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**The complexity of the relationship between spontaneous brain activity
and glucose metabolism**

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Abstract

Brain glucose metabolism as assessed by [^{18}F]FDG positron emission tomography (PET) is expected to be significantly related to resting-state functional MRI (rs-fMRI) activity and functional connectivity (FC), but the underlying coupling model is still incompletely understood. Employing simultaneous acquisitions, we related [^{18}F]FDG standard uptake value ratio (SUVR) to 50 features pertaining to rs-fMRI 1) signal, 2) hemodynamic response, 3) static and 4) time-varying FC, and 5) phase synchronization. To assess which rs-fMRI variables better describe SUVR across regions, we employed a hierarchical approach, identifying the model at population level, and then estimating it on individual data. Multilevel modelling explained around 40% of the SUVR variance, with signal-related features as the most relevant fMRI variables. When the model was used to characterize between-network variability of the SUVR-fMRI coupling, the ranking changed. We demonstrate that local activity and synchronization are the most important predictors of glucose metabolism, while large-scale FC properties gain importance within specific networks.

Introduction

Brain glucose consumption can be assessed *in vivo* by [^{18}F]fluorodeoxyglucose positron emission tomography ([^{18}F]FDG PET) acquisitions¹, usually through semi-quantitative proxies like the standard uptake value ratio (SUV_R)². As evidenced by [^{18}F]FDG studies, glucose metabolism displays significant regional variability. The reasons behind this heterogeneity in glucose expense, however, remain largely unexplained. Crucially, most of the remarkable metabolic budget of the brain, ~25% of energy in the face of only 2% of body weight, is spent during rest^{3,4}. This ‘dark energy’ of the brain⁵ with unclear functional meaning is expected to be mainly employed for maintaining resting potentials and subthreshold synaptic transmission⁶, since most of the energy budget of a neuron is utilized at the level of the synapses, rather than in the neuron’s body⁷.

The regional differences in brain metabolism are thus likely to be explained by variability in spontaneous activity, which has been extensively explored with blood-oxygen-level-dependent (BOLD) resting-state functional magnetic resonance imaging (rs-fMRI)^{8,9}. In addition to spontaneous activity, the functional relationships between activity patterns of different brain regions may relate to glucose consumption as well¹⁰. To this purpose, rs-fMRI can be used to derive the so-called “functional connectivity” (FC), i.e., the statistical relation between BOLD signal fluctuations in different brain regions; this approach has led to the identification of a functional architecture of resting-state networks (RSNs) that recapitulate clusters of regions activated for specific functions^{11,12}. FC can be estimated in a static fashion (sFC), but also with time-varying approaches (tvFC), which interpret FC as non-stationary and changing across adjacent time windows¹³; notably, both might prove relevant to metabolic consumption.

Metrics derived from network science can then be used to characterize the topology of sFC and tvFC, with correlations between areas represented as ‘edges’ connecting ‘nodes’, and nodes described in terms of their centrality (‘hubness’), number of connections, and so on^{14,15}.

While rs-fMRI studies have provided a wide range of information on the properties of spontaneous activity, the physiological underpinnings of these results remain poorly understood, as the BOLD signal arises from a complex combination of cerebral blood volume (CBV), blood flow (CBF) and metabolic rate of oxygen (CMRO₂)^{17,18}, and is indirectly and nonlinearly related to neuronal activity through the hemodynamic response function (HRF)¹⁹; importantly, it is also subjected to significant contamination from systemic modulations, both hemodynamic (heart rate variability, vasomotion etc.) and respiratory (e.g., respiratory volume variability)²⁰.

Building upon the previous considerations, the relationship between the information provided by rs-fMRI and [^{18}F]FDG PET across brain regions needs to be thoroughly investigated with two main aims.

89 First, to better understand the sources of regional metabolic variability. In particular, we might
90 wonder: 1) how much is the ‘dark energy’ of the brain related to local activity probed by the BOLD
91 signal? 2) how much is instead related to local synchronization of the BOLD signal, i.e., a possible
92 measure of neural population excitatory-inhibitory balance? 3) does inter-regional static synchrony
93 play a more relevant role than more dynamic, time-varying interactions?

94 Second, the biological basis of the BOLD signal needs to be further characterized, an effort that would
95 help turn rs-fMRI into a more specific biomarker; [¹⁸F]FDG PET, being tightly linked to neural
96 activity⁷, despite its typically low temporal resolution, can provide important insight.

97 Some evidence on this relationship has started to emerge from sequential and simultaneous [¹⁸F]FDG
98 PET/fMRI acquisitions²¹. In particular, the mean BOLD signal and the amplitude of its low frequency
99 fluctuations (ALFF) have been found to be associated with [¹⁸F]FDG SUVR across voxels²², with
100 stronger correlations in specific brain regions^{23,24}. With regard to the coupling between FC and
101 metabolism, moderate associations between SUVR and global FC metrics were detected^{23,25}, with
102 stronger and more consistent correlations for the regional homogeneity (ReHo) of BOLD (up to
103 Pearson’s $r = 0.8$), which is an index of local synchronization^{26,27}. The topology of FC was also found
104 to be important, with more central nodes having a stronger relationship between their FC and
105 metabolic consumption²³. In addition, the relationship between SUVR and local and global FC has
106 been described as a power law or exponential model, especially in some specific networks^{25,28}. The
107 variability in the [¹⁸F]FDG-fMRI coupling across networks has been highlighted in multiple previous
108 studies^{23,24}, with demarcation between visual and default mode regions on one side, and frontoparietal
109 regions on the other²⁸. When the [¹⁸F]FDG-fMRI coupling is assessed across subjects, however, much
110 lower correlations between SUVR and rs-fMRI variables are detected in many studies^{23,26,27}. In
111 summary, somewhat inconsistent results emerge from the literature, with bivariate spatial correlations
112 between [¹⁸F]FDG PET and a handful of BOLD-derived metrics (ALFF, ReHo, voxel-wise FC)
113 ranging from 0 to 0.64 in explained variance (R^2), and substantial differences across brain regions
114 and networks, as well as a low correlation across subjects even in simultaneous acquisitions^{23,27}.

115 Notably, no study has ever attempted a multivariate integration of a wider range of rs-fMRI features,
116 as well as a multilevel prediction of SUVR both at the population level and at the subject/network
117 level.

118 We set out to fill these gaps in knowledge with a fully data-driven approach using simultaneously
119 acquired [¹⁸F]FDG PET and rs-fMRI data from two separately published datasets of 26 subjects^{23,31}.
120 After preliminary assessment of 50 rs-fMRI-derived variables, pooled into 5 categories, i.e., 1) signal,
121 2) HRF, 3) sFC, 4) tvFC, and 5) phase coherence (PC)²⁹ (see **Table 1** for the list of the features, their
122 acronyms and a brief description) we set out to address the following questions.

123 1. which is the strength of the bivariate association between these rs-fMRI features and SUVR across
124 the whole brain? And then, since regions with high vs. low metabolic consumption are expected to
125 have quite different structural and functional properties^{1,3,4}, does this coupling change according to
126 the ranking of brain nodes based on SUVR?

127 2. is it possible to explain group level SUVR variance across regions by combining rs-fMRI features,
128 for the first time, into a multiple regression model? Is the group of selected features more populated
129 by local or large-scale brain network metrics, and does it account for between-subject variability
130 (BSV)³⁰? Finally, which of the previously identified rs-fMRI features are more important to explain
131 SUVR when multilevel modelling is performed across RSNs, i.e., which is the between-network
132 variability (BNV) of the SUVR-fMRI association?

