Brain Spect Perfusion and Pet Metabolism as Discordant Biomarkers in Major Depressive Disorder

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Abstract

Background: Brain SPECT perfusion and PET metabolism have been, most often interchangeably, proposed to study the underlying pathological process in major depressive disorder (MDD). The objective of this study is to document similarities and inconsistencies between these two biomarkersaccording to global characteristics of the disease.

We conducted a retrospective pilot study in 16 patients sufferingfrom MDDwho underwent, during a same current episode, a cerebral perfusion SPECT with ^{99m}Tc-HMPAO and a metabolic PETwith a ^{18}F-FDG. Whole-brain voxel-based SPM(T) maps were generated in correlation with the number of depressive episodes and in correlation with the depression duration, separately for the two exams (p-voxel and p-cluster<0.005, uncorrected).

Results: No significant correlations were found between brain PET metabolism and either the number of depressive episodes or the duration of the disease. On the contrary, significant correlations were found with SPECT perfusion: the increased number of depressive episodes was correlated with decreased perfusion of the right insula cortex; the increased depression duration was correlated with bilateral decreased perfusion of the anterior cingulum cortex.

Conclusions: The study demonstrates that brain perfusion and glucose metabolismare not equivalent biomarkers inMDD,highlighting the value of brain perfusion SPECT despite less favorable instrumentation detection compared to metabolic PET.

Background

Major depressive disorder (MDD) is a common mental health disorder, now the first cause of disability worldwide and a major contributor to the overall global burden of diseases according to the World Health Organization. It has been estimated that 15–30% of patients are resistant to antidepressants and cognitive behavioral treatment[1].

The current diagnosis and course evaluation of MDD rely on clinical examination. To date, the risk of misdiagnosis remains present because of the lack of noninvasive and quantifiable assessments of all depression dimensions[2]. Furthermore, in case of antidepressant resistance, several promising treatments are proposed (pharmacological, noninvasive and invasive neuromodulation). Nonetheless, the physiopathology of depression and the neural and biological mechanisms of treatments efficacy are still not fully understood. In this context, neuroimaging biomarkers are needed for diagnosing, predicting the course of the disorder, guiding the choice of therapy as well as monitoring the response to these therapies.

Since 2008 with the development of the “Rdoc Research” program, brain SPECT with ^{99m}Tc-ECD or ^{99m}Tc-HMPAo and ^{18}F-FDG PET have been proposed to respectively study regional blood flow and glucose metabolism in a range of psychiatric disorders including MDD[3]. These two biomarkers are believed to

characterize the global synaptic activity through the neurovascular coupling. They have been used to help in the neurological differential diagnosis of depression, and more recently considered to better understand the underlying pathological process in MDD and to predict response and non-response outcomes to neuromodulation therapies such as repetitive transcranial magnetic stimulation (rTMS) or Deep Brain stimulation (DBS) in Treatment Resistant Depression (TRD)[4,5]. In this line, some regions seem particularly involved, especially in treatment resistant cohorts: the frontal cortex and more broadly the limbic system. Nevertheless, the genuine overlap across PET/SPECT studies is globally more limited and slows down the clinical integration of these biomarkers in the patient's evaluation. The main explanations of these discrepancies are the small size and clinical heterogeneity of inclusions, as well as the variability of neuroimaging techniques, radiotracers and statistical models [6]. One alternative hypothesis would be that neuroimaging biomarkers are not as equivalent as anticipated in MDD, especially for SPECT perfusion and PET metabolism.

The objective of this study is to document similarities and inconsistencies between brain SPECT perfusion and PET metabolism according to the global characteristics of the disease, and particularly the number of previous depressive episodes and the depression duration, in a same group of patients with MDD.

Methods

Subjects

We conducted a retrospective pilot study. The database concerned patients with a psychiatric follow-up in Sainte Marguerite University Hospital (Marseille, France) from January 2011 through July 2019. Our inclusion criteria were patients over the age of 18 suffering from TRD, who underwent a cerebral SPECT with ^{99m}Tc-HMPAo and a ^{18}F-FDG PET with an interval delay of less than 18 months during a same current major depressive episode (according to DSM-IV criteria). These SPECT examinations had been performed to initially explore differential diagnoses. The selected patients were subsequently included in the HrTMS trial which included a metabolic PET imaging evaluation before treatment with ethical and regulatory authorizations (ClinicalTrials.gov: NCT02559466; Registry Identifier ID RCB: 2015-A00345-44)[5,7]. Patients with bipolar depression, schizophrenia and neurologic comorbidities were excluded.

