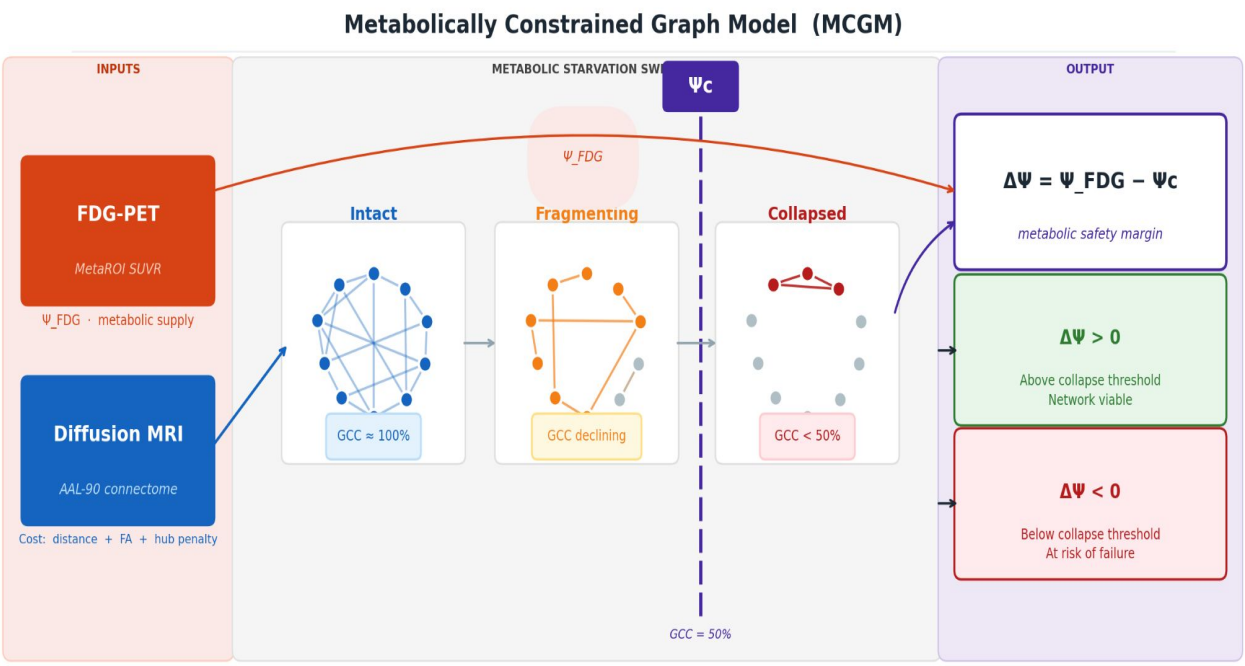
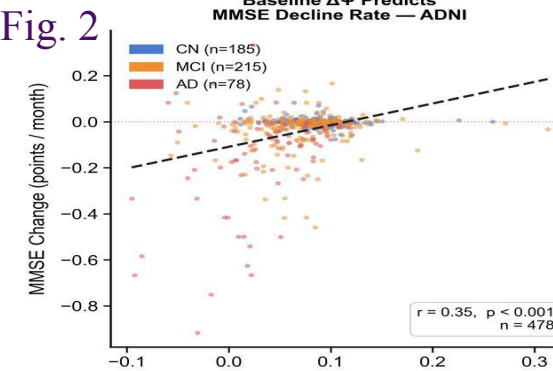
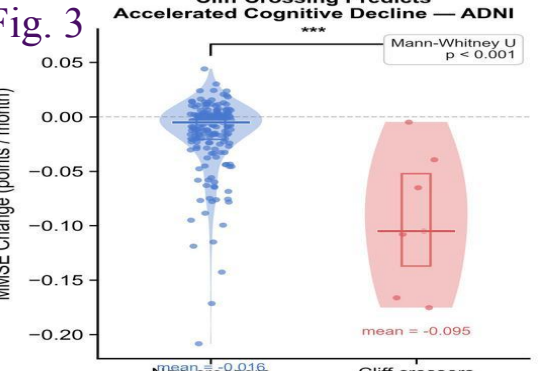
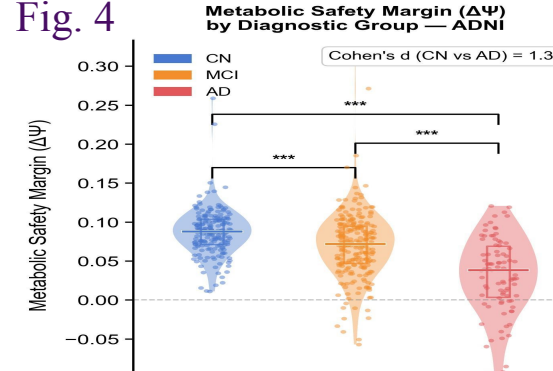
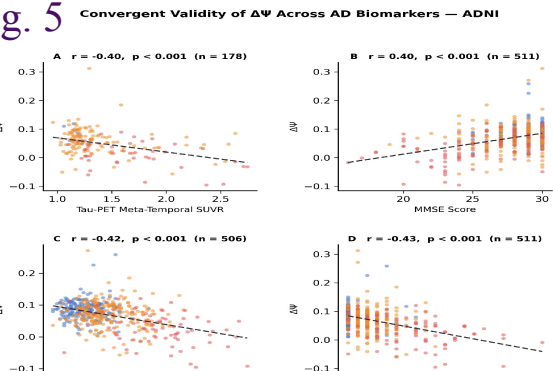
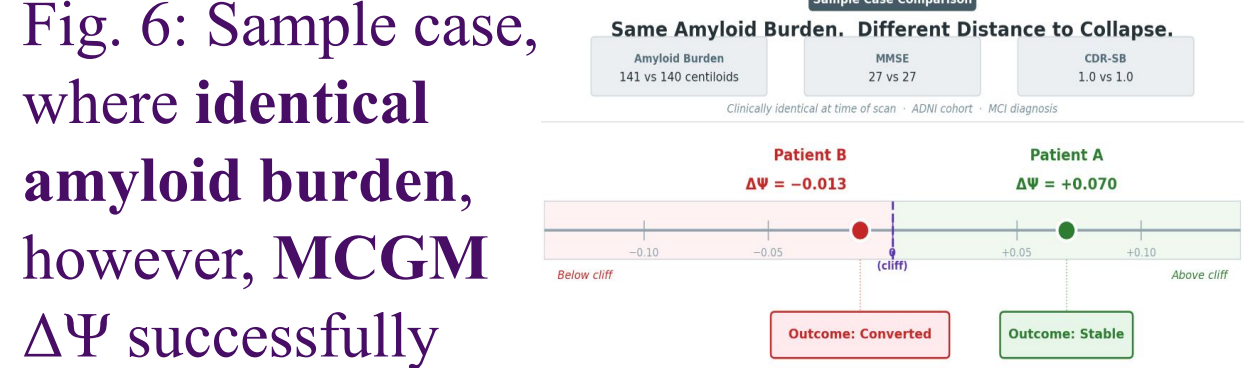


Metabolic Safety Margin As A Multimodal Biomarker Of Network Vulnerability And Predictor Of Cognitive Decline In Alzheimer's Disease

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The Metabolic Safety Margin ($\Delta\Psi$) is a multimodal biomarker quantifying proximity to network failure. Integrating connectivity and metabolism, $\Delta\Psi$ predicts cognitive decline. Individuals crossing the failure threshold decline six times faster, making it a robust prognostic tool across the Alzheimer’s disease spectrum.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES
- Alzheimer's disease (AD) disrupts cerebral metabolism and structural connectivity, yet established biomarkers (amyloid PET, tau PET, and atrophy) primarily index pathologic burden rather than proximity to functional network failure. Consequently, individuals with comparable pathology may differ substantially in their risk of near-term cognitive decline. - We introduce Metabolic Safety Margin ($\Delta\Psi$), derived from our proposed Metabolically Constrained Graph Model (MCGM) that mimics the brain as a weighted structural connectome, constructed from diffusion MRI tractography using the AAL-90 atlas. In MCGM, each edge carries a biophysically derived metabolic cost incorporating tract length, white matter integrity (FA), and hub connectivity penalty with a subject-specific