133

134 ***Table 1 – Extracted rs-fMRI features and their categories***

135 Fifty fMRI-derived variables, divided according to the pool to which they belong: 1) signal, 2)
136 hemodynamic response function (HRF), 3) static functional connectivity (sFC), 4) time-varying
137 functional connectivity (tvFC), 5) phase coherence (PC). See **Supplementary Methods** for full
138 description of the features.
139

Pools	rs-fMRI Variables
Signal	med-BOLD : median of the BOLD time series
	MAD-BOLD : median absolute deviation (MAD) of the BOLD time series
	skew-BOLD : skewness of the BOLD time series
	ApEn-BOLD : approximate entropy (ApEn) of the BOLD time series
	rApEn-BOLD : range ApEn of the BOLD time series
	AR-BOLD : reflection coefficient of the first-order autoregressive AR(1) model fit to BOLD time series
	ALFF : amplitude of low frequency fluctuations (ALFF) of BOLD time series
	ReHo : regional homogeneity of BOLD time series
	MAD-ReHo : MAD of the time-varying ReHo (tvReHo)
	CV-ReHo : CV% of tvReHo
	peaks-BOLD : number of BOLD pseudo-events
HRF	peak-HRF : height of HRF peak
	hrf-DEG : degree (DEG) of HRF correlation matrix
	hrf-STR : strength (STR) of HRF correlation matrix
	hrf-CC : clustering coefficient (CC) of HRF correlation matrix
	hrf-BC : betweenness centrality (BC) of HRF correlation matrix
	hrf-EC : eigenvector centrality (EC) of HRF correlation matrix
	hrf-LE : local efficiency (LE) of HRF correlation matrix
	hrf-GE : global efficiency (GE) of HRF correlation matrix
sFC	s-DEG : DEG of sFC
	s-STR : STR of sFC
	s-CC : CC of sFC
	s-BC : BC of sFC
	s-EC : EC of sFC
	s-LE : LE of sFC
	s-GE : GE of sFC

tvFC	mdiff-DEG: temporal median of the absolute value of 1 st order differentials (mdiff) of DEG time series
	mdiff-STR: mdiff of STR time series
	mdiff-CC: mdiff of CC time series
	mdiff-BC: diff of BC time series
	mdiff-EC: mdiff of EC time series
	mdiff-LE: mdiff of LE time series
	mdiff-GE: mdiff of GE time series
	CV-DEG: coefficient of variation (CV%) of DEG time series
	CV-STR: CV% of STR time series
	CV-CC: CV% of CC time series
	CV-BC: CV% of BC time series
	CV-EC: CV% of EC time series
	CV-LE: CV% of LE time series
	CV-GE: CV% of GE time series
	SampEn-DEG: sample entropy (SampEn) of DEG time series
	SampEn-STR: SampEn of STR time series
	SampEn-CC: SampEn of CC time series
	SampEn-BC: SampEn of BC time series
	SampEn-LE: SampEn of LE time series
	SampEn-GE: SampEn of GE time series
PC	med-LEig: median of the Leading Eigenvector (LEig)'s time series
	MAD-LEig: MAD of LEig time series
	CV-LEig: CV% of LEig time series
	mdiff-LEig: mdiff of LEig time series

Results

Feature extraction and preliminary evaluation of rs-fMRI variables

The flowchart describing the preprocessing and preliminary analysis of the [¹⁸F]FDG PET and rs-fMRI data is shown in **Figure 1** (see the **Methods** section for details).

The [¹⁸F]FDG PET variable of interest is the SUVR, which was extracted for every region of the Schaefer cortical atlas³² (200 parcels, supplemented by 18 subcortical regions³³) in each subject, and will be considered as the dependent variable in every modelling approach from here onward.

The 50 rs-fMRI variables, extracted at the single-subject level and *a priori* subdivided into 5 pools, are reported in **Table 1**: the signal pool (1) contains features related to the basic statistics of the BOLD time series (median, variance, skewness), its complexity, its low-frequency fluctuations (ALFF), local coherence (ReHo) and high-amplitude events (peaks-BOLD); in the HRF pool (2), then, we placed the amplitude of the HRF peak, calculated using a blind deconvolution method³⁴, and the HRF correlation structure across regions described by means of graph properties; the sFC pool (3) characterizes FC calculated across the entire fMRI scan with graph theory metrics; the tvFC pool (4) assesses graph metrics' temporal variability across sliding windows¹³; finally, the PC pool (5) characterizes FC as coherence of BOLD phase²⁹.

158 **Figure 1 – Flowchart of rs-fMRI and [¹⁸F]FDG PET processing, feature extraction and analysis.**
 159 Both rs-fMRI time series and [¹⁸F]FDG SUVR data were parceled using the Schaefer cortical atlas
 160 (200 ROIs) and 18 subcortical ROIs. The parcel-wise rs-fMRI data were used to extract fifty features
 161 representative of five pools, i.e., 1) signal, 2) HRF, 3) sFC, 4) tvFC, 5) PC. The PET-fMRI coupling
 162 was investigated using bivariate correlation and multivariable multilevel modelling across subjects
 163 and across fMRI-based RSNs.

168 The Spearman's correlation matrix between the 50 rs-fMRI variables at group median level (i.e., by
169 taking the parcel-wise median value of each feature across subjects) was computed (**Figure 2a**), in
170 order to assess the relationships between the extracted features and their degree of redundancy: the
171 clustering into 5 pools provided by *a priori* knowledge was fairly consistent with the observed
172 correlation structure, with signal, HRF and sFC features (*upper block*) being clearly distinguished
173 from tvFC features (*lower block*), which they are negatively correlated with, and PC variables
174 demonstrating lower correlation with the rest. However, it was also noticeable that strong correlations
175 between many variables were present, especially for the tvFC pool, and that a feature selection step
176 was going to be necessary to use these variables in a numerically sound multivariable model of
177 SUVR: the condition number $\kappa(X)$, which quantifies the level of correlation between predictors in a
178 multiple regression context (i.e., their multicollinearity), was high ($\kappa(X) = 70.58$), way beyond the
179 acceptability range³⁵, and this is known to result in unstable and unreliable models (see **Methods**).

180

181

182 **SUVR vs. rs-fMRI: bivariate relationships**

183 Before moving to the multiple regression framework, we began by investigating bivariate associations
184 between SUVR and the extracted rs-fMRI variables at the group level, in the so-called naïve average
185 data approach (NAD), as done by many previous studies^{23,25,26}; here, however, a much wider range
186 of fMRI-derived variables was explored. Many significant spatial associations between SUVR and
187 rs-fMRI features were detected across the 218 analyzed regions, as assessed through Spearman's rank
188 correlation ($p = 0.05$ significance level) with false discovery rate (FDR) multiple comparison
189 correction³⁶. The correlation coefficients are reported in **Figure 2b**.

190

191

192 **Figure 2 – Bivariate correlations among rs-fMRI variables, and between rs-fMRI variables and**
 193 **SUVR.** The pattern of Spearman's correlations (FDR-corrected, non-significant values shown in

194 white) among rs-fMRI features, assessed at the group level and divided according to the pool to which

195 they have been assigned (1) signal, 2) HRF, 3) sFC, 4) tvFC, 5) PC), is shown in (a). The rs-fMRI

196 features are tested for association with group median SUVR across 218 brain regions (b) via

197 Spearman's correlations (significant values after FDR correction are indicated with an asterisk).

200 The strongest *positive* associations were with 1) ReHo ($\rho = 0.45$, $p < 0.001$), 2) s-BC ($\rho = 0.4$, $p <$
 201 0.001), and 3) SampEn-BC ($\rho = 0.44$, $p < 0.001$), i.e., respectively 1) a measure of local
 202 synchronization of BOLD, 2) a sFC graph metric, betweenness centrality (BC), which describes a
 203 node in terms of its *global* connections in a graph, and 3) a measure of temporal complexity of the
 204 BC time series. The strongest *negative* correlations were mdiff-BC ($\rho = -0.42$, $p < 0.001$) and CV-
 205 BC ($\rho = -0.42$, $p < 0.001$) in the tvFC pool, both measures of temporal variability of BC.
 206 In general, it can be noted that positive associations emerged for the majority of the signal-based,
 207 HRF and sFC-related features, while tvFC metrics displayed a consistent and never previously
 208 reported negative association with SUVR (**Figure 2b**). Notable exceptions amongst signal-based
 209 features are rApEn-BOLD ($\rho = -0.31$, $p < 0.001$), a measure of BOLD signal complexity, and peaks-
 210 BOLD ($\rho = -0.34$, $p < 0.001$), which quantifies the number of signal peaks exceeding one standard
 211 deviation from the baseline: both exhibited negative relationships with SUVR. Amongst tvFC
 212 features, SampEn-BC ($\rho = 0.44$, $p < 0.001$) shows a strong positive coupling with SUVR, in contrast
 213 to the behavior of the other tvFC metrics. Interestingly, the dynamics of local synchronization, i.e.,
 214 MAD-ReHo and CV-ReHo, displays a positive association with SUVR as well.
 215 Overall, it can be noted that the detected spatial correlations were at best moderate.

