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The Brain-Derived Neurotrophic Factor Val66Met Polymorphism Moderates an Effect of Physical Activity on Working Memory Performance

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Abstract

Physical activity enhances cognitive performance, yet individual variability in its effectiveness limits its widespread therapeutic application. Genetic differences might be one source of this variation. For example, carriers of the methionine-specifying (Met) allele of the brain-derived neurotrophic factor (*BDNF*) Val66Met polymorphism have reduced secretion of BDNF and poorer memory, yet physical activity increases BDNF levels. To determine whether the *BDNF* polymorphism moderated an association of physical activity with cognitive functioning among 1,032 midlife volunteers (mean age = 44.59 years), we evaluated participants' performance on a battery of tests assessing memory, learning, and executive processes, and evaluated their physical activity with the Paffenbarger Physical Activity Questionnaire. *BDNF* genotype interacted robustly with physical activity to affect working memory, but not other areas of cognitive functioning. In particular, greater levels of physical activity offset a deleterious effect of the Met allele on working memory performance. These findings suggest that physical activity can modulate domain-specific genetic (*BDNF*) effects on cognition.

Keywords

BDNF, physical activity, working memory, executive function, genetics, visual memory, episodic memory

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Introduction

Physical activity enhances cognitive function in both healthy and impaired populations (Hillman, Erickson, & Kramer, 2008). For instance, randomized clinical trials have demonstrated that increased physical activity improves executive function, processing speed, and memory performance in older adults (Colcombe & Kramer, 2003). In schizophrenia, physical-activity interventions are considered a propitious treatment for enhancing brain function (Pajonk et al., 2010), and in attention-deficit hyperactivity disorder, physical activity may improve cognitive performance and reduce attentional deficits (Gapin, Labban, & Etnier, 2011). Consistent with this view, results of meta-analyses and critical reviews have suggested that physical activity enhances cognition in a domain-specific fashion, with the largest effects for executive functions (Colcombe & Kramer, 2003; Erickson & Kramer, 2009; P. J. Smith et al., 2010).

Despite consensus about the relative benefits of physical activity for cognitive and brain health, such effects vary appreciably among individuals. One proposed explanation for this individual variability is that genetic

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factors moderate the salutary effects of physical activity on cognition (Kramer & Erickson, 2007). It is conceivable that variants of certain genes might attenuate beneficial effects of physical activity, whereas others might augment its effects. For example, physically inactive individuals carrying the apolipoprotein E (*APOE*) ε4 allele are at a greater risk for amyloid-plaque deposition than are their more active counterparts (Head et al., 2012).

In addition to *APOE*, other polymorphisms influence cognitive and brain function and share putative causal pathways with physical activity. For example, a nonsynonymous single nucleotide polymorphism in the gene encoding brain-derived neurotrophic factor (*BDNF*) has been related to cognitive function and brain morphology, albeit inconsistently (Mandelman & Grigorenko, 2012). In this functional polymorphism, a methionine-specifying (Met) allele at amino acid 66 of the *BDNF* gene, as compared with the alternate valine-specifying (Val) allele, is associated with decreased levels of BDNF-protein secretion and distribution (Egan et al., 2003), with corresponding deficits in episodic and working memory function (Z. Y. Chen, Bath, McEwen, Hempstead, & Lee, 2008). Yet the BDNF protein is also closely linked to physical activity (Erickson, Miller, & Roecklein, 2012). Rodent models demonstrate that physical activity enhances learning and memory by increasing the production and secretion of BDNF (Neeper, Gomez-Pinilla, Choi, & Cotman, 1995; Vaynman, Ying, & Gomez-Pinilla, 2004). For example, blocking BDNF or deleting the tropomyosin-receptor-kinase B (TrkB) receptor effectively abolishes the neurogenic and learning-related benefits associated with exercise (Li et al., 2008; Vaynman et al., 2004). In humans, extended periods of exercise increase hippocampal volume, which in turn is associated with increased serum BDNF (Erickson et al., 2011).

