Association of Suicidal Status, Inflammation Markers, and Resting-State Functional Activity and Connectivity in Patients With Major Depressive Disorder

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Abstract

Background: This study aimed to identify (1) neural markers of suicide attempt using resting-state functional magnetic resonance imaging (rs-fMRI) and (2) associations between rs-fMRI metrics and resting-state functional connectivity (rs-FC), suicidal phenotype, and peripheral blood inflammation markers.

Methods: Inflammation markers (C-reactive protein [CRP], interleukin [IL]-1β, IL-2, and IL-6, and tumor necrosis factor-α TNF-α) and rs-fMRI metrics were measured in 20 healthy controls (HCs) and 42 patients with unipolar depression according to the *DSM-5* criteria (n = 21 suicide attempters [SAs] in the last 8 days and n = 21 affective controls [ACs] without lifetime suicidal history) between February 1 and November 30, 2017. Amplitude of low-frequency fluctuation (ALFF), regional homogeneity (ReHo), voxel-mirrored homotopic connectivity, and rs-FC were estimated in prefrontal cortex, anterior cingulate cortex, and insula.

Results: Participants were mainly women (age: 40–48 years). Only CRP concentration was higher in SAs than in ACs and HCs (3.55 [0.5; 13.3] vs 0.6 [0.3; 4.4] vs 0.8 [0.3; 13.9] mg/L, respectively, $P < 10^{-3}$). ALFF values in the pars opercularis of the inferior frontal gyrus (IFG) were lower in SAs than in ACs and HCs (all $P < 10^{-2}$), even after controlling for suicidal ideation intensity and CRP level. Suicidal ideation was negatively correlated with all rs-fMRI metrics (except ReHo of left side) of this region in patients. The rs-FC values of bilateral anterior cingulate cortex, left orbital IFG, and middle frontal orbital gyrus were higher in SAs than in ACs and HCs (all $P < .05$).

Conclusions: Resting-state activity and connectivity in regions involved in language, cognitive control, and decision-making may be associated with suicidal behaviors, but not with inflammation markers.

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Transnosographic features suggest that suicidal behavior has its own physiopathology and should be considered a specific clinical entity. According to the *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition (*DSM-5*),[1] suicidal behavior could be a separate diagnosis, emphasizing the relevance of identifying specific biomarkers.[2]

Identifying the neural substrates of suicidal behavior is key to understanding suicide etiology and might help to reduce suicide rates among psychiatric patients by promoting the development of novel therapeutic strategies based on behavioral neuroscience and brain stimulation.

Neuroimaging studies have shown structural and functional brain abnormalities in the prefrontal cortex, insula, and striatal regions and also in the connections between these brain areas.[3] Disturbances in the structure and function of brain regions can lead to brain network alterations, including the ability of brain regions to coordinate their activity in a system. Resting-state functional magnetic resonance imaging (rs-fMRI) has been used to explore the intrinsic activity or resting-state brain networks. In their review, Serafini et al[4] showed that vulnerability to suicidal behavior might be associated with abnormalities of the frontolimbic and frontoparietal-cerebellar pathways and with negative blood-oxygenation-level–dependent (BOLD) responses in the anterior regions of the default mode network. Moreover, a recent electroencephalography-based study reported that the regulation of intrinsic brain networks is altered in patients with depression and history of suicidal attempt in the last 6 months compared with healthy controls (HCs).[5] However, differences in acquisition/analysis methods and in population characteristics among fMRI studies limit the finding interpretability. Some studies focused on adolescents,[6–9]

Clinical Points

- Resting-state activity of the ventrolateral prefrontal cortex was altered in suicide attempters (SAs), possibly contributing to language impairment and poor decision-making and cognitive control.
- High C-reactive protein concentration was associated with history of suicidal acts, but none of the tested peripheral inflammatory markers (C-reactive protein, interleukin [IL]-1β, IL-2, and IL-6, and tumor necrosis factor-α) was associated with resting-state functional magnetic resonance imaging metrics.
- The relevance of meditation-based psychotherapies in recent suicide attempters needs to be thoroughly studied because these approaches modify the resting-state activity of prefrontal brain regions and reduce suicidal ideation.

and others included adults.[10–14] Importantly, "suicidality" has been operationalized differently among studies (eg, suicidal ideation, history of suicide attempts, or composite assessment).[8,15]

Suicidal ideation and behaviors are still considered a symptom or a consequence of a concomitant psychiatric disorder, mainly major depressive disorder (MDD).[16] However, rs-fMRI studies showed that in patients with MDD, resting-state functional connectivity (rs-FC) of the left amygdala-right insula/left superior orbitofrontal area and right amygdala-left middle temporal area was higher in depressed suicide attempters (SAs) than in controls.[12] Such enhanced rs-FC in limbic regions may contribute to emotional dysregulation. Moreover, the functional network connectivity between insular-default mode network and insular-cerebellum was decreased in SAs, reflecting impaired internal processing.[11] In addition, the amplitude of low-frequency fluctuation (ALFF) values were significantly higher in the right superior and left middle temporal and occipital regions and significantly lower in the left superior and middle frontal gyri in SAs than in controls.[6,17] Lastly, regional homogeneity (ReHo) in the right posterior cingulate cortex was increased in SAs compared with nonattempters.[18] It is important to disentangle the neural underpinnings of suicidal ideation and attempt.[19,20] Indeed, connectivity patterns between cognitive control network and salience and default mode networks were different in SAs and suicide ideators.[19] A study showed that ALFF value changes (decreased in the frontoparietal network and increased in hippocampus) could be used to distinguish SAs from suicide ideators, psychiatric controls, and HCs.[20]

Two meta-analyses reported that the blood concentrations of the proinflammatory cytokines interleukin (IL)-1β and IL-6 are significantly increased and those of the anti-inflammatory IL-2 are decreased in SAs compared with nonsuicidal patients and HCs.[21,22] Similarly, C-reactive protein (CRP) concentration in blood was higher in SAs than in depressed nonattempters, independently of the interval after the suicide attempt.[23] Interestingly, CRP basal level has been associated with rs-FC in the default mode network, including in the ventromedial prefrontal cortex,[24–26] that in turn was correlated with anhedonia severity in patients with MDD.[25] Moreover, IL-6 covaried with connectivity of the medial prefrontal cortex in HCs[27] and in patients with bipolar disorder.[28] However, data on associations between cytokines and rs-fMRI metrics in patients with MDD are still lacking. Moreover, it is important to investigate homogeneous populations while controlling for the presence of major depression to better characterize the association between suicidal, resting-state activity, and inflammatory status.[29]

Therefore, the aims of our study were (1) to identify neural markers in a homogeneous sample of SAs using rs-fMRI and (2) to find possible associations between rs-fMRI metrics/connectivity, suicidal phenotype, and peripheral inflammation markers in patients with MDD. We hypothesized that between-group differences of intrinsic activity in prefrontal areas may be independent of the suicidal ideation intensity and may correlate with peripheral proinflammatory cytokines.

