups were analyzed using ANOVA for cytokine values taken as continuous variables and the Chi-square tests for cytokine values taken as categorical variables. As the distribution of the blood concentrations of each cytokine type was skewed, data were first log-transformed, if the concentration of that cytokine had a log-normal distribution, and also categorized into tertiles. For IL-2 the undetectable rate was higher than 50%; therefore, IL-2 levels were categorized in two groups (detectable and undetectable).

To identify potential confounders, the association between cerebral activation and group (SA, AC, HC), age, treatment, mood disorder and childhood maltreatment was tested using the Pearson's correlation coefficient for continuous independent variables and the Student's *t*-test or ANOVA for categorical independent variables.

The relationship between cerebral activation and cytokine values was examined using partial correlations for cytokines taken as continuous variables and analysis of covariance for cytokines taken as categorical variables, adjusted for group, physical neglect during childhood, and antidepressant intake. The normality of the residuals was verified.

Significance was set at $p < 0.05$. Analyses were performed using SPSS Statistics 21 (SPSS, Inc., Chicago) and SAS (version 9.4; SAS Inc, Cary, North Carolina).

3. Results

3.1. Clinical, sociodemographic and biological data in the three groups

Age, educational level, and NART score were comparable in the three groups (SA, AC and HC) (Table 1). As expected, HC had lower levels of subclinical self-reported depressive symptoms (BDI score) and anxiety (STAI scores) compared with the two patient groups. The number of past major depressive episodes and the age at first major depressive episode were comparable between SA and AC. Similarly, mood characteristics (i.e., BDI score, HAMD score, number of manic episodes and major depressive episodes) and anxiety (STAI scores) were similar in the two patient groups. Conversely, emotional neglect was more frequently reported in the SA than AC group, and emotional abuse in the AC than HC group. Diagnosis of bipolar disorder and intake of antipsychotics and benzodiazepines were more frequent in the SA than AC group (Table 1). In the SA group, the mean number of suicide attempts was 3.23 (SD = 2.64). The mean interval between the last suicide attempt and the inclusion date was 4.48 (SD = 5.08) years. The age at first suicide attempt was 25.50 years (SD = 8.23). For the most severe suicide attempt (RRRS), the mean risk score was 8.82 (SD = 2.96) and the mean rescue factor was 12.06 (SD = 1.39) (rescue factor). The total SIS score was 14.53 (SD = 4.45). Finally, baseline IL-1β, IL-2, IL-6 and TNF-α blood levels, assessed as continuous or

Table 1
Sociodemographic, clinical characteristics and childhood traumatisms in healthy controls (HC), affective controls (AC) and suicide attempters (SA).

	HC N = 19		AC N = 40		SA N = 42			
Variable	Mean (± SD)		Mean (± SD)		Mean (± SD)		p	Post-Hoc comparisons
Socio-demographic and clinical characteristics								
Level of education (in years)	14.05 (± 2.01)		14.60 (± 1.97)		13.45 (± 4.01)		0.23	
Age (in years)	39.14 (± 7.95)		35.48 (± 7.69)		38.82 (± 9.67)		0.15	
Social distress score (NTS)	57.00 (± 12.21)		66.73 (± 15.43)		64.90 (± 13.52)		0.05	HC < AC
Age of first suicide attempt (in years)					25.50 (± 8.23)		–	
Number of suicide attempts					3.23 (± 2.64)		–	
Age at first major depressive disorder (in years)			23.68 (± 7.40)		24.05 (± 8.19)		0.83	
Number of major depressive disorders			0.48 (± 1.38)		1.17 (± 1.97)		0.07	
Number of manic episodes			0.45 (± 1.22)		0.67 (± 1.54)		0.16	
BDI score	0.42 (± 0.96)		4.40 (± 4.98)		4.19 (± 4.12)		0.002	HC < AC, SA
HAMD score	2.63 (± 2.69)		3.35 (± 4.42)		3.71 (± 3.64)		0.59	
STAI state score	27.37 (± 5.92)		37.25 (± 11.91)		35.55 (± 10.03)		0.001	HC < AC, SA
STAI trait score	30.47 (± 5.70)		44.85 (± 11.11)		46.55 (± 10.77)		< 0.0001	HC < AC, SA
NART score	20.84 (± 6.27)		21.83 (± 2.94)		22.38 (± 3.76)		0.66	
	n	%	n	%	n	%		
Bipolar disorder			14	35.00	25	59.52	0.03	
Antidepressant intake			10	25.00	7	16.67	0.42	
Anticonvulsant intake			3	7.50	6	14.29	0.48	
Antipsychotic intake			1	2.50	8	19.05	0.03	
Benzodiazepine intake			2	5.00	9	21.43	0.03	
Lithium intake			3	7.50	4	9.52	0.99	
Childhood trauma questionnaire								
Score physical abuse								
None/ low	18	94.74	35	87.50	39	92.86	NA	
Moderate/ severe	1	5.26	5	12.50	3	7.14		
Score emotional neglect								
None/ low	17	89.47	28	70.00	23	54.76	0.03	AC < SA
Moderate/ severe	2	10.53	12	30.00	19	45.24		
Score physical neglect								
None/ low	18	94.74	34	85.00	35	83.33	0.47	
Moderate/ severe	1	5.26	6	15.00	7	16.67		
Score sexual abuse								
None/ low	18	94.74	33	82.50	34	80.95	0.37	
Moderate/ severe	1	5.26	7	17.50	8	19.05		
Score emotional abuse								
None/ low	18	94.74	26	65.00	25	59.52	0.02	HC < AC
Moderate/ severe	1	5.26	14	35.00	17	40.48		

