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Short Report

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Long-term prognostic value and clinical correlates of brain [¹⁸F]-FDG PET in patients with post-COVID-19 condition and neurocognitive disorders: a prospective cohort study

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Short communication

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ABSTRACT: (250 words max)

Purpose: Brain [^{18}F]-FDG-PET often reveals cerebral hypometabolism in post-COVID-19 patients experiencing neurocognitive issues, but its prognostic value remains uncertain. We evaluated the long-term utility of [^{18}F]-FDG PET in this population.

Materials and Methods: We reviewed the prospective SYNPOCov cohort (NCT05610436), including WHO-defined post-COVID-19 patients with confirmed SARS-CoV-2 who underwent brain PET scans and had ≥ 1 year of follow-up. Final clinical outcomes were adjudicated as good (no residual disability), partial (improvement but persistent disability), or stable by an expert adjudication committee. PET scans were compared with those of age- and sex-matched pre-pandemic healthy controls ($n=39$). Regional metabolic values were extracted from significant clusters (voxel-level $p < 0.005$; cluster-level $p < 0.05$, FWE-corrected) and associated with demographic and clinical data.

Results: Seventy patients were included (48.3 ± 11.9 years; 69% female; 26.4 ± 9.5 months follow-up), of whom 19, 34, and 17 were classified as having good, partial, and stable clinical outcomes respectively. Baseline imaging demonstrated hypometabolism in four clusters: right frontal, parietal and lateral temporal cortex, and cerebellum. Metabolic values in the right frontal and lateral temporal clusters were significantly lower in previously hospitalized patients and with pre-Omicron variants ($p \leq 0.04$ and $p \leq 0.03$ respectively). However, neither baseline regional metabolism nor its longitudinal evolution on follow-up PET scans ($n=30$) was associated with long-term clinical outcome.

Conclusion: Brain [^{18}F]-FDG PET remains a valuable biomarker of cerebral involvement in post-COVID-19 neurocognitive disorder, revealing metabolic signatures associated with acute disease severity and viral variant. While not predictive of long-term outcome, PET findings improve understanding of factors underlying persistent cerebral dysfunction.

Key Words: long COVID, brain FDG-PET, neurocognitive disorders, prognostic value.

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INTRODUCTION

Post-COVID-19 condition (PCC), recognized by the World Health Organisation [1], refers to the persistence of COVID-19 symptoms three months after the initial infection, affecting up to 6% of initially infected patients [2]. Persistent neurological symptoms, notably fatigue, cognitive impairment, and sleep disturbances, are highly prevalent (20 % of patients) and severely impact quality of life and working ability [3–5]. Given the scale of the pandemic, PCC represents a major global public health challenge.

Brain [^{18}F]-FDG PET has emerged as a valuable tool in the context of PCC, both for differential diagnosis and for the objective detection of brain damage in patients presenting with cognitive impairment [6]. A characteristic pattern of cerebral neuronal dysfunction in cases of long-term COVID-19 has been identified, primarily involving hypometabolism of the orbitofrontal cortex, temporal regions, the brainstem and the cerebellum [7]. Although it is often presumed that these metabolic changes reflect functional and potentially reversible neuroinflammatory processes, their long-term course remains uncertain. A recent study [8] demonstrated that, in patients who had previously been hospitalized in an intensive care unit, cerebral hypometabolism and neuropsychological impairments had not improved significantly after one year. However, it is still unclear whether the severity of these functional brain abnormalities determines the clinical course of patients.

In this context, our study aimed to evaluate the prognostic value of initial brain [^{18}F]-FDG PET in PCC patients. Our primary objective was to determine if regional brain metabolism correlates with long-term clinical outcomes of patients after at least one year of follow-up. Furthermore, as the determinants of this metabolic phenotype remain poorly understood, we sought to identify the demographic and clinical factors influencing cerebral metabolism within this population.

MATERIAL AND METHODS

The database from the SYNPOCov prospective single-center cohort (NCT05610436), including consecutive PCC patients with neurocognitive disorders, between January 2021 and December 2023 was locked. All patients fulfilled the 2021 WHO definition of post-COVID-19 condition [1] and had virologically confirmed SARS-CoV-2 infection. We analyzed data from patients who underwent brain [^{18}F]-FDG PET at initial diagnostic workup and who received standardized clinical follow-up comprising at least two consultations over a minimum period of one year, as well as data from a subgroup of patients with follow-up PET.

Each patient was assessed at the time of diagnosis and during follow-up to determine the number and type of symptoms, the degree of disability, and social outcome, as well as to administer validated clinical questionnaires (a list of all symptoms assessed, and questionnaires performed is provided in Supplementary Table 1). Information regarding the initial infection, specifically whether the patient received outpatient or inpatient care, the variant type (Omicron or pre-Omicron variants), and any comorbidities, including psychiatric history, was also collected. At last follow-up, patients were classified by an expert adjudication committee (FG and EL), acting in strict blindness to one another and to all PET results, into three groups based on outcome: (i) good (absence of residual disability, group 1), (ii) partial (clinical improvement with persistent significant disability, group 2), and (iii) no recovery (stable persistent significant disability, group 3). Cases of classification disagreement between the two experts were reviewed to reach a consensus.

PET was performed in accordance with recent guidelines [9] and acquired on a digital system (Vereos, Philips®) with identical machine, acquisition, reconstruction, and correction parameters between the initial PET scan and the one-year follow-up PET scan, for patient who underwent follow-up PET imaging.