METHODS

Participants

The study sample, recruited between February 1 and November 30, 2017, included 20 HCs (individuals without any history of psychiatric disorders according to the *DSM-5* criteria and no lifetime history of suicide attempt) and 42 patients with MDD [21 SAs with history of suicide attempt in the last 8 days and 21 affective controls (ACs) without lifetime history of suicide attempt].

HCs were recruited through advertisement. Patients (SAs and ACs) were recruited among the inpatients of the Department of Emergency Psychiatry and Acute Care, Montpellier Academic Hospital, France. All participants were right-handed, and Caucasian adults aged between 18 and 70 years. All patients (ACs and SAs) had a current depressive episode according to the *DSM-5* criteria. Exclusion criteria were current neurological or inflammatory disease; CRP >10 mg/L; current antibiotic or anti-inflammatory treatment; history of head trauma with loss of consciousness; current substance misuse, excluding tobacco; lifetime history of manic or hypomanic episode, schizophrenia, or schizoaffective disorder according to the *DSM-5*; pregnancy and breastfeeding; and contraindication to magnetic resonance imaging.

The study was conducted in accordance with the Consolidated Standards of Reporting Trials ethical guidelines. All participants gave their written informed consent. The study was approved by Montpellier University Hospital (CPP Sud Méditerranée IV) ethics committee (N°ID-RCB: 2016-01267-44 (CPP Sud Méditerranée IV) and registered in ClinicalTrials.gov (NCT03052855). Participants received a financial compensation of 50 euros.

Clinical Assessment

Participants underwent a standardized interview led by a psychiatrist to determine the depression score and to assess psychopathology according to the *DSM-5* criteria using the Mini-International Neuropsychiatric Interview, version 7.0.0. Depressive symptomatology was assessed using the clinician-rated Inventory of Depressive Symptomatology,[30] current psychological pain using a 10-point Likert scale,[31] suicidal ideation intensity in the week before inclusion using the Columbia-Suicide Severity Rating Scale (C-SSRS),[32] and suicidal intent with the Suicidal Intent Scale.[33] The number of past suicide attempts and the lethality of the last attempt were recorded. All psychotropic treatments (name and daily dose) in the last 24 hours before MRI were recorded, and the medication load was calculated for each patient.[34]

Laboratory Analyses

Blood samples were collected after overnight fasting, between 7:00 and 9:00 AM, the day after admission, in 5-mL ethylenediaminetetraacetic acid–coated tubes (BD Vacutainer, Franklin Lakes, NJ). High-sensitivity CRP in serum was measured with the immunoturbidimetric method and a cobas 8000 modular analyzer (Roche Diagnostic, Meylan, France). Reagents and calibrators were used according to the manufacturer's guidelines with analytic measuring ranges set at 0.3–350 mg/L.

Plasma was separated by centrifugation at 3,000 ×*g* at room temperature for 20 minutes and stored at −80°C for batch analysis by multiplex or enzyme-linked immunosorbent assay of IL-1β, IL-6, and IL-2, and tumor necrosis factor-α (TNF-α). Analytes with >30% missing data were excluded from the analysis (IL-1β and IL-2).

Brain MRI

Brain MRI was performed using a 3T MRI scanner with a 32-channel head coil (MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany) at the I2FH platform, Neuroradiology Department, Montpellier Hospital.

A high-resolution 3DT1 magnetization-prepared rapid gradient-echo sequence was acquired with the following parameters: repetition time (TR)/echo time (TE) = 2,300/2.900 ms, time of inversion = 900 ms, flip angle = 9°, voxel size = 1.2 ×1 ×1 mm^3, and 176 sagittal slices. During rs-fMRI gradient echo-echo planar image acquisition (TR/TE = 3,000/30 ms, flip angle = 80°, voxel size = 3.4 × 3.4 × 3.4 mm^3, 42 transverse slices, 200 volumes measures, and acquisition time = 10 min), participants were instructed to keep the eyes closed, lie still, and not think about anything in particular.

MRI Data Preprocessing

Imaging data were preprocessed using MATLAB (The MathWorks Inc, MA) and SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). All images were reoriented using the anterior commissure as reference. Standard Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) segmentation was performed on T1 images to extract gray matter, white matter, and cerebrospinal fluid posterior probability distribution. A dedicated DARTEL template was then used to normalize all T1 images (Ashburner).[35]

Resting-state images were processed using a standard processing pipeline that included signal heterogeneity correction using ANTS NI4TK, slice timing, motion correction, coregistration on the T1 images, normalization (based on the T1 images), and spatial smoothing (full width at half maximum = 6 mm).

Resting-State Metrics

ALFF, ReHo, and voxel-mirrored homotopic connectivity (VMHC) were estimated to evaluate local alterations of signal fluctuations.

VMHC is considered one of the most salient features of the brain intrinsic functional architecture[36] because it assesses the functional homotopy (ie, interhemispheric rs-FC) by quantifying the functional connectivity between a voxel and its mirrored counterpart in the contralateral hemisphere. ALFF, ReHo, and VMHC maps were prepared with the REST toolbox (Resting-State fMRI Data Analysis Toolkit V1.8, REST-Group, http://www.restfmri.net). Functional images were detrended and filtered (0.01–0.08 Hz). Smoothing was performed after ReHo score calculation to avoid artificially increasing the similarity between neighboring voxels. Maps were z-scored. The average gray matter ALFF, ReHo, and VMHC values were extracted from 116 regions using the Automated Anatomical Labelling (AAL) parcellation atlas (AAL 116 toolbox[37]). Based on our previous fMRI studies[38–40] and literature data,[3] analyses focused on regions implicated in suicidal vulnerability (Supplementary Figure 1): (1) orbitofrontal cortex (OFC), particularly the inferior frontal orbital gyrus, the middle frontal orbital gyrus, and the medial frontal orbital gyrus; (2) ventrolateral prefrontal cortex (VLPFC), particularly the pars opercularis of the inferior frontal gyrus (IFG); (3) dorsal prefrontal cortex; particularly the middle frontal gyrus; (4) anterior cingulate cortex (ACC); and (5) insula. The corresponding

