

NAME OF PRESENTING AUTHOR: McKenna E. Williams

EMAIL ADDRESS OF PRESENTING AUTHOR: mewillia@health.ucsd.edu

## Genetic and environmental influences on Alzheimer's disease neuroimaging signatures

McKenna E. Williams<sup>1,2,3</sup>, Nathan A. Gillespie<sup>4</sup>, Tyler R. Bell<sup>1,3</sup>, Anders M. Dale<sup>5,6</sup>, Jeremy A. Elman<sup>1,3</sup>, Lisa T. Eyler<sup>3,7</sup>, Christine Fennema-Notestine<sup>3,5</sup>, Donald J. Hagler, Jr.<sup>5</sup>, Linda K. McEvoy<sup>5</sup>, Michael C. Neale<sup>4</sup>, Matthew S. Panizzon<sup>1,3</sup>, Chandra A. Reynolds<sup>8</sup>, Mark Sanderson-Cimino<sup>1,2,3</sup>, Carol E. Franz<sup>1,3</sup>, William S. Kremen, PhD<sup>1,3</sup>

<sup>1</sup>Center for Behavior Genetics of Aging, University of California San Diego, La Jolla, CA, USA

<sup>2</sup>Joint Doctoral Program in Clinical Psychology, San Diego State University/University of California, San Diego, CA, USA

<sup>3</sup>Department of Psychiatry, University of California San Diego, La Jolla, CA, USA

<sup>4</sup>Virginia Institute for Psychiatric and Behavior Genetics, Virginia Commonwealth University, VA, USA

<sup>5</sup>Department of Radiology, University of California San Diego, La Jolla, CA, USA

<sup>6</sup>Department of Neuroscience, University of California San Diego, La Jolla, CA, USA

<sup>7</sup>Desert Pacific Mental Illness Research Education and Clinical Center, VA San Diego Healthcare System, CA, USA

<sup>8</sup>Department of Psychology, University of California Riverside, Riverside, CA, USA

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### ABSTRACT:

Composite scores of MRI-based morphometrics in brain regions associated with Alzheimer's disease (AD) pathology have been developed to distinguish early AD-related atrophy from normal age-associated brain changes. These composite scores, commonly termed 'AD signatures,' are associated with increased risk of progression to mild cognitive impairment or AD and with symptom severity. Genetic and environmental influences on AD signatures have not been examined. Moreover, given that aging is associated with atrophy in areas that overlap with regions in AD signatures, it is unknown if they capture unique AD-related variance or simply reflect general brain aging. Here, we used a cortical thickness/hippocampal volume signature (CTHV), a mean diffusivity (MD) signature, and an MRI-based measure of predicted brain age ( $n=310-502$ ) in biometrical analyses to determine 1) the genetic and environmental etiology of each AD signature and the measure of brain age, and 2) sources of covariance among these three phenotypes. Participants were from the Vietnam Era Twin Study of Aging (age=56.18, SD=2.61). Heritability estimates were similar for the signatures and predicted brain age (0.68-0.71). Phenotypic correlations ranged from -0.46 to 0.27. Genetic correlations among the three phenotypes were moderate but significant: 0.33 [95%CI:0.19,0.47] (CTHV signature and predicted brain age); -0.55 [95%CI:-0.66,-0.42] (MD signature and predicted brain age); and -0.36 [95%CI:-0.51,-0.20] (CTHV and MD signatures). Despite similar heritability estimates and significant genetic correlations among the three phenotypes, our findings are consistent with genetic influences unique to each AD signature that were not shared with those contributing to general brain aging.

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