Data collection

Sociodemographic characteristics recorded include gender, age, marital status and education level. Clinical data included illness duration, number of depressive episodes, melancholic and psychotic characteristics as well as pharmaco-resistance and global severity according to the structured clinical Interview for DSM-IV (SCID-IV)[8]. Data concerning severity scales such as MADRS or Beck were not available in all patients for the two-evaluation time-points. Treatment data recorded included all antidepressants, antipsychotics, and mood stabilizers as well as invasive and non-invasive brain stimulation (electroconvulsive therapy, rTMS and deep brain stimulation and vagal nerve stimulation).

SPECT and PET acquisitions

SPECT and PET were performed for all subjects, with the same SPECT and PET cameras, and under the same conditions. ^{18}F-FDG PET was performed using an integrated PET/CT camera (Discovery ST, GE Healthcare, Waukeskha, WI, USA). ^{18}F-FDG was injected intravenously 30 minutes beforehand at the activity of 150 MBq, and PET images were acquired over a period of 15 minutes. SPECT with ^{99m}Tc-HMPAO acquisition was performed using a double-headed rotating gamma camera (ECAM, Siemens) equipped with a fanbeam collimator. ^{99m}Tc-HMPAO was injected intravenously 15 minutes beforehand at the activity of 740 MBq, and SPECT images were acquired over a period of 20 minutes. Images were initially converted from the DICOM to the NifTi format using MRIcro (www.mricro.com) and transferred to SPM. Whole-brain statistical analysis was performed at the voxel level using SPM12 software (Wellcome Department of Cognitive Neurology, University College, London, UK) after spatial normalization (the Montreal Neurological Institute atlas) and smoothing with a Gaussian filter (8 mm full-width at half-maximum) to blur individual variations in gyral anatomy and to increase the signal-to-noise ratio. Whole-brain voxel-based SPM (T) maps were generated in correlation with the number of depressive episodes and in correlation with the depression duration, separately for the two exams (p-voxel < 0.005 uncorrected, p-cluster < 0.05 uncorrected).

Statistical analysis

Data were presented in proportions or mean and standard deviations. Characteristics were compared for each patient between PET and SPECT acquisition dates using the Student t-test or the Mann–Whitney U-test for continuous variables, a chi-square test, or Fisher's exact test for categorical variables. Mean PET/SPECT values were extracted at the individual level for significant cluster(s) to calculate Spearman correlations. The statistical significance level was set at $p < 0.05$ in a two-sided test.

Results

Baseline characteristics

A total of 16 subjects were included in the study. Patient characteristics are described in Table 1. Patients were mostly women with a mean age above 50 years old. Our sample included 4 men (25%) and 12 women (75%), 81.3% of patients were single, and 66.7% had less than 12 years of education. They all presented TRD with a mean number of depressive episodes estimated at 2.31 ± 1.9. Among this group, 13 patients suffered from a severe current episode, and melancholic criteria were present in 6 patients. The mean interval delay between PET and SPECT acquisitions was 4.37 months ± 4.89 (20 days to 13 months). No significant changes were found between these two-time point evaluations, especially for clinical characteristics and treatments. However, age and disease duration did show statistically significant differences with a respective difference of 5.28 months ($p = 0.02$) 1.44 months ($p = 0.023$), since SPECT was systematically performed before PET in these patients.

Table 1
Demographic and clinical characteristics of patients at PET and SPECT day acquisitions (n = 16)

