Title: Integrating Brain Imaging and Real-World Behavioral Data to Understand Alzheimer's Progression

Alzheimer's disease (AD) is a progressive neurodegenerative disorder affecting over 7 million individuals in the United States, with projections estimating a rise to 13 million by 2050 without effective interventions [1]. Traditional clinical assessments often provide only episodic snapshots of cognition and may miss subtle, early-stage functional decline [16]. Neuroimaging techniques, such as functional MRI (fMRI) and EEG, have been instrumental in identifying early neural changes in AD, including hippocampal atrophy and disruptions in the default mode network (DMN) connectivity [4][11]. However, these methods are typically confined to controlled laboratory environments, limiting their ecological validity [10]. In contrast, wearable actigraphy devices enable continuous, ecologically valid monitoring of behavioral rhythms, including sleep, activity, and circadian patterns-domains disrupted early in AD progression [9][21]. These devices capture real-world data over extended periods, providing insights into daily functioning that traditional assessments might overlook [20] [6]. While prior studies have utilized repositories such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the National Sleep Research Resource (NSRR) to explore neural and behavioral data separately, integration poses challenges due to differing cohorts and data structures [2]. Ontology-based data harmonization addresses this by mapping elements across datasets to a shared conceptual framework, facilitating interoperability and enabling cross-cohort analyses. For instance, the Alzheimer's Disease Data Element Ontology (ADEO) has successfully harmonized data between ADNI and the National Alzheimer's Coordinating Center (NACC) [5]. This project integrates ADNI neuroimaging and NSRR actigraphy data via ontology harmonization. By enabling semantic alignment of heterogeneous datasets, this approach facilitates comprehensive analyses previously unattainable. While neuroimaging often lacks ecological validity, actigraphy provides continuous, real-world monitoring of behavioral rhythms [13]. Integrating these modalities allows for holistic understanding of AD progression across neural and behavioral dimensions [12]. The fusion of these data types through ontology-based harmonization enables identification of novel digital biomarkers reflecting subtle changes in brain structure/function and daily behavioral patterns, potentially leading to earlier diagnosis and intervention strategies. The framework developed is scalable and adaptable, allowing incorporation of additional datasets and facilitating reproducibility in future research, advancing AD research with new avenues for early detection and personalized intervention strategies.

Proposed Study Design: Two complementary studies apply this framework to identify digital biomarkers and build predictive models of Alzheimer's progression using harmonized neural and behavioral data.

Study 1. Associations between neuroimaging biomarkers and real-world activity patterns in AD using harmonized datasets: Hippocampal atrophy and default mode network (DMN) dysfunction are associated with cognitive decline in Alzheimer's disease (AD) [4][15], while disrupted sleep and circadian rhythms indicate elevated AD risk [9][20][21]. This study examines these relationships using structural MRI data from ADNI ($n = 300$) and actigraphy data from NSRR ($n = 500$, age ≥ 65), harmonized via the Alzheimer's Disease Data Element Ontology (ADEO) [5]. Despite differing cohorts, ADEO enables semantic alignment for meta-level analyses without subject-level pairing [2][5]. The hypothesis posits that lower hippocampal volume and reduced DMN connectivity correspond to poorer sleep efficiency and attenuated activity rhythms, including increased sleep fragmentation and reduced daytime activity [8][9][15]. Multivariable regression will be used, adjusting for age, sex, and cognitive status; results will include standardized beta coefficients and FDR-corrected p-values ($p < 0.05$). Integrating ecologically valid behavioral data with neuroimaging markers enables the discovery of digital biomarkers reflecting functional decline in early AD, advancing scalable, real-world monitoring approaches [3].