217 *SUVR-fMRI associations are strengthened in low SUVR nodes*

218 As the relationship between [^{18}F]FDG PET and rs-fMRI could be spatially heterogeneous,
 219 Spearman's correlations were also re-evaluated across groups of nodes selected according to linearly
 220 increasing percentiles of the SUVR distribution, i.e., by progressively retaining the highest SUVR
 221 values, from the 1st up to the 85th percentile, as well as linearly decreasing percentiles of the same
 222 distribution, i.e., by retaining the lowest SUVR values, from the 100th to the 15th (**Supplementary**
 223 **Figure S1**). The purpose of the analysis was to verify whether SUVR-fMRI associations would be
 224 strengthened in high SUVR nodes or, conversely, in low SUVR nodes, as SUVR provides a clear
 225 ranking of brain regions, that is expected to be related to crucial structural and functional properties,
 226 e.g., neuron-to-glia ratio, richness in neuroreceptors, excitatory-inhibitory activity^{1,3,4}.
 227 Spearman's correlations ($p = 0.05$ significance level, FDR-corrected) between parcel-wise SUVR and
 228 all 50 rs-fMRI features (*rows*) are shown in **Figure 3a**, for each of the threshold levels along the
 229 SUVR distribution (*columns*). Going towards nodes with high SUVR (*right side of Figure 3a*) does
 230 not lead to any relevant effect for most features (except for three measures): therefore, hardly any
 231 strengthening of SUVR-fMRI relationships is detected in high SUVR nodes.
 232 Interestingly, however, a marked increase in many of the bivariate associations can be observed by
 233 selecting nodes with low values of SUVR (*left side of Figure 3a*), with highly significant correlations
 234 even after FDR correction.

235 **Figure 3 – The SUVR-*fMRI* correlation changes strongly in low SUVR nodes.**

236 Spearman's correlations (FDR-corrected, non-significant values shown in white) between SUVR and
237 all fifty rs-fMRI features (*y axis*) across nodes selected according to linearly increasing (*x axis - right*)
238 and decreasing (*x axis - left*) percentiles of SUVR (**a**). The dashed black line shows the percentile
239 with maximum correlation across features (i.e., nodes in the 1st - 40th percentile range). The histogram
240 (**b**), on the right, highlights the chosen percentile in the SUVR distribution and the range of percentiles
241 included in the correlation. The brain regions shown on the left, plotted on the cortical surface and
242 subcortex, are the parcels over which correlations are assessed.

We then identified the percentile threshold corresponding to the highest total correlation value across features: the spatial pattern of the 87 nodes below the 40th percentile of the SUVR distribution is shown in **Figure 3b**. These parcels, where the SUVR-fMRI association is emphasized, mainly belong to temporal/limbic areas (including hippocampus), sensorimotor cortices, and subcortical regions, such as cerebellum and globus pallidus (**Supplementary Figure S1**).

This finding suggests the presence of *nonlinear* relationships between [¹⁸F]FDG SUVR and most rs-fMRI features: tighter and more linear associations are present across a limited range of low SUVR nodes, with weaker coupling as SUVR gets higher. This nonlinear association was thus further characterized (see **Supplementary Results**), expanding on previous studies which were focused on specific networks and features^{25,28}.

SUVR vs. rs-fMRI: multivariable multilevel model

We then set out to assess which combination of rs-fMRI features was better able to explain SUVR across brain regions with multiple regression and multilevel modelling, in a fully data-driven way. In multilevel modelling, the model structure is usually known, or selected at the lower level, i.e., at the individual level³⁰. However, as significant BSV in the SUVR-fMRI association is expected, especially for the rs-fMRI features, we chose to identify the model predictors at the population level (NAD approach), thus exploiting the denoising properties of averaging. The model structure selected at the group median level was then used for multilevel modelling across subjects to characterize the BSV of the SUVR-fMRI association, as shown in (**Figure 4, top**), trying to fully capitalize on the fact that [¹⁸F]FDG and rs-fMRI data were acquired in the same subjects.

Maximum explanatory power of SUVR:

To assess the maximum explanatory power provided by the fMRI-derived features, we began by fitting an ordinary least squares (OLS) multiple regression model employing *all* the available features in a log-linear form (i.e., exploring the relationship between SUVR and the log-transformed rs-fMRI explanatory variables), to account for the detected nonlinearity (**Supplementary Results**): it can in fact be noted that the log-linear pairwise relationship between SUVR and each of the rs-fMRI features outperformed to the linear model in many occasions (62%). From now we will call this log-linear model.

The OLS model had an R² value of 0.62: the maximum explanatory power thus reaches up to around 60% of the SUVR variance, without fully saturating the variance despite marked overparameterization (i.e., 50 rs-fMRI predictors). Due to the high number of predictors and the presence of multicollinearity, the precision of numerous parameter estimates (expressed as coefficients of variation, CVs%)³⁷ was low, as expected (**Supplementary Figure S3c**).

280 **Figure 4 – Multilevel modelling approach for subjects and networks.** The multivariable model
 281 structure defined at the population level for the SUVR-fMRI relationship was used in a hierarchical
 282 model. The multilevel approach was first applied to individual data with subjects (S , *top*), then with networks (N , *bottom*): fixed effects θ_S and θ_N describe the population
 283 parameters, and random effects η_{Si} and η_{Nj} describe how much each subject i or network j deviates
 284 from the population fixed effects for each of the selected parameters, i.e., the between-subject
 285 variability (BSV) and between-network variability (BNV) of the SUVR-fMRI model.
 286

290 Assessment of a parsimonious and informative group level multivariable model:

291 Multiple feature selection approaches (eleven methods) were then explored. The results of each and
292 the reason for the choice of the optimal approach are detailed in **Supplementary Results**.

293 The chosen feature selection process was performed in two stages. First, a sign-constrained non-
294 negative least squares (NNLS) estimator³⁸ was employed; then, the NNLS estimates were refined
295 with a second stage of feature selection with elastic net regression³⁹. The reached solution was optimal
296 in comparison with the other ten methods, in terms of both goodness of fit ($R^2 = 0.411$) and precision
297 of the estimates ($CVs\% \mu \pm \sigma = 66.73 \pm 17.79 \%$). The selected rs-fMRI predictors are: 1) ApEn-
298 BOLD, 2) rApEn-BOLD, 3) ReHo, 4) CV-ReHo, 5) peaks-BOLD, 6) hrf-LE, 7) s-BC, 8) CV-BC, 9)
299 med-LEig.

300 The first five predictors belong to the signal and local synchronization pool, while the other four to
301 the remaining groups of rs-fMRI features, suggesting only an *indirect* relationship with the large-
302 scale network connectivity measures. Notably, most of the identified rs-fMRI predictors were chosen
303 with high consistency across the employed feature selection methods, which highlights the robustness
304 of their association with SUVR (**Supplementary Figure S4, Supplementary Figure S5**).