	At PET day acquisition	**At SPECT day acquisition**	**p-value**
Demographic Characteristics			
Age (years, mean ± SD)	50.50 ± 16.3	50.06 ± 16.7	**p = 0.020**
Study level	5 (33.3%)	5 (33.3%)	p = 1.000
>12 years	10 (66.7%)	10 (66.7%)	p = 1.000
≤ 12 years			
Marital status	13 (81.3%)	13 (81.3%)	p = 1.000
Single	3 (18.8%)	3 (18.8%)	p = 1.000
Couple			
Clinical Characteristics			
Depression duration (months)	136.44 ± 120	132.56 ± 121.48	**p = 0.023**
Number of depressive episodes	2.31 ± 1.9	2.31 ± 1.9	p = 1.000
SCID severity			
mild	2 (12.5%)	2 (12.5%)	p = 1.000
moderate	1 (6.3%)	1 (6.3%)	p = 1.000
severe	13 (81.3%)	13 (81.3%)	p = 1.000
Melancholic features	6 (37.5%)	6 (37.5%)	p = 1.000
Treatments			
SSRI	5 (31.3%)	7 (43.8%)	p = 0.500
SNRI	6 (37.7%)	5 (31.3%)	p = 0.300
Tricyclics	2 (12.5%)	2 (12.5%)	p = 1.000
MAOI	1 (6.3%)	1(6.3%)	p = 1.000
Pramipexole	1 (6.3%)	1 (6.3%)	p = 1.000
Antipsychotics, first generation	1(6.3%)	1(6.3%)	p = 1.000
Antipsychotics, second generation	3 (18.8%)	4 (25%)	p = 0.607

SCID: structured clinical Interview for DSM-IV; SSRI: selective serotonin reuptake inhibitors; MAOI: monoamine oxidase inhibitors

	At PET day acquisition	At SPECT day acquisition	p-value
Mood stabilizers	0	0	p = 1.000
Others	3 (18.8%)	2 (12.5%)	p = 0.350

SCID: structured clinical Interview for DSM-IV; SSRI: selective serotonin reuptake inhibitors; MAOI: monoamine oxidase inhibitors

Brain PET metabolism and SPECT perfusion findings

No significant SPM (T) results were found for PET metabolism in correlation with either the number of depressive episodes or the depression duration. On the contrary, significant correlations were found with SPECT perfusion: the increased number of depressive episodes was correlated with decreased perfusion of the right insula cortex (T-voxel max = 4.52, k = 515), and the increased depression duration was correlated with bilateral decreased perfusion of the anterior cingulum cortex (ACC) (T-voxel max = 5.31, k = 236). Spearman's correlations on extracted clusters confirmed negative correlation between the number of depressive episodes and perfusion of the right insula (r=-0.621, p = 0.01) and between depression duration and perfusion of the ACC (r=-0.676, p = 0.004). These same clusters were extracted for PET metabolism without significant correlation (r=-0.240 for metabolism of the right insula cortex and the number of depressive episodes; r = 0.074 for metabolism of the ACC and the depression duration). These results are presented in Fig. 1 and Fig. 2.

Discussion

We conducted a retrospective pilot study in a sample of 16 patients suffering from TRD who all underwent a cerebral perfusion SPECT with ^{99m}Tc-HMPAO and a metabolic PET with ^{18}F-FDG. No relevant clinical changes were found upon evaluation at these two-time points, especially for disease characteristics and treatments. Whole-brain voxel-based analysis reveals inconsistent results between SPECT perfusion and PET metabolism, and could thus at least in part explain previous variability of findings in the literature for these two biomarkers[6]. Significant negative correlations were found with SPECT perfusion between number of episodes and the right insula perfusion, and between the depression duration and bilateral ACC perfusion, while no relationship was obtained for PET metabolism.

Number of episodes and illness duration are considered as risk factors of pharmaco-resistance and involved in depression recurrence[9,10]. They also may signal risk of residual symptoms such as sleep disturbances, executive impairments and anxiety[11]. Correlations with these two variables have already been described in few previous neuroimaging studies. A voxel-based study of 127 subjects suffering from TRD showed a weak negative correlation between the duration of illness and brain ^{99m}Tc-ECD SPECT perfusion in bilateral cingulate and orbital cortices[12]. A recent MRI meta-analysis including morphometry studies found a significant gray matter reduction in the rostral part of the anterior cingulum related to illness duration and repeated depressive episodes[13]. Moreover, our findings are concordant with another

^{18}F-FDG PET study: in 18 hospitalized patients with unipolar depression, Mayberg et al. revealed no significant relationship between brain metabolism and illness chronicity[14].