collapse threshold (Ψ_c). $\Delta\Psi$ quantifies the distance between current metabolic state and predicted network failure, providing a measure of network resilience rather than accumulated pathology alone. The framework was successfully evaluated with Alzheimer’s Disease Neuroimaging Initiative (ADNI) dataset.	 Fig. 1 The MCGM’s (depicted in Fig. 1) edge costs incorporate inter-regional distance, tract FA, and a hub-connectivity penalty, capturing the metabolic burden of long-range, highly connected pathways. Metabolic supply is progressively withdrawn in a starvation sweep, edges are pruned in descending cost order, and the collapse threshold (Ψ_c) is defined as the point where the giant connected component falls below 50% of nodes. FDG-PET MetaROI SUVR provides the current metabolic supply (Ψ_{FDG}). The Metabolic Safety Margin is calculated as: $\Delta\Psi = \Psi_{FDG} - \Psi_c$ - Positive $\Delta\Psi$ indicates metabolic reserve above the collapse threshold, whereas - negative $\Delta\Psi$ indicates a network operating below its predicted failure point.	 Fig. 2  Fig. 3  Fig. 4  Fig. 5  Fig. 6 - Fig. 2: $\Delta\Psi$ declined across the Alzheimer’s spectrum: CN (0.087), MCI (0.070), AD (0.032) (Cohen’s $d = 1.36$, $p < 0.001$). - Fig. 3: Below-threshold status ($\Delta\Psi < 0$) increased with severity: 0% (CN), 4.2% (MCI), 24.4% (AD). - Fig. 4: Baseline $\Delta\Psi$ predicted MMSE decline below-threshold participants declined 6X faster. - Fig. 5: $\Delta\Psi$ correlated with ADAS-Cog 13 ($r = -0.39$), CDR-SB ($r = -0.43$), and tau PET ($r = -0.40$) (all $p < 0.001$). - Fig. 6: Sample case, where identical amyloid burden, however, MCGM $\Delta\Psi$ successfully predicted divergent 36-month outcome.	