Off-Equilibrium Fluctuation-Dissipation Theorem Paves the Way in Alzheimer's Disease Research

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INTRODUCTION: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive cognitive decline. Although traditional methods have provided insights into brain dynamics in AD, they have limitations in capturing non-equilibrium dynamics across

disease stages. Recent studies suggest that dynamic functional connectivity in resting-state networks (RSNs) may serve as a biomarker for AD, but the role of deviations from dynamical equilibrium remains underexplored.

OBJECTIVE: This study applies the off-equilibrium fluctuation-dissipation theorem (FDT)~\cite{Monti2024} to analyze brain dynamics in AD, aiming to compare deviations from equilibrium in healthy controls, patients with mild cognitive impairment (MCI), and those with AD. The goal is to identify potential biomarkers for early AD detection and understand disease progression's mechanisms.

METHODS: We employed a model-free approach based on FDT to analyze functional magnetic resonance imaging (fMRI) data, including healthy controls, MCI patients, and AD patients. Deviations from equilibrium in resting-state brain activity were quantified using fMRI data. In addition, we performed model-based simulations incorporating Amyloid-Beta (\ab{}), tau burdens, and Generative Effective Connectivity (GEC) for each subject.

RESULTS: Our findings show that deviations from equilibrium increase during the MCI stage, indicating hyperexcitability, followed by a significant decline in later stages of AD, reflecting neuronal damage. Model-based simulations incorporating \ab{} and tau burdens closely replicated these dynamics, especially in AD patients, highlighting their role in disease progression. Healthy controls exhibited lower deviations, while AD patients showed the most significant disruptions in brain dynamics.

DISCUSSION: The study demonstrates that the off-equilibrium FDT framework can accurately characterize brain dynamics in AD, providing a potential biomarker for early detection. The increase in non-equilibrium deviations during the MCI stage followed by their decline in AD offers a mechanistic explanation for disease progression. Future research should explore how combining this framework with other dynamic brain measures could further refine diagnostic tools and therapeutic strategies for AD and other neurodegenerative diseases.