The insula and anterior cingulum cortices are known to be involved in TRD[6,15]. The insula is particularly involved in the emotional identification a stimulus, and in the affective state in response to it. Resting-state hyperactivity of the insula has been linked in MDD to pathological self-focused mental ruminative behaviors[16]. On the other hand, the ACC modulates the link between ventral and dorsal networks involved in regulation of emotion. Dorsal ACC is specifically implicated in executive functions through the cognitive control network and its subgenual subdivision focused on emotional experience and processing[17]. Furthermore, the insula and ACC both belong to the salience network which participates in judgement alteration and negative thoughts in MDD[18]. They also both interact with the default mode network, and contribute to the alteration of attentional system and to the introspection in MDD[19].

PET is one of the main neuroimaging techniques evaluated in recent psychiatry research[15]. Indeed, PET is usually preferred to SPECT because of better spatial resolution. Cerebral glucose metabolism and cerebral perfusion have been considered as coupled for a long time because the brain consumes roughly 20% of total body oxygen and 25% of total body glucose. The most important energy source for the brain is the adenosine triphosphate (ATP), produced almost entirely by the oxidative metabolism of glucose[20]. However, their consistent correlations are presently questioned, in part justified by other mechanisms of blood flow regulation which could produce a different cartography of cerebral perfusion from the metabolic one. This has already been highlighted in healthy subjects[21]. Furthermore, neurovascular uncoupling between glucose and oxygen metabolism, via oxygen depletion and induction of downstream hypoxia response pathways, could play a key role in neurodegenerative diseases[22]. And it does not seem excluded that psychiatric disease could also increase differences between brain metabolic and perfusion cartographies, involving the same neurovascular uncoupling mechanisms.

The main limitations were a retrospective design and a small sample size. Our results concerned patients with TRD, and they are not generalizable to all patients suffering from MDD. The interval delay between the two acquisitions was significant and resulted in mild differences considering age and disease duration, which were ultimately irrelevant in number of months. To our knowledge, this is the first study which focuses on a single group of patients. This choice produced a better homogeneity by excluding interindividual differences.

Conclusions

The study demonstrates that brain perfusion and glucose metabolism are not equivalent biomarkers in TRD, highlighting the value of brain perfusion SPECT despite less favorable spatial resolution and image quality compared to metabolic PET. These findings motivate a more frequent use of this more available imaging technique in future psychiatric research.

Declarations

Ethics approval and consent to participate

This word has been performed in accordance with the Declaration of Helsinki, with written consent of patients and approvement of local ethics committee (ClinicalTrials.gov: NCT02559466; Registry Identifier ID RCB: 2015-A00345-44).

Consent for publication

Not applicable

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request

Competing interests

The authors declare that they have no competing interests

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Authors’ contribution

MT: analysis and interpretation of clinical and PET/SPECT data; drafting the work; final approval

LB: analysis and interpretation of clinical and PET/SPECT data; revision of the work; final approval

TK: acquisition of clinical data; revision of the work; final approval

GF: analysis and interpretation of clinical and PET/SPECT data; revision of the work; final approval

CL: conception and design of the study; acquisition of clinical data; revision of the work; final approval

RR: conception and design of the study; acquisition, analysis and interpretation of clinical data; drafting the work; final approval

EG: conception and design of the study; acquisition, analysis and interpretation of PET/SPECT data; drafting the work; final approval