Table 1.
Description of the Sample

	HCs (n = 21) Median [min; max] or N (%)	ACs (n = 21) Median [min; max] or N (%)	SAs (n = 20) Median [min; max] or N (%)	*P* value	Post hoc
Age, y	40 [24; 64]	48 [19; 66]	47.5 [19; 65]	.670	
Women	14 (66.7)	15 (71.4%)	17 (85)	.445	
Married/in a couple	15 (71.4)	8 (38.1%)	8 (40)	.054	
Education level, y	14 [2; 20]	12 [2; 18]	11 [2; 17]	**.020**	**HCs>SAs**
BMI	21.38 [18.07; 37.11]	20.76 [15.92; 31.17]	22.24 [16.53; 33.77]	.560	
Current eating disorder	-	0 (0)	2 (10)	.232	
Current anxious disorder	-	16 (76.2%)	13 (65)	.657	
Lifetime alcohol use disorder	-	3 (14.3%)	2 (10)	.999	
Number of depressive episodes	-	2 [0; 7]	2 [0; 10]	.770	
Duration of current depressive episode, wk	-	13 [2; 209]	14 [0; 209]	.695	
IDSC-30 total score	-	49 [32; 61]	50.5 [33; 66]	.278	
Current psychological pain	0 [0; 2]	5 [2; 10]	7 [0; 10]	**$<10^{-3}$**	**SAs, ACs > HCs**
C-SSRS, SI intensity	-	14 [0; 25]	21.5 [16; 25]	**$<10^{-3}$**	**SAs >ACs**
Number of lifetime suicide attempts	-	-	2.0 [1; 20]	-	
Age at first suicide attempt, y	-	-	31.5 [14; 64]	-	
Lethality of last suicide attempt	-	-	3 [2; 4]	-	
Medication load	-	3 [1; 5]	3 [1; 6]	.638	
Antidepressant intake	-	5 (23.8%)	3 (15)	.697	
Antipsychotic intake	-	1 (4.8%)	5 (25)	.093	
Anxiolytic/hypnotic intake	-	12 (57.1%)	15 (75)	.381	
CRP, mg/L	0.8 [0.3; 13.9]	0.6 [0.3; 4.4]	3.55 [0.5; 13.3]	**$<10^{-3}$**	**SAs > ACs, HCs**
IL-6, pg/mL	35 [5; 75]	47.5 [5; 265]	40 [5; 4,355]	.530	
TNF-α, pg/mL	45.45 [9.09; 12 7.27]	45.45 [9.09; 10 00]	59.09 [9.09; 11 572.73]	.780	

Boldface indicates statistical significance.
Abbreviations: ACs = affective controls, BMI = body mass index, CRP = C-reactive protein, C-SSRS = Columbia-Suicide Severity Rating Scale, HCs = healthy controls, IDSC-30 = clinician-rated Inventory of Depressive Symptomatology, IL-6 = interleukin-6, SA = suicide attempter, SI = suicidal ideation, TNF-α = tumor necrosis factor-α.

regions in the AAL atlas included 7 regions in each hemisphere.

Resting-State Functional Connectivity

A region of interest–to–region of interest (ROI-to-ROI[tnq_query9])–based analysis was performed using the CONN toolbox (version 21.a, www.nitrc.org/projects/conn) based on the chosen a priori regions previously described with the AAL atlas. Additional preprocessing included denoising with voxel-wise removal of linear trends over each patient's rs-fMRI dataset and temporal low-pass filtering ($0.009\ \text{Hz} < f < 0.08\ \text{Hz}$). The BOLD signal of white matter, cerebrospinal fluid, and movement parameters were used as covariates to remove unwanted physiologic and motion artifact effects. First-level analyses used a weighted general linear model to estimate the Fisher-transformed bivariate correlation coefficients between ROIs (gray matter only). Second-level, random-effects analyses were carried out for the rs-FC values on a ROI-to-ROI basis.

Statistical Analyses

Statistical analyses were performed with R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). A general linear model was used to model each regional measure as an outcome, while adjusting for age, sex, and education level. To identify the main group effects, a type II analysis of variance was performed with the fitted model. A false discovery rate (FDR) procedure was used for each set of rs-fMRI metrics and for rs-FC to correct for multiple comparisons, and post hoc analyses were performed for regions with a FDR $P < .05$. Exploratory correlation analyses were performed to examine possible associations between rs-fMRI metrics with a main group effect and clinical variables (depression, psychological pain intensity, and suicidal ideation intensity) in all patients as well as suicidal intent and lethality of last suicide attempt in SAs. Exploratory correlation analyses were also performed to identify possible associations between rs-fMRI metrics and peripheral inflammation markers in all patients (adjustment for sex and age). All correlation analyses were followed by multiple comparison correction (FDR).

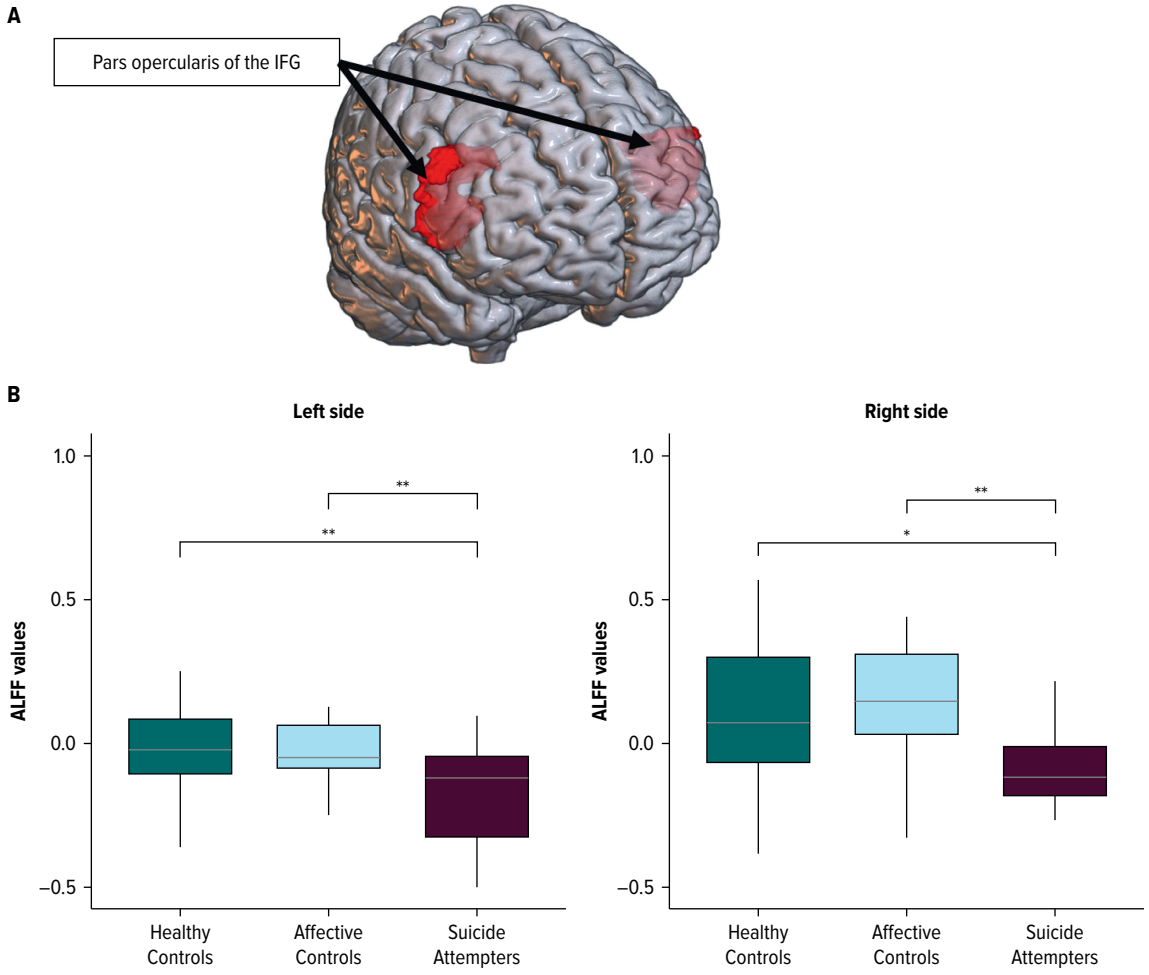
RESULTS

Description of the Sample

The whole sample included 46 (74%) women, and the mean age was 44 (SD = 14) years. The mean IDSC

Figure 1.