NA: Test not applicable.

Table 2
Serum cytokine levels in healthy controls (HC), affective controls (AC) and suicide attempters (SA).

	HC N = 19		AC N = 40		SA N = 42		
Variables	n	%	n	%	n	%	p-value
IL-1β (pg/ml)[(1)]	0.37 (0.06)		0.46 (0.05)		0.42 (0.04)		0.46
IL-1β (pg/ml)							
< 0.31	9	47.37	12	30.00	12	28.57	0.50
[0.31–0.51]	6	31.58	12	30.00	16	38.10	
> 0.51	4	21.05	16	40.00	14	33.33	
IL-6 (pg/ml) [(1)]	0.59 (0.10)		0.73 (0.07)		0.74 (0.09)		0.50
IL-6 (pg/ml)							
< 0.51	8	42.11	9	22.50	16	38.10	0.06
[0.51–0.96]	7	36.84	19	47.50	8	19.05	
> 0.96	4	21.05	12	30.00	18	42.86	
TNF-α (pg/ml) [(1)]	0.56 (0.07)		0.83 (0.09)		0.77 (0.08)		0.08
TNF-α (pg/ml)							
< 0.50	10	52.63	10	25.00	15	35.71	0.29
[0.50–1.12]	5	26.32	16	40.00	12	28.57	
> 1.12	4	21.05	14	35.00	15	35.71	
IL-2 (pg/ml)							
< 0.94	13	68.42	28	70.00	23	54.76	0.32
≥0.94	6	31.58	12	30.00	19	45.24	

[(1)] geometric mean (SD).

categorical variables, were comparable in the three groups (Table 2). No significant association was found between current treatments and cytokine levels, thus excluding any effect of psychotropic drug intake on the inflammatory parameters.

3.2. Associations between cerebral activation during the Cyberball game explicit social exclusion and clinical, sociodemographic and biological variables (Supplementary Table 1)

No significant association was found between the mean cerebral activation during the Cyberball game (ESE vs. INC) and group (SA, AC, HC), age, and type of mood disorder (unipolar or bipolar disorder). Similarly, use of antipsychotics, anticonvulsants, benzodiazepines or lithium was not associated with cerebral activation. Only antidepressant intake was negatively associated with left insula activation (ESE vs. INC). Moreover, physical neglect was negatively associated with right ACC activation (ESE vs. INC), but not the other CTQ subscores (Supplementary Table 1).