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Not applicable

References

1. Thase ME. Treatment-resistant depression: prevalence, risk factors, and treatment strategies. J Clin Psychiatry. 2011;72:e18.
2. Fried EI, Epskamp S, Nesse RM, Tuerlinckx F, Borsboom D. What are 'good' depression symptoms? Comparing the centrality of DSM and non-DSM symptoms of depression in a network analysis. J Affect Disord. 2016;189:314–20.
3. Zhang K, Zhu Y, Zhu Y, Wu S, Liu H, Zhang W, et al. Molecular, Functional, and Structural Imaging of Major Depressive Disorder. Neurosci Bull. 2016;32:273–85.
4. Fonseka TM, MacQueen GM, Kennedy SH. Neuroimaging biomarkers as predictors of treatment outcome in Major Depressive Disorder. J Affect Disord. 2018;233:21–35.
5. Tastevin M, Richieri R, Boyer L, Fond G, Lançon C, Guedj E. Brain PET metabolic substrate of TMS response in pharmaco-resistant depression. Brain Stimulation: Basic Translational Clinical Research in Neuromodulation. 2020;13:683–5.
6. Fitzgerald PB, Laird AR, Maller J, Daskalakis ZJ. A Meta-Analytic Study of Changes in Brain Activation in Depression. Hum Brain Mapp. 2008;29:683–95.
7. Tastevin M, Baumstarck K, Groppi F, Cermolacce M, Lagrange G, Lançon C, et al. Double cone coil rTMS efficacy for treatment-resistant depression: A prospective randomized controlled trial. Brain Stimul. 2019. doi:10.1016/j.brs.2019.09.009.
8. Williams Janet FMichaelB, Spitzer Robert BW L., Gibbon Miriam. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Clinical Trials Version (SCID-CT. 2007.
9. Bennabi D, Aouizerate B, El-Hage W, Doumy O, Moliere F, Courtet P, et al. Risk factors for treatment resistance in unipolar depression: a systematic review. J Affect Disord. 2015;171:137–41.
10. Buckman JEJ, Underwood A, Clarke K, Saunders R, Hollon SD, Fearon P, et al. Risk factors for relapse and recurrence of depression in adults and how they operate: A four-phase systematic review and meta-synthesis. Clin Psychol Rev. 2018;64:13–38.
11. Serafini G, Nebbia J, Cipriani N, Conigliaro C, Erbuto D, Pompili M, et al. Number of illness episodes as predictor of residual symptoms in major depressive disorder. Psychiatry Res. 2018;262:469–76.

12. Richieri R, Boyer L, Faget-Agius C, Farisse J, Mundler O, Lançon C, et al. Determinants of brain SPECT perfusion and connectivity in treatment-resistant depression. Psychiatry Res. 2015;231:134–40.
13. Bora E, Fornito A, Pantelis C, Yücel M. Gray matter abnormalities in Major Depressive Disorder: a meta-analysis of voxel based morphometry studies. J Affect Disord. 2012;138:9–18.
14. Mayberg HS, Brannan SK, Mahurin RK, Jerabek PA, Brickman JS, Tekell JL, et al. Cingulate function in depression: a potential predictor of treatment response. Neuroreport. 1997;8:1057–61.
15. Gong B, Naveed S, Hafeez DM, Afzal KI, Majeed S, Abele J, et al. Neuroimaging in Psychiatric Disorders: A Bibliometric Analysis of the 100 Most Highly Cited Articles. J Neuroimaging. 2019;29:14–33.
16. Sliz D, Hayley S. Major Depressive Disorder and Alterations in Insular Cortical Activity: A Review of Current Functional Magnetic Imaging Research. Front Hum Neurosci 2012; 6. doi:10.3389/fnhum.2012.00323.
17. Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. Trends in Cognitive Sciences. 2000;4:215–22.
18. Manoliu A, Meng C, Brandl F, Doll A, Tahmasian M, Scherr M, et al. Insular dysfunction within the salience network is associated with severity of symptoms and aberrant inter-network connectivity in major depressive disorder. Front Hum Neurosci 2014; 7. doi:10.3389/fnhum.2013.00930.
19. Bessette KL, Jenkins LM, Skerrett KA, Gowins JR, DelDonno SR, Zubieta J-K, et al. Reliability, Convergent Validity and Time Invariance of Default Mode Network Deviations in Early Adult Major Depressive Disorder. Front Psychiatry 2018; 9. doi:10.3389/fpsyt.2018.00244.
20. Reilly P. Head injury: pathophysiology and management of severe closed injury. London: Chapman and Hall Medical; 1997.
21. Henriksen OM, Vestergaard MB, Lindberg U, Aachmann-Andersen NJ, Lisbjerg K, Christensen SJ, et al. Interindividual and regional relationship between cerebral blood flow and glucose metabolism in the resting brain. J Appl Physiol. 2018;125:1080–9.
22. Watts ME, Pocock R, Claudianos C. Brain Energy and Oxygen Metabolism: Emerging Role in Normal Function and Disease. Front Mol Neurosci 2018; 11. doi:10.3389/fnmol.2018.00216.