ALFF Metrics for the Pars Opercularis of the IFG: (A) Localization and Delimitation of the Pars Opercularis of the IFG in the AAL Atlas; (B) Average ALFF Values for the Right and Left Pars Opercularis in Each Group



*P < .05, **P < .01.
Abbreviations: AAL = Automated Anatomical Labelling, ALFF = amplitude of low-frequency fluctuation, IFG = inferior frontal gyrus.

score was 35 (SD = 25) (ie, moderate depressive symptomatology), without between-group differences. The mean C-SSRS score (suicidal ideation intensity) was 11 (SD = 10) and was higher in SAs than in ACs. The mean CRP concentration was 2.7 (SD = 3.4) mg/L and was higher in SAs than in HCs. The sociodemographic and clinical characteristics of the different groups are presented in Table 1.

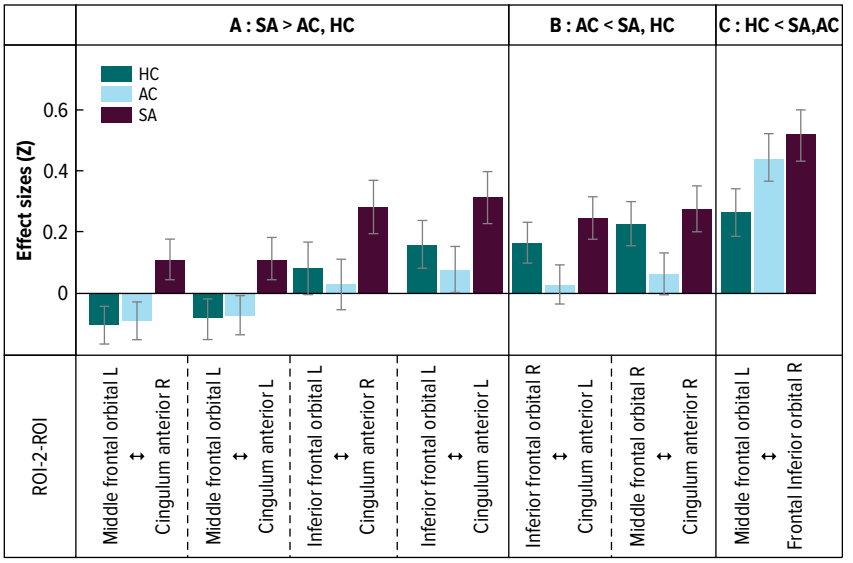
Main Group Effect on rs-fMRI

Overall, a main group effect on ALFF values was observed in the left and right pars opercularis of IFG (F = 6.75, P = .033 and F = 5.66, P = .040, respectively). After post hoc correction for multiple testing, the ALFF values in the pars opercularis of IFG were lower in SAs than in controls (ACs and HCs) (Figure 1). This result remained significant after adjustment for suicidal ideation intensity and CRP concentration (not shown). There was no main group effect on ReHo and VMHC values.

Overall, main group effects on rs-FC were mainly observed between ROIs of the OFC and ACC and within the OFC. After post hoc correction for multiple testing, the rs-FC values of bilateral ACC and left pars orbitalis of the IFG and middle frontal orbital gyrus were higher in SAs compared to ACs and HCs. The rs-FC values of the left middle frontal orbital gyrus and right inferior frontal orbital gyrus were higher in patients (SAs and ACs) than in HCs. The rs-FC values of inferior frontal orbital gyrus, left ACC, left middle frontal orbital gyrus, and right ACC were lower in ACs than in SAs and HCs (Figure 2).

Figure 2.

Significant Between-Group Comparisons for the rs-FC Values in the Identified ROIs Related to Suicidal Vulnerability[a]



[a]Comparison of the effect size of the Fisher-transformed correlation coefficients in the 3 groups is shown, including the 95% CI. Only significant ROI-to-ROI rs-FC values are shown (FDR *P* value < .05).
Abbreviations: AC = affective controls, FDR = false discovery rate, HC = healthy controls, L = left, R = right, ROI = region of interest, rs-FC = resting-state functional connectivity, SA = suicide attempters.

Correlations Between rs-fMRI, Clinical Measures, and Inflammatory Markers in All Patients (ACs and SAs)

The correlations between suicidal ideation intensity and all rs-fMRI metrics in the pars opercularis (except for the ALFF and ReHo of the left side) were significant after FDR correction. Table 2. Moreover, the correlation between psychological pain and rs-FC of left middle frontal gyrus and left insula remained significant after FDR correction (Supplementary Tables 1–4). No correlation between peripheral inflammation markers (CRP, IL-6, and TNF-α), rs-fMRI metrics (Table 3), and rs-FC (Supplementary Tables 6 and 7) remained significant after FDR correction in patients (ACs and SAs).

DISCUSSION

The main result of this study is the association between resting-state activity of the pars opercularis of the IFG and suicide attempt and suicidal ideation in patients with MDD. Specifically, the difference in ALFF values for the left pars opercularis of the IFG between SAs and controls remained significant even after controlling for suicidal ideation, despite the negative correlation between ALFF values in the same region and suicidal ideation intensity. This should encourage us to thoroughly investigate the hypothesis that the neurobiology underpinnings of suicidal ideation and act overlap but are not identical.[41] Our results are in accordance with previous studies showing lower ALFF values in the VLPFC in SAs compared with depressed patients[20,42] as well as decreased IFG functional connectivity in SAs compared with HCs[43] and in patients at high compared with low suicidal risk.[15] As ALFF is directly correlated with task-based BOLD responses,[44] our results may indicate altered functioning of the pars opercularis associated with impaired verbal fluency[45] and response inhibition,[46] both involved in the suicidal process.[47,48] Indeed, individuals who are less able to verbalize emotions or distress are more likely to use nonverbal communication, such as self-harm.[49] Moreover, impaired response inhibition in patients with left IFG damage is a significant predictor of future suicidal ideation or act.[47] Our results strengthen the hypothesis that altered activity of the pars opercularis of the IFG may exacerbate suicidal ideation and act, possibly through its association with language impairment and its involvement in the circuits mediating cognitive control.