Given that increased production and secretion of BDNF is considered one of the primary mechanisms by which exercise affects learning and memory, it is conceivable that the *BDNF* polymorphism might moderate beneficial effects of physical activity on cognitive performance. There are several ways in which such an interaction could occur. First, physical activity might offset poorer cognitive performance associated with the *BDNF* Met allele by boosting performance to the level seen in individuals homozygous for the Val allele. Such an interaction would suggest that cognitive deficits associated with the Met allele might be overcome through participation in greater amounts of physical activity. Alternatively, physical activity might magnify genotype-dependent differences in cognitive function, such that *BDNF* Val homozygotes, who typically perform better than Met-allele carriers, also benefit preferentially from the cognition-enhancing effects of physical activity.

Method

Participants

All data were derived from participants of the University of Pittsburgh Adult Health and Behavior (AHAB) project, described in detail elsewhere (Manuck, Phillips, Gianaros, Flory, & Muldoon, 2010). The AHAB project provides a registry of behavioral and biological data on midlife community volunteers (30–54 years of age) recruited via mass-mail solicitation from communities of southwestern Pennsylvania. Registry data include sociodemographic measurements; psychiatric history and symptomatology; aspects of social and cognitive functioning; information on lifestyles, habits, and routines; and DNA extracted for the study of genetic variation associated with registry phenotypes (Bleil, Gianaros, Jennings, Flory, & Manuck, 2008; Manuck et al., 2010). Exclusion criteria for AHAB have been described previously (Manuck et al., 2010) and included the following: clinical history of atherosclerotic cardiovascular disease; chronic kidney or liver disease; cancer treated in the preceding year; major neurologic disorders or psychotic illness; pregnancy; and use of insulin, glucocorticoid, antiarrhythmic, psychotropic, or prescription weight-loss medications. In addition, night-shift workers and nonnative English speakers were excluded from participation.

AHAB data employed in our study included measurements obtained on 1,295 participants with estimated IQ scores of 80 or higher. To reduce the possibility of admixture, we selected the 1,081 non-Hispanic Caucasian participants in this sample. A standard score below 80 on an index in the Wechsler suite of cognitive-assessment scales (see the Cognitive Assessments section) is often interpreted as indicative of borderline cognitive dysfunction; therefore, we also excluded 49 individuals who scored beneath this threshold to mitigate confounding by mental impairment or learning disorder (Sattler & Ryan, 2009). Our final sample consisted of 1,032 participants (mean age = 44.59 years; 52.13% female, 47.87% male; see Table 1).

Genotyping

Genomic DNA was isolated from peripheral white blood cells using the PureGene kit (Gentra Systems, Minneapolis, MN). The Val66Met polymorphism at the *BDNF* locus was genotyped using the amplification conditions reported by Cheng et al. (2005) and detection by fluorescence polarization as described by X. Chen, Levine, and Kwok (1999). Genotypes were assigned by comparison with the genotypes of individuals of known *BDNF* genotype run in parallel. Using conventions from prior studies (Krueger et al., 2011), we combined participants heterozygous for

Table 1. Results From the Factor Analysis

Measure	Working memory	Episodic memory	Switching	Visuo-spatial memory
Spatial 1-back accuracy	.812	—	—	—
Spatial 2-back accuracy	.741	—	—	—
Letter 1-back accuracy	.785	—	—	—
Letter 3-back accuracy	.699	—	—	—
Logical Memory I recall	—	.893	—	—
Logical Memory II recall	—	.895	—	—
Logical Memory II recognition	—	.815	—	—
Trail Making Test Part A time	—	—	.825	—
Trail Making Test Part B time	—	—	.766	—
Backward spatial span	—	—	−.622	—
Visual-reproduction recall	—	—	—	.889
Visual-reproduction recognition	—	—	—	.662

Note: Factor analysis with varimax rotation resulted in four factors: working memory, episodic memory, switching, and visuo-spatial memory. These four factors accounted for a cumulative total of 67.02% of the variance. Shown here are the loadings for 12 measures that generated the factors. Values with an absolute value of less than .40 are not shown.

the Val and Met alleles with those homozygous for the Met allele into a single group because of the low frequency of Met homozygotes (n = 40). This resulted in a final sample of 361 Met carriers and 671 Val homozygotes for analysis. Allele frequencies were in conformity with Hardy-Weinberg equilibrium, $\chi^2(1, N = 1{,}032) = 0.04$, $p > .05$.