Voxel-by-voxel analyses at the group level were performed via the statistical parametric mapping software SPM 25, run in MATLAB 2025b (MathWorks, Inc., Sherborn, MA). Analyses were performed with t-tests to compare patients with a local database (NCT03345290) of 39 age- and sex-matched pre-pandemic healthy controls and for each group of patients, depending on their final clinical outcomes, each other. A paired comparison between PET performed at inclusion and at follow-up for patient with 2 PET was also performed. Age, sex +/- viral variant or hospitalisation status were treated as continuous or binary variables and used as covariates. A p-voxel value < 0.005 and a p-cluster value < 0.05 with familywise error (FWE) correction, were considered significant. The statistical SPM analyses searched for both hyper and hypometabolism. Significant clusters of metabolisms were extracted at the individual level using Marsbar [10]. Analyses of variance (ANOVA), Student's t-tests

or Welch's t-tests, and multivariable regression analyses were performed to assess associations between PET-derived metabolic measures and patients' health outcomes and clinical characteristics. A correction for multiple comparisons was applied to the primary analyses. Statistical significance was defined as a two-sided p value < 0.05. All analyses were conducted using R software (version 4.6.0).

RESULTS

We analyzed data of 70 patients (age 48.3 ± 11.9 ; 69% women), of whom 30 (age 47.7 ± 8.5 ; 63.3% women) had undergone two PET at one year (See Supplemental Figure 1 for flowchart). Demographic characteristics and information regarding acute SARS-CoV-2 infection are presented in the Table 1. Clinical assessment at baseline and last follow-up are presented in Supplemental Table 1. Mean time interval between the initial clinical visit and the baseline PET was 4.9 ± 4.6 months, and the overall clinical follow-up duration (interval between the first and second clinical visits) was 26.4 ± 9.5 months. At the last follow-up, the outcome was classified as good (group 1) for 19 patients (27%), partial (group 2) for 34 patients (49%), and no recovery (group 3) for 17 patients (24%) (Table 1).

At diagnosis, compared to healthy pre-pandemic healthy control, PCC patients presented four significant hypometabolic clusters: right frontal cortex, right parietal cortex, right temporal region, and cerebellum (Figure 1).

Regarding the primary outcome measure, voxel-by-voxel SPM analyses failed to identify any significant hypometabolic or hypermetabolic clusters associated with the final clinical outcome. Extracted regional metabolic values confirmed this lack of association (Supplemental Text), revealing nearly identical distributions across all clinical trajectories. In the subgroup of patients with longitudinal imaging (n=30), voxel-by-voxel comparisons of initial and follow-up PET scans did not reveal any significant longitudinal metabolic changes and no association with the final outcome was observed.

To respond to our second objective, all demographical and clinical variables presented in Supplemental Table 1 were associated with the metabolic values of extracted clusters in the whole population. Results of univariate analyses are presented in Supplemental Table 2. In multivariate regression analyses, only men status ($\beta = -3.0$, 95%CI [-5.6, -0.53], $p=0.02$), prior hospitalization ($\beta = -3.8$, 95%CI [-7.1, -0.55], $p=0.02$) and infection with a pre-Omicron variant ($\beta = -2.9$, 95%CI [-5.6, -0.14], $p=0.04$) remained independent predictors of extracted clusters hypometabolism (illustrated in Figures 2 and 3).

DISCUSSION

This prospective cohort study aimed to assess the long-term prognostic value of brain [^{18}F]-FDG PET in patients with PCC. Our main finding highlights that neither the severity of initial regional cerebral hypometabolism nor longitudinal variation of metabolic values reliably predicted the long-term clinical outcome in patients with PCC. Interestingly, our exploratory secondary analyses demonstrated that the initial metabolic phenotype is strongly dependent on the severity of the acute phase of the infection, in particular regarding the hospitalisation status and infection with variants preceding Omicron.

Since even if the use of [^{18}F]-FDG-PET for PCC diagnosis has largely been evaluated [11], no study has previously investigated the predictive value of PET for long-term clinical outcomes in a clinically well-characterized prospective cohort of patients.

The lack of correlation between cerebral metabolism and long-term outcome suggests that PCC disability cannot be explained solely by the extent of focal neuroinflammation or neuronal dysfunction. Persistent symptoms are probably driven by multiple interacting mechanisms, including immune, psychological and autonomic factors [11,12]. Consistently, metabolic values were not associated with MoCA scores. Nevertheless, [^{18}F]-FDG PET remains valuable for differential diagnosis and objective assessment of brain involvement in PCC [6].

First-reported factors associated with [^{18}F]-FDG PET hypometabolism have been identified. Patients infected with pre-Omicron variants or requiring hospitalisation showed more pronounced hypometabolism, linking brain metabolic abnormalities with initial disease severity and viral virulence. The third independent factor identified in multivariate analyses is well reported in literature as men status is associated to a lower global metabolism in the brain [13].

Our study has several limitations. Follow-up imaging scans were performed according to clinical need rather than a systematic protocol, introducing selection bias: the [^{18}F]-FDG were not re-checked if the first one was interpreted as normal. Secondly, our classification of clinical outcomes (good, partial, stable), although assessed by a blinded expert panel, remains a pragmatic categorization that may oversimplify the nuanced fluctuations in patients with PCC and the objective reality of the patients' disability.

As a conclusion, although [^{18}F]-FDG is a reliable objective biomarker for identifying brain involvement, with metabolic pattern influenced by the severity of the disease, it cannot, however, serve as a standalone prognostic tool for predicting long-term clinical recovery in individual patients.

172 Management of PCC must therefore remain comprehensive and clinically oriented, as functional
173 neuroimaging explores only one aspect of this persistent multifactorial condition.