Our second main result is that connectivity between ACC and orbital parts of IFG and middle frontal gyrus was higher in SAs than in controls (ACs and HCs). The lower rs-FC in ACs than in HCs suggests that there is not a continuum between HCs, ACs, and SAs, but rather a specific pathophysiology of suicidal vulnerability which

Table 2.

Correlation Between Clinical Characteristics and rs-fMRI Metrics

	Correlation between psychological pain (VAS) and rs-fMRI measures in patients (ACs and SAs)			Correlation between depression severity (IDSC-30) and rs-fMRI measures in patients (ACs and SAs)			Correlation between suicidal ideation intensity (C-SSRS) and rs-fMRI measures in patients (ACs and SAs)			Correlation between suicidal intent (SIS) and rs-fMRI measures in SAs		
	ALFF	ReHo	VMHC	ALFF	ReHo	VMHC	ALFF	ReHo	VMHC	ALFF	ReHo	VMHC
Middle frontal (L)	0.05	−0.22	−0.08	0.12	−0.15	−0.15	0.2	0.03	−0.09	0.02	−0.09	−0.08
Middle frontal (R)	0.15	−0.09	−0.17	0.01	−0.19	−0.19	0.1	−0.16	−0.21	0.04	0.08	−0.04
Middle frontal orbital (L)	0.04	0.03	0.1	0.06	0	0.01	0.17	0.17	0.06	0.21	0.31	0.24
Middle frontal orbital (R)	−0.04	0.04	0.1	0.06	0.05	0.02	0.22	0.04	−0.03	−0.03	0.04	0.23
Pars opercularis IFG (L)	−0.16	**−0.38***	−0.25	0	−0.07	**−0.33***	**−0.32***	−0.16	**−0.41****	−0.43	−0.32	−0.29
Pars opercularis IFG (R)	0.2	**−0.34***	−0.24	−0.27	−0.1	**−0.34***	**−0.41****	**−0.34***	**−0.47****	−0.36	−0.09	−0.38
Inferior frontal orbital (L)	−0.15	−0.29	0.2	−0.18	−0.07	−0.04	0.02	0.05	0.22	0.25	0.41	0.25
Inferior frontal orbital (R)	−0.25	−0.09	0.15	−0.23	0.02	−0.05	0.06	0.1	0.21	0.14	0.41	0.11
Medial frontal orbital (L)	−0.07	−0.12	0.04	0.2	0.23	0.25	0.24	0.26	0.22	0.04	0.29	0.19
Medial frontal orbital (R)	−0.09	0.07	0.05	0.15	0.22	0.25	0.29	0.1	0.2	−0.22	0.25	0.14
Insula (L)	−0.01	−0.13	−0.09	−0.22	−0.01	−0.12	−0.18	0.31	0.11	−0.15	−0.09	−0.27
Insula (R)	−0.12	0.01	−0.07	−0.24	−0.03	−0.18	−0.25	0.24	−0.01	−0.19	0.08	−0.24
Anterior cingulum (L)	−0.04	−0.06	0.17	−0.27	0.05	0.22	0.13	0.17	0.18	−0.16	0.31	0.12
Anterior cingulum (R)	−0.07	0.01	0.16	−0.09	0.12	0.22	0.03	0.1	0.25	−0.23	0.04	0.16

**P value < .01; *P value < .05 without correction for multiple tests. Correlations in bold were significant after correction for multiple tests.

Abbreviations: ACs = affective controls, C-SSRS = Columbia-Suicide Severity Rating Scale, IDSC-30 = clinician-rated Inventory of Depressive Symptomatology, IFG = inferior frontal gyrus, L = left side, R = right side, rs-fMRI = resting-state functional magnetic resonance imaging, SA = suicide attempter, SIS = Suicidal Intent Scale, TNF-α = tumor necrosis factor-α, VAS = visual analog scale.

Table 3.

Correlation Between Levels of Peripheral Inflammatory Markers and rs-fMRI Metrics in Patients

	Correlation between IL-6 concentration and rs-fMRI measures in patients (ACs and SAs)			Correlation between TNF-α concentration and rs-fMRI measures in patients (ACs and SAs)			Correlation between CRP concentration and rs-fMRI measures in patients (ACs and SAs)		
	ALFF	ReHo	VMHC	ALFF	ReHo	VMHC	ALFF	ReHo	VMHC
Middle frontal (L)	−0.03	0.01	0.01	−0.17	−0.01	0.02	−0.07	−0.11	0.25
Middle frontal (R)	−0.13	−0.13	−0.02	−0.26	−0.16	−0.01	−0.2	−0.12	0.19
Middle frontal orbital (L)	−0.27	−0.16	−0.17	−0.2	−0.16	−0.17	−0.02	−0.24	0.15
Middle frontal orbital (R)	−0.28	−0.06	−0.12	−0.27	−0.02	−0.11	−0.03	−0.09	0.22
Pars opercularis IFG (L)	−0.07	−0.13	0.12	0.02	−0.09	0.14	−0.15	−0.07	0.14
Pars opercularis IFG (R)	0.07	−0.02	0.11	0.12	0	0.14	−0.43	−0.17	0.01
Inferior frontal orbital (L)	−0.09	−0.01	0.03	0	−0.01	0	−0.01	−0.14	0.06
Inferior frontal orbital (R)	−0.18	0.03	0.01	−0.13	0.03	−0.01	−0.16	−0.16	0.09
Medial frontal orbital (L)	−0.18	−0.13	−0.13	−0.2	−0.14	−0.13	−0.05	0.03	0.27
Medial frontal orbital (R)	−0.12	−0.02	−0.1	−0.13	−0.01	−0.09	0.07	−0.01	0.12
Insula (L)	0.38*	−0.11	−0.08	0.29	−0.08	−0.04	0.04	0.26	0.1
Insula (R)	0.46**	−0.17	−0.05	0.47**	−0.14	−0.01	−0.01	0.25	0.04
Anterior cingulum (L)	0.33	0.15	0.37*	0.33	0.14	0.38*	−0.09	−0.22	−0.25
Anterior cingulum (R)	0.26	0.06	0.33	0.25	0.06	0.35*	0.05	−0.17	−0.11

**P value < .01; *P value < .05 without correction for multiple tests.

Abbreviations: ACs = affective controls, ALFF = amplitude of low-frequency fluctuation, CRP = C-reactive protein, IFG = inferior frontal gyrus, IL-6 = interleukin-6, L = left side, R = right side, ReHo = regional homogeneity, rs-fMRI = resting-state functional magnetic resonance imaging, SA = suicide attempter, TNF-α = tumor necrosis factor-α, VHMC = voxel-mirrored homotopic connectivity.

