

BDNF Val66Met genetic polymorphism modulates cognition across the menopausal transition

Mateja Perović¹, Madeline Wood Alexander^{2,3}, Yuen Yan Wong³, Jessica Z.K. Caldwell⁴, Jennifer S. Rabin^{2,3} & Liisa A.M. Galea^{1,2}

1 Centre for Addiction and Mental Health; 2 University of Toronto; 3 Sunnybrook Research Institute; 4 University of Wisconsin-Madison

Introduction

Menopause has been theorized as a major contributing factor to the greater prevalence of Alzheimer's disease (AD) in women than men^{1,2}. The brain-derived neurotrophic factor (BDNF) Val66Met single nucleotide polymorphism modulates AD risk in women³, however, no studies of BDNF Val66Met effects on cognitive aging have considered menopause effects.

Methods

We examined non-linear cognitive trajectories across the menopausal transition as a function of BDNF Val66Met and final menstrual period (FMP)-centered age using generalized additive mixed models.

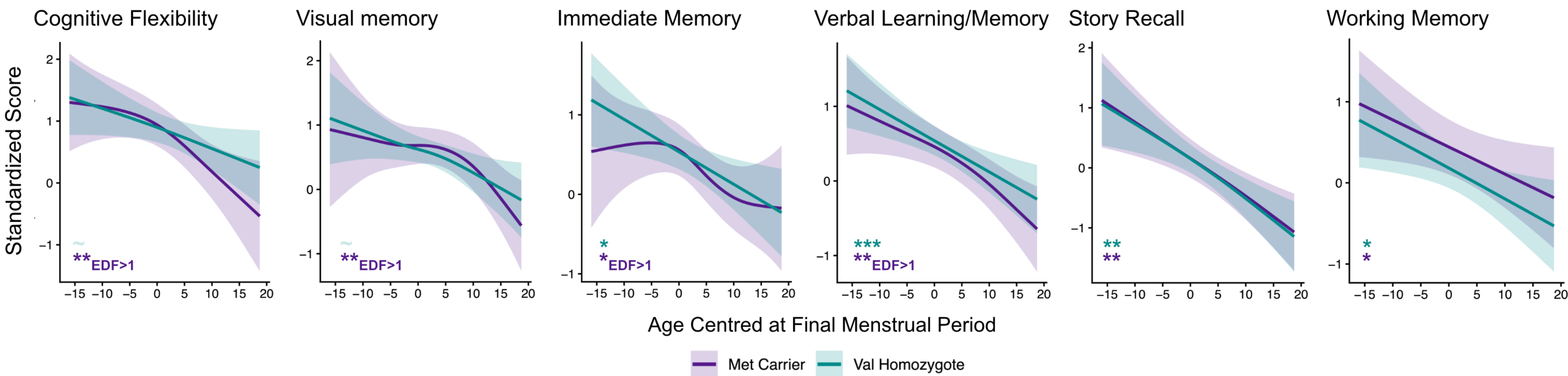
Further, we identified cognitive profiles in a cross-sectional sample of post-menopausal women using latent profile analysis. We examined profile membership using multinomial regression.

	Longitudinal (baseline information)	Post-menopausal (cross-sectional data)
N	143 (30.4% Met)	349 (32.1% Met)
Age	46.3±4.1	57.5±5
Education	15.9±2.9	16±2.8
Age at FMP	52.7±3.4	49±4.8

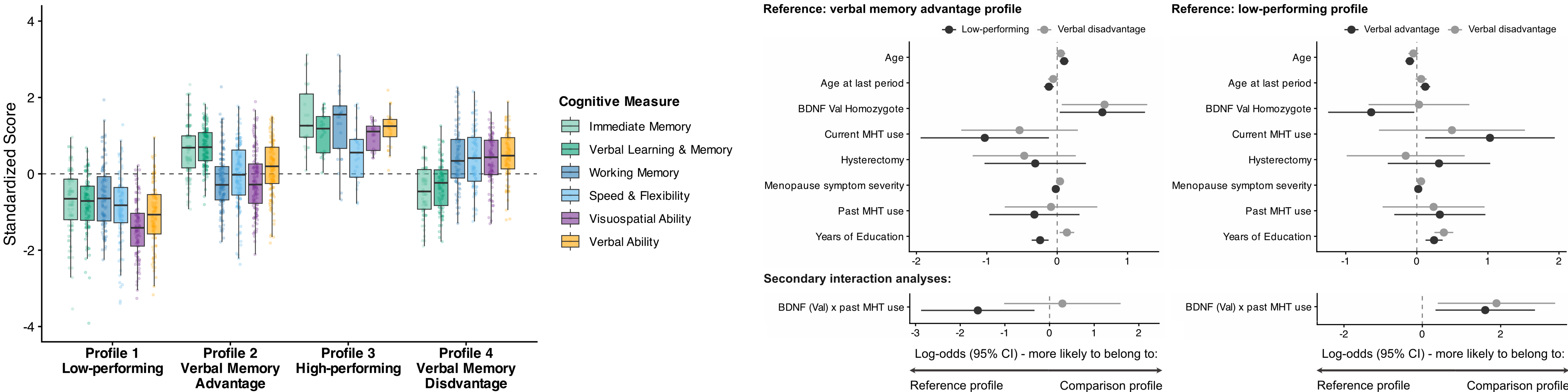
Data source: Wisconsin Registry for Alzheimer's Prevention. Outcomes: pre-derived cognitive factor scores⁴.

Results

Longitudinal cognitive trajectories across the menopausal transition. Negative associations between cognitive performance and age were seen across domains. However, only Met carriers exhibited significant non-linear trajectories in cognitive flexibility (EDF=2.4,p=0.004), visual memory (EDF=2.9,p=0.005), immediate (EDF=3.1,p=0.039) and verbal learning and memory (EDF=1.9,p=0.002), characterized by acceleration of decline around the age of final menstrual period (* $p < 0.05$; ** $p < 0.001$; *** $p < 0.001$; ~ $p = 0.05$; EDF>1 indicates a non-linear effect).



Post-menopausal cognitive profiles. Latent profile analysis yielded four cognitive profiles (visualized below). Having a Met allele (OR=0.53, $p=0.038$), menopause hormone therapy use (OR=0.7, $p=0.027$), and later age at final menstrual period (OR=0.9, $p=0.001$) was associated with higher odds of being in the verbal memory advantage group relative to the low-performing group. Follow-up interaction analyses indicated that past menopause hormone therapy use modulated the association between BDNF Val66Met and cognitive profile membership (OR=4.99, $p=0.013$; OR=6.64, $p=0.013$).



Conclusions

BDNF Val66Met is a meaningful moderator of female cognitive aging. Met carriers show accelerated cognitive decline around the age of final menstrual period, and reduced benefits of past menopause hormone therapy use post-menopause relative to Val homozygotes. These findings align with prior evidence of increased hormonal sensitivity in Met carriers during reproductive years⁵. The menopausal transition may thus present a critical inflection point for expression of genetic susceptibility to cognitive decline.