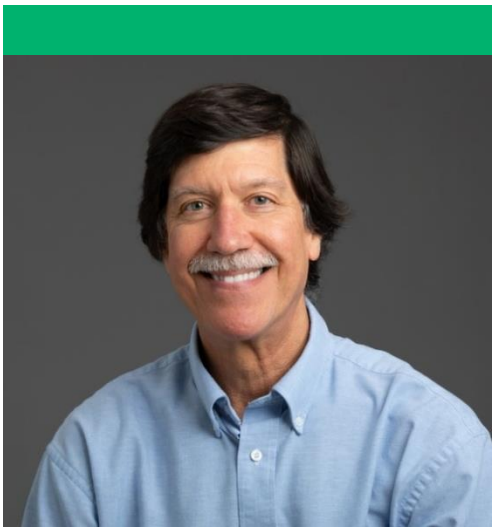
RUSH

# David A. Bennett, MD



The Robert C. Borwell Professor of Neurological Sciences

## Advancement of Medicine

Over the past three decades, we have systematically built a platform to identify risk factors and novel drug discovery for neurologic conditions of the central nervous system. We identified numerous risk factors for loss of cognitive and motor function, as well as numerous pathologies and resilience factors. **We are now discovering new potential therapeutic targets to treat and prevent the loss of cognitive and motor function.** Over the past 15 years, we have generated an unprecedented multi-omic, multi-brain region and blood database to drive drug discovery in the cognition space. This database also drives discovery in the motor function space, as it generates omic data for spinal cord and muscle conditions and multiple sclerosis. Finally, we generated induced pluripotent stem cells from 110 autopsied participants, with another 70 cells under construction and funding secured to develop an additional 30 cells. Rush Alzheimer's Disease Center, or RADC, resources are distributed globally via our Resource Sharing Hub.

### Research

The current National Institutes of Health salary cap cannot entirely cover the salaries of senior investigators who receive full project funding from federal sources. Thus, proceeds from my endowed professorship were used to supplement the salaries of two full professors with long track records of bringing millions in external funding to Rush.

### Grants

In 2025, I was awarded two grants from the National Institute on Aging and one private foundation grant. The RADC as a whole, under my leadership, was awarded 12 grants. Below, I list 10 important publications of the 100+ publications I co-authored in 2025.

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## Publication Highlights – Abbreviated

Vialle RA, de Paiva Lopes K, Li Y, Ng B, Schneider JA, Buchman AS, Wang Y, Farfel JM, Barnes LL, Wingo AP, Wingo TS, Seyfried NT, De Jager PL, Gaiteri C, Tasaki S, **Bennett DA**. Structural variants linked to Alzheimer's disease and other common age-related clinical and neuropathologic traits. *Genome Med*. 2025 Mar 4;17(1):20.

- This study highlights the utility of including analysis of structural variants for elucidating mechanisms underlying genome-wide association study loci and provides a valuable resource for the characterization of the effects of structural variants in neurodegenerative disease pathogenesis.

Zhao J, Gu T, Gao C, Miao G, Palma-Gudiel H, Yu L, Yang J, Wang Y, Li Y, Lim J, Li R, Yao B, Wu H, Schneider JA, Seyfried N, Grodstein F, De Jager PL, Jin P, **Bennett DA**. Brain 5-hydroxymethylcytosine alterations are associated with Alzheimer's disease neuropathology. *Nat Commun*. 2025 Mar 22;16(1):2842.

- Our study presents a large-scale, genome-wide atlas of 5-hydroxymethylcytosine in the Alzheimer's brain and offers insight into the mechanism underlying Alzheimer's disease pathogenesis.

Buchman AS, Wang T, de Paiva Lopes K, Zammit AR, Oveisgharan S, Seyfried N, Wang Y, DeJager P, Nag S, Tasaki S, Yu L, **Bennett DA**. Identifying motor resilience proteins associated with motor decline in older adults. *J Gerontol A Biol Sci Med Sci*. 2025 Jul 24;80(8):glaf144.

- Cortical proteins may provide motor resilience for both linear and non-linear motor decline. Further drug discovery targeting resilience proteins may yield therapies that can reduce motor impairment even in the absence of treatments for Alzheimer’s disease and related dementia pathologies.

Aron L, Ngian ZK, Qiu C, Choi J, Liang M, Drake DM, Hamplova SE, Lacey EK, Roche P, Yuan M, Hazaveh SS, Lee EA, **Bennett DA**, Yankner BA. Lithium deficiency and the onset of Alzheimer's disease. *Nature*. 2025 Sep;645(8081):712-721.

- These findings reveal the physiological effects of endogenous lithium in the brain and indicate that disruption of lithium homeostasis may be an early event in the pathogenesis of

Alzheimer's disease. Lithium replacement with amyloid-evading salts is a potential approach to the prevention and treatment of Alzheimer's disease.

Oveisgharan S, Yu L, Yang J, Agrawal S, Vialle R, de Paiva Lopes K, Tasaki S, Wang Y, Petyuk VA, Young-Pearse TL, Menon V, Zhao J, Miao G, Barnes LL, Schneider JA, De Jager PL, Seyfried N, **Bennett DA**. Cortical gray matter proteins associated with cerebral amyloid angiopathy in community-dwelling older adults: an autopsy study. *Neurology*. 2025 Sep 23;105(6):e214024.

- This study suggests two molecular pathways underlying cerebral amyloid angiopathy, with a larger effect size for the pathway including SFRP1 and APOE protein and C-terminally truncated amyloid beta before position 40.