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does not overlap with depression vulnerability. The ACC receives information from the OFC and is implicated in learning associations between actions and reward vs punishment outcomes.[50] It has been shown that the rs-FC between these regions is altered in patients with depression and suicidal ideation.[51] Interestingly, studies in HCs found that the rs-FC of OFC and ACC was positively associated with risk taking (ie, the tendency to

take risks when making decisions or aim for goals)[52] and risk preference (ie, the preference for risky choices over safe alternatives) with a mediating effect of self-control.[53] Our results add to the hypothesis of the involvement of a dysfunctional frontocingulate connectivity that may underlie altered decision-making toward risk,[54] impulsivity, and self-control[55] in SAs.

Our findings strengthen the relevance of meditation-based psychotherapies for SAs. Meditation modifies[55] the activity of prefrontal brain regions,[56] as indicated by the ALFF increase during meditation compared with resting.[57] Moreover, emotional regulation, in the framework of mindfulness training, has been linked to corticolimbic modulation.[56] It has been shown that mindfulness training decreases the association between depressive symptomatology and suicidal ideation in patients with history of suicidal depression.[58] Moreover, in SAs, acceptance and commitment therapy is more effective than relaxation in reducing the intensity of suicidal ideation, even after 3 months of follow-up.[59] Meditation-based psychotherapies also improve decision-making[60] that is altered in SAs due to altered VLPFC functioning.[40]

The analysis of peripheral inflammation markers showed that high CRP concentration was associated with history of suicidal acts, as previously reported.[23] However, CRP was not associated with rs-fMRI metrics or rs-FC in patients (SAs and ACs). In the present analysis, CRP was considered a continuous variable and not a categorical variable (cutoff >3 mg/L) as done by Aruldass et al[24] who found a link between rs-FC and high CRP. The correlation between proinflammatory cytokine concentration and the rs-fMRI metrics did not remain after FDR correction. Of note, previous studies reported a negative correlation between IL-6 and functional connectivity in insula-involving networks.[24,61] Untargeted proteomic approaches to study inflammatory markers might be more suitable to identify possible associations with rs-fMRI metrics in patients with depression. In addition, future studies should focus on the hypothalamic-pituitary-adrenal axis because it may exert a modulatory influence on suicide risk through its dysregulation and its association with inflammatory pathways and neuroplasticity.[62]

Our study has several limitations. First, the sample size was small. However, our main results are mainly consistent with literature data. Second, the potential association between rs-fMRI, lethality of last suicidal act, and number of past suicide attempts could not be assessed due to the variable distribution. Third, in this study, only few factors involved in the inflammatory pathway were investigated. The association between rs-fMRI metrics and other peripheral inflammatory markers cannot be excluded and should be investigated in larger samples. Fourth, body mass index (BMI) was not considered in our analyses despite its association with inflammatory status because the small sample size did not allow including many covariables. However, BMI values were not different between groups. Fifth, a cross-sectional methodology was used, and specific causal links could not be investigated. However, SAs with a recent history of suicide attempt (in the last 8 days) were recruited in order to increase the sample homogeneity and to emphasize the impact of the suicide attempt rather than depression. Indeed, most previous studies included depressed subjects with lifetime history of SA, limiting the possibility to determine whether and to what extent inflammatory markers are related to current depression or to a previous suicidal act. Nevertheless, the selection of such a specific sample may limit the generalizability of our results. Sixth, a ROI approach was chosen. Nevertheless, many statistical tests were carried out by including clinical and biological peripheral markers. Therefore, multiple testing corrections were performed to reduce the risk of false-positive results.

To conclude, our study showed that the VLPFC resting-state activity was altered in SAs and was influenced by the suicidal ideation intensity. Moreover, SA was associated with altered rs-FC between ACC and OFC, which may contribute to choose risky outcomes. These findings support the relevance of meditation-based therapy for these patients. It is also important to identify specific subgroups of suicidal patients who might have increased vulnerability to inflammation that influences cerebral activity and who might benefit from anti-inflammatory agents. Finally, rs-fMRI metrics could be candidate biomarkers to detect patients at risk in order to improve suicide prevention.

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The Journal of Clinical Psychiatry

Supplementary Material

Article Title: Association of Suicidal Status, Inflammation Markers, and Resting-State Functional Activity and Connectivity in Patients With Major Depressive Disorder

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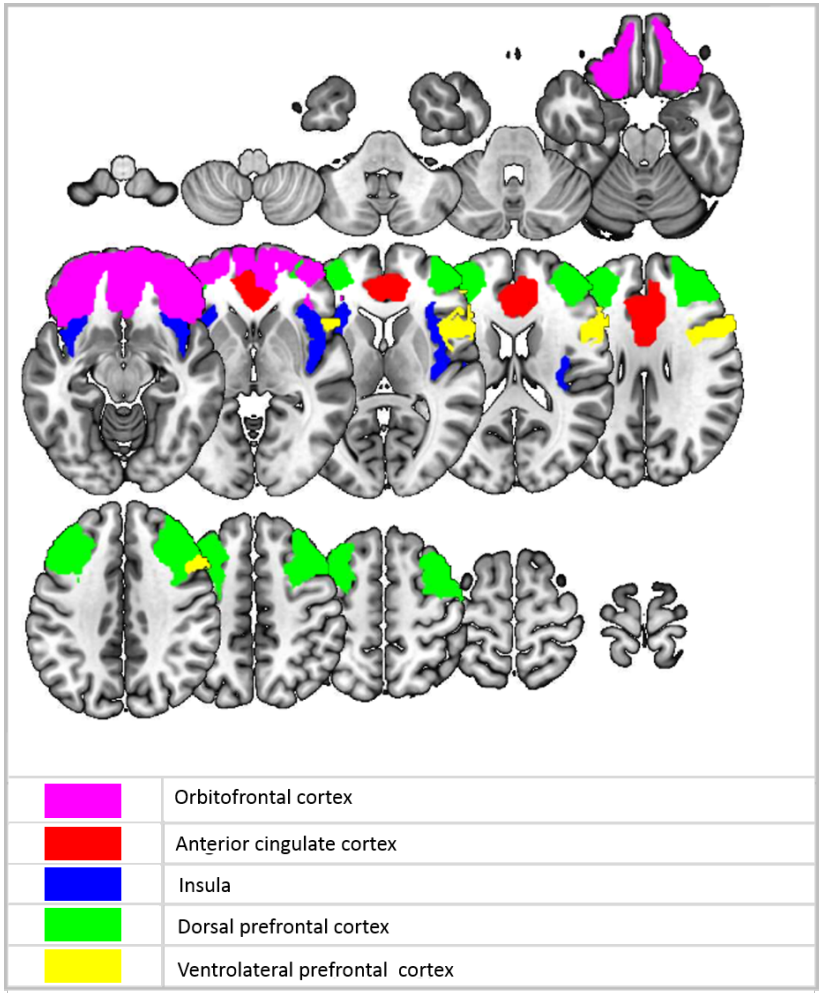
LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

