

Cross-species Analysis Of Circadian Dysfunction In Alzheimer’s Disease: Integrating Human Neuroimaging and *C. elegans*

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A cross-species pipeline linking human MRI biomarkers with *C. elegans* molecular assays reveals that EGCG and resveratrol restore circadian rhythmicity disrupted by CK1δ/ε inhibition, establishing a scalable translational framework to identify and evaluate viable therapeutic targets for circadian dysfunction in Alzheimer's disease.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES
Alzheimer’s disease (AD) is characterized by progressive cognitive decline and profound circadian dysregulation. Degeneration of the hypothalamus disrupts sleep-wake cycles, further exacerbating disease burden. This study establishes a cross-species translational framework connecting human neuroimaging biomarkers with <i>Caenorhabditis elegans</i> molecular assays to identify candidates capable of restoring circadian rhythmicity.	Using MRI and clinical data from 660 individuals (ADNI database), a Circadian Dysfunction Index (CDI) was constructed by integrating hypothalamic and ventricular volumes with caregiver-reported sleep and appetite changes. To interrogate conserved molecular mechanisms, <i>C. elegans</i> were treated with the CK1 delta/epsilon inhibitor SR-3029 to perturb the LIN-42/KIN-20 pathway (an analog of the mammalian PER/CLOCK system). Four therapeutic candidates—curcumin, resveratrol, epigallocatechin gallate (EGCG), and melatonin—were screened for their ability to rescue rhythmic molting behavior.	Analysis of clinical neuroimaging data revealed that lower hypothalamic volumes significantly correlated with higher CDI scores, establishing a robust structural marker for human circadian disruption. In the parallel <i>C. elegans</i> model, EGCG produced the most robust phenotypic recovery, successfully restoring rhythmic molting periodicity from an impaired 840–920 minutes back to near-wild type levels (640 minutes). These coupled datasets validate the translational pipeline, mapping out clear structural and behavioral parameters for the next phase of targeted computational screening.	This cross-species integration demonstrates that bridging human clinical neuroimaging with in vivo <i>C. elegans</i> models provides a powerful framework for tracking circadian dysfunction. The robust phenotypic recovery demonstrated by EGCG provides a scalable, data-driven platform for therapeutic discovery. Future directions will leverage high-throughput computational screening to map the precise structural mechanics of the KIN-20 kinase pathway, accelerating targeted intervention points for restoring biological rhythms in neurodegeneration.	[1] ADNI. 2016. Alzheimer’s Disease Neuroimaging Initiative. adni.loni.usc.edu. [2] Lamberti et al. 2024. <i>Sci Rep</i> 14(1). doi:10.1038/s41598-024-62303-9. [3] Goukasian et al. 2019. <i>Dement Geriatr Cogn Disord Extra</i> 9(2):281–93. [4] Monsalve et al. 2011. <i>Curr Biol</i> 21(24):2033–45. CONTACT  Arjun Gupta American High School arjgupta007@gmail.com ALZHEIMER’S ASSOCIATION 