To test for possible genetic substructure in this sample, we genotyped an additional 15 genome-spanning single-nucleotide polymorphisms for analysis using the program Structure (Falush, Stephens, & Pritchard, 2003). A model with admixture, uncorrelated allele frequencies, individual alpha parameters, and an independent F statistic (fixation index) was run assuming one, two, or three subpopulations. For each model, we used a burn in of 40,000 simulations, followed by 80,000 repetitions, and compared the likelihoods of models' fitting the data. Because the likelihood of data's fitting a model with two subpopulations (k = −15,904) and three subpopulations (k = −16,846) did not exceed that of its fitting a model with one population (k = −16,846), no further adjustments were made for stratification.

Cognitive assessments

Trail Making Test. In Part A of the Trail Making Test, the participant connected the numbers 1 through 26 in ascending order as quickly as possible without removing the pencil from the page. In Part B, the participant alternated between connecting numbers and letters in ascending and alphabetical order (Reitan, 1992). Part B is considered a measure of executive function or switching, but performance on Part B can be compared with performance on Part A to control for baseline differences in processing speed. Time taken in seconds to complete each test was the primary outcome variable. Longer durations indicated worse performance.

Logical Memory I and II. In these subtests of the Wechsler Memory Scale–-Third Edition (WMS-III; Wechsler, 1997), participants were read two stories (Stories A and B). For Logical Memory I, Story A was read once and then, immediately after administration, the participant verbally recalled any information from the story. Story B was read twice, and the participant was instructed to verbally recall any information from the story immediately after each presentation. For Logical Memory II, the participant was asked to recall both Stories A and B 25 to 35 min after the initial presentation. Following free recall, the participants were asked yes-or-no questions about both stories. Memory performance was defined as the following: total number of freely recalled units from both stories immediately following presentation (Logical Memory I recall), total number of freely recalled units from both stories after the delay (Logical Memory II recall), and total number of correctly answered yes-or-no questions about both stories after the delay (Logical Memory II recognition).

Visual reproduction. This subtest of the WMS-III (Wechsler, 1997) includes recall and recognition components for nonverbal stimuli. Five line drawings were presented sequentially for 10 s each. The participant was asked to draw each image immediately after presentation. In the recall component, the participant was asked to draw each image after a 25- to 35-min delay. In the recognition component, the participant chose the

drawings that had been presented, one at a time, from an array of drawings. In each condition, the scores for all five drawings were summed to produce the total score.

Letter* n-*back. In the letter *n*-back test, participants viewed a series of letters presented sequentially for 500 ms each with an intertrial interval of 2,000 ms. Participants performed 1-back and 3-back tests, each consisting of 56 trials (50% match trials, 50% nonmatch trials). In the 1-back test, participants were instructed to respond by pressing a button when the currently presented letter was the same as the previously presented letter (match condition) but to press a different button when the current letter did not match the previously presented letter (nonmatch condition). Instructions were similar for the 3-back test, except that participants responded according to whether the currently presented letter was the same as or different from the letter presented three trials previously. The outcome measures were the number of correct responses for each test.

Spatial* n-*back. The spatial *n*-back was analogous to the letter *n*-back except that spatial locations, rather than letters, were to be remembered. In the spatial *n*-back, participants viewed a series of dot patterns presented sequentially for 500 ms each with an intertrial interval of 2,000 ms. Again, there were 56 trials per condition (50% match trials, 50% nonmatch trials). In the 1-back test, participants were instructed to respond by pressing a button when the currently presented dot pattern was the same as the previously presented pattern and a different button when the two patterns differed. Instructions were similar for the 2-back test, but participants were instructed to respond when the dot pattern matched or did not match the dot pattern presented two trials previously. The outcome measures were the number of correct responses in each condition. Spatial working memory tasks are usually more difficult than verbal working memory tasks; the different *n*-back conditions (2-back for spatial and 3-back for letter) were chosen to make the accuracy and performance across tasks more equivalent.