Study 2. Predicting Cognitive Decline in MCI Using Multimodal Machine Learning on Harmonized Neuroimaging and Actigraphy Data: This study aims to predict 2-year cognitive decline in mild cognitive impairment (MCI) by integrating neuroimaging and actigraphy data from the ADNI cohort ($n = 150$) using ontology-based harmonization [7][5]. Features such as hippocampal volume and sleep efficiency will inform supervised models (e.g., SVMs, neural networks) [14]. Stratified 5-fold cross-validation will assess performance via AUC-ROC, with DeLong's test used to compare against unimodal baselines [18]. We hypothesize multimodal models will outperform unimodal ones, offering a clinically relevant framework for early Alzheimer's detection [17][19].

References:

[1] Alzheimer's Association. (2025). *American Perspectives on Early Detection of Alzheimer's Disease in the Era of Treatment*. https://www.alz.org/getmedia/ef8f48f9-ad36-48ea-87f9-b74034635c1e/alzheimers-facts-and-figures.pdf

[2] Cui, L., Zeng, N., Kim, M., Mueller, R., Hankosky, E. R., Redline, S., & Zhang, G.-Q. (2018). X-search: An open access interface for cross-cohort exploration of the National Sleep Research Resource. *BMC Medical Informatics and Decision Making, 18*(1). https://doi.org/10.1186/s12911-018-0682-y

[3] Chudzik, A., Śledzianowski, A., & Przybyszewski, A. W. (2024). *Machine learning and digital biomarkers can detect early stages of neurodegenerative diseases*. MDPI. https://www.mdpi.com/1424-8220/24/5/1572

[4] Greicius, M. D., Srivastava, G., Reiss, A. L., & Menon, V. (2004). Default-mode network activity distinguishes Alzheimer's disease from healthy aging: Evidence from functional MRI. *Proceedings of the National Academy of Sciences, 101*(13), 4637–4642. https://doi.org/10.1073/pnas.0308627101

[5] Hao, X., Li, X., Zhang, G.-Q., Tao, C., Schulz, P. E., & Cui, L. (2023). An ontology-based approach for harmonization and cross-cohort query of Alzheimer's disease data resources. *BMC Medical Informatics and Decision Making, 23*(S1). https://doi.org/10.1186/s12911-023-02250-z

[6] James, B. D., Boyle, P. A., Bennett, D. A., & Buchman, A. S. (2012). Total Daily Activity Measured With Actigraphy and Motor Function in Community-dwelling Older Persons With and Without Dementia. *Alzheimer Disease & Associated Disorders, 26*(3), 238–245. https://doi.org/10.1097/wad.0b013e31822fc3cb

[7] Lee, M.-W., Kim, H. W., Choe, Y. S., Yang, H. S., Lee, J., Lee, H., Yong, J. H., Kim, D., Lee, M., Kang, D. W., Jeon, S. Y., Son, S. J., Lee, Y.-M., Kim, H.-G., Kim, R. E. Y., & Lim, H. K. (2024). A multimodal machine learning model for predicting dementia conversion in Alzheimer's disease. *Scientific Reports*. https://pmc.ncbi.nlm.nih.gov/articles/PMC11133319/

[8] Li, C., Fronczek-Poncelet, J., Lange, D., Hennecke, E., Kroll, T., Matusch, A., Aeschbach, D., Bauer, A., Elmenhorst, E., & Elmenhorst, D. (2019). Impact of acute sleep deprivation on dynamic functional connectivity states. *Human Brain Mapping, 41*(4), 994–1005. https://doi.org/10.1002/hbm.24855

[9] Lim, A. S. P., Kowgier, M., Yu, L., Buchman, A. S., & Bennett, D. A. (2013). Sleep Fragmentation and the Risk of Incident Alzheimer's Disease and Cognitive Decline in Older Persons. *Sleep, 36*(7), 1027–1032. https://doi.org/10.5665/sleep.2802

[10] Loosen, A. M., Kato, A., & Gu, X. (2024). Revisiting the role of computational neuroimaging in the era of integrative neuroscience. *Neuropsychopharmacology*. https://doi.org/10.1038/s41386-024-01946-8

