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Comprehensive Insights into Neural Activity and Metabolic Processes: Disentagling the Glycolytic Pathway to Examine the Resting-State [18F]FDG-PET/fMRI Coupling

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Functional connectivity (FC) is used for investigating brain network organization. Given that the brain consumes 20% of the body's glucose to support functions, understanding the relationship between glucose consumption and FC is essential for comprehending brain physiology (Raichle, 2006). Some studies have linked FC with the semiquantitative metabolic indices *SUVR* (Standardized Uptake Value Ratio) or the quantitative overall metabolic fractional uptake, *Ki* [ml/cm3/min], revealing a partial relationship. However, no studies have assessed how different components of the glycolytic process relate to network structure as expressed through FC.

fMRI and PET were collected for 42 healthy subjects (HCs) (Volpi et al., 2023). The fMRI data were band-pass filtered in the range 0.008-0.1 Hz (F1) to maximize the presence of spontaneous low-frequency oscillations, and in the range 0.008-0.21 Hz (F2) to include hemodynamic contributions. fMRI and PET signals were parcellated using a clustered version of the Yan functional atlas (Yan et al., 2023), plus 12 subcortical (AAL3). Individual FC matrices were obtained by calculating Pearson correlation. Static PET images were normalized to SUVR, while two-compartment kinetic modelling was applied to dynamic data to assess *K1*, *k2*, *k3* rate constants and to calculate *Ki* using Variational Bayesian inference (Castellaro et al., 2017).
Partial Least Square Correlation was applied between *K1* and *FCSTR* (nodal strength) and repeated between *k3*, *Ki*, *SUVR* and *FCSTR* (Figure 1a). The generalizability of significant multivariate correlations was tested via 7-fold cross-validation. For each generalizable pair, a regression line was established, defining a 90th percentile normality band of HC distances from the line.

The strongest relationship between the influx parameter *K1* and *FCSTR* was in F2 (r=0.66). As the scatterplot between *K1* and *FCSTR* scores shows (Figure 1b), brain regions with higher glucose transport often exhibit stronger functional connectivity.
While a positive correlation between *SUVR* and *FCSTR* was observed specifically in F1 (r=0.75), the scatterplot (Figure 1c) reveals a broader spread around the regression line, indicating higher variability across subjects.
The *k3-FCSTR* and *Ki-FCSTR* pairs showed a non-generalizability results and for this reason are not reported.

The stronger *K1-FCSTR* coupling in F2 was expected, as this band includes more hemodynamic contributions, which appear essential for linking the two metabolic and functional information sources (Amend et al., 2019). The modest yet reliable correlation between *SUVR* and *FCSTR* may be attributable to SUVR being a semi-quantitative measure compared to the quantitative FDG-PET analysis: *SUVR* cannot disentangle the different physiological processes describing brain glucose consumption kinetics (better described by *K1*), hindering a full understanding of its relationship with FC (Palombit et al., 2022; Volpi et al., 2024). The *k3-FCSTR* and *Ki-FCSTR* couplings do not surpass the level of statistical significance, highlighting that the major contribution to brain metabolic processes and the network, as described by FC and summarized in the strength graph measure, is sensitive only to blood flow and BBB permeability.

This study shows that the hemodynamic part of the BOLD signal is also crucial in studying its relationship with brain metabolism, as it is linked to glucose and oxygen supply.

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