BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Neale, Michael, C.

eRA COMMONS USER NAME (credential, e.g., agency login): MCNEALE

POSITION TITLE: Distinguished Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Bedford College, University of London	BSc	1980	Psychology
Institute of Psychiatry, University of London	PhD	1985	Psychology

A. **Personal Statement**

As the developer of OpenMx, a globally-adopted statistical modeling package for analyses of continuous, ordinal and binary data, especially data from relatives. The versatile open source software has been downloaded around 2 million times. I have collaborated and coauthored articles with MPI Dr. Gillespie for over 25 years. I bring extensive expertise in statistical genetic modeling to the VETSA Wave 5 project. Our 20-year partnership with the Vietnam Era Twin Study of Aging (VETSA) has produced over 25 co-authored publications with collaborators, including a landmark study mapping genetic correlations of the human cortex (Chen et al., 2012, Science), which advanced ADRD-related neuroimaging research. With over 500 peer-reviewed publications, an h-index of 107 (ISI), and awards like the James Shields Award for twin studies, my methodological innovations have shaped genetic epidemiology.

Dr. Gillespie and I have analyzed high-dimensional longitudinal data, including VETSA's NULISA biomarker panel and neuroimaging measures, to uncover causal pathways and heterogeneity in ADRD risk factors, delivering high-impact results. My expertise in Mendelian randomization, extended through novel twin-design and longitudinal integrations (Minica et al., 2018), directly supports Aim 1's causal association tests between ADRD risk factors and late-life outcomes. For Aim 2, I will develop advanced models to evaluate heterogeneity, including pathology levels (2B) and early-life influences from age 20 (2D), leveraging OpenMx's matrix algebra and numerical optimization for rapid, robust analysis of complex datasets. Our joint work on longitudinal twin models ensures precise handling of VETSA's multi-decade data.

Our Leadership Plan, refined over decades of collaboration, ensures seamless MPI coordination and analytical precision. Our 25-year partnership, proven through consistent delivery of groundbreaking analyses, guarantees that we will achieve VETSA Wave 5's aims, advancing ADRD research through impactful publications and presentations.

Citations:

a. Boker S, **Neale** MC, Maes H, et al. OpenMx: An Open Source Extended Structural Equation Modeling Framework. Psychometrika. 2011;76(2):306-317. PMCID: PMC3525063.
b. Gillespie NA, Elman JA, McKenzie RE, Tu XM, Xian H, Reynolds CA, Panizzon MS, Lyons MJ, Eglit GML, **Neale** MC, Rissman R, Kremen WS, Franz C. The heritability of blood-based biomarkers related to risk of Alzheimer's Disease in a population-based sample of early old-age men. Alzheimer's & Dementia. 2023;20(1):356-65. PMCID: PMC10843753.
c. Chen CH, Gutierrez ED, Thompson W, Panizzon MS, Jernigan TL, Eyler LT, Fennema-Notestine C, Jak AJ, **Neale** MC, Franz CE, Lyons MJ, Grant MD, Fischl B, Seidman LJ, Tsuang MT, Kremen WS, Dale

AM. Hierarchical genetic organization of human cortical surface area. Science. 2012;335(6076):1634-1636. PMCID: PMC3690329.

d. Gillespie NA, **Neale** MC, Panizzon MS, McKenzie RE, Tu XM, Xian H, Reynolds CA, Lyons MJ, Rissman RA, Elman JA, Franz C, Kremen WS. Testing the causal impact of plasma amyloid on total Tau using a genetically informative sample of adult male twins. Aging Brain, accepted.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

1976–1977: Nursing Auxiliary, Coney Hill Mental Hospital, Gloucester, UK

1983–1986: Research Worker/Lecturer, Department of Psychology, Institute of Psychiatry, University of London

1986–1989: Research Associate, Department of Human Genetics, Virginia Commonwealth University (VCU)
1989–1992: Assistant Professor, Department of Human Genetics, VCU

1992–1999: Associate Professor, Department of Psychiatry, VCU

2000–Present: Professor, Departments of Psychiatry and Human Genetics, VCU

2003–Present: External Professor, Department of Biological Psychology, Free University of Amsterdam, NL
2005–Present: Associate Director, Virginia Institute for Psychiatric & Behavioral Genetics, VCU