Figures

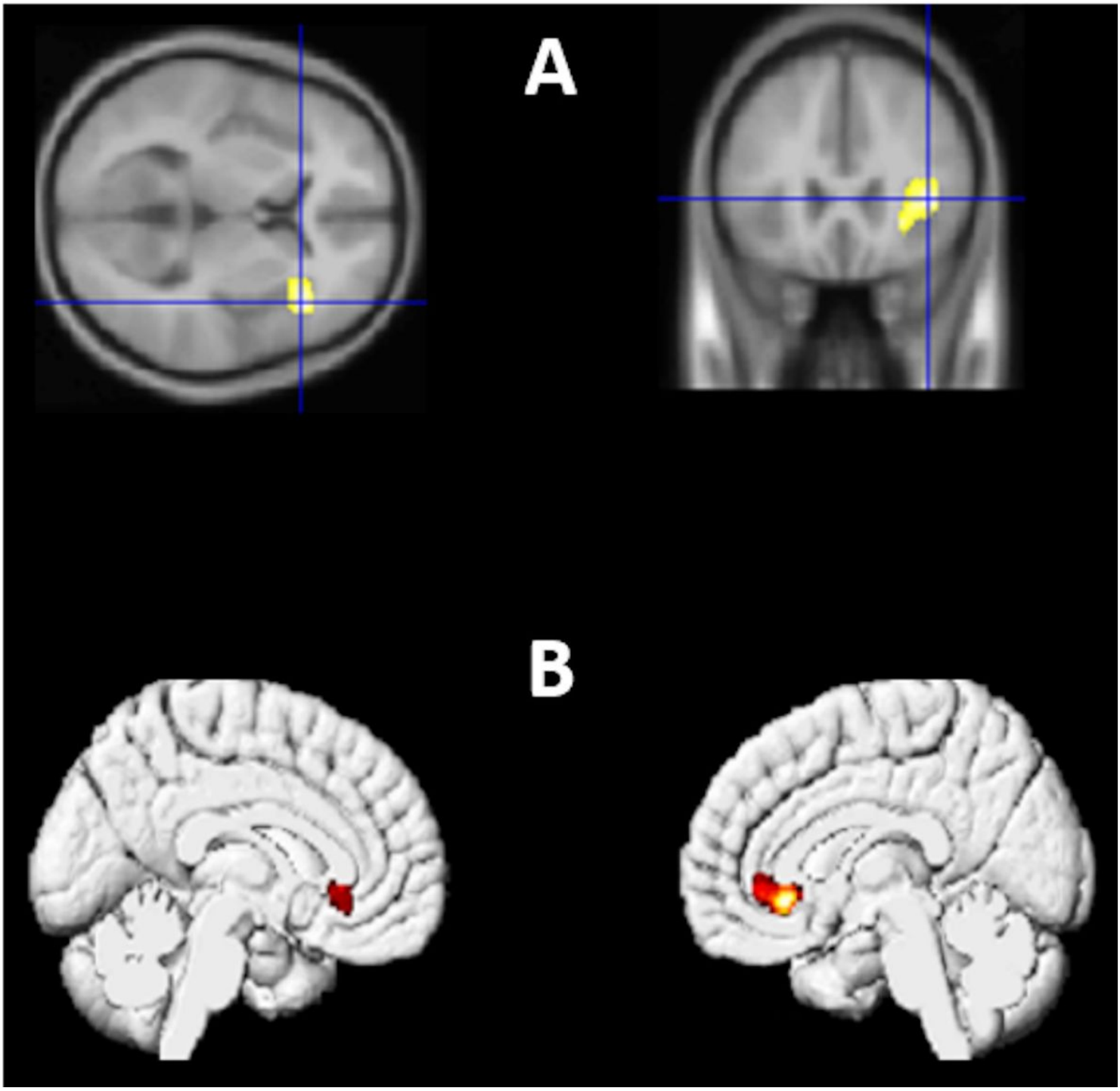

Figure 1

Anatomical localization of significant perfusion SPECT findings (p-voxel < 0.005 uncorrected, p-cluster < 0.05 uncorrected).A) : the increased number of depressive episodes was correlated with decreased perfusion of the right insula cortex (T-voxel max= 4.52, k=515). B) the increased depression duration was correlated with bilateral decreased perfusion of the anterior cingulum cortex (T-voxel max= 5.31, k=236).