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176 **DECLARATIONS**

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180 All authors contributed to the study conception and design. Material preparation, data collection and
181 analysis were performed by all authors. The first draft of the manuscript was written by Heyer and all
182 authors commented on previous versions of the manuscript. All authors read and approved the final
183 manuscript.

184 The datasets generated during and analysed during the current study are available from the
185 corresponding author on reasonable request.

186 This is an observational study. The University Hospital Center Research Ethics Committee has
187 confirmed that no ethical approval is required. National Clinical Trial number: NCT05610436.

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Table 1. Characteristics of the whole study cohort and the subgroup with longitudinal [^{18}F]-FDG follow-up.

	Initial PET	Follow up PET
Numbers of patient, n	70	30
Age (years), mean +/- standard deviation	48.3 $\pm$ 11.9	47.7 $\pm$ 8.5
Sex (women, n (%))	48 (69%)	19 (63%)
Professional activity before the Covid-19 pandemic, n (%)	61 (87%)	28 (93.3%)
Healthcare professional, n (%)	17 (24%)	12 (40%)
Time between initial infection and first consultation (months), median (Q1, Q3)	15 (8, 23)	14.5 (7, 26)
Hospitalization, n (%)	10 (14%)	6 (20%)
PreOmicron variant, n (%)	49 (70%)	23 (77%)
Psychiatric history, n (%)	26 (37%)	11 (37%)
Cardiovascular risk factors, n (%)	35 (50%)	14 (46.6%)
Respiratory diseases, n (%)	22 (31%)	11 (36.6%)
Charlson Comorbidity Index, n (%)		
0	57 (81%)	25 (83.3%)
1	6 (8.6%)	2 (6.7%)
2	5 (7.1%)	3 (10%)
3	1 (1.4%)	0 (0.0%)
4	1 (1.4%)	0 (0.0%)
Clinical outcome		
Group 1, n (%)	19 (27%)	4 (13%)
Group 2, n (%)	34 (49%)	21 (70%)
Group 3, n (%)	17 (24%)	5 (16%)

Group 1: good (no residual disability); Group 2: partial (improvement but persistent disability); Group 3: no recovery (stable persistent disability)

Figures

Figure 1. Surface rendering of the significant hypometabolic clusters in PCC patients compared to healthy controls (p-voxel < 0.005, p-cluster < 0.05 FWE-corrected). Clusters: right prefrontal cortex (X: 42; Y: 58 ; Z: -10, T-voxel max 4.75), right parietal cortex (X:54 ; Y: -22 ; Z: 52, T-voxel max 4.56), right lateral temporal region (X: 66; Y:-10 ; Z: -38, T-voxel max 4.29) and cerebellum (X:16 ; Y: -54 ; Z: -30, T-voxel max 4.09).

Figure 2. Box plots of the regional metabolic values in the right frontal and lateral temporal clusters according to hospitalization status (A, B) and viral variant (C, D). The central horizontal line represents the median, the cross (x) indicates the mean, the box spans the interquartile range (IQR), and the whiskers extend to the minimum and maximum values. P-values were derived from Welch Two Sample t-tests. A reduction in metabolic activity was observed in frontal and temporal clusters in hospitalized patients and patients with pre-Omicron variant.

Figure 3. Hypometabolic clusters identified during voxel-by-voxel SPM analyses (p-voxel value < 0.005 and p-cluster value < 0.05, with FWE correction). A: all patients with age and sex as covariates; B: all patients with age, sex and hospitalisation status as covariates; C: all patients with age, sex and viral variant as covariates. Progressive reduction of significant hypometabolic clusters when adjusting for hospitalization status (B), and their quasi-complete disappearance when adjusting for the pre-Omicron variant (C), suggest that these factors contribute to the hypometabolic brain pattern observed in PCC patients.

Supplemental Text:

Methods

Following an injection of 2 MBq/kg [¹⁸F]-FDG, the patient underwent neurosensory rest for 30 min. Patients were scanned in the supine position with a single bed for an acquisition time of 15 min. All patients were instructed to fast for at least six hours before injection and had a blood glucose level < 10 mmol/L.

The brain [¹⁸F]-FDG-PET images were normalized into the MNI space (National Institute of Montreal) and smoothed via filtering with a 3-dimensional isotropic Gaussian kernel with 4 mm full-width-at-half-maximum. An inclusive mask including the whole cortex, the olfactory bulb, thalamus and basal ganglia, brainstem, and cerebellum, excluding the white matter and cerebrospinal fluid was used to take into account all the brain areas involved in the long COVID hypometabolic pattern. Proportional scaling was performed to give the same global metabolic value to each PET examination.

Results

For the subgroup of patients who underwent longitudinal imaging (n=30), the follow-up PET was performed 16.1 ± 7.1 months after the initial PET, and the mean clinical follow up was 29.4 ± 9.6 months.

For instance, mean proportional scaled metabolic values in the cerebellum cluster were 86.9 ± 4.6 kBq/ml for group 1, 88.1 ± 5.7 kBq/ml for group 2, and 89.4 ± 7.1 kBq/ml for group 3 (p=0.77). Similar strictly overlapping metabolic distributions were observed in the right frontal, right parietal, and right temporal clusters (p≥0.77).

No significant association was found between the metabolic values of extracted clusters from the second PET scan and clinical outcomes (p≥0.81).

