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Sex-dependent effect of the BDNF Val66Met polymorphism on executive functioning and processing speed in older adults: evidence from the health ABC study

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ABSTRACT

Brain-derived neurotrophic factor (BDNF) Val66Met polymorphism may be an important source of heterogeneity seen in cognitive aging, although the specific relationship between this polymorphism and cognition remains controversial and may depend on the sex of participants. We assessed 2668 older black and white adults and fit linear mixed models to digit symbol substitution test (DSST) performance assessed in years 0 (baseline), 4, 7, and 9 to examine the interaction between sex and BDNF genotype on the intercept (i.e., estimated baseline DSST) and change in DSST over 9 years, adjusted for covariates. Sex interacted with BDNF genotype to predict DSST intercept ($F[1,1599] = 7.4$, $p < 0.01$) and 9-year change ($F[1,1183] = 4.1$, $p = 0.04$) in white participants only. Initially, white male Val/Val carriers had lower DSST scores (37.6, $SE = 0.8$) in comparison with male Met carriers (difference, −1.7; 95% CI, −3.2 to −0.3) and female Val/Val carriers (difference, −5.6; 95% CI, −6.8 to −4.3). White female Met carriers showed a slower rate of change (annual rate of change = −0.6, $SE = 0.1$) in comparison with female Val/Val carriers (difference, −0.2; 95% CI, −0.4 to −0.02) and male Met carriers (difference, −0.3; 95% CI, −0.5 to −0.02). Our findings suggest that BDNF Val66Met and sex should be considered in future endeavors aimed at treating or preventing neurodegenerative disorders.

1. Introduction

Aging is characterized by multifaceted changes within several cognitive domains and the brain regions that subserve them (Salthouse, 2011). Notably, aging negatively impacts executive functions and processing speed, cognitive processes that are significantly associated with the ability to perform activities of daily living and all-cause mortality (Pavlik et al., 2003; Royall et al., 2004). However, the deleterious effects of aging are not equally seen across individuals, and a significant proportion of the population maintains cognitive function even into older age (Hayden et al., 2011; Wilson et al., 2002). Understanding the sources of this variation in cognitive aging will be crucial for future endeavors aiming to treat or prevent neurodegenerative disorders such as Alzheimer's disease (AD). Importantly, genetic studies suggest that allelic variation within the neuroplasticity-related gene encoding for brain-derived neurotrophic factor (BDNF) may be a potential source of the heterogeneity seen in cognitive aging, although the exact relationship between polymorphisms within this gene and cognitive decline remain controversial.

BDNF is a neurotrophin critically involved in neuronal proliferation, differentiation and survival, synaptic plasticity, and the cellular mechanisms required for learning and memory (Cowansage et al., 2010). A common single-nucleotide polymorphism (SNP) is found within the prodomain region of the human BDNF gene, resulting in an amino acid substitution of valine (Val) to methionine (Met) at position 66, termed the Val66Met substitution. Frequency of the variant Met allele within the general population ranges from ~4% in African Americans to ~30% in Caucasians and ~50% in Asians (Petryshen et al., 2010; Pivac et al.,

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2009; Shimizu et al., 2004). The Met allele alters intracellular trafficking of the precursor form of BDNF (proBDNF), reducing the activity-dependent neuronal secretion of the mature form of BDNF by approximately 30% while total central BDNF levels remain normal compared with Val/Val carriers (Chen et al., 2008; Egan et al., 2003). Functionally, the direction of the relationship between this SNP and cognitive decline remains controversial.

Although it has been suggested that the Val allele may be neuroprotective and related to higher cognition and the Met allele is related to impaired cognitive function (Chen et al., 2008), the evidence regarding the association between the BDNF Val66Met polymorphism and cognitive performance is not straightforward. Earlier cross-sectional studies found that compared with homozygous Val carriers, Met carriers presented with reduced episodic memory and smaller hippocampal volume in younger adults (Egan et al., 2003; Hariri et al., 2003), as well as reduced verbal learning and memory and processing speed in older adults (Kennedy et al., 2015; Miyajima et al., 2008). Longitudinal declines in verbal learning and memory were greater in middle-aged Met allele carriers at risk for AD (Boots et al., 2017). However, in contrast to these findings, other studies have failed to find a significant association between the Met allele and cognitive decline in participants at risk for AD (Honea et al., 2013; Lim et al., 2013; Weinstein et al., 2014). Interestingly, studies have even found the opposite, with greater cognitive performance in Met carriers compared with Val/Val carriers in different populations, including patients with Parkinson's disease, AD, and mild cognitive impairment, as well as in cognitively healthy older adults (Erickson et al., 2008; Feher et al., 2009; Gajewski et al., 2012, 2011; Harris et al., 2006; Nagata et al., 2012; van der Kolk et al., 2015).

These conflicting results may be because of several reasons, including the specific cognitive domain under investigation as many of the original studies have focused on memory-based tasks and there is suggestion that executive functions may show a greater association with this polymorphism (Mandelman and Grigorenko, 2012), the age of participants, and differences in cognitive status between populations. Importantly, a recent meta-analysis indicated that performance on memory-based tasks was greater in Val/Val carriers, whereas performance on tasks assessing executive functions was greater in Met carriers (Toh et al., 2018). Furthermore, the biological sex of participants may help explain discrepancies in the relationship between the BDNF Val66Met polymorphism and cognition, as sex differences exist in the effect of the Met allele on several outcomes, including hippocampal blood flow, volume of the dorsolateral prefrontal cortex, and on AD risk (Fukumoto et al., 2010; Nemoto et al., 2006; Wei et al., 2012). And, importantly, older women may show less age-associated decline across certain cognitive domains, including executive functions and processing speed (Gerstorf et al., 2011; McCarrey et al., 2016; McDowell et al., 2004).