305

306 Multivariable multilevel model across subjects:

307 The hierarchical modelling framework was then applied to the individual data using the identified
308 predictors, to characterize the BSV of the SUVR-fMRI association. The log-linear model identified
309 at the group level was re-estimated using a linear mixed-effect (LME) approach³⁰. The fixed-effect
310 (θ_s) parameter estimates, which represent the equivalent of the parameters estimated at the group
311 median level, are reported in (**Figure 5a**) with their standard errors (SEs). To get an accurate ranking
312 of the most relevant predictors in explaining SUVR, the estimated θ_s were ordered by their relative
313 contribution to the model using dominance analysis (DA)⁴⁰ (**Figure 5b**). In terms of general
314 dominance (see **Methods**), at the top was ReHo (48% of the total R^2), followed by peaks-BOLD
315 (19%), CV-BC (11.74%), CV-BC (10.50%), s-BC (8.02%), ApEn-BOLD (3.67%), med-Leig
316 (2.60%), hrf-LE (1.47%), rApEn-BOLD (0.02%). Notably, the features belonging to the signal pool
317 collectively accounted for 76.17% of the hierarchical model R^2 . The random effects (η_{si}) describe
318 the deviation from the group value of the parameters for a specific subject i , i.e., how much the
319 parameters of each subject i are distant from the group-level estimates θ_s (**Supplementary Figure**
320 **S7b**). In this case we found that the BSV in the SUVR-fMRI association is clearly non-negligible. In
321 fact, the group-level θ_s estimates are very close to those obtained using the NAD approach,
322 confirming the adequacy of the average approach in describing the relationship between the variables.
323 However, as expected, the R^2 of the overall model, i.e., considering BSV, was lower and equal to
324 0.245, due to the capability of the multilevel mixed-effect approach to keep into account both

325 between- and within-subject variability. The R^2 values of the subject-level models are reported in
326 **Supplementary Figure S7a**, and they display high variability (from 0.05 to 0.45).
327 The median across subjects of the model's residuals v_{Si} , which highlight how well the SUVR of each
328 region is explained by the identified model, can be visualized in **Figure 5c**. Notably, high positive
329 values are present in posteromedial cortex (posterior cingulate cortex (PCC) in particular) and
330 subcortex (putamen): these areas identify nodes with high SUVR values which are not satisfactorily
331 explained by the available rs-fMRI features. Importantly, this deficiency in explanatory power is
332 highly consistent across subjects, as evidenced by the low variability (CVs%) of the residuals in those
333 areas (**Figure 5d**).
334

335 **Figure 5 – Multivariable multilevel modelling of SUVR across subjects.** The multivariable log-
 336 linear model predictors chosen at the group NAD level are shown. Parameter estimates and standard
 337 errors for the fixed effects θ_S , which represent the parameters that best explain SUVR across regions
 338 at the group level (a). The relative importance weights produced by dominance analysis (DA),
 339 highlighting the proportion of the multivariable multilevel model R^2 explained by each predictor
 340 (general dominance) (b). Across-subject median (c) and CVs% (d) of weighted residuals v_{Si} of the
 341 multilevel model, plotted on the brain cortex and subcortex.
 342

345 **SUVR vs. rs-fMRI: multilevel model across networks**

346 Finally, the log-linear model with the 9 selected rs-fMRI predictors was tested in its ability to describe
347 the expected network-level variability of the SUVR-fMRI association (BNV), i.e., by considering
348 only the parcels referring to specific brain networks. RSNs were here grouped according to the
349 Schaefer' functional atlas in its 17-RSN partition³², supplemented by 18 subcortical anatomical
350 regions³³. A multilevel modelling framework was again employed, but with RSNs as the grouping
351 factor for individual level data, instead of subjects (**Figure 4, bottom**).

352 The fixed effects θ_N and their SEs for the between-network model are reported in (**Figure 6a**). ReHo
353 and peaks-BOLD are still highly relevant parameters in describing the SUVR across networks,
354 together with ApEn-BOLD and CV-BC; rApEn-BOLD and hrf-LE, instead, lose importance, and
355 their fixed effect θ_N becomes irrelevant (with a SE range crossing the zero-line). To confirm the
356 ranking, DA was performed in this context as well: ReHo was still the most important predictor in
357 terms of general dominance (explaining 23.24% of the model's R^2), followed by CV-BC (19.85%),
358 peaks-BOLD (16.39%), s-BC (15.19%), ApEn-BOLD (11.46%), med-LEig (9.65%), CV-ReHo
359 (2.55%), hrf-LE (1.80%), rApEn-BOLD (0.13%) (**Figure 6b**).

360 Notably, the R^2 of model prediction considering network-wise estimates is markedly lower than when
361 subjects are used to cluster nodes. As shown in (**Figure 6c**), the single RSNs are highly heterogeneous
362 in terms of model R^2 , ranging from around 0 to 0.32, with an overall prediction with $R^2 = 0.147$.

363 **Figure 6 – Multilevel SUVR modelling across networks – parameter estimates and explained**
 364 **variance.** The nine features chosen at the group level are shown. Parameter estimates and standard
 365 errors for the fixed effects θ_N , which represent the parameters that best explain SUVR across regions
 366 in an average network (a). Relative importance weights produced by dominance analysis (DA) in
 367 terms of the proportion of the between-network model R^2 explained by each predictor (general
 368 dominance) (b). Network-wise R^2 values, representing the percentage of SUVR variance explained
 369 by the mixed-effect model at the network level, plotted on the cortical surface and subcortex (c).
 370

373 The BNV of the SUVR-fMRI association is measured by the random effects η_{Nj} for each network,
374 with some RSNs displaying significant distance from the model estimates θ_N of the “average-
375 network”. To better assess this variability, the nine rs-fMRI predictors’ parameter estimates ψ_{Nj} (i.e.,
376 sum of fixed effects θ_N and random effects η_{Nj} for every network j) were plotted (**Figure 7a**). We
377 can observe that most predictors included in the multivariable model display heterogeneity across
378 networks in their relationship with SUVR, with either positive or negative associations depending on
379 the specific RSN, which cannot be captured by the average situation described by the fixed effects
380 θ_N of (**Figure 6a**). Some predictors show notably consistent spatial patterns, and therefore, to assess
381 their similarity, the correlation between their random effects was evaluated across networks (**Figure**
382 **7b**). Notably, although uncorrected for multiple comparisons, significant correlations ($p < 0.05$) can
383 be found between the patterns of ReHo, CV-ReHo, hrf-LE and med-LEig, with strong positive
384 weights for somatomotor network B (SM(B)) and also control network (CTR(C)). Another interesting
385 pattern emerges for CV-BC, which displays both positive (CTR(A), VIS(B)) and negative weights
386 (TEMP/PAR, LIMBIC(A), SAL/VAN(A), DMN(B)).

387 Finally, the network-wise ψ_{Nj} values were correlated across predictors, to assess how similar the
388 RSNs were to one to another in terms of their SUVR-fMRI coupling (**Figure 7c**). When considering
389 only significant correlations ($p < 0.05$, uncorrected), an interesting pattern emerges: some RSNs are
390 fairly isolated from the rest of the brain in their SUVR-fMRI association pattern (e.g. DMN(A),
391 DMN(C), VIS(A), VIS(B), SM(A), CTR(A)), with only 1-2 significant correlations with other RSNs;
392 other RSNs, instead, have many significant correlations, and thus are similar to many other networks
393 in their SUVR-fMRI coupling (SAL/VAN(A), DAN(A), DAN(B), CTR(B), CTR(C), DMN(B),
394 LIMBIC(B), SUB).