2017–Present: Distinguished Professor, Department of Psychiatry, VCU

Honors

1983: Thompson Memorial Award for Behavior Genetics

1994: Cattell Award, Society for Multivariate Experimental Psychology

2000: Fulker Award, Behavior Genetics Association

2004: James Shields Award for Outstanding Contribution to Twin Studies

2004: Fulker Award, Behavior Genetics Association

2005: MERIT Award, National Institute on Drug Abuse

2009: Tanaka Award, Society for Multivariate Experimental Psychology

2017: Distinguished Scholarship Award, Virginia Commonwealth University

C. Contributions to Science

Current projects that I would like to highlight include:

R25DA026119 Neale (PI) 09/01/2009–04/30/2024 (NCE through 04/30/2025)
Research Education in Statistical Genetics of Substance Abuse
Provides predoctoral and postdoctoral training in statistical genetics, supporting VETSA's analytical framework.
Role: PI

R01AG022381 Kremen (PI) 07/01/2015–03/31/2025
The VETSA Longitudinal MRI Twin Study of Aging
Studies cognitive and brain aging in veteran twins, directly supporting VETSA Wave 5's neuroimaging analyses.
Role: PI Subcontract

R01AG050595 Kremen (PI) 03/01/2002–05/31/2025
The VETSA Longitudinal Twin Study of Cognition and Aging
Examines genetic and environmental causes of cognitive aging in VETSA twins, supporting Aim 2D.
Role: PI Subcontract

U01DA041120 Neale, Bjork (MPI) 9/30/2015-3/31/2027 ABCD-USA Consortium: Research Project Site at VCU. One of four sites at which data are collected from twins, the study examines neuroimaging, psychopathology, substance use, and relevant cultural factors to examine the causes and consequences of substance use.
Role: MPI

R01 MH125902
Kendler, K. (PI), Role: co-investigator
12/2021-10/2026
Title: An Integrative Approach to the Etiology of Internalizing Disorders in the Lifelines Cohort

1. Development of OpenMx and Mx for Twin-Based Analyses: I pioneered the development of Mx and OpenMx, open-source software packages that combine matrix algebra interpreters with numerical optimizers, enabling flexible multivariate and longitudinal analyses of twin and family data. OpenMx, an R package, is downloaded ~1,000 times monthly and used globally for genetic modeling, including ADRD studies in VETSA. These tools support Aim 1's causal inference via Mendelian randomization and Aim 2's heterogeneity analyses by processing high-dimensional neuroimaging and biomarker data (e.g., NULISA panel).

a. Boker S, Neale MC, Maes H, et al. OpenMx: An Open Source Extended Structural Equation Modeling Framework. Psychometrika. 2011;76(2):306-317. PMCID: PMC3525063.
b. Neale MC, Hunter MD, Pritikin JN, et al. OpenMx 2.0: Extended Structural Equation and Statistical Modeling. Psychometrika. 2016;81(2):535-549. PMCID: PMC4516707.
c. Gillespie NA, Neale MC, Panizzon MS, McKenzie RE, Tu XM, Xian H, Reynolds CA, Lyons MJ, Rissman RA, Elman JA, Franz C, Kremen WS. Testing the causal impact of plasma amyloid on total Tau using a genetically informative sample of adult male twins. Aging Brain, accepted.
d. Gillespie NA, Elman JA, McKenzie RE, Tu XM, Xian H, Reynolds CA, Panizzon MS, Lyons MJ, Eglit GML, Neale MC, Rissman R, Kremen WS, Franz C. The heritability of blood-based biomarkers related to risk of Alzheimer's Disease in a population-based sample of early old-age men. Alzheimer's & Dementia. 2023;20(1):356-65. PMCID: PMC10843753.