Supplemental Table 1. Descriptive statistics of clinical characteristics at initial consultation and follow-up consultation

Initial Consultation						Follow-up consultation					
Characteristics	G1 (n=19)	G2 (n=34)	G3 (n=17)	Total (N=70)	P*	Characteristics	G1 (n=19)	G2(n=34)	G3 (n=17)	Total (N=70)	P*
Number of symptoms. median [Q1 ; Q3]	7 [5;10]	9.5 [7;11]	10 [8;11]	9 [7;11]	0.01	Number of symptoms. median [Q1 ; Q3]	3 [2;4]	7 [5;8]	10 [7;11]	6.5 [4;9]	<0.001
Asthenia. n (%)	19/19 (100%)	34/34 (100%)	17/17 (100%)	70/70 (100%)	/	Asthenia. n (%)	12/19 (63%)	33/34 (97%)	17/17 (100%)	62/70 (89%)	<0.001
Cardiopulmonary symptoms. n (%)	14/19 (74%)	34/34 (100%)	17/17 (100%)	65/70 (93%)	<0.001	Cardiopulmonary symptoms. n (%)	5/19 (26%)	26/34 (76%)	16/17 (94%)	47/70 (67%)	<0.001
Anosmia/Agueusia. n (%)	6/19 (32%)	10/34 (29%)	7/17 (41%)	23/70 (33%)	0.89	Anosmia/Agueusia. n (%)	1/19 (5%)	9/34 (26%)	8/17 (47%)	18/70 (26%)	0.02
Cognitive impairment. n (%)	19/19 (100%)	34/34 (100%)	17/17 (100%)	70/70 (100%)	/	Cognitive impairment. n (%)	12/19 (63%)	33/34 (97%)	16/17 (94%)	61/70 (87%)	<0.001
Arthromyalgia. n (%)	10/19 (53%)	28/34 (82%)	15/17 (88%)	53/70 (76%)	0.006	Arthromyalgia. n (%)	4/19 (21%)	25/34 (74%)	15/17 (88%)	44/70 (63%)	<0.001
Digestive symptoms. n (%)	9/19 (47%)	22/34 (65%)	14/17 (82%)	45/70 (64%)	0.07	Digestive symptoms. n (%)	4/19 (21%)	15/34 (44%)	10/17 (59%)	29/70 (41%)	0.03
Hyperventilation syndrome. n (%)	9/18 (50%)	27/34 (79%)	15/17 (88%)	51/69 (74%)	0.007	Hyperventilation syndrome. n (%)	2/19 (11%)	14/33 (42%)	14/16 (88%)	30/68 (44%)	<0.001
Postural tachycardia syndrome. n (%)	7/19 (37%)	7/34 (21%)	6/17 (35%)	20/70 (29%)	0.35	Postural tachycardia syndrome. n (%)	2/19 (11%)	3/34 (9%)	3/17 (18%)	8/70 (11%)	0.88
Clinical scores:						Clinical scores:					
Montral Cognitive Assessment. median [Q1 ; Q3]	25 [22.5;27.5]	25 [23.2;27]	25 [22;27]	25 [22;27]	>0.99	Montral Cognitive Assessment. median [Q1 ; Q3]	27 [26;28.2]	27 [26;28]	26 [23;28]	27 [25;28]	0.24
HAD Anxiety subscale. median [Q1 ; Q3]	8 [6;13]	9 [5;15]	8 [6;12]	8 [6;13]	>0.99	HAD Anxiety subscale. median [Q1 ; Q3]	5 [3;8]	9 [5;11.8]	10 [6;13]	8 [4.8;11]	0.015
HAD Anxiety >10. n (%)	8/19 (42%)	11/33 (33%)	7/17 (41%)	26/69 (38%)	0.64	HAD Anxiety >10. n (%)	3/17 (18%)	10/34 (29%)	8/17 (47%)	21/68 (31%)	0.17
HAD Depression subscale. médiane [Q1 ; Q3]	7 [4.5;11]	7 [6;11]	9 [6;13]	8 [5;12]	0.42	HAD Depression subscale. médiane [Q1 ; Q3]	4 [1;6]	7.5 [3;11]	13 [9;15]	7.5 [3;11]	0.002
HAD Depression >10. n (%)	7/19 (37%)	11/33 (33%)	8/17 (47%)	26/69 (38%)	0.92	HAD Depression >10. n (%)	1/17 (6%)	12/34 (35%)	10/17 (59%)	23/68 (34%)	0.004
Chalder global scale. median [Q1 ; Q3]	24 [23;28.8]	29 [25;31.2]	30 [29;31]	29 [23.5;31]	0.021	Chalder global scale. median [Q1 ; Q3]	14.5 [11.8;22]	24 [20;29]	30 [27;31]	23 [17.5;29]	<0.001
Chalder physical scale. median [Q1 ; Q3]	17 [14;19]	18.5 [14.8;20.2]	19.5 [18;21]	18 [15;20]	0.07	Chalder physical scale. median [Q1 ; Q3]	9.5 [7;14]	14 [13;19]	19 [18;21]	14 [12.2;19]	<0.001
Chalder mental scale. median [Q1 ; Q3]	9 [7;11.8]	10.5 [9;12]	11 [10;12]	10.5 [9;12]	0.06	Chalder mental scale. median [Q1 ; Q3]	5.5 [4;8]	9 [7;12]	11 [9;12]	9 [6.2;11]	<0.001

* Comparison between G1 versus (G2+G3). Khi2 test for qualitative variables and Mann Whitney test for quantitative variables.