395

396 **Figure 7 – Multilevel SUVR modelling across networks – multivariable network-level estimates.**
 397 Individual network parameter estimates (ψ_{Nj} , sum of fixed effects θ_N and random effects η_{Nj} , which
 398 describe the variability from the fixed effect for each RSN j), plotted on the brain surface for each
 399 predictor (a). Correlation matrix (non-significant values in white, $p = 0.05$, uncorrected) of the nine
 400 predictors' random effects η_{Nj} across RSNs (b). Correlation matrix (non-significant values in white,
 401 $p = 0.05$, uncorrected) of the RSNs' parameter estimates ($\psi_{Nj} = \theta_N + \eta_{Nj}$) across predictors (c).
 402

Discussion

In this work, we thoroughly investigated the spatial relationship between a wide range of features extracted from rs-fMRI and simultaneously acquired [^{18}F]FDG PET, while also accounting for the variability across subjects (i.e., BSV) and networks (i.e., BNV) in this relationship.

Relationship between SUVR and rs-fMRI through bivariate correlation

In addition to the rs-fMRI variables that have already been associated to SUVR, i.e., ALFF, ReHo, sFC strength^{22,23,25}, we extended our assessment to a wide variety of previously unexplored features, such as time-varying functional connectivity (tvFC) and HRF-related variables.

To our knowledge, the relationship between [^{18}F]FDG metabolism and FC temporal variability has never been tested before. While it is established that regions with stronger static FC tend to have higher cerebral blood flow⁴¹ and higher energy metabolism²⁵, possibly reflecting the fact that they are also more strongly connected anatomically⁴² (with recent work highlighting that structural connectivity graph properties are positively associated with [^{18}F]FDG SUVR^{43,44}), the tvFC coupling with glucose metabolism is not established.

We found that tvFC (as captured by graph theory metrics' temporal variability) has a moderate-strong negative association with SUVR. The interpretation of this finding can be supported by knowing that sFC and tvFC graph metrics are negatively correlated, as clearly shown by the correlation matrix among rs-fMRI predictors (**Figure 2a**) and that the higher the strength of a static correlation across the entire rs-fMRI acquisition, the lower its temporal variability across time windows from the same acquisition⁴⁵. However, examination of the relationships between tvFC and sFC graph metrics with SUVR suggests that a different pattern of correlations emerges, with tvFC-SUVR associations not being just the *inverse* of the sFC findings (**Figure 2b**). Similarly to our findings with [^{18}F]FDG, tvFC has been previously linked to L-[1- ^{11}C]leucine PET, with regions having strong protein turnover displaying less temporal variability of their graph properties⁴⁶.

Interestingly, this negative association stands out when compared to CV-ReHo, which is instead positively associated with SUVR, implying that the dynamics of local synchronization vs. global FC may have different neurobiological underpinnings: this is in line with a rs-fMRI study which showed that, unlike with FC, static ReHo and time-varying ReHo are *positively* correlated⁴⁷.

Additionally, a strong negative relationship is found between SUVR and the number of BOLD pseudo-events (peaks-BOLD), which is related to the interpretation of the BOLD signal as a point process, with sparse neural events governing its dynamics⁴⁸. While puzzling at first, one interpretation might come from considering that higher local oxygen consumption by active neurons is associated with decreased positive BOLD fluctuations⁴⁹, and therefore the higher the number of BOLD peaks and extreme events, the lower the oxidative metabolism and SUVR might be in that region.

439 We then examined how these relationships would be modulated by selecting parcels according to
440 their ranking in the SUVR distribution. In order to better probe the spatial relationship between SUVR
441 and rs-fMRI, which is heterogeneous across the brain^{23,28}, we chose to explore the changes in
442 correlations selecting nodes from the SUVR standpoint, instead of according to FC properties^{24,25}.
443 Interestingly, nodes with progressively higher SUVR, which are expected to be the richest in terms
444 of receptor density, local activity and inter-regional communications^{1,3,4}, did not show different
445 relationships between metabolism and rs-fMRI, but the correlations with most rs-fMRI features
446 became significantly stronger when considering nodes with progressively lower SUVR (**Figure 3**).
447 This finding suggests that only in nodes with lower metabolism is the [¹⁸F]FDG-fMRI relationship
448 emphasized, implying the presence of a nonlinear association for most of the rs-fMRI features, not
449 just for the previously explored metrics^{25,28}, with high SUVR nodes remaining unexplained by the
450 available features. This nonlinear association was also assessed through model selection, with either
451 an exponential, a power law or a log-linear relationship attributed to the majority (86%) of the
452 evaluated bivariate associations (see **Supplementary Results**). The nonlinearity of the coupling
453 between glucose consumption and BOLD is partly expected: 1) known nonlinearity exists in the
454 associations between BOLD and neuronal activity¹⁸, to which glucose metabolism is instead linearly
455 related⁷; 2) nonlinear models such as power laws are common in biology, and in particular in
456 metabolic budget²⁵; 3) the [¹⁸F]FDG coupling with local and global FC^{25,28} has been previously
457 described with a power law within specific areas; 4) nonlinear relationships between cerebral blood
458 flow and glucose metabolism have been reported⁵⁰.

459

460 ***The multivariable multilevel model***

461 To our knowledge, this is the first study to investigate the [¹⁸F]FDG-fMRI coupling using a
462 multivariable approach, attempting to identify the best subset of metrics, among a wide range of
463 fMRI-derived variables, to explain SUVR variability across regions. Moreover, to fully capitalize on
464 the fact that PET and fMRI data were acquired in the same subjects, we employed a multilevel
465 modelling approach, with the selection of the best features performed at the group (higher) level, and
466 modelling performed at the individual (lower) level, to characterize the between-subject variability
467 of the SUVR-fMRI association (**Figure 4, top**). The selected model consisted of nine rs-fMRI
468 variables (**Figure 5 a, b**) which represented all pools of features: signal (ApEn-BOLD, rApEn-
469 BOLD, peaks-BOLD, ReHo, CV-ReHo), HRF (hrf-LE), sFC (s-BC), tvFC (CV-BC), PC (med-Leig).
470 The strongest predictors are related to the BOLD signal and its local synchronization properties
471 (peaks-BOLD, ReHo), which consistently emerged as relevant across all feature selection methods
472 (**Supplementary Results**). The fact that the SUVR-fMRI spatial coupling is emphasized when local

BOLD variables are involved might reflect the interplay between excitatory and inhibitory neural populations⁵¹, which regulate CBF, a main ingredient in many fMRI-related features^{17,18,52,53}. Overall, the explanatory power provided by BOLD rs-fMRI reached a 40% of the SUVR variance at the group level (24% across subjects). Zones of polarization in the model residuals emerged in subcortical (putamen), posteromedial (PCC), and lateral frontal regions, which could mainly be attributed to outliers with higher metabolism (**Figure 5c**), which are poorly explained by the available rs-fMRI features in a consistent manner across subjects (**Figure 5d**). These results point to the idea that the BOLD signal and FC, even though related to CBV, CMRO₂ and CBF^{17,18}, reflect the metabolic architecture established by [¹⁸F]FDG SUVR only partially, even in simultaneously acquisitions, and that rs-fMRI FC and its graph metrics cannot be considered a proxy of glucose metabolism.

Moreover, the individual model R² values were variable across subjects, highlighting the fact that the SUVR-fMRI relationship displays significant between-subject variability, with subjects whose BOLD signal and FC architecture are more related to SUVR, and others that have hardly any relationship.

Next, we used the multilevel modelling approach and the identified predictors to characterize between-network variability, exploiting the fMRI-derived RSNs to group the individual data in a network-by-network fashion (**Figure 4, bottom**).

Importantly, the rs-fMRI predictors selected for the between-subject model proved to still be relevant for evaluating the between-network SUVR-fMRI association, but their ranking, as assessed by dominance analysis, changed noticeably (**Figure 6b**), with static and dynamic FC features (CV-BC in particular) gaining importance in the model.

Moreover, when the network-wise effects are considered, significant positive and negative associations emerge for each of the nine predictors (**Figure 7a**). These patterns of predictors have some degree of similarity across networks, with a cluster of RSNs (subcortical, limbic, salience, dorsal attention etc.) being highly correlated, which implies they have a similar SUVR-fMRI multivariable association pattern (**Figure 7c**). Other networks, instead, seem to be more isolated in their SUVR-fMRI coupling (default mode, visual, somatomotor etc.), possibly reflecting their enrichment in high SUVR nodes (DMN, VIS) that are more difficult to explain using fMRI features (**Figure 5c**).

