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Functional and Metabolic Network Signatures of Mitochondrial Specialization in the Human Brain

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Introduction
Despite representing only ~2% of body mass, the human brain consumes about 20% of the body's total energy (Raichle 2006). Most of this energy fuels spontaneous activity at rest and is produced through oxidative phosphorylation (OxPhos), powered by mitochondria. A recently developed voxelwise atlas of mitochondrial respiratory capacity offers an unprecedented view of this key bioenergetic function (Mosharov et al. 2025). Yet, how this spatial distribution of mitochondrial features aligns with the brain's functional and metabolic network organization remains unknown. Here, we test whether mitochondrial phenotypes are structured according to intrinsic network architecture.

Methods
We analyzed all gray matter voxels from a biochemically profiled human brain slab (n = 249; figure panel a), each characterized by six mitochondrial features: enzymatic activities of CI, CII, and CIV; mitochondrial density (MitoD); tissue respiratory capacity (TRC); and mitochondrial respiratory capacity (MRC). High-resolution 7T resting-state fMRI (n = 58 subjects) and dynamic [¹⁸F]FDG PET (n = 20 subjects) data were coregistered to the slab's stereotaxic space to derive voxelwise Functional Connectivity (FC) and Metabolic Connectivity (MC) matrices (figure panel b). For each OxPhos feature, we first computed its correlation across nodes with the FC- or MC-weighted mean in each node's network neighbors (figure panel c). Significant correlations would suggest network-driven effects in regional variability of mitochondrial features. We then constructed a Mitochondrial Profile Similarity (MPS) matrix by computing Pearson's correlation between the mitochondrial feature profiles of each voxel pair. We applied Louvain community detection to both FC and MC (γ = 0.8–2.0, step 0.1) to identify network modules, and tested whether MPS values were greater within modules than between them (ΔMPS = average MPS within – average MPS between modules, figure panels d–i). All analyses accounted for spatial autocorrelation (SA) and network geometry using SA-preserving and degree- and edge-length-preserving null models.

Results
Across nodes, all mitochondrial features were significantly associated with the MC-weighted neighborhood averages (all $p < 0.01$ vs. both null models). For FC, significant effects were found for CI, CIV, TRC, and MRC (all $p < 0.05$ vs. both null models), suggesting that mitochondrial features, particularly oxidative capacity, are shaped by network-level interactions, with stronger effects for MC than FC. In the modularity analysis, FC showed higher within-modules than between-modules MPS across most γ values ($p < 0.001$), with effects strengthening at higher γ and pointing to increased mitotype coherence at finer community resolutions. For MC, significant effects were observed only at the finest resolutions, peaking at $\gamma = 1.6$ ($p = 0.006$), suggesting a higher degree of scale specificity.

Discussion
Our findings show that mitochondrial specialization is closely embedded within the brain's functional and metabolic networks. Connectivity modules appear to act as bioenergetic niches, harboring distinct mitotypes. Regional differences in oxidative capacity are influenced by network-level interactions, suggesting that mitochondrial organization is not merely a local property but also reflects systems-level constraints. Together, these results provide a mechanistic link between intrinsic connectivity and energy metabolism, offering a framework for understanding how mitochondrial phenotypes support human brain function.

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