We sought to determine whether the BDNF Val66Met polymorphism interacts with sex to influence rate of change in the digit symbol substitution test (DSST), a test of executive functioning and processing speed, in older adults. To that aim, we conducted a secondary analysis of data from the Health, Aging and Body Composition (Health ABC) Study—a 10-year longitudinal, cohort study of cognitively healthy older adults. Importantly, peripheral BDNF levels decline with increasing chronological age and this decline is related to cognitive impairment, which may be more pronounced in women than men (Komulainen et al., 2008; Weinstein et al., 2014). Previously, a cross-sectional analysis of a subsample of the parent Health ABC cohort showed a strong sex-related difference in serum BDNF levels as well as a trend for a main effect of BDNF polymorphism that was not explored in relationship to biological sex (Nettiksimmons et al., 2014). Therefore, we conducted an exploratory analysis to determine whether BDNF genotype differences in peripheral BDNF levels differed by sex.

2. Methods

2.1. Study design and participants

The Health ABC study is a 10-year prospective, epidemiologic, biracial cohort study of older adults 70–79 years of age at baseline. The present study involves 2668 of the 3075 community-dwelling black and white participants without dementia who were recruited in 1997 from Memphis, TN, or Pittsburgh, PA, with complete baseline data on the main measures of interest (i.e., cognition, sex, BDNF genotyping). All eligible participants gave written informed consent and institutional review boards at the University of Tennessee Memphis, the University of Pittsburgh, and the University of California San Francisco gave study approval.

2.2. Measurements

2.2.1. Descriptive variables and covariates

Baseline demographics and health characteristics were assessed at the baseline in 1997/1998. Demographics included age, race (white or black), sex, and educational attainment ($<$ or $\geq$high school). Health-related characteristics included depressive symptoms as assessed with the 20-item Center for Epidemiologic Studies–Depression Scale (CES-D) (Radloff, 1977) with scores above 16 indicative of depression. Diabetes status was determined by self-report and confirmed by medication use. Gait speed (m/s) was assessed over a 6-meter walkway. Self-reported time spent walking was assessed annually from year 0 to year 9 using a standardized questionnaire developed for the Health ABC study and modeled on a previous questionnaire (Taylor et al., 1978). Based on previous work suggesting a link between physical activity and the BDNF Val66Met polymorphism (Erickson et al., 2013), we used the average time spent walking across all time points for the current analyses.

2.2.2. Cognitive functioning

The DSST was administered to participants in years 0, 4, 7, and 9 after the baseline to measure executive functioning and information processing. The test consists 9 digit-symbol pairs, and participants must fill in as many corresponding symbols for the given digits within 90 seconds. The DSST score is the total number of items correctly coded, with higher scores indicating better executive functioning. Global cognitive performance was measured in years 1, 5, 8, and 10 with the modified Mini-Mental Status Examination (3MS) (Teng and Chui, 1987), with scores ranging from 0 to 100 and scores lower than 80 indicating cognitive impairment.

2.2.3. DNA collection and BDNF genotyping

DNA was extracted from whole-blood samples (Gentra Systems, Minneapolis, MN) and the Val66Met polymorphism (rs6265) was determined using standard methods (Nettiksimmons et al., 2014).

2.2.4. BDNF serum levels

BDNF was measured in serum from fasting blood samples obtained from a random subset of 1000 participants without possible dementia (score on the 3MS $<$ 80) in year 2 of the Health ABC study (Nettiksimmons et al., 2014). Serum was stored at -70°C and shipped to R&D Systems' Analytical Testing Service (Minneapolis, MN) for measurement of BDNF using an enzyme-linked immunosorbent assay with a detection limit of 1250 pg/mL. Average intra- and inter-assay coefficients of variation were $<$10%. Platelet count was measured in samples obtained in year 3 as previously reported (Nettiksimmons et al., 2014). Data from 77 participants were excluded for technical reasons, and 166 participants were further excluded because of missing DSST scores or important covariates.

2.3. Statistical analyses

Linear mixed models were fitted using the lme4 package (Version 1.14) (Bates et al., 2015) in R version 3.4.3 (Team, 2017). Analyses used restricted maximum likelihood estimation using all available data from each participant with at least the baseline data. Restricted maximum likelihood estimation is an implicit imputation procedure under the assumption that data are missing at random (Enders, 2013). This approach has been shown to provide less biased estimates and to increase generalizability in comparison with deletion approaches that remove individuals with missing follow-up data (Elobeid et al., 2009). The intercepts were specified as a random effect. Time was entered as a within-subjects repeated measure (year 0 [baseline], 4, 7, 9). Sex (females, males) and BDNF genotype (Met carrier, Val/Val carrier) and their interactions with time (i.e., sex × time, BDNF genotype × time, sex × BDNF genotype × time) were entered as between-subjects fixed effects. Based on previous findings, the following covariates and their interactions with time were also included as fixed effects: depression score (CES-D score), average self-reported time spent walking (minutes per week), age, education, diabetes status, and study site (Memphis, Pittsburgh) (Hosang et al., 2014; Kennedy et al., 2015; Zhou et al., 2013). In addition, slope score was specified as a random effect, and because of potential racial differences (Petryshen et al., 2010; Pivac et al., 2009; Rosano and Lopez, 2015; Shimizu et al., 2004), we stratified based on participant race (white versus black). We report only the highest-order interaction that was significant (e.g., 3-way interaction). Post hoc pairwise comparisons were conducted with z-score contrasts. Statistical significance was set at a two-tailed alpha = 0.05 for each analysis.

