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Glucose Metabolism echoes Long-Range Temporal Correlations in the Human Brain

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Introduction
Long-range temporal correlations (LRTC) are a ubiquitous property of healthy brain activity and, under the Critical Brain Hypothesis, reflect proximity to critical states. In line with this, these scale-free dynamics diminish during loss of consciousness - signaling a departure from criticality - and rebound upon recovery. Yet their implications for individual-level metabolic regulation remain unclear. Here, we relate LRTC in resting-state fMRI, quantified by the Hurst exponent, to glucose metabolism measured with [¹⁸F]FDG PET.

Methods
We analyzed a multimodal dataset comprising resting-state fMRI and dynamic [¹⁸F]FDG PET from 43 healthy adults. The Hurst exponent was estimated via a wavelet-based approach using the Schaefer 400 7 Networks atlas augmented with the Tian subcortical atlas (S1). Dynamic [¹⁸F]FDG PET was fitted with the two-compartment Sokoloff model to obtain microparameters K₁ (tracer inflow), k₂ (tracer efflux), and k₃ (phosphorylation by hexokinase). The macroparameter K_i (net uptake) captured overall kinetics (Figure 1 panel a). We correlated the Hurst exponent with [¹⁸F]FDG parameters at group and individual levels, assessing significance with spatial-autocorrelation-preserving null models (Figure panels b-c). Interindividual variability was tested by regressing mean Hurst exponents against [¹⁸F]FDG parameters while controlling for age, sex, and head motion (Figure panel d). We further extended analyses to two PET tracers: [¹¹C]UCB-J (synaptic density) and L-[¹-¹¹C]Leucine (cerebral protein synthesis rate, rCPS). The hurst exponent map was regressed onto these biological properties. Predictor importance was assessed by dominance analysis, and model performance was evaluated with distance-dependent cross-validation (Figure panel e).

Results
Across subjects and regions, Hurst exponents were consistently >0.5, indicating persistent dynamics. The Hurst exponent showed a strong positive association with K_i ($r = 0.65$, $p_{SMASH} < 0.0001$). Among microparameters, k₃ displayed a robust linear relationship with Hurst values ($r = 0.44$, $p_{SMASH} < 0.0001$), replicating at the single-subject level. At the interindividual level, higher mean Hurst exponents were associated with faster [¹⁸F]FDG phosphorylation (k₃), indicating that individuals with stronger LRTC exhibit faster hexokinase-mediated phosphorylation (model $R^2 = 0.20$; $\beta = 0.32$, $t = 3.28$, $p = 0.002$). In the multilinear model, the weighted combination of K_i, synaptic density, and rCPS explained a substantial fraction of LRTC variance (67%, $p_{SMASH} < 0.0001$). Dominance analysis identified rCPS as the strongest predictor of the Hurst exponent (general dominance: 58%), followed by glucose metabolism (25%). Distance-dependent cross-validation indicated good generalizability.

Discussion
LRTC are pervasive in spontaneous brain activity and couple systematically with metabolism across regions and individuals. At the individual level, stronger LRTC corresponded to faster [¹⁸F]FDG phosphorylation, linking intrinsic neural dynamics to metabolic utilization. Beyond glucose, synaptic density and protein synthesis also contributed, suggesting that sustaining temporally persistent dynamics requires energy as well as ongoing molecular remodeling. Overall, scale-free fluctuations - while supporting efficient information processing - carry a substantial metabolic cost.

Primary author: FACCA, Massimiliano (University of Padova, Padova Neuroscience Center (PNC))

Co-authors: Ms RIDOLFO, Anna (University of Padova, Padova Neuroscience Center (PNC)); Dr CELLI, Miriam (University of Padova, Department of Neuroscience); Ms TARRICONE, Claudia (University of Padova, Padova Neuroscience Center (PNC)); Dr MAZZONETTO, Ilaria (Venetian Institute of Molecular Medicine (VIMM)); Dr VOLPI, Tommaso (Department of Radiology and Biomedical Imaging, Yale University, New Haven, CT, USA); Prof. VLASSENKO, Andrei G. (Neuroimaging Laboratories at the Mallinckrodt Institute of Radiology, Washington University School of Medicine, St Louis, MO, USA); Prof. GOYAL, Manu S. (Neuroimaging Laboratories at the Mallinckrodt Institute of Radiology, Washington University School of Medicine, St Louis, MO, USA); Prof. CORBETTA, Maurizio (University of Padova, Padova Neuroscience Center (PNC)); Prof. BERTOLDO, Alessandra (University of Padova, Padova Neuroscience Center (PNC))

Presenter: FACCA, Massimiliano (University of Padova, Padova Neuroscience Center (PNC))

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