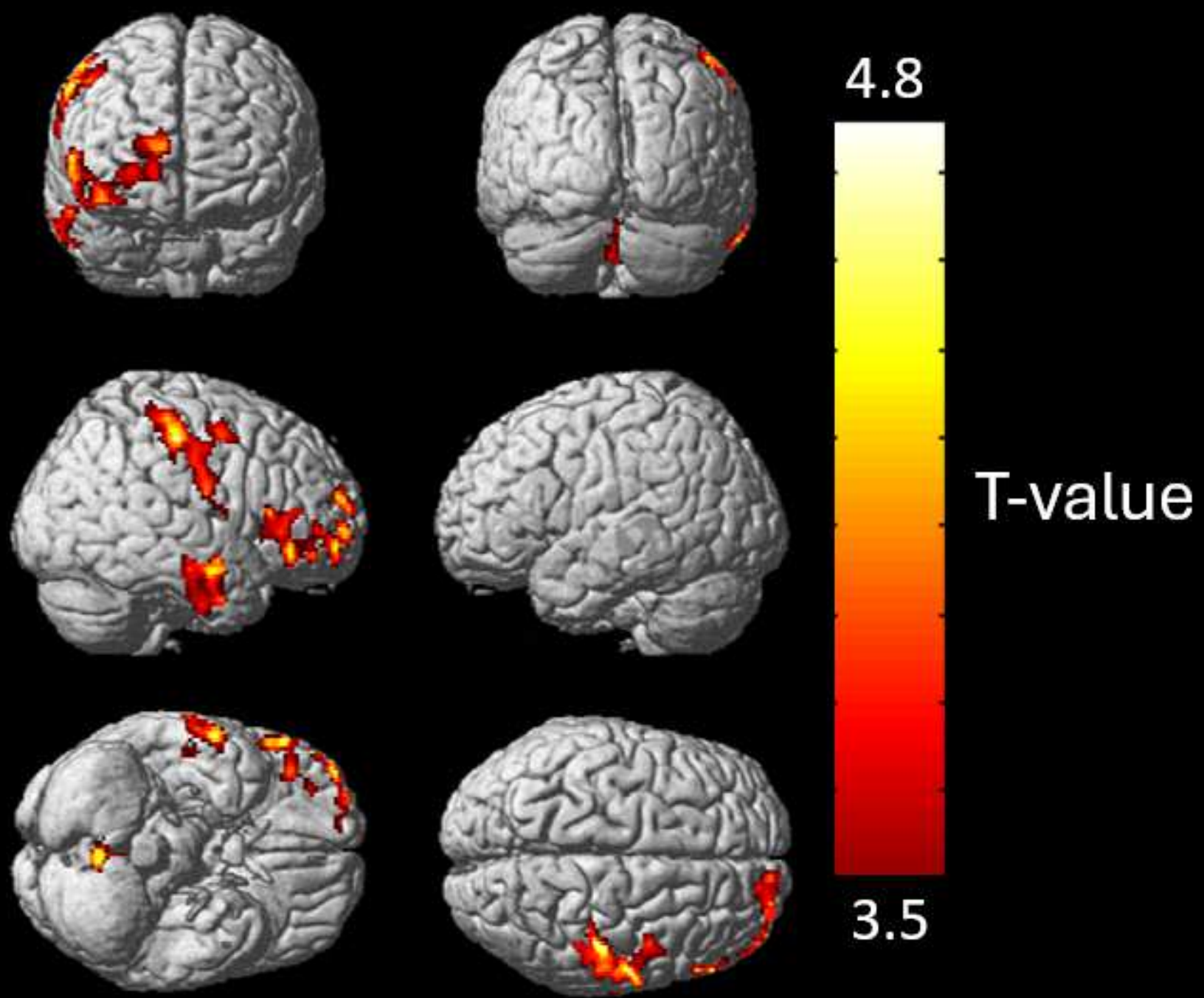
Supplemental Table 2: Variables significantly associated or correlated with metabolic values at initial [¹⁸F]-FDG PET in univariate analyses. P-values were derived from Welch Two Sample t-test or Correlation. All these analyses are purely exploratory.

Variables	Brain areas	p-value	Associations/Correlations
INITIAL PET			
DEMOGRAPHIC VARIABLES			
Age	Cerebellum	0.011	Positive correlation: older age is associated with higher cerebellar metabolism.
Hospitalization status	Right frontal and temporal	0.0376 and 0.0247	Patients who were hospitalized presented lower metabolism.
PreOmicron variant	Right frontal and temporal	0.0199 and 0.0191	Patients with pre-Omicron variant presented lower metabolism.
Charlson Comorbidity Index	Cerebellum	0.006	Positive correlation: high Charlson Comorbidity Index is associated with higher cerebellar metabolism.
Professional activity before Covid-19 pandemic	Cerebellum	0.010	Patients who are in employment have lower cerebellar metabolism.
Cardiovascular risk factors	Cerebellum	0.048	Presence of cardiovascular risk factors is associated with higher cerebellar metabolism.
CLINICAL VARIABLES			
Fever ¹	Right Parietal	0.003	Fever is associated with a lower metabolism in the right parietal lobe.
Ageusia ¹	Right Frontal	0.041	Ageusia is associated with a lower right frontal metabolism.
Sleep disorder ¹	Right Parietal	0.026	A sleep disorder is associated with a higher right parietal metabolism.
HAD Depression subscale (score > 10) ²	Cerebellum	0.03	A score > 10 to the HAD depression subscale is associated with a lower cerebellum metabolism at follow up.
Fever ²	Right Parietal	0.002	Fever is associated with higher metabolism in the right parietal lobe at follow up.
Skin and appendage disorders ²	Right Temporal	0.005	Skin and appendage disorders is associated with a lower right temporal metabolism at follow up.