3. Results

3.1. Genotype frequency

The sample consisted of 1618 white and 1050 black participants. In white participants, the genotype distribution was 66.4% Val/Val, 30.2% Val/Met, and 3.4% Met/Met, and this distribution fit the Hardy-Weinberg equilibrium ($\chi^2 = 0.005$, $p = 0.94$). In black participants, the genotype distribution was 91.0% Val/Val, 8.9% Val/Met, and 0.2% Met/Met, and this was in conformity with Hardy-Weinberg equilibrium ($\chi^2 = 0.023$, $p = 0.88$). The genotype frequency significantly differed between whites and blacks ($\chi^2 = 214.50$, $p < 0.001$), as previously reported (Petryshen et al., 2010; Shimizu et al., 2004). Following conventions established in the field, Met/Met participants and Val/Met participants were combined into a single group because of the low frequency of the Met/Met genotype (less than 5%). The frequency of the two genotypes did not differ between males and females in either whites ($\chi^2 = 0.009$, $p = 0.93$) or blacks ($\chi^2 = 1.62$, $p = 0.20$). See Table 1 for final group numbers in white and black participants.

3.2. Demographics and baseline characteristics by BDNF genotype and sex

Table 1 provides the baseline characteristics of the Health ABC sample, stratified by race, genotype, and sex. Among white participants, groups did not significantly differ at the baseline in age, education level, diabetes status, depression, or global cognition (all p's > 0.17). Among black participants, groups did not significantly differ at the baseline on any variable examined (all p's > 0.20).

3.3. Sex difference in the association between BDNF genotype and change in executive functioning

Table 2 summarizes the main effects of, and interactions between, sex and BDNF genotype on the DSST intercept and slope, stratified by participant race. Among white participants, sex interacted with BDNF genotype to predict the DSST intercept ($F[1,1599] = 7.4$, $p < 0.01$) and slope ($F[1,1183] = 4.1$, $p = 0.04$). Fig. 1 depicts differences in the DSST intercept in white participants (panel A) and black participants (panel C), as well as annual rate of change in white participants (panel B) and black participants (panel D) as a function of sex and BDNF genotype. In white participants, initially, male Val/Val carriers had a lower DSST scores (37.6, SE = 0.8) in comparison with male Met carriers (difference, −1.7; 95% CI, −3.2 to −0.3) and female Val/Val carriers (difference, −5.6; 95%

Table 1
Demographics and the baseline characteristics across BDNF Val66Met genotype in male and female white and black participants in the Health ABC study

Variable	Val/Val carriers		Met carriers		
	Males	Females	Males	Females	p value of interaction[a]
White participants					
N (%)	564 (34.9)	510 (31.5)	287 (17.7)	257 (15.9)	0.93
Age, mean (SD)	73.9 (2.9)	73.6 (2.8)	73.7 (2.9)	73.4 (2.7)	0.89
Education < high school, %	224 (39.7)	275 (53.9)	118 (41.1)	135 (52.5)	0.60
Weight kg, mean (SD)	81.3 (12.9)	67.0 (12.6)	81.4 (11.5)	65.0 (11.8)	0.12
Diabetes, %	76 (13.5)	40 (7.8)	37 (12.9)	18 (7.0)	0.85
CES-D, mean (SD)	3.8 (4.5)	5.5 (5.9)	4.3 (4.9)	5.3 (6.0)	0.17
Baseline 3MS, mean (SD)	92.3 (5.9)	93.5 (5.4)	92.7 (5.4)	93.9 (5.4)	0.98
Gait speed (m/s), mean (SD)	1.3 (0.2)	1.2 (0.2)	1.3 (0.2)	1.2 (0.2)	0.61
Average self-reported time spent walking (min/wk), mean (SD)	136.4 (288.6)	84.7 (108.3)	129.9 (163.9)	96.2 (125.4)	0.99
Black participants					
N (%)	388 (37.0)	567 (54.0)	45 (4.3)	50 (4.8)	0.20
Age, mean (SD)	73.5 (2.8)	73.2 (2.9)	73.5 (2.7)	73.2 (3.0)	0.86
Education < high school, %	272 (70.1)	405 (71.4)	35 (77.8)	38 (76.0)	0.88
Weight kg, mean (SD)	81.7 (15.1)	76.0 (15.7)	80.2 (12.8)	74.5 (17.6)	0.99
Diabetes, %	91 (23.5)	117 (20.6)	6 (13.3)	7 (14.0)	0.72
CES-D, mean (SD)	4.4 (4.9)	4.9 (5.2)	3.0 (3.8)	5.0 (5.6)	0.20
Baseline 3MS, mean (SD)	86.3 (8.3)	88.1 (7.8)	88.0 (6.7)	88.5 (7.8)	0.50
Baseline gait speed (m/s), mean (SD)	1.1 (0.2)	1.0 (0.2)	1.1 (0.2)	1.1 (0.1)	0.26
Average self-reported time spent walking (min/wk), mean (SD)	103.0 (158.1)	54.4 (91.5)	105.2 (201.1)	63.3 (95.9)	0.85

Key: BDNF, brain-derived neurotrophic factor; CES-D, Center for Epidemiologic Studies–Depression Scale; 3MS, modified Mini-Mental Status Examination.
[a] p values testing sex by BDNF Val66Met genotype interaction from 2-way analysis of variance for continuous variables and logistic regression for categorical variables.

Table 2
Summary of main effects of sex and BDNF Val66Met genotype, and their interaction on DSST intercept and slope, stratified by participant race

Predicting intercept	*F* value	Degrees of freedom	*p* value
Predicting DSST in white participants			
Sex	51.1	1, 1598	<0.001
BDNF genotype	0.2	1, 1599	0.66
Sex × BDNF genotype	7.4	1, 1599	<0.01
Predicting change over time			
Time	61.9	1, 1260	<0.001
Sex × Time	2.2	1, 1184	0.14
BDNF genotype × Time	1.0	1, 1184	0.32
Sex × BDNF genotype × Time	4.1	1, 1183	0.04
Predicting DSST in black participants			
Sex	14.4	1, 1034	<0.001
BDNF genotype	4.7	1, 1034	0.03
Sex × BDNF genotype	0.1	1, 1034	0.82
Predicting change over time			
Time	39.5	1, 736	<0.001
Sex × Time	0.01	1, 787	0.94
BDNF genotype × Time	0.02	1, 789	0.89
Sex × BDNF genotype × Time	0.01	1, 792	0.92

Key: BDNF, brain-derived neurotrophic factor; DSST, digit symbol substitution test. Not shown are the effects of the covariates: age, CES-D, education, clinical site, average amount of self-reported time spent walking, and diabetes.