3.3. Association between peripheral inflammatory markers and cerebral activation during Cyberball game explicit social exclusion (Figs. 1 and 2, Supplementary Table 2a and b)

In unadjusted associations, the plasma level of IL-1β was negatively associated with activation of right OFC during ESE vs. INC ($p = 0.01$). The negative association between IL-1β and right ACC activation (ESE

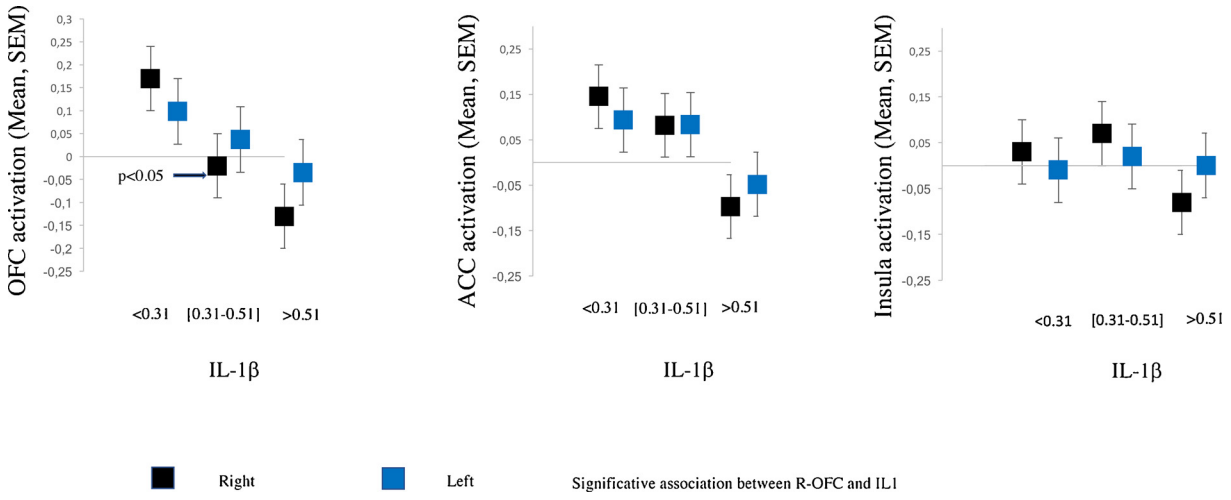

Fig. 1. Crude association between OFC, ACC and Insula activation and basal level of IL-1β.

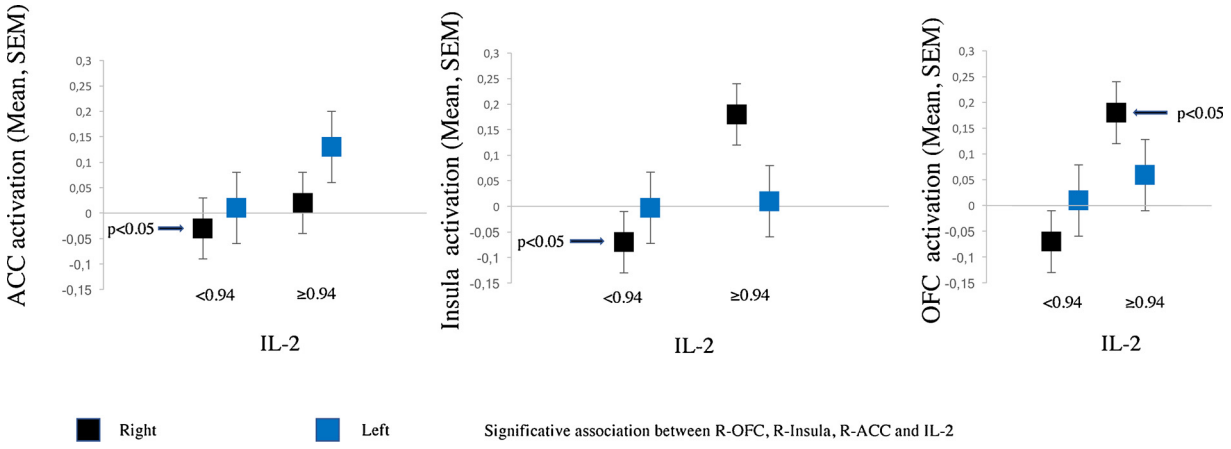

Fig. 2. Crude association between ACC, Insula and OFC activation and basal level of IL-2.