$\Delta\Psi$ measures remaining functional reserve, distance to network collapse, not accumulated pathology, offering a mechanistically grounded complement to amyloid biomarkers. - Individuals matched on amyloid and cognition differ substantially in $\Delta\Psi$, stratifying clinical risk from a single multimodal assessment. $\Delta\Psi$ predicts MCI-to-AD conversion prospectively (AUC = 0.67, $p = 0.007$), identifying individuals at highest collapse risk before clinical diagnosis $\Delta\Psi$ correlates with longitudinal cognitive decline (ADAS-Cog $r = -0.42$), tracking trajectory. - The framework is potentially generalizable to Neurodegenerative diseases. Preliminary results on simulated PD connectome degeneration, the same framework predicts motor-first circuit failure consistent with basal ganglia hub disruption, PPMI validation in progress.	- Jack CR Jr, et al. (2018). NIA-AA research framework: Toward a biological definition of Alzheimer's disease. Alzheimer's & Dementia - Landau SM, et al. (2011). Associations between cognitive, functional, and FDG-PET measures of decline in AD and MCI. Neurobiology of Aging. - LaMontagne PJ, et al. (2019). OASIS-3: Longitudinal neuroimaging, clinical, and cognitive dataset for normal aging and Alzheimer's disease. - Petersen RC, et al. (2010). Alzheimer's Disease Neuroimaging Initiative (ADNI): - Vaishnavi SN, et al. (2010). Regional aerobic glycolysis in the human brain.
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