¹Initial consultation; ²Follow-up consultation

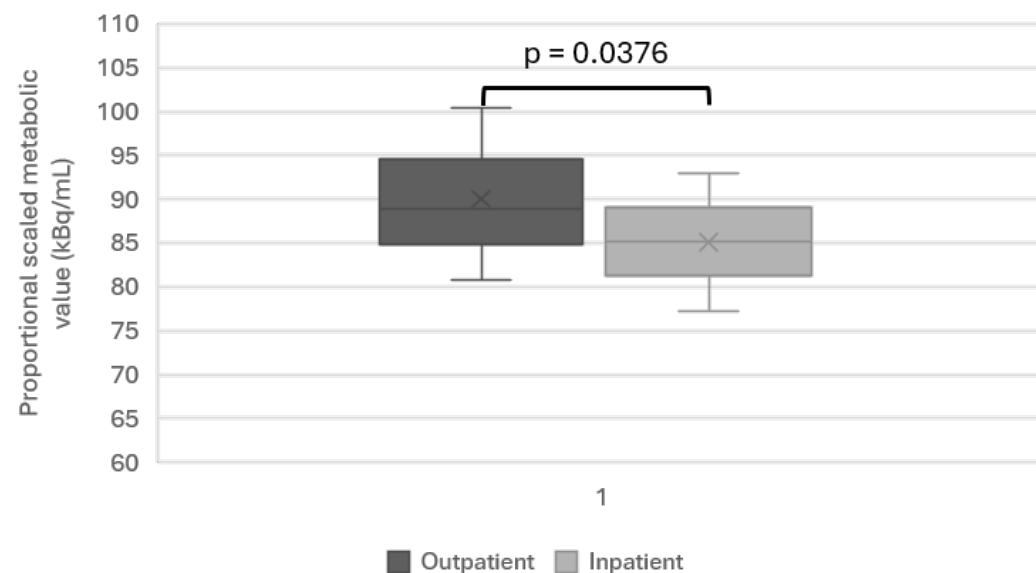
Supplemental Figure

Supplemental Figure 1. Flowchart

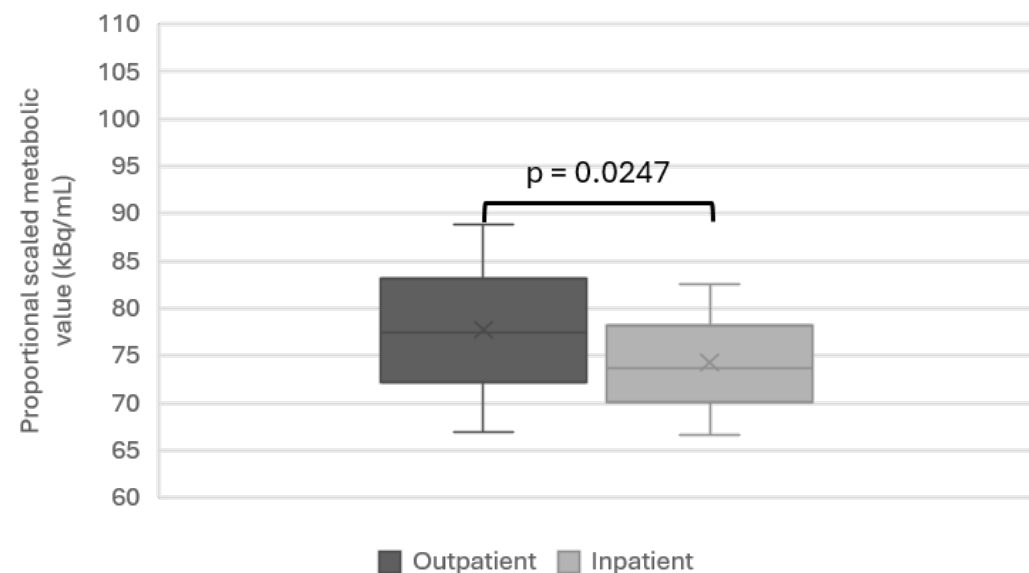


A