Supplementary material

Supplementary Figure 1: Regions involved in suicidal vulnerability



Supplementary Table 1: Correlations between the rs-FC of region pairs and psychological pain intensity in patients (ACs and SAs)

	Middle frontal L	Middle frontal R	Middle frontal Orbital L	Middle frontal Orbital R	Pars opercularis of the IFG L	Pars opercularis of the IFG R	Inferior frontal Orbital L	Inferior frontal Orbital R	Medial frontal Orbital L	Medial frontal Orbital R	Insula L	Insula R	Anterior cingulum L	Anterior cingulum R
Middle frontal L		-0.22	-0.03	-0.02	-0.24	-0.32*	-0.23	-0.27	-0.26	-0.34*	-0.45*	-0.41*	-0.28	-0.24
Middle frontal R			-0.26	-0.17	-0.31	-0.34*	-0.29	-0.30	-0.25	-0.28	-0.27	-0.24	-0.11	-0.05
Middle frontal Orbital L				-0.05	0.02	-0.03	-0.15	-0.21	-0.21	-0.16	0.11	-0.05	-0.10	-0.15
Middle frontal Orbital R					-0.05	-0.14	-0.06	-0.22	-0.31	-0.21	0.19	-0.09	0.05	0.09
Pars opercularis of the IFG L						0.02	-0.05	0.09	0.01	-0.03	-0.16	-0.06	-0.07	-0.02
Pars opercularis of the IFG R							-0.10	0.08	-0.08	-0.13	-0.04	0.04	-0.12	-0.13
Inferior frontal Orbital L								-0.05	-0.30	-0.17	0.13	0.03	-0.32	-0.25
Inferior frontal Orbital R									-0.22	-0.12	0.17	0.03	-0.20	-0.10
Medial frontal Orbital L										-0.11	0.02	-0.08	-0.23	-0.23
Medial frontal Orbital R											0.15	0.11	-0.14	-0.19
Insula L												-0.10	-0.20	-0.21
Insula R													-0.14	-0.17
Anterior cingulum L														-0.09
Anterior cingulum R														

* non-corrected p-value < 0.05; colored cells: FDR p-value <0.05

Supplementary Table 2. Correlations between the rs-FC of regions pairs and depression severity in patients (ACs and SAs)

	Middle frontal L	Middle frontal R	Middle frontal Orbital L	Middle frontal Orbital R	Pars opercularis of the IFG L	Pars opercularis of the IFG R	Inferior frontal Orbital L	Inferior frontal Orbital R	Medial frontal Orbital L	Medial frontal Orbital R	Insula L	Insula R	Anterior cingulum L	Anterior cingulum R
Middle frontal L		0.14	0.17	0.19	0.04	0.09	0.19	0.15	0.17	0.18	0.20	0.30		0.08
Middle frontal R			0.26	0.19	0.18	0.07	0.41*	0.14	0.13	0.13	0.14	0.24	-0.08	-0.23
Middle frontal Orbital L				-0.23	-0.02	0.04	-0.27	-0.26	-0.06	0.06	-0.07	0.03	0.13	0.15
Middle frontal Orbital R					0.10	0.04	-0.41*	-0.18	-0.26	-0.11	-0.28	-0.12	0.05	0.01
Pars opercularis of the IFG L						0.08	-0.03	0.04	0.06	0.09	0.18	0.19	0.15	0.20
Pars opercularis of the IFG R							0.22	0.11	-0.12	-0.09	0.17	0.28	0.09	-0.01
Inferior frontal Orbital L								-0.23	-0.08	0.03	0.13	0.26	0.04	0.13
Inferior frontal Orbital R									-0.14	-0.04	-0.09	0.11	0.08	0.10
Medial frontal Orbital L										0.19	-0.16	-0.09	-0.16	-0.09
Medial frontal Orbital R												0.03	-0.21	-0.14
Insula L												0.17	0.10	0.09
Insula R													0.17	0.15
Anterior cingulum L														0.32*
Anterior cingulum R														

* non-corrected p-value < 0.05; colored cells: FDR p-value <0.05

Supplementary Table 3. Correlations between the rs-FC and suicidal ideation intensity in patients (ACs and SAs)

	Middle frontal L	Middle frontal R	Middle frontal Orbital L	Middle frontal Orbital R	Pars opercularis of the IFG L	Pars opercularis of the IFG R	Inferior frontal Orbital L	Inferior frontal Orbital R	Medial frontal Orbital L	Medial frontal Orbital R	Insula L	Insula R	Anterior cingulum L	Anterior cingulum R
Middle frontal L		0.01	0.05	-0.10	0.06	0.02	0.16	0.03	0.28	0.19	0.11	0.04	-0.02	0.01
Middle frontal R			-0.02	-0.08	0.17	0.02	0.22	0.12	0.33*	0.31*	0.04	0.05	0.02	-0.08
Middle frontal Orbital L				-0.13	-0.16	0.01	-0.04	-0.11	0.04	0.13	0.25	0.16	-0.09	-0.22
Middle frontal Orbital R					-0.22	-0.05	0.03	0.05	0.01	0.10	0.15	0.10	0.04	-0.04
Pars opercularis of the IFG L						0.06	-0.25	-0.30	-0.21	-0.33*	0.16	0.10	-0.02	-0.08
Pars opercularis of the IFG R							-0.18	-0.17	-0.03	-0.09	0.02	0.01	-0.01	-0.18
Inferior frontal Orbital L								-0.11	0.03	0.03	0.31	0.21	0.01	-0.02
Inferior frontal Orbital R									-0.11	-0.04	0.23	0.14	0.03	0.01
Medial frontal Orbital L										0.11	0.13	0.03	0.24	0.30
Medial frontal Orbital R											0.07	0.09	0.25	0.29
Insula L												-0.04	-0.04	-0.10
Insula R													-0.02	-0.13
Anterior cingulum L														0.31
Anterior cingulum R														

* non-corrected p-value < 0.05; colored cells: FDR p-value <0.05

Supplementary Table 4. Correlations between the rs-FC of region pairs and suicidal intent of the last suicide attempt in SAs