vs INC) was almost significant (p = 0.05) when IL-1β was evaluated as categorical variable, and became significant when IL-1β was taken as continuous variable (p = 0.02). Detectable IL-2 level was positively associated with activation (ESE vs INC) of the right ACC, insula and OFC (p = 0.02, p = 0.002, p = 0.004, respectively) (Supplementary Table 2a). These associations remained significant after adjustment for group (Supplementary Table 2b). The negative relationship between IL-1β (as categorical variable) and right OFC activation (ESE vs. INC) remained significant after adjustment for physical childhood neglect (p = 0.01), as well as the positive association between IL-2 and ACC, insula and OFC activation (ESE vs. INC) (p = 0.03, p = 0.002, p = 0.007, respectively, data not shown). Similarly, the associations between IL-1β (as categorical variable) and right OFC activation (p = 0.009) and between IL-2 and ACC, insula and OFC activation (p = 0.02, p = 0.001, p = 0.004, respectively) remained significant also after adjustment for antidepressant intake (data not shown). No significant association was found between IL-6 and TNF-α plasma levels and cerebral activation (ESE vs INC) in unadjusted and adjusted models.

4. Discussion

To our knowledge, this is the first study to explore the link between basal peripheral inflammatory markers and neuroanatomical features of social rejection in euthymic patients with mood disorders, by taking into account their history of suicide attempt.

Our results show that basal inflammation leads to a decrease of the neural response to a social exclusion game in a clinical population, but without any influence of the suicidal status. Previous studies conducted in suicidal patients reported altered levels of peripheral cytokines (Ducasse et al., 2015) or modified cerebral activation in response to experimental social distress (Olié et al., 2017). However, they did not assess plasma cytokine level and cerebral activation together. The patients (SA and AC groups) in our study were euthymic at the time of the evaluation and had a personal history of major depressive episodes with or without suicide attempt. Our results suggest that the relationship between basal inflammation and brain activation may not be a trait marker of suicidal vulnerability. In the meta-analysis conducted by Ducasse et al. (2015), the involvement of IL-2 in suicidal behavior reflected a psychiatric "state", because biological samples were collected within one month following the suicide attempt (Ducasse et al., 2015). Additional studies should explore the influence of the pathological state (i.e., recent suicide attempt) to discriminate between suicidal "trait" and "state" and inflammation markers.

The absence of interactions between suicidal status and the immune-brain relationships in our study could also be explained by a weakness of the Cyberball game in reflecting highly salient social stress. However, Eisenberger et al., (2007) reported a relationship between neural correlates of experimental social exclusion and feelings of social distress in the real word. Specifically, daily feelings of social distress were higher in individuals with increased activation in brain regions involved in pain and emotion processing (dorsal ACC, amygdala, periaqueductal gray) during scan-based social exclusion (Eisenberger et al., 2007). Moreover, this strategy has been already used to evaluate neural

correlates of social rejection in psychiatric populations, including patients with mood disorders. For instance, compared with controls, patients with current unipolar depression showed greater amygdala, insula, and ventrolateral prefrontal cortex activation in response to the social exclusion condition during the Cyberball game (Kumar et al., 2018). In our study, we did not find any effect of mood disorders on the relationship between inflammation markers and brain activation during experimental social exclusion. Differently from the study by Kumar et al. (2018), we included euthymic individuals with a diagnosis of unipolar or bipolar disorder, and we focused on trait markers.

During ESE, activation of different brain regions was associated with IL-1β and IL-2 plasma levels. The activation of right OFC was negatively associated with the plasma level IL-1β, a pro-inflammatory cytokine (Dinarello, 2011), and positively associated with the concentration of IL-2, an anti-inflammatory cytokine (Banchereau et al., 2012). This suggests that activation of the right OFC decreases during social exclusion compared with inclusion when the basal inflammation level increases. Some mechanistic hypotheses were proposed to explain the interaction between blood cytokines and brain function. In humans, peripheral cytokines can enter the central nervous system by binding to transport molecules of the blood brain barrier and alter the functioning of specific brain regions (Miller and Raison, 2015). Peripheral IL-1β affects brain function by influencing various metabolic pathways, such as serotonin reuptake and excretion (Zhu et al., 2010), BDNF down-regulation (Goshen et al., 2008), NMDA receptor activation (Tilleux and Hermans, 2007), or kynurenine pathway activation (Steiner et al., 2011). The link between IL-1β and OFC was specifically assessed in animal models. In rats, IL-1β may directly exert a complex modulation of neuron firing within OFC (Lukáts et al., 2005). However, the biological mechanisms underlying IL-1β negative association with OFC activation remain unclear in humans.