CI, −6.8 to −4.3). Among females, there was no significant difference in DSST intercept between Met and Val/Val carriers (difference, −1.3; 95% CI, −2.8 to 0.3). The effect of BDNF genotype on the DSST intercept in males was significantly different from its effect in females (difference, 3.0, 95% CI, 0.8–5.2).

With regard to slope scores, in white participants all groups showed significant decreases in DSST scores over time (all p's $<$ 0.001); however, female Met carriers showed a slower rate of change in DSST (annual rate of change, −0.6, $SE = 0.1$) in comparison with female Val/Val carriers (difference, −0.2; 95% CI, −0.4 to −0.02) and male Met carriers (difference, −0.3; 95% CI, −0.5 to −0.02). The effect of BDNF genotype on the DSST rate of change in males was significantly different from its effect in females (difference, 0.3, 95% CI, 0.01–0.6). No other between-group differences were observed (all p's > 0.08).

Among black participants, there was no significant interaction between sex and BDNF genotype on either DSST intercept ($p = 0.82$; Fig. 1 panel C) or slope ($p = 0.92$; Fig. 1 panel D); however, there was a main effect of sex ($F[1,1034] = 14.4$, $p < 0.001$) and BDNF genotype ($F[1,1034] = 4.7$, $p = 0.03$) on the DSST intercept (see Table 2). As depicted in Fig. 2, females had higher initial DSST scores than males (panel A; difference, 4.9; 95% CI, 3.5–6.3), and Met carriers had higher intercepts than Val/Val carriers (panel B; difference, 2.6; 95% CI, 0.2–5.0). No differences by sex or genotype were observed on slope scores (all p's > 0.89).

3.4. Sex difference in the association between BDNF genotype and change in global cognitive functioning

Table 3 summarizes the main effects of, and interactions between, sex and BDNF genotype on the 3MS intercept and slope,

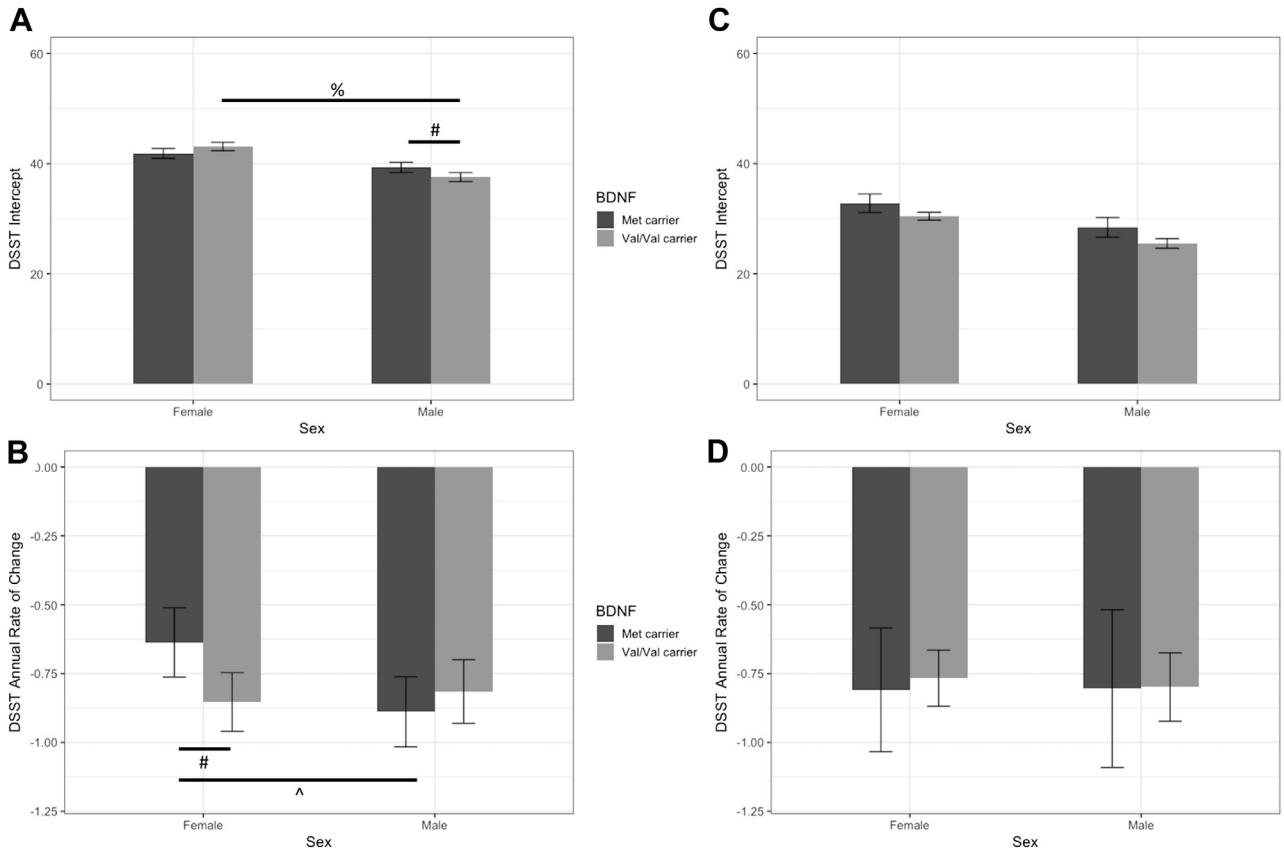

Fig. 1. Estimated digit symbol substitution test (DSST) intercepts in white participants (panel A) and black participants (panel C), as well as annual rate of change (slope) in white participants (panel B) and black participants (panel D) separated by sex and BDNF genotype. Values are adjusted for clinical site, depression, age, education, self-reported time spent walking, and prevalent diabetes. Error bars represent standard errors. A significant interaction was found between sex and BDNF genotype in white participants (panels A and B) but not black participants (panels C and D). # indicates significant difference between Met carriers and Val/Val carriers; % indicates significant difference between female and male Val/Val carriers; ^ indicates significant difference between female and male Met carriers. Abbreviations: BDNF, brain-derived neurotrophic factor.