2. Causal Inference Methods for ADRD: My work on Mendelian randomization and direction-of-causation models has advanced causal inference in genetic epidemiology, directly supporting Aim 1's goal of testing causal associations among ADRD risk factors. By integrating molecular genetic data with twin designs, I have developed methods to test assumptions of no pleiotropy and no reverse causation, critical for VETSA's analyses of ADRD biomarkers and cognitive outcomes.

a. Minica CC, Dolan CV, Boomsma DI, de Geus E, Neale MC. Extending Causality Tests with Genetic Instruments: An Integration of Mendelian Randomization with the Classical Twin Design. Behav Genet. 2018;48(4):337-349. PMCID: PMC6028857.
b. Gillespie NA, Neale MC, Panizzon MS, McKenzie RE, Tu XM, Xian H, Reynolds CA, Lyons MJ, Rissman RA, Elman JA, Franz C, Kremen WS. Testing the causal impact of plasma amyloid on total Tau using a genetically informative sample of adult male twins. Aging Brain, accepted.
c. Kremen WS, Panizzon MS, Elman JA, Granholm EL, Andreassen OA, Dale AM, Gillespie NA, Gustavson DE, Logue MW, Lyons MJ, Neale MC, Reynolds CA, Whitsel N, Franz CE. Pupillary dilation responses as a midlife indicator of risk for Alzheimer's disease: association with Alzheimer's disease polygenic risk. Neurobiol Aging. 2019;83:114-21. PMCID: WOS:000499079800012.
d. Neale MC, Kendler KS. Models of comorbidity for multifactorial disorders. Am J Hum Genet. 1995;57(4):935-953. PMCID: PMC1801512.

3. Neuroimaging Twin Analyses for ADRD: I have led twin-based analyses of neuroimaging data, including VETSA studies, to uncover genetic influences on brain structure and function relevant to ADRD, supporting Aim 2's focus on heterogeneity. My collaboration with Dr. Kremen on VETSA data has produced high-resolution genetic correlation maps of cortical areas, revealing genetically homogeneous regions linked to ADRD risk. These methods inform analyses of VETSA's neuroimaging and biomarker data.

a. Chen CH, Gutierrez ED, Thompson W, Panizzon MS, Jernigan TL, Eyler LT, Fennema-Notestine C, Jak AJ, Neale MC, Franz CE, Lyons MJ, Grant MD, Fischl B, Seidman LJ, Tsuang MT, Kremen WS, Dale AM. Hierarchical genetic organization of human cortical surface area. Science. 2012;335(6076):1634-1636. PMCID: PMC3690329.
b. Elman JA, Panizzon MS, Gillespie NA, Hagler DJ, Fennema-Notestine C, Eyler LT, McEvoy LK, Neale MC, Lyons MJ, Franz CE, Dale AM, Kremen WS. Genetic architecture of hippocampal subfields on standard resolution MRI: How the parts relate to the whole. Hum Brain Mapp. 2019;40(5):1528-1540. PMCID: PMC6397064.
c. Sanderson-Cimino M, Panizzon MS, Elman JA, Tu X, Gustavson DE, Puckett O, Cross K, Notestine R, Hatton SN, Eyler LT, McEvoy LK, Hagler DJ, Neale MC, Gillespie NA, Lyons MJ, Franz CE, Fennema-Notestine C, Kremen WS. Periventricular and deep abnormal white matter differ in associations with cognitive performance at midlife. Neuropsychology. 2021;35(3):252-264. PMCID: PMC8500190.
d. Williams ME, Gillespie NA, Bell TR, Dale AM, Elman JA, Eyler LT, Fennema-Notestine C, Franz CE, Hagler DJ, Lyons MJ, McEvoy LK, Neale MC, Panizzon MS, Reynolds CA, Sanderson-Cimino M, Kremen WS. Genetic and Environmental Influences on Structural and Diffusion-Based Alzheimer's Disease Neuroimaging Signatures Across Midlife and Early Old Age. Biol Psychiatry Cogn Neurosci Neuroimaging. 2023;8(9):918-27. PMCID: PMC9827615.