Our study also showed that IL-2 plasma level is positively associated with activation of the right insula, right ACC and right OFC in ESE vs INC. Animal studies evaluated the pathways that might link blood IL-2 and prefrontal cortex function. In rats, peripheral IL-2 challenge enhances the release of metabolites (N-acetylaspartate and myoinositol), and triggers microglial activation in the prefrontal region (Schneider et al., 2012). In mice, IL-2 controls acetylcholine release from the septal region that connects with the cingulate cortex (Meola et al., 2013). Additional studies are needed to better understand the potential pathways underlying the link between IL-2 and the central nervous system in humans. Finally, in agreement with the study by Slavich et al. (2010), we did not find any association between IL-6 and TNF-α plasma levels and cerebral activity during experimental social exclusion (Slavich et al., 2010).

Our results suggest a role of the baseline immune status in processing social stressors in prefrontal regions (i.e., right ACC, insula and OFC), adding to previous results showing the coupling between dynamic variation of blood cytokines during experimental social stressor or experimental inflammatory challenge and activation of ACC and amygdala (Muscatell et al., 2016a,b; Inagaki et al., 2012; Muscatell et al., 2016b). Growing evidence shows that psychosocial stress induces the production of pro-inflammatory cytokines (such as IL-1β) in peripheral blood myeloid cells, a process partly mediated by stress catecholamines (Miller and Raison, 2015). In turn, IL-1β can enter the brain through the humoral route and alter brain functioning. Hence, the innate immune system is a key factor that contributes to the processing of social threats in association with other self-protective mechanisms. As proposed by Eisenberger et al. (2017), inflammation organizes the behavioral and neural response to social stress in an adaptive way. In healthy individuals, this leads to a state of heightened inflammation to avoid social threats or to increase sensitivity to social exclusion (Eisenberger et al., 2017). Inflammatory status and brain activation dynamically interact. Our results provide a complementary understanding of the link between basal cytokine levels and brain activation in euthymic patients with affective disorders/suicidal vulnerability exposed to ESE. Peripheral cytokines and brain activity may be considered as two parts of a social warning system (Slavich and Irwin, 2014) and they might interact in a balanced relationship or "homeostasis". In response to social threats, basal level of peripheral cytokines and activation of neural structures may compensate one another, tending towards a state of equilibrium. Therefore, one could hypothesize that basal inflammation might prevent excessive neural activation in response to the perception of social exclusion and consequently the emergence of a non-adapted depressive reaction. The basal inflammation modulation of the neural response to social exclusion could be independent of psychiatric conditions, particularly suicidal vulnerability.

Our study has some limitations. First, we recruited medicated patients, but this reflects real-life conditions. However, our main results remained unchanged after adjustment for treatment intake. Moreover, psychotropic treatment did not affect the cytokine plasma level in our clinical sample. Second, only women were included. This allowed excluding a sex effect, but limits the generalization of our results. Indeed, women are more sensitive to social exclusion (Eisenberger et al., 2009; Weik et al., 2010). Third, we did not control the results for smoking status and body mass index. Finally, the HC group was smaller than the AC and SA groups (19 subjects vs 40 and 42). However, our main objective was to study the effect of history of suicidal behavior in patients with mood disorders (SA vs AC) on the relationship between inflammatory cytokines and brain activation during ESE. The HC group was included only to determine whether this relationship was influenced by a personal history of mood disorder.

5. Conclusion

This study evaluated the association between baseline inflammatory status and cerebral activation during ESE in patients with mood disorders with and without history of suicide behaviors. Our results show that this association is not a trait marker linked with suicidal vulnerability. We suggest that basal inflammation prevents the hyperactivation of brain regions sensitive to social rejection in situations of social exclusion and helps to maintain the homeostasis of the social warning system in conditions of mood stability. Additional studies are needed to explore the role of the pathological "state" (i.e., current mental disorders) and its influence on the brain immune relationships in conditions of social stress.

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Conflicts of interest

Authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2018.09.041.

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