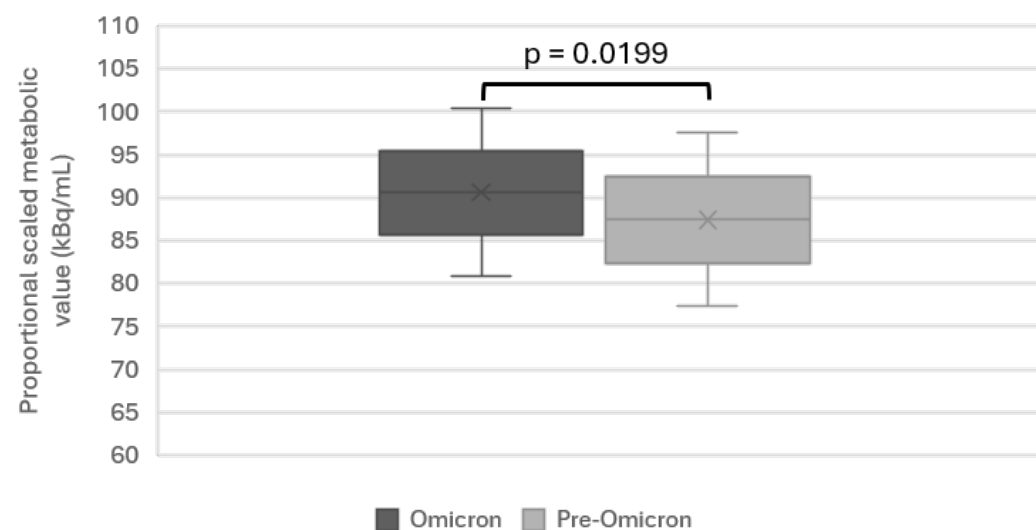
Right frontal cluster

**B**

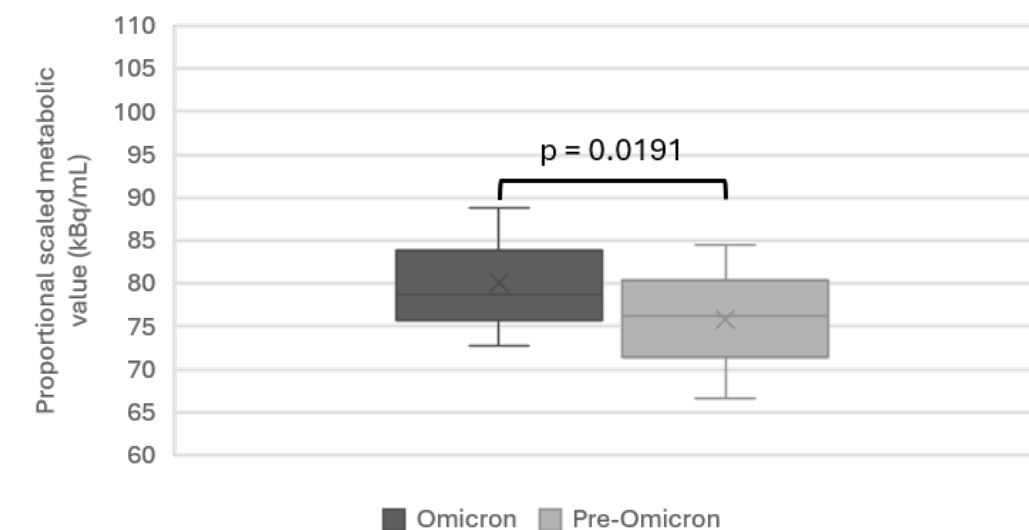
Right lateral temporal cluster

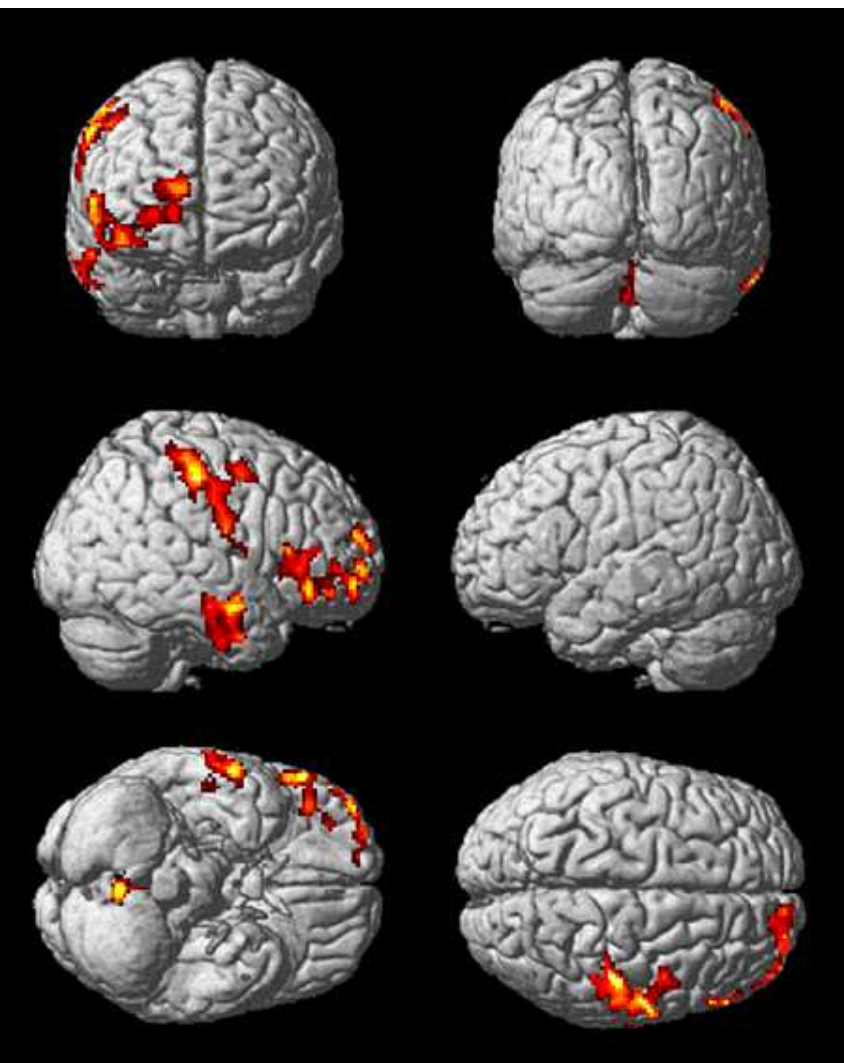
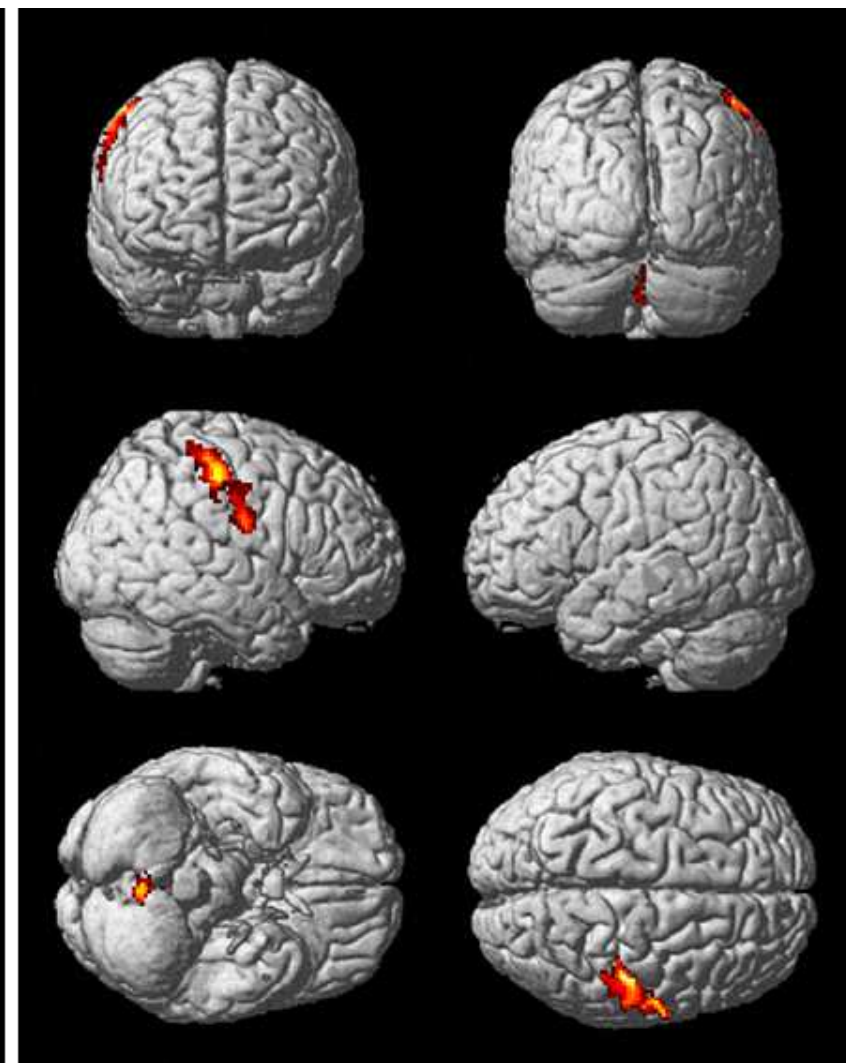