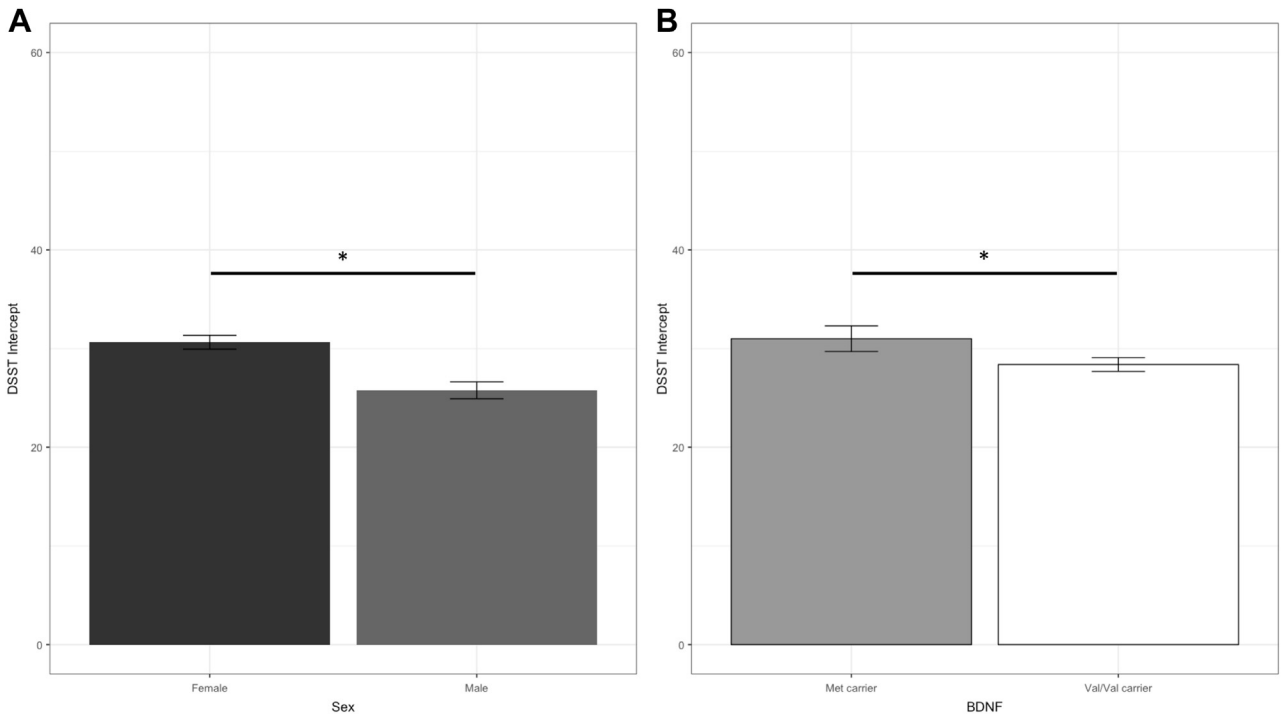

Fig. 2. Estimated digit symbol substitution test (DSST) intercepts separated by sex (panel A) and BDNF genotype (panel B) in black participants. Values are adjusted for clinical site, depression, age, education, self-reported time spent walking, and prevalent diabetes. Error bars represent standard errors. * indicates significant difference between groups. Abbreviations: BDNF, brain-derived neurotrophic factor.

stratified by participant race. In black and white participants, there was a main effect of sex on the 3MS intercept ($p < 0.001$) and significant decrease in 3MS scores over time ($p < 0.001$), but no main effect of BDNF genotype or interaction of BDNF genotype and sex. As shown in Fig. 3, black women had higher initial 3MS scores than black men (difference, 1.7, 95% CI, 0.8–2.6) and white women had higher 3MS scores than white men (difference, 1.5, 95% CI, 1.0–2.0).

3.5. Sex difference in the association between BDNF genotype and BDNF levels

Serum BDNF levels were measured in a random subset of participants. Limitations in sample size precluded our ability to stratify analyses by race. Therefore, race was entered into the model as a covariate. A limited number of extreme values were found; therefore as previously carried out (Nettiksimmons et al., 2014), the data were trimmed to exclude the top and bottom 1% to reduce the possibility of undue influence of extreme values (final n = 742). An analysis of covariance, adjusting for age, CES-D, education, clinical site, diabetes, race, and platelet count found a significant interaction between sex and BDNF genotype (F[1731] = 3.9, $p = 0.049$, partial $\eta^2 = 0.005$; see Fig. 4). Male Met carriers (n = 74) showed significantly lower levels of BDNF compared with male Val/Val carriers (n = 256) (difference, −2.059 ng/mL; 95% CI, −4.090 to −0.028) and female Met carriers (n = 84) (difference, −3.330 ng/mL; 95% CI, −5.782 to −0.878).