4. Longitudinal Modeling of ADRD Risk Factors: My development of longitudinal twin models, including growth curve and latent class models, supports Aim 2D's focus on early-life influences on later-life ADRD risk. These methods enable VETSA to model heterogeneity in cognitive and biomarker trajectories across decades, leveraging early adulthood data. My work with VETSA has elucidated genetic and environmental contributions to cognitive aging.

a. Logue MW, Panizzon MS, Elman JA, Gillespie NA, Hatton SN, Gustavson DE, Andreassen OA, Dale AM, Franz CE, Lyons MJ, Neale MC, Reynolds CA, Tu X, Kremen WS. Use of an Alzheimer's disease polygenic risk score to identify mild cognitive impairment in adults in their 50s. Mol Psychiatry. 2019;24(3):421-430. PMCID: PMC6110977.
b. Franz CE, Hatton SN, Elman JA, Warren T, Gillespie NA, Whitsel NA, Puckett OK, Dale AM, Eyler LT, Fennema-Notestine C, Hagler DJ, Hauger RL, McKenzie R, Neale MC, Panizzon MS, Pearce RC, Reynolds CA, Sanderson-Cimino M, Toomey R, Tu XM, Williams M, Xian H, Lyons MJ, Kremen WS. Lifestyle and the aging brain: interactive effects of modifiable lifestyle behaviors and cognitive ability in men from midlife to old age. Neurobiol Aging. 2021;108:80-89. PMCID: PMC8862767.
c. Gustavson DE, Elman JA, Reynolds CA, Eyler LT, Fennema-Notestine C, Puckett OK, Panizzon MS, Gillespie NA, Neale MC, Lyons MJ, Franz CE, Kremen WS. Brain reserve in midlife is associated with executive function changes across 12 years. Neurobiol Aging. 2024;141:113-120. PMCID: PMC11246793.
d. Williams ME, Elman JA, McEvoy LK, Andreassen OA, Dale AM, Eglit GML, Eyler LT, Fennema-Notestine C, Franz CE, Gillespie NA, Hagler DJ, Hatton SN, Hauger RL, Jak AJ, Logue MW, Lyons MJ, McKenzie RE, Neale MC, Panizzon MS, Puckett OK, Reynolds CA, Sanderson-Cimino M, Toomey R, Tu XM, Whitsel N, Xian H, Kremen WS. 12-year prediction of mild cognitive impairment aided by Alzheimer's brain signatures at mean age 56. Brain Communications. 2021;23(3):1-14.

5. Genetic Epidemiology of Complex Traits: I have applied twin and family designs to study the etiology of complex traits, including ADRD, substance use, and psychiatric disorders. My work with VETSA has identified genetic influences on ADRD biomarkers and cognitive outcomes, supporting Aim 2's heterogeneity analyses. These studies inform precision prevention strategies by elucidating shared genetic and environmental pathways.

a. Buchholz E, Gillespie NA, Hunt JF, Reynolds CA, Rissman RA, Schroeder A, Cortes I, Bell T, Lyons MJ, Kremen WS, Franz CE. Midlife cumulative deficit frailty predicts Alzheimer's disease-related plasma biomarkers in older adults. Age Ageing. 2024;53(3):afae028. PMCID: PMC10921085.
b. Garduno AC, Laughlin GA, Bergstrom J, Tu XM, Cummins KM, Franz CE, Elman JA, Lyons MJ, Reynolds CA, Neale MC, Gillespie NA, Xian H, McKenzie RE, Toomey R, Kremen WS, Panizzon MS, McEvoy LK. Alcohol use and cognitive aging in middle-aged men: The Vietnam Era Twin Study of Aging. J Int Neuropsychol Soc. 2023;29(3):235-245. PMCID: PMC9592679.
c. Kremen WS, Panizzon MS, Elman JA, Granholm EL, Andreassen OA, Dale Twiggs AM, Gillespie NA, Gustavson DE, Logue MW, Lyons MJ, Neale MC, Reynolds CA, Whitsel N, Franz CE. Pupillary dilation

responses as a midlife indicator of risk for Alzheimer's disease: association with Alzheimer's disease polygenic risk. Neurobiol Aging. 2019;83:114-121. PMCID: WOS:000499079800012.

d. Warrington NM, Freathy RM, Neale MC, Evans DM. Using structural equation modelling to jointly estimate maternal and fetal effects on birthweight in the UK Biobank. Int J Epidemiol. 2018;47(4):1229-1241. PMCID: PMC6124615.

I have authored or coauthored over 600 peer-reviewed articles; my H- indexes are 107 and 148 for ISI and Google, respectively. A list of almost 950 publications arising from my funded research and educational programs can be found at: https://www.ncbi.nlm.nih.gov/sites/myncbi/michael.neale.1/bibliography/40595238/public/?sort=date&directi on=descending.