

A growing body of evidence suggests that dementia is a result of the complex interplay between neurodegenerative and cerebrovascular processes, influenced by genetic, demographic, and lifespan environmental exposures. Current dementia prediction work relies on either biomarkers or itemized risk factors, lacking an integrated understanding of how neurobiological mechanisms interact with non-modifiable and modifiable risk factors and lead to diverse neurodegeneration trajectories. To address this challenge, we propose a novel deep systems biology model to characterize the dementia-specific state evolution of functional fluctuations (using functional MRI), where the identified abnormal system behaviors underlying functional dynamics allow us to presage the risk of developing dementia. Following this spirit, we further introduce risk factors as the system control variables, which allows us to elucidate the synergistic effect of risk profiles on dementia through the lens of brain function. We have evaluated our dementia prediction model on the ADNI database, where we not only achieved the highest prediction accuracy but also dissected a system-level underpinning of how various risk factors collectively modify the progression of dementia.