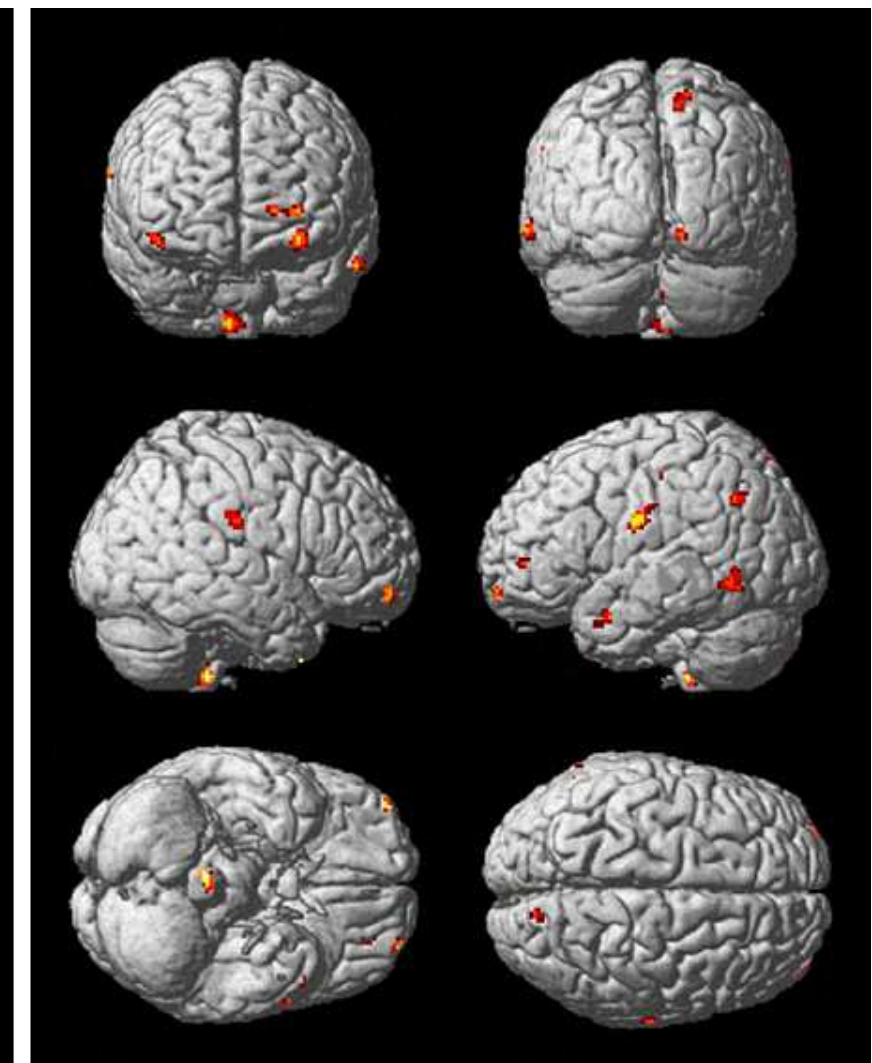
**C**

Right frontal cluster

**D**

Right lateral temporal cluster





Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementalfigure1.pptx](#)