4. Discussion

We found evidence that there is an interaction between sex and BDNF Val66Met polymorphism to influence rate of decline over time on a test of executive functioning and processing speed but not on a test of global cognition in cognitively healthy, older adults. Specifically, female Met carriers showed the least amount of decline in performance on the DSST compared with male Met carriers and Val/Val carriers of both sexes over 10 years. This is one of few longitudinal studies to explore the association between the BDNF Val66Met polymorphism and declines in executive functioning over time and is unique in examining the role of sex. Our finding adds to the growing body of literature showing that sex differences exist in the effect of the BDNF Val66Met polymorphism on brain and behavior (Foltynie et al., 2005; Fukumoto et al., 2010; Jiang

Table 3
Summary of main effects of sex and BDNF Val66Met genotype, and their interaction on 3MS intercept and slope, stratified by participant race

Predicting intercept	*F* value	Degrees of freedom	*p* value
Predicting 3MS in white participants			
Sex	26.5	1, 1546	<0.001
BDNF genotype	3.3	1, 1560	0.07
Sex × BDNF genotype	0.7	1, 1547	0.42
Predicting change over time			
Time	15.1	1, 1140	<0.001
Sex × Time	0.001	1, 1056	0.98
BDNF genotype × Time	0.5	1, 1070	0.46
Sex × BDNF genotype × Time	0.1	1, 1045	0.72
Predicting 3MS in black participants			
Sex	15.3	1, 1008	<0.001
BDNF genotype	3.2	1, 1043	0.08
Sex × BDNF genotype	0.9	1, 1023	0.34
Predicting change over time			
Time	30.0	1, 645	<0.001
Sex × Time	0.3	1, 619	0.58
BDNF genotype × Time	0.2	1, 888	0.65
Sex × BDNF genotype × Time	0.2	1, 770	0.67

Key: BDNF, brain-derived neurotrophic factor; 3MS, modified Mini-Mental Status Examination.
Not shown are the effects of the covariates: age, CES-D, education, clinical site, average amount of self-reported time spent walking, and diabetes.

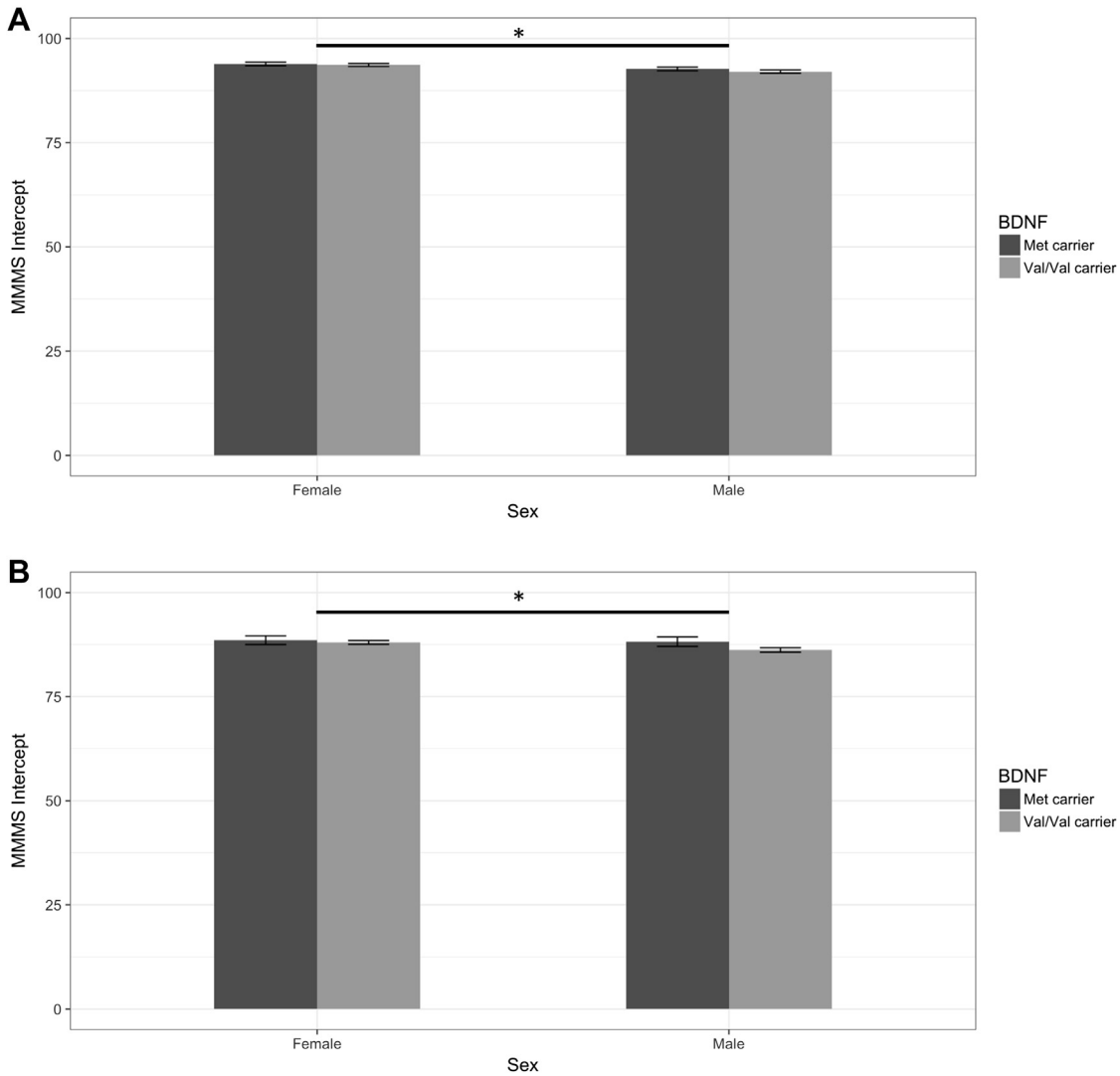

Fig. 3. Estimated modified Mini-Mental State Examination (3MS) intercepts separated by sex and BDNF genotype in white participants (panel A) and black participants (panel B). Values are adjusted for clinical site, depression, age, education, self-reported time spent walking, and prevalent diabetes. Error bars represent standard errors. * indicates significant difference between females and males, regardless of BDNF genotype. Abbreviations: BDNF, brain-derived neurotrophic factor.

et al., 2017; Kim et al., 2016; Marrocco et al., 2017; Nemoto et al., 2006; Wei et al., 2012) and highlights the importance of incorporating sex-based analyses into studies examining the role of genetic variability in cognitive aging.