Grodstein F, Wilson RS, Graham EK, Mroczek DK, **Bennett DA**. Trends over 45 years in personality traits among older populations. *J Gerontol B Psychol Sci Soc Sci*. 2025 Nov 5;80(12):gbaf212.

- We found associations of later birth cohort with lower neuroticism and higher conscientiousness among older adults. Findings suggest that personality at older ages is amenable to population-level shifts, with implications for health.

Lopes KP, Vialle RA, Green G, Fujita M, Gaiteri C, Menon V, Schneider JA, Wang Y, De Jager PL, Habib N, Tasaki S, **Bennett DA**. Gene module-trait network analysis uncovers cell type specific systems and genes relevant to Alzheimer's disease. *Acta Neuropathol Commun*. 2025 Nov 4;13(1):222.

- Our work provides cell-specific molecular networks modeling the molecular events leading to Alzheimer's disease.

Oveisgharan S, Yu L, Wang Y, Yang J, Vialle R, Lopes KP, Tasaki S, Young-Pearse TL, De Jager PL, Petyuk VA, Schneider JA, Seyfried NT, **Bennett DA**. Amyloid beta binding partners in the brain tissue of older adults. *Alzheimers Dement*. 2025 Nov;21(11):e70882.

- Identification of amyloid beta binding partners that mediate the association between amyloid beta and tau tangles may provide new targets for Alzheimer's disease treatment.

Farfel JM, Capuano AW, Nag S, Sampaio MCM, Gibbons J, Wilson RS, **Bennett DA**. The pathology, Alzheimer's and related dementias study (PARDoS): design and characteristics of the first 4700+ Brazilian participants. *Neuroepidemiology*. 2025 Dec 2:1-33.

- Here, we present the study design, demographic characteristics of the first 4,790 autopsied participants and clinical characteristics of the first 4,283 participants with informant interviews.

Buchman AS, Yu L, Oveisgharan S, Tickotsky N, de Paiva Lopes K, Zammit AR, VanderHorst V, Klein HU, Nag S, **Bennett DA**. Associations of pathologic Parkinson's disease (PD) and co-pathologies with cognitive decline and progression of Parkinsonian signs in decedents with subclinical disease. *Acta Neuropathol*. 2025 Dec 22;151(1):1.

- The associations of Lewy bodies with cognition and Parkinsonism may vary with the severity of nigral neuronal loss and, together, with its co-pathologies, account for a minority of late-life progressive Parkinsonism and cognitive decline. Synucleinopathies in older adults without clinical Parkinson's disease may be underestimated.

## Invited Presentations – Abbreviated

- Deconstructing the Complexity of AD/ADRD: From Translational Epidemiology to Precision Medicine. USC Center for Personalized Brain Health Research Symposium: Advances in Personalized Brain Health. February 25, 2025. Los Angeles, CA.
- Charting a Path to Precision Medicine for Alzheimer's Disease. Consortium pour l'Identification précoce de la Maladie d'Alzheimer-Québec (CIMA-Q). May 16, 2025. Montréal, QC, CA.
- Charting a Path to Precision Medicine for Alzheimer's Disease. 5th U.S.-Israel Alzheimer's Disease Conference. University of Tel Aviv. June 5, 2025. Tel Aviv, Israel.
- Aging, Cognitive and Motor Function, and Genetics. Instituto Nacional de Salud Pública. June 19, 2025. Cuernavaca, Morelos.
- Genetics of Cognitive and Motor Function. Instituto Nacional de Salud Pública. June 19, 2025. Cuernavaca, Morelos.
- Preliminary Findings and Opportunities for Studies of Pollution in the USA, Brazil, and Mexico. Santiago Exposome Symposium: Integrating Environmental Exposures into Research on Alzheimer's Disease and Related Dementias. September 25, 2025. Santiago, Chile.
- Deconstructing the Complexity of AD/ADRD: From Translational Epidemiology to Precision Medicine "Charting a path to precision medicine for brain diseases." 2nd Annual Carol and

Gene Ludwig Center Symposium. Genetics and Biology of Resilience and Resistance to Alzheimer's Disease. Columbia University Medical Center. October 9, 2025. New York City, NY.

- Charting a Path to Precision Medicine for AD/ADRD. Canadian Consortium on Neurodegeneration in Aging (CCNA). October 15, 2025. Calgary, AB, CA.
- Risk Factors, Pathology, Resilience, and the Clinical Expression of Alzheimer's Disease. 112th Canadian Conference on Dementia. October 16, 2025. Calgary, AB, CA.

## The Year Ahead: 2026 and Beyond

After generating an unprecedented multi-omic brain platform for novel drug target discovery in human brains from non-Latino white people, we are now generating similar data on brains and multiple other organs from Brazilian study participants with a broad range of life characteristics across age, sex, race and socioeconomic status. In fact, one of the awarded grants in 2025 is to generate more data on Brazilian study participants, and we anticipate two additional such grants to be awarded early in 2026. One of the expected awards will collect brain, bone, teeth and lung samples for studies of metal and particulate matter pollutants. We continue to generate brain cell lines from our autopsied participants to conduct experiments that get us closer to precision medicine for brain diseases. Finally, we believe in open science and will continue to share our findings across the field.

## With Gratitude

As always, thank you for your generous support of our work. These funds are instrumental in ensuring Rush and the RADC continue to conduct excellent aging and Alzheimer's disease research.