These findings add to and enrich previous work highlighting between-network variability in the SUVR-fMRI association through bivariate associations^{23,28}.

Notably, the regions where SUVR-fMRI *bivariate* correlations are higher (**Figure 3**) seem to fall into networks with fairly high R² values in the *multivariable* model (**Figure 6c**), confirming that the SUVR-fMRI coupling is emphasized in these regions. It is also important to underline that marked

regional heterogeneity has also been described in the coupling between [^{18}F]FDG SUVR and local CBF⁵⁴, which is likely to underlie some of the variability detected here due to CBF contributions to rs-fMRI variables.

Limitations

A comprehensive understanding of the relationship between [^{18}F]FDG PET and rs-fMRI will require simultaneous assessment of other features, such as CBF and CMRO₂, ideally probed by [^{15}O]H₂O PET⁵⁵ and [^{15}O]O₂ PET⁵⁶ respectively, which would thoroughly describe the effects of hemodynamics and oxidative and non-oxidative metabolism, possibly bridging the gap between these measures. Additionally, while the dataset employed here consists of standard rs-fMRI acquisitions (single-echo, TR of 2s, voxel size 3-4 mm, duration ~10 minutes), the BOLD-[^{18}F]FDG coupling would likely be improved by more advanced rs-fMRI methods (e.g. multi-echo imaging⁵⁷), recordings of physiological variables (respiratory volume, end-tidal CO₂ and heart rate)²⁰, and regression of the CBF contribution⁵² out of the BOLD signal and local coherence features.

For what concerns [^{18}F]FDG PET, it must also be remembered that SUVR, which was employed here as well as in all the literature on [^{18}F]FDG-fMRI coupling^{22,23,25,27,28}, may offer a biologically confounded view of glucose consumption: SUVR is in fact a semi-quantitative and relative index, which results from interactions between the rate constants of the [^{18}F]FDG compartmental model, i.e., K_1 (ml/cm³/min), describing tracer uptake through the blood-brain barrier, k_2 (min⁻¹), describing its efflux into the venous blood, and k_3 (min⁻¹), quantifying the phosphorylation rate of the hexokinase in neurons and glia^{1,2}. There is therefore the possibility that some of the contribution of CBF to the [^{18}F]FDG-fMRI coupling comes from SUVR, which is in fact highly correlated with the early, CBF-related frames of [^{11}C]PiB PET in healthy controls⁵⁹, as well as with PET-derived CBF estimates⁵⁴. It is therefore likely that PET kinetic modelling will help disentangle the biological processes underlying both BOLD rs-fMRI and static PET estimates.

Conclusion

In conclusion, we thoroughly investigated for the first time the spatial relationship between [^{18}F]FDG SUVR and a wide range of features derived from rs-fMRI (pooled into 1) signal, 2) HRF, 3) sFC, 4) tvFC and 5) PC-based features) using simultaneous PET/fMRI data. Selection of low SUVR parcels led to a strengthening of SUVR-fMRI associations, implying the presence of a nonlinear relationship for many features. Moreover, a novel multivariable multilevel modelling framework was employed to identify the best subset of rs-fMRI predictors able to explain regional SUVR variance, highlighting that predictors based on the BOLD signal and its local synchronization (ReHo and BOLD pseudo-events, in particular) are the ones that are more tightly related to [^{18}F]FDG SUVR across brain

543 regions. This suggests a local contribution of CBF that should be tested for and, possibly, regressed
544 out from the BOLD signal.

545 Notably, the overall explanatory power provided by rs-fMRI on the regional metabolic variability did
546 not exceed 40% of the variance at the group level, with significant variability across subjects. When
547 multilevel modelling of the SUVR-fMRI coupling was carried out across networks, the selected
548 predictors were still relevant for description of RSN metabolism, but noticeable variability across
549 networks was present: new positive and negative associations emerged, and sFC and tvFC network
550 features gained importance. In conclusion, SUVR variability across parcels is only partly expression
551 of brain network organization described by rs-fMRI.

552

553

554	List of abbreviations:
555	ALFF, amplitude of low frequency fluctuations
556	ApEn, approximate entropy
557	BC, betweenness centrality
558	BNV, between-network variability
559	BOLD, blood oxygen level dependent
560	BSV, between-subject variability
561	CBF, cerebral blood flow
562	CBV, cerebral blood volume
563	CMRO ₂ , cerebral metabolic rate of oxygen
564	CTR, control network
565	CV, coefficient of variation
566	DAN, dorsal attention network
567	DMN, default mode network
568	FC, functional connectivity
569	FDG, fluorodeoxyglucose
570	FDR, false discovery rate
571	fMRI, functional magnetic resonance imaging
572	HRF, hemodynamic response function
573	LE, local efficiency
574	LIMBIC, limbic network
575	LME, linear mixed-effect
576	MAD, median absolute deviation
577	med-LEig, median of Leading Eigenvectors
578	OLS, ordinary least squares
579	NAD, naïve average data
580	NNLS, non-negative least squares
581	PC, phase coherence
582	PET, positron emission tomography
583	rApEn, range approximate entropy
584	ReHo, regional homogeneity
585	rs-fMRI, resting-state fMRI
586	RSN, resting-state network
587	SAL/VAN, salience/ventral attention network
588	SE, standard error

589 sFC, static FC
590 SM, somatomotor network
591 STR, strength
592 SUB, subcortical regions
593 SUVR, standard uptake value ratio
594 TEMP/PAR, temporo-parietal network
595 tvFC, time-varying FC
596 VIS, visual network
597
598
599
600

Methods

Data and Imaging protocols

The dataset includes 26 healthy subjects from two studies: 11 subjects (8 males; 52.2 ± 10.4 years), hereby referred to as dataset A (Munich)²³, and 15 subjects (6 males; 64.7 ± 7.9 years), i.e., dataset B (Naples)³¹. Subjects were scanned in *eyes open* condition while looking at a fixation cross. Exclusion criteria included a history of psychiatric or neurological disorders, use of psychoactive drugs or treatment with CNS-active medications, pregnancy, and MR-related contraindications. The subjects provided their informed written consent according to the Code of Ethics of the World Medical Association and the Institutional Review Board and Ethics Committee at the Technische Universität München, for dataset A, and the SDN Foundation, for dataset B. Both centers simultaneously collected [¹⁸F]FDG PET and rs-fMRI data accompanied by a structural MR image on two identical Biograph mMR 3T scanners (Siemens Healthcare, Erlangen, Germany) equipped with the standard-supply head-neck coil (12-channel).

Dataset A: MRI data consisted in a structural magnetization prepared rapid acquisition gradient echo (MPRAGE) T1-weighted (T1w) image (TR/TE = 2300/2.98 ms, FA = 9°, 1 mm isotropic voxel size with 0.5 mm gap), 300 volumes of T2*-weighted gradient-echo echo-planar imaging (GE-EPI) with TR/TE = 2000/30 ms and voxel size of 3 mm isotropic (0.6 mm inter-slice gap). PET acquisition consisted in a saturated list mode (10 min duration), started 30 minutes post-injection and reconstructed with voxel size of $3.7 \times 2.3 \times 2.7$ mm³.

Dataset B: MRI data consisted in a similar T1- MPRAGE structural image and 240 volumes of GE-EPI for rs-fMRI with 4 mm isotropic voxel and TR/TE = 1920/32 ms. Simultaneous PET/fMRI measurements started 30 min post-injection, and PET images were acquired in sinogram mode for 15 min with reconstruction voxel size of $1.12 \times 1.12 \times 2.0$ mm³.

The interested reader should refer to the respective papers^{23,31} for more detailed information on each dataset.