Findings from previous studies in humans have been equivocal, with the Met allele associated with negative, positive, or null effects on cognitive performance and decline over time (Boots et al., 2017; Egan et al., 2003; Erickson et al., 2008; Feher et al., 2009; Gajewski et al., 2012, 2011; Hariri et al., 2003; Harris et al., 2006; Honea et al., 2013; Kennedy et al., 2015; Lim et al., 2013; Miyajima et al., 2008; Nagata et al., 2012; van der Kolk et al., 2015; Weinstein et al., 2014). Our finding that the Met allele is associated with less decline in females lends further support for the protective effect of the Met allele on executive functioning in older adults that are cognitively healthy. Van der Kolk et al. (2015) also found this beneficial effect of the Met allele on executive function in older adults with Parkinson's disease. The Met variant may also be protective against declines in executive functions and processing speed in participants with multiple sclerosis (Zivadinov et al., 2007) and systemic lupus erythematosus (Oroszi et al., 2006), suggesting that the positive effect of the Met allele is not disease specific. Interestingly, the effect of the Met allele may not generalize to all races and ethnicities. In our analysis of the Health ABC study, in black participants, Met allele carriers had higher intercepts (initial performance on the executive functioning task) than Val/Val carriers. However, the black Met and Val/Val carriers did not differ in slope, indicating that all participants declined similarly over time. Racial and ethnic differences are found in the frequency of the Met allele, ranging from 0% in sub-Saharan African populations to over 50% in Asian populations (Petryshen et al., 2010; Pivac et al., 2009; Shimizu et al., 2004). These substantial differences place the BDNF Val66Met polymorphism within the top 1% of genes in terms of allelic variability between populations across the world (Vulturar et al., 2016). Relevant to the present study is the significantly lower frequency of the Met allele in the people of African decent, with frequencies ranging from 0% to 15% (Petryshen et al., 2010). Thus the large differences in allelic frequency coupled with the possible racial differences in functional effects of the Met allele, highlight the need to take into account population diversity in the BDNF Val66Met polymorphism in future studies.

The effects of the Met allele on the brain are highly complex and a number of explanations have been proposed to address the

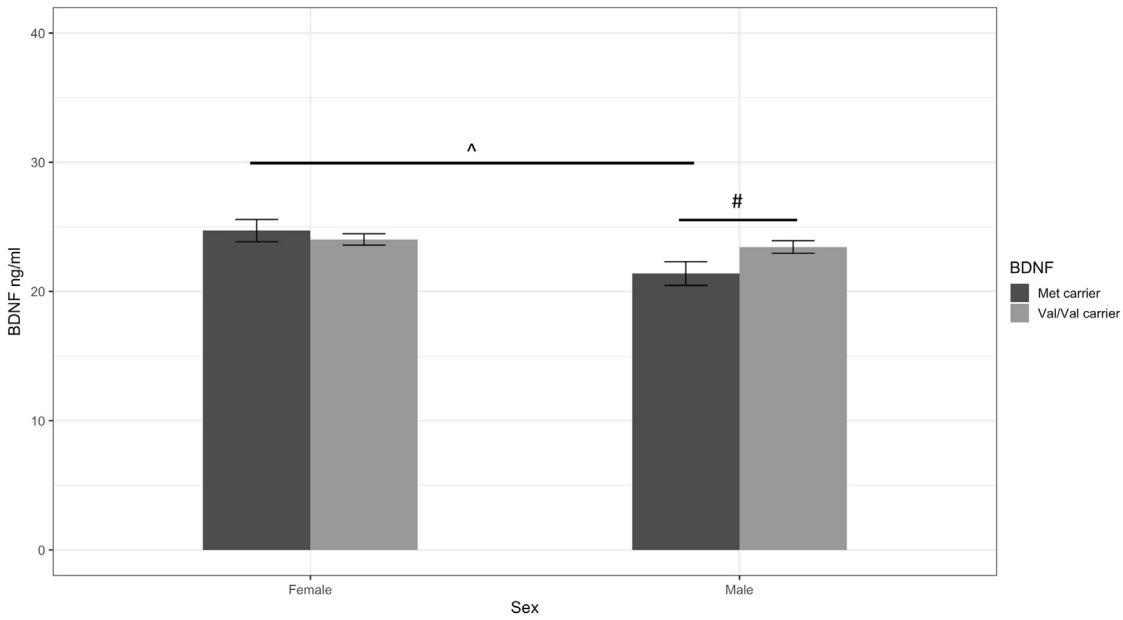

Fig. 4. Circulating serum levels of BDNF (ng/mL) in year 2 by sex and BDNF Val66Met genotype in white and black participants in the Health ABC study. Values are adjusted for age, CES-D, education, clinical site, race, diabetes and platelet count. # indicates significant difference between Met carriers and Val/Val carriers; ^ indicates significant difference between female and male Met carriers. Abbreviations: BDNF, brain-derived neurotrophic factor.