	Middle frontal L	Middle frontal R	Middle frontal Orbital L	Middle frontal Orbital R	Pars opercularis of the IFG L	Pars opercularis of the IFG R	Inferior frontal Orbital L	Inferior frontal Orbital R	Medial frontal Orbital L	Medial frontal Orbital R	Insula L	Insula R	Anterior cingulum L	Anterior cingulum R
Middle frontal L		-0.10	0.18	-0.01	-0.11	-0.20	-0.19	-0.24	-0.23	-0.36	-0.03	-0.16	-0.47*	-0.45*
Middle frontal R			0.14	0.02	-0.06	-0.19	0.03	0.04	0.11	-0.12	0.10	-0.10	-0.15	-0.27
Middle frontal Orbital L				-0.32	0.02	0.23	-0.07	-0.08	-0.45*	-0.24	-0.05	-0.26	-0.38	-0.35
Middle frontal Orbital R					-0.16	-0.01	0.05	0.10	-0.37	-0.10	0.07	-0.06	-0.05	-0.12
Pars opercularis of the IFG L						0.01	-0.02	-0.12	0.01	-0.07	0.11	0.02	-0.17	-0.07
Pars opercularis of the IFG R							0.23	0.25	0.04	-0.24	0.33	0.22	-0.21	-0.26
Inferior frontal Orbital L								-0.18	-0.09	-0.02	-0.17	-0.12	-0.09	0.01
Inferior frontal Orbital R									0.06	0.06	-0.06	-0.11	-0.08	-0.06
Medial frontal Orbital L										-0.15	-0.06	0.01	0.19	0.14
Medial frontal Orbital R											0.01	0.04	0.21	0.14
Insula L												-0.20	-0.16	-0.02
Insula R													-0.14	-0.07
Anterior cingulum L														0.25
Anterior cingulum R														

* non-corrected p-value < 0.05; colored cells: FDR p-value <0.05

Supplementary Table 5, Correlations between the rs-FC of region pairs and CRP concentration in patients (ACs and SAs)

	Middle frontal L	Middle frontal R	Middle frontal Orbital L	Middle frontal Orbital R	Pars opercularis of the IFG L	Pars opercularis of the IFG R	Inferior frontal Orbital L	Inferior frontal Orbital R	Medial frontal Orbital L	Medial frontal Orbital R	Insula L	Insula R	Anterior cingulum L	Anterior cingulum R
Middle frontal L		0.19	0.07	-0.10	-0.08	-0.22	0.05	-0.02	0.16	0.03	-0.06	-0.07	0.12	0.11
Middle frontal R			0.02	-0.12	0.07	0.01	0.11	0.14	0.12	0.20	-0.01	0.01	0.07	-0.01
Middle frontal Orbital L				-0.23	0.14	-0.01	0.16	-0.07	0.28	0.24	0.13	0.09	-0.03	0.03
Middle frontal Orbital R					-0.06	-0.20	0.15	-0.09	0.41*	0.32	-0.21	-0.15	0.03	0.10
Pars opercularis of the IFG L						-0.23	0.01	0.01	0.05	0.09	0.03	0.01	0.17	0.12
Pars opercularis of the IFG R							-0.08	0.09	0.06	0.28	-0.09	-0.03	-0.02	-0.06
Inferior frontal Orbital L								-0.08	0.23	0.24	0.11	0.03	0.16	0.24
Inferior frontal Orbital R									0.10	0.17	0.19	0.16	0.11	0.11
Medial frontal Orbital L										-0.04	0.16	0.16	0.17	0.29
Medial frontal Orbital R											0.19	0.30	0.02	0.09
Insula L												-0.27	-0.01	-0.05
Insula R													-0.04	-0.05
Anterior cingulum L														0.03
Anterior cingulum R														

* non-corrected p-value < 0.05; colored cells: FDR p-value <0.05

Supplementary Table 6. Correlations between the rs-FC of region pairs and TNF-alpha concentration in patients (ACs and SAs)

	Middle frontal L	Middle frontal R	Middle frontal Orbital L	Middle frontal Orbital R	Pars opercularis of the IFG L	Pars opercularis of the IFG R	Inferior frontal Orbital L	Inferior frontal Orbital R	Medial frontal Orbital L	Medial frontal Orbital R	Insula L	Insula R	Anterior cingulum L	Anterior cingulum R
Middle frontal L		0.19	0.08	0.25	0.26	0.06	0.06	0.17	-0.09	0.04	-0.05	0.12	0.05	0.26
Middle frontal R			0.06	0.29	0.14	0.03	0.14	0.20	-0.17	-0.04	-0.04	0.15	-0.02	0.08
Middle frontal Orbital L				0.05	0.16	-0.11	0.05	0.01	0.03	0.06	0.02	0.08	-0.05	0.06
Middle frontal Orbital R					0.22	0.13	-0.07	0.01	0.01	0.06	0.08	0.29	0.07	0.21
Pars opercularis of the IFG L						-0.08	0.16	0.08	-0.03	0.01	0.02	0.05	0.18	0.24
Pars opercularis of the IFG R							0.08	0.18	0.02	0.05	-0.31	-0.10	0.16	0.20
Inferior frontal Orbital L								-0.09	-0.05	-0.01	-0.02	-0.07	-0.17	-0.10
Inferior frontal Orbital R									-0.08	-0.03	-0.21	0.09	-0.04	0.07
Medial frontal Orbital L										0.14	-0.05	-0.14	-0.13	-0.11
Medial frontal Orbital R											0.01	0.02	-0.05	-0.06
Insula L												-0.31	0.02	-0.03
Insula R													0.13	0.18
Anterior cingulum L														-0.12
Anterior cingulum R														

Supplementary Table 7. Correlations between the rs-FC of region pairs and IL-6 concentration in patients (ACs and SAs)

	Middle frontal L	Middle frontal R	Middle frontal Orbital L	Middle frontal Orbital R	Pars opercularis of the IFG L	Pars opercularis of the IFG R	Inferior frontal Orbital L	Inferior frontal Orbital R	Medial frontal Orbital L	Medial frontal Orbital R	Insula L	Insula R	Anterior cingulum L	Anterior cingulum R
Middle frontal L		0.22	0.09	0.25	0.27	0.09	0.06	0.16	-0.07	0.06	-0.02	0.15	0.07	0.27
Middle frontal R			0.06	0.31	0.17	0.05	0.12	0.19	-0.14	0.01	-0.03	0.16	0.01	0.10
Middle frontal Orbital L				0.05	0.18	-0.09	0.08	0.04	0.02	0.06	0.01	0.07	-0.06	0.06
Middle frontal Orbital R					0.23	0.15	-0.03	0.05	0.01	0.06	0.09	0.28	0.07	0.22
Pars opercularis of the IFG L						-0.04	0.17	0.08	-0.02	0.01	0.06	0.07	0.20	0.27
Pars opercularis of the IFG R							0.08	0.18	0.03	0.07	-0.31	-0.08	0.18	0.22
Inferior frontal Orbital L								-0.06	-0.04	0.01	-0.03	-0.09	-0.16	-0.09
Inferior frontal Orbital R									-0.09	-0.03	-0.19	0.10	-0.04	0.07
Medial frontal Orbital L										0.15	-0.03	-0.11	-0.11	-0.09
Medial frontal Orbital R											0.03	0.04	-0.01	-0.03
Insula L												-0.35	0.05	0.01
Insula R													0.15	0.21
Anterior cingulum L														-0.09*
Anterior cingulum R														

* non-corrected p-value < 0.05; colored cells: FDR p-value <0.05