Data pre-processing

All subjects were identically pre-processed to obtain local metabolism information from [¹⁸F]FDG PET data, and BOLD-based measures from rs-fMRI data, employing a pipeline similar to the Human Connectome Project (HCP) minimal preprocessing pipeline⁶⁰ with the addition of PET processing.

635 *Structural imaging pre-processing*

636 Structural T1w images were N4 bias field-corrected⁶¹, skull-stripped, and segmented into grey matter
637 (GM), white matter (WM) and cerebrospinal fluid. The brain cortex was delineated with Freesurfer
638 (*recon-all* volume and surface reconstruction pipelines)⁶², obtaining pial and GM-WM interface
639 surfaces. Manual editing was performed to correct for surface delineation errors. Generated surfaces
640 were resampled over the *fs_LR* mesh provided by *Conte69* atlas (symmetric-hemisphere mesh of 32k
641 nodes) to obtain aligned cortical surfaces for each subject. The Schaefer functional atlas³² was used
642 to parcellate cortical surfaces into 200 parcels, grouped according to Yeo's 17 RSNs scheme¹² into
643 Central Visual (VIS(A)), Peripheral Visual (VIS(B)), Somatomotor A (SM(A)), Somatomotor B
644 (SM(B)), Temporal Parietal (TP), Dorsal Attention A (DAN(A)), Dorsal Attention B (DAN(B)),
645 Salience/Ventral Attention A (VAN(A)), Salience/Ventral Attention B (VAN(B)), Control A
646 (CTR(A)), Control B (CTR(B)), Control C (CTR(C)), Default Mode A (DMN(A)), Default Mode B
647 (DMN(B)), Default Mode C (DMN(C)), Limbic A (L(A)) and Limbic B (L(B)). The cortical regions
648 were supplemented by 18 subcortical regions extracted from Freesurfer (bilaterally: Caudate,
649 Putamen, Accumbens, Pallidum, Amygdala, Hippocampus, Thalamus, Ventral diencephalon,
650 Cerebellar cortex) and delineated in single-subject space employing the Multi-Atlas Label Fusion
651 (MALF) method³³. Parcels corresponding to subcortical regions were assigned to the Subcortical
652 (SUB) group.

653

654 *PET data pre-processing*

655 [¹⁸F]FDG PET images, after normalization to injected dose and subject's body weight, were linearly
656 resampled in T1w space with FSL's *flirt*⁶³ and intensity-normalized by the whole-brain average
657 uptake⁶⁴:

$$658 \quad SUV = \frac{[^{18}\text{F}]\text{FDG concentration [MBq/ml]}}{\frac{\text{injected dose [MBq]}}{\text{body weight [kg]}}} \quad SUVR = \frac{SUV_{\text{target}}}{SUV_{\text{reference}}}$$

659 SUVR maps were then parcellated in the same way as the rs-fMRI data, and parcel-wise SUVR was
660 computed as the median value of the vertices inside a region. All pre-processing steps avoided any
661 further spatial smoothing on both [¹⁸F]FDG and rs-fMRI data.

662

663 *Functional MRI data pre-processing*

664 The first four rs-fMRI volumes were discarded to avoid non-equilibrium magnetization effects. The
665 remaining volumes were corrected for slice timing difference by realigning them to the median
666 volume, using FSL's *mcflirt*⁶³. A template EPI volume was obtained with *antsBuildTemplate*⁶⁵ from
667 realigned rs-fMRI data and used to estimate an affine transform (*flirt*, FSL), subsequently employed
668 to map main tissue segmentations obtained from the pre-processed T1w image to the native EPI

space. Nuisance signals consisted in motion traces and their first order derivatives complemented by the first five temporal principal components, obtained after principal component analysis of WM and CSF EPI signals, explaining 70% and 50% of the average variance across subjects⁶⁶, which were regressed out from all brain voxels in native EPI space⁶⁷. Regression residuals were finally resampled first to the T1w space and then on top of the mid-thickness cortical surface mesh with Connectome Workbench⁶⁸. Finally, the BOLD signal was high-pass filtered with a cut-off of 0.008 Hz. No low-pass filter was applied, as the higher frequency components (0.1-0.25 Hz) of BOLD are likely to provide relevant neural information⁶⁹. The vertex-wise BOLD signal was parcellated according to the Schaefer cortical atlas and the supplementary subcortical MALF parcels as previously described.

rs-fMRI feature extraction

Feature extraction as well as subsequent analyses were performed in MATLAB (ver. 2020a, The Mathworks, Natick, MA). 50 different features were extracted from the BOLD signal, either at the vertex or the parcel level. The extracted features were chosen as descriptors of different aspects of the BOLD 1) signal, 2) HRF, 3) sFC, 4) tvFC, and 5) PC. A list of the features and their acronyms is reported in **Table 1**. A detailed description of the features and how they were extracted can be found in the **Supplementary Methods**. The extracted features were then employed first in a bivariate correlation analysis against SUVR, and then in a multivariable multilevel modelling procedure to verify how much SUVR variance could be explained across the whole brain at the group level, as well as accounting for individual level information.

Bivariate analysis of the metabolism-fMRI relationship

rs-fMRI features vs. glucose metabolism across all brain regions

The bivariate relationship between node-wise SUVR and rs-fMRI properties was assessed at the group level (naïve average data approach, NAD), employing the region-wise median values across subjects for SUVR and each of the 50 extracted features. The association between fMRI-derived features and metabolism across nodes was separately tested via Spearman's rank bivariate correlation (significance level 0.05, corrected for multiple comparisons using the Benjamini-Hochberg FDR approach³⁶).

rs-fMRI features vs. metabolism in specific clusters of nodes

The spatial heterogeneity in the [¹⁸F]FDG PET-fMRI relationship, which has previously been reported^{23,25}, was probed by selecting clusters of nodes with increasingly high or increasingly low SUVR. The threshold level was determined by considering linearly increasing percentiles of the

704 SUVR distribution over all nodes, in the range going from the 1st to 85th percentiles, with step 1 (from
 705 218 up to 33 nodes); moreover, in the opposite direction, nodes were selected according to linearly
 706 decreasing percentiles of SUVR, from the 100th to the 15th percentile (from 218 down to 33 nodes).
 707 Selected nodes at every level are reported in the binary matrix in **Supplementary Figure S1**. For
 708 each threshold level, Spearman's correlation between SUVR and all fMRI-derived features was
 709 calculated across the selected nodes, and FDR-corrected for multiple comparisons across thresholds
 710 and rs-fMRI features (significance level 0.05)³⁶. The absolute values of Spearman's correlation were
 711 summed across the 50 fMRI variables for each percentile, to determine which threshold had the
 712 maximum correlation across features.

713
 714

715 **Multivariable modelling of the SUVR-fMRI relationship at the group level**

716 The relationship between SUVR and each of the 50 rs-fMRI properties ($fMRI_{ip}$, for $i = 1, \dots, 218$
 717 regions, and $p = 1, \dots, 50$) was then tested with four different bivariate models:

718 1) a linear model,

$$719 \quad SUVR_i = \alpha_p + \beta_p \cdot fMRI_{ip}$$

720 2) a mono-exponential model,

$$721 \quad SUVR_i = \alpha_p \cdot e^{\beta_p \cdot fMRI_{ip}}$$

722 3) a power law model,

$$723 \quad SUVR_i = \alpha_p \cdot fMRI_{ip}^{\beta_p}$$

724 4) a log-linear model,

$$725 \quad SUVR_i = \alpha_p + \beta_p \cdot \log fMRI_{ip}$$

726 which were compared in terms of their residual sum of squares (RSS). This bivariate model selection
 727 process led to choose the log-linear model for multiple regression modelling (see **Supplementary**
 728 **Results**).