discrepancies found in the literature in addition to ethnicity, including age differences between subjects. Specifically, it has been suggested that the Met allele is detrimental to cognitive and brain structure and function at younger ages but confers some neuroprotection at more advanced ages (Erickson et al., 2008; Feher et al., 2009; Gajewski et al., 2012, 2011; Harris et al., 2006; Honea et al., 2013; Nagata et al., 2012; van der Kolk et al., 2015; Voineskos et al., 2011). Indeed, our findings support this claim as the Met allele was associated with less decline in executive processing over time in older adults, and also extend previous findings by showing that this protective effect was exclusive to females. The protective effects with aging may be related to differential effects of the two proBDNF variants resulting from the Met66 allele versus the Val66 allele on synaptic plasticity. ProBDNF is the precursor form of BDNF, and is itself biologically active, regulating neuronal morphology and physiology in a manner that is opposite of the mature BDNF form (Hempstead, 2015). Specifically, proBDNF, through activation of the p75 receptor, induces apoptosis, reduces spine density and dendritic complexity, and facilitates long-term depression in the hippocampus (Buhusi et al., 2017; Koshimizu et al., 2009; Woo et al., 2005; Yang et al., 2014). The proBDNF molecule consists of 2 regions: the N-terminal prodomain region that is cleaved from the C-terminal mature domain region. The prodomain contains the Val66Met SNP. Recently, the Val66 variant, but not the Met66 variant, was shown to be responsible for the proBDNF depression of synaptic activity (Kailainathan et al., 2016), suggesting a possible explanation for the protective effects of the Met allele in cognitive aging. However, the role of biological sex in these relationships has yet to be investigated.

Interestingly, the BDNF Val66Met polymorphism has been associated with risk for major depression (Zhao et al., 2018) although the relationship may be more pronounced in males than females as seen in a meta-analysis of 14 studies (Verhagen et al., 2010). Furthermore, inflammation has been proposed to play a role in the pathogenesis of major depression, potentially by modulating BDNF levels. Specifically, systemic immune challenges and increased proinflammatory cytokines such as IL-1β lead to reduced BDNF expression (Calabrese et al., 2014). A recent study examined for the first time the association between the Val66Met polymorphism and inflammation in depressed patients and found, in a mainly female sample (84.9% female), that carriers of the polymorphism presented with higher circulating BDNF and lower levels of TNF-α, a proinflammatory cytokine (Caldieraro et al., 2018). Thus, taken together, these results suggest that the BDNF Val66Met polymorphism has complex effects on the brain and body, which may be dependent on participant characteristics including sex, psychiatric health, and inflammatory status.

Support for a sex difference in the effect of the BDNF Val66Met polymorphism on cognition was recently shown using a knock-in mouse model in which young adult female carriers of the Met allele but not males showed impaired hippocampus-dependent spatial memory (Marrocco et al., 2017). Importantly, ovariectomy negated the cognitive impairment seen in female Met carriers, suggesting that circulating ovarian hormones such as estradiol interact with the Met allele to induce cognitive deficits (Marrocco et al., 2017). At first glance, this may seem contradictory with our finding that the Met allele was beneficial for executive functioning. However, our female participants were well past the onset of menopause and were thus most likely in an estrogen-deficient state similar to ovariectomized female mice. The possible modulation of Met allele effects by estradiol was also recently demonstrated in humans as aberrant hippocampal recruitment during an executive functioning task was seen in female Met carriers only after pharmacologic treatment with estradiol (Wei et al., 2017). Thus, the neuromodulatory role of estradiol may interact with the Met allele to help further explain discrepancies within the literature.

Mechanistically, we provide preliminary evidence that circulating serum levels of BDNF were reduced in Met allele carriers, although somewhat surprisingly this effect was only seen in males. BDNF is released from neurons via two possible pathways: regulated secretory pathway or the constitutive pathway (Thomas and Davies, 2005). The Met variant is believed to retard intracellular trafficking of proBDNF, which leads to reduced regulated activity-dependent secretion of the mature form of BDNF (Egan et al.,

2003) but not influencing constitutive (nonregulated) secretion (Chen et al., 2005). Thus, it may be the case that in female Met carriers there is a compensatory upregulation of the constitutive BDNF pathway. Interestingly some studies find greater levels of BDNF in various brain regions such as the hippocampus, amygdala, and prefrontal cortex (Bakos et al., 2009; Bland et al., 2005; Hayley et al., 2015; Snigdha et al., 2011), as well as in the peripheral circulation (Bus et al., 2012; Driscoll et al., 2012; Golden et al., 2010), in females than males, although our findings suggest that this may only be the case for Met carriers. Future studies are required that specifically examine the activity-dependent and constitutive secretory BDNF pathways in female and male Met allele carriers.

The present study is limited by the number of homozygous Met carriers that was very small, preventing a dose-response exploration of the Met allele. In the Health ABC study, BDNF levels were measured cross-sectionally in year 2 of the study when cognitive testing was not conducted. This, in conjunction with the small samples size, preclude our ability to conduct mediation analyses to determine whether serum BDNF levels at the time of cognitive testing underlie the effect of the interaction between sex and the BDNF Val66Met polymorphism on DSST performance. Although we were able to assess the effect of the BDNF polymorphism and sex on the 3MS, we were unable to specifically examine performance on a memory-based task. Furthermore, the DSST assesses performance across several domains, including processing speed, sustained attention, and working memory. Thus, it is unclear which specific domain the BDNF Val66Met polymorphism is influencing. The BDNF gene contains several functionally important SNPs (Huang et al., 2007; Miyajima et al., 2008). We were only able to conduct analyses using one BDNF SNP (i.e., rs6265). Future studies should explore sex-dependent effects of other BDNF SNPs in older populations.

5. Conclusions

The present findings suggest that the Met allele is associated with less decline in executive functioning and processing speed over time in older white females but not white males. Interestingly, although in black participants the Met allele was associated with greater performance on the test of executive functioning but not with less decline over time, this was irrespective of sex. Furthermore, we found that circulating serum levels were lower in male Met carriers compared with all other groups. Our findings that sex and possibly race are important moderators of the relationship between the BDNF Val66Met polymorphism and executive functioning highlight the complexity of this polymorphism's effects on the brain and suggests new avenues of inquiry for future studies.

Disclosure statement

The authors have no actual or potential conflicts of interest.

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