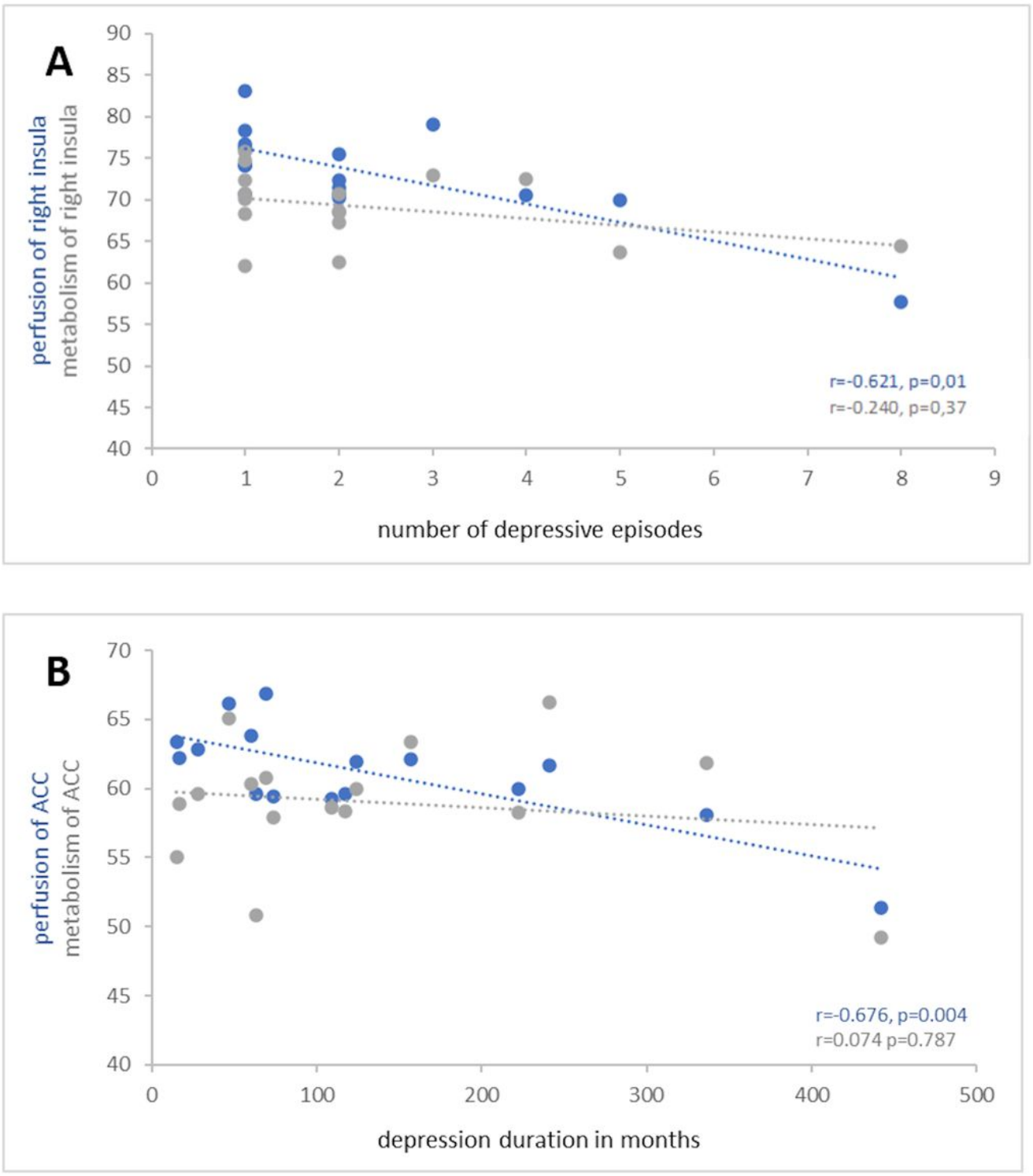

Figure 2

Scatter plot of Spearman's correlations on extracted clusters.A) The increased number of depressive episodes was correlated with decreased SPECT perfusion of the right insula cortex (r=-0.621, p=0.01). No correlation was found between the number of depressive episodes and PET metabolism, and especially the metabolism of the right insula cortex (r=-0.240, p=0.37). B) The increased depression duration was correlated with bilateral decreased SPECT perfusion of the anterior cingulum cortex (ACC; r=-0.676,

p=0.004). No correlation was found between the depression duration and PET metabolism, and especially the metabolism of ACC (r=0.074, p=0.787).