[11] Michels, L., Riese, F., Meyer, R., Kälin, A. M., Leh, S. E., Unschuld, P. G., Luechinger, R., Hock, C., O'Gorman, R., Kollias, S., & Gietl, A. (2021). EEG-fMRI Signal Coupling Is Modulated in Subjects With Mild Cognitive Impairment and Amyloid Deposition. *Frontiers in Aging Neuroscience, 13*. https://doi.org/10.3389/fnagi.2021.631172

[12] Modupe Odusami, R., Maskeliūnas, R., & Damaševičius, R. (2023). Optimized Convolutional Fusion for Multimodal Neuroimaging in Alzheimer's Disease Diagnosis: Enhancing Data Integration and Feature Extraction. *Journal of Personalized Medicine, 13*(10), 1496–1496. https://doi.org/10.3390/jpm13101496

[13] Sanchez-Ortuno, M. M., Edinger, J. D., Means, M. K., & Almirall, D. (2010). Home is where sleep is: An ecological approach to test the validity of actigraphy for the assessment of insomnia. *Journal of Clinical*

Sleep Medicine, 6(1), 21–29. https://pubmed.ncbi.nlm.nih.gov/20191934/

[14] Settimi, M., Tchoudnovski, D., Ntale, I., Colelli, D. R., Costa, Y. S., Mitchell, S., Masellis, M., Lam, B., Lim, A., Chung, F., Ramirez, J., Goubran, M., Black, S. E., & Boulos, M. I. (2025). Examining the association between sleep apnea and total hippocampal volumes in cognitive impairment. *Alzheimer's Dementia, 21*(4), e70183. https://doi.org/10.1002/alz.7018

[15] Sherman, S. M., Mumford, J. A., & Schnyer, D. M. (2015). Hippocampal activity mediates the relationship between circadian activity rhythms and memory in older adults. *Neuropsychologia, 75*, 617–625. https://doi.org/10.1016/j.neuropsychologia.2015.07.020

[16] Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., Iwatsubo, T., Jack, C. R., Kaye, J., Montine, T. J., Park, D. C., Reiman, E. M., Rowe, C. C., Siemers, E., Stern, Y., Yaffe, K., Carrillo, M. C., Thies, B., Morrison-Bogorad, M., & Wagster, M. V. (2011). Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia, 7*(3), 280–292. https://doi.org/10.1016/j.jalz.2011.03.003

[17] Venugopalan, J., Tong, L., Hassanzadeh, H. R., & Wang, M. D. (2021). Multimodal Deep Learning Models for early detection of Alzheimer's disease stage. *Scientific Reports*. https://www.nature.com/articles/s41598-020-74399-w

[18] Wang, X., Zhou, S., Ye, N., Li, Y., Zhou, P., Chen, G., & Hu, H. (2024). Predictive models of Alzheimer's disease dementia risk in older adults with mild cognitive impairment: A systematic review and critical appraisal. *BMC Geriatrics*. https://pmc.ncbi.nlm.nih.gov/articles/PMC11188292/

[19] Wen, J.,Thibeau-Sutre, E., Diaz-Melo, M., Samper-Gonzalez, J., Routier, A., Bottani, S., Dormont, D., Durrleman, S., Burgos, N., & Colliot, O. (2020). Convolutional Neural Networks for classification of Alzheimer's disease: Overview and reproducible evaluation. *arXiv.org*. https://arxiv.org/abs/1904.07773

[20] Winer, J. R. (2024). The role of actigraphy in detecting and characterizing the early phases of Alzheimer's disease. *SLEEP, 47*(5). https://doi.org/10.1093/sleep/zsae076

[21] Winer, J. R., Lok, R., Weed, L., He, Z., Poston, K. L., Mormino, E. C., & Zeitzer, J. M. (2024). Impaired 24-h activity patterns are associated with an increased risk of Alzheimer's disease, Parkinson's disease, and cognitive decline. *Alzheimer's Research & Therapy, 16*(1). https://doi.org/10.1186/s13195-024-01411-0