729 At the NAD level, a multiple linear regression approach was employed to verify how much of the
 730 group-wise SUVR variance could be explained by the linear combination of different fMRI-based
 731 features. The ordinary least squares (OLS) problem was formulated as follows:

$$732 \quad y = X\beta + \varepsilon$$

733 where y and ε are $n \times 1$ vectors of the response/dependent variable (i.e., SUVR) and the model error,
 734 and $X \in \mathbb{R}^{n \times p}$ is the matrix of p regressors (i.e., log-transformed rs-fMRI predictors), or design
 735 matrix. Before performing OLS regression, all predictors were z-scored, i.e., centered and scaled by
 736 their standard deviation (SD). The outcome variable, i.e., SUVR, was z-scored as well, so no model
 737 intercept needed to be estimated. The solution to the OLS problem was obtained as

$$738 \quad \hat{\beta} = (X^T X)^{-1} X^T y$$

The model design matrix consisted of 50 parameters. The model was formulated as follows:

$$SUVR_i = \beta_1 \cdot \log fMRI_{i1} + \beta_2 \cdot \log fMRI_{i2} + \dots + \beta_p \cdot \log fMRI_{ip} + \varepsilon_i$$

for each observation $i = 1, \dots, n$. The relationships amongst the predictors were evaluated by Spearman's correlation (**Figure 2**), to assess the presence of strong correlations (i.e., multicollinearity). Since high multicollinearity amongst predictors is known to result in lower precision, switched signs of the coefficients, and a lack of statistical significance of the multivariable model³⁵, the ill-conditioning of the design matrix was quantified using the condition number, i.e.,

$$\kappa(X) = \frac{\sigma_{\max}(X)}{\sigma_{\min}(X)}$$

with $\sigma_{\max}(X)$ and $\sigma_{\min}(X)$ as the highest and lowest singular values of X , respectively. As a rule of thumb, $\kappa(X)$ requires attention if higher than 30³⁵.

The OLS fit was obtained with all the rs-fMRI variables and interpreted as the highest possible predictive power that could be extracted from the available features. However, it is well-known that, in the case of overparameterized linear models, OLS is generally not useful, as many CVs% (i.e., percent error variance divided by the absolute value of the parameter estimates) are too high (CVs% > 100%) and the model is not *a posteriori* identifiable, so it should be rejected³⁷. As discussed, performing feature selection at the individual level would lead to unstable estimates, so we continued to work at the group (i.e., NAD) level.

Eleven feature selection strategies, namely non-negative least squares (NNLS), elastic net regression, hierarchical clustering, stepwise selection, and general-to-specific modelling in different combinations were tested and compared to identify the best group of features to explain SUVR variability at group level. More details are in (**Supplementary Figure S4, Supplementary Table S1, Supplementary Methods**).

Full hierarchical modelling of the SUVR-fMRI relationship

As a NAD approach like the one described so far is statistically sound and unbiased only in case of low between-subject variability, a multilevel population modelling approach (mixed-effect model) was employed in order to characterize in a single stage both the group-level (fixed) and individual-level (random) effects³⁰ contributing to the relationship between the selected rs-fMRI variables and SUVR (**Figure 4, top**). First, the link between model and SUVR was described at individual level by the following equation:

$$y_{Si} = F_{Si}(X_{Si}, \psi_{Si})$$

$$z_{Si} = y_{Si} + v_{Si}$$

with y_{Si} as the SUVR model prediction for the i th subject ($i = 1, \dots, m$), which is a function of X_{Si} (the fixed-effects design matrix composed by the features extracted from the rs-fMRI data of

subject i), and the parameters to be estimated for subject i , ψ_{Si} ; z_{Si} is the vector of the measured
 SUVR data of subject i and v_{Si} is the within-subject variability, or residual unexplained variability,
 assumed to be normally distributed with zero mean and variance σ_i^2 .

Second, at population level, ψ_{Si} was described by a function combining population parameters (or
 fixed effects, θ_S), and random variability of individual parameters around the population mean (or
 random effects, η_{Si}), according to the following assumptions:

$$\eta_{Si} \sim N(0, \Omega_S)$$

$$\psi_{Si} = \theta_S + \eta_{Si}$$

where η_{Si} is assumed to be Gaussian, with zero mean, independent across individuals and with
 covariance matrix Ω_S (another population parameter); as a consequence, ψ_{Si} have a normal
 distribution as well. The matrix Ω_S was assumed to be full.

The intra-individual (first level) model structure was composed by the nine features selected with the
 NAD approach, here at single-subject level. Data normalization was performed within subjects via z-
 scoring. The inter-individual model (second level) describing the BSV of the parameters was set
 according to the aforementioned assumptions.

This estimation requires solving the penalized least squares problem, i.e., the penalized weighted
 residual sum of squares (PWRSS),

$$PWRSS(\Omega_S, \theta, y_{Si} | Z_{Si}) = WRSS(\Omega_S, \theta_S, y_{Si} | Z_{Si}) + \| y_{Si} | Z_{Si} \|^2$$

with Z_{Si} as the random-effects design matrix. This nonlinear optimization problem was solved using
 the restricted maximum likelihood (REML) estimation method⁷⁰. The standard errors (SE) were
 calculated for each θ_S parameter estimate as the square root of the diagonal of their covariance matrix.
 The overall and subject-wise multilevel model R^2 were also evaluated. The residual unexplained
 variability v_{Si} was evaluated by calculating its median and variability (CV%) across subjects.

The hierarchical modelling approach was also performed across networks (N) in order to characterize
 between-network variability. RSNs were used as the grouping factor instead of subjects in a model
 formulated as follows:

$$y_{Nj} = F_{Nj}(X_{Nj}, \psi_{Nj})$$

$$z_{Nj} = y_{Nj} + v_{Nj}$$

with j as the j th network ($j = 1, \dots, q$). Normalization of SUVR and rs-fMRI variables was performed
 via z-scoring within RSNs.

The random effects η_{Nj} and the resulting individual parameters ψ_{Nj} were evaluated in terms of their
 correlation structure, both across RSNs (1st dimension) and across the nine predictors (2nd dimension),
 as seen in **(Figure 7b, c)**.

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Relative importance analysis to determine predictor importance

Relative importance analysis^{40,71} was employed as a supplement to the results of hierarchical modelling. This type of analysis allows to appropriately partition the model’s explained variance amongst multiple predictors when there is still significant multicollinearity, which makes typical indicators of importance (e.g., standardized regression coefficients) flawed. Dominance analysis (DA), in particular, works by rank-ordering the predictors in term of relative importance by comparing the additional contributions they make to the R^2 of all possible subset models. Specifically, we assessed the *general dominance* of the variables, which is established for one predictor over another when the average of its conditional contributions over all model sizes is greater than that of the other. The obtained general dominance weights are also measures of relative effect sizes, as they sum to the model R^2 : the percent contribution to the model R^2 was therefore calculated and reported. While DA was originally proposed for OLS models, it was later extended to multilevel models⁴⁰. In order to apply DA to hierarchical models, a null model with no predictors must be provided, and the slopes of first-level models must be considered fixed even when they are random in the identified model, to simplify dominance evaluation. DA was used to assess the extent to which each selected variable was driving the prediction in the context of the LME models across subjects (S) and across networks (N), as they were still affected by non-negligible multicollinearity.

829 **Data availability**

830 The multimodal [¹⁸F]FDG PET and rs-fMRI data used in the present study can be accessed via
831 request to the groups who performed the original studies^{23,31}. Data sharing will be subject to the
832 policies and procedures of the institution where each dataset was collected.

833 The codes and processed data that support the conclusions of this research work can be accessed via
834 request to the corresponding authors.

835

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840

841 **Author contributions:**

842 T.V. and A.B. designed the study, performed the analysis, interpretation of the data, and the drafting
843 of the article. E.S. contributed to the preprocessing of the data and to the drafting of the article. M.C.
844 contributed to the interpretation of the data and to the drafting of the article. M.A. designed and
845 collected the data for the original study for dataset B and contributed to revision of the draft. All
846 authors approved the final version of the article to be published.

847

848 **Competing interests:**

849 The authors declare no competing interests.

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