Backward spatial span. In this subtest of the WMS-III (Wechsler, 1997), the examiner tapped a series of cubes in a specific sequence, with increasing sequence lengths as the test continued. The participant was then required to tap the same sequence in the reverse order. The outcome measure for this task was the span length, or the total number of correctly tapped cubes in a single sequence.

Physical-activity assessment

The Paffenbarger Physical Activity Questionnaire is a widely used instrument for estimating weekly kilocalories expended (Paffenbarger, Wing, & Hyde, 1978) from self-reported activities of daily living (e.g., stairs climbed, blocks walked) and leisure activities requiring physical exertion (e.g., sports, recreational pursuits), indexed to both frequency and duration. As employed in AHAB, the Paffenbarger questionnaire was referenced to average weekly levels of physical activity, as experienced over the past year. This instrument has high reliability (Ainsworth, Leon, Richardson, Jacobs, & Paffenbarger, 1993) and convergent validity with several objective measures of physical activity and fitness, including maximal oxygen uptake (Nowak et al., 2010), dual-energy X-ray absorptiometry (Shedd et al., 2007), and body mass index (Choo et al., 2010). The Paffenbarger questionnaire is predictive of health conditions that are related to physical activity, including myocardial infarction (Chomistek, Chiuve, Jensen, Cook, & Rimm, 2011), total cholesterol and fasting blood glucose (Choo et al., 2010), bone density (Shedd et al., 2007), and inflammatory biomarkers (McFarlin et al., 2006). From responses to this questionnaire, an estimate of average weekly energy expenditure, in kilocalories, was calculated (Paffenbarger et al., 1978).

Statistical analysis

Normality of distribution was examined for all study variables, of which only our physical-activity index (kilocalories per week) showed significant (positive) skew. This measure was therefore normalized by logarithmic transformation prior to analysis. Additionally, to reduce the number of dependent variables for primary statistical analyses, we first subjected the 12 cognitive tests to an exploratory factor analysis, with varimax rotation (SPSS Version 20). Four factors were identified as having eigenvalues above 1 and corroborated by scree test. These accounted, respectively, for 30.94%, 16.79%, 10.25%, and 9.03% of total variance. The first factor (working memory) consisted primarily of accuracy rates on the letter and spatial *n*-back tasks. The second factor (episodic memory) included the logical-memory scores from the immediate- and delayed-recall tasks. A third factor (switching) consisted of scores from parts A and B of the Trail Making Test and from the backward-spatial-span tests, and the fourth factor (visuo-spatial memory) consisted of visual-reproduction-test scores. See Table 1 for factors and loadings.

Linear regression was used for all analyses, and sex and education were entered as covariates because of their modest association with physical activity and several of the cognitive variables. Also entered were *BDNF* genotype (heterozygous or homozygous Met genotype vs. homozygous Val genotype, coded 1 and 0, respectively), physical activity (kilocalories per week; log-transformed), and their interaction product. Each of the four factor scores served as dependent variables in primary analyses, with a statistical threshold of $p < .01$. In

secondary analyses, parallel regressions (at a statistical threshold of $p < .05$) were run on individual cognitive tests comprising any factor that revealed a significant *BDNF* × Physical Activity interaction. To decompose significant *BDNF*-by-physical-activity interactions, we recentered the kilocalories variable at 1.5 standard deviations below the mean (i.e., at 6.38) and recomputed the linear regression analyses. This analysis examined if main effects of *BDNF* appeared at lower levels of physical activity.

Results

There were no significant associations between *BDNF* and any demographic measures (all *p*s > .20), but there were modest correlations between kilocalories and sex ($r = -.06$, $p < .03$) and between kilocalories and education ($r = .07$, $p < .02$), such that males and participants with higher levels of education engaged in slightly higher amounts of physical activity. Age was not significantly correlated with kilocalories ($r = -.02$, $p < .45$) and did not differ by genotype ($t = 0.61$, $p < 0.54$); it therefore was not included as a covariate in the regression models. All analyses reported in the following section were conducted using sex and education as covariates. Average demographic and physical-activity values are summarized in Table 2.

Main effects of physical activity and BDNF *on cognitive performance*

Greater amounts of physical activity were associated with higher scores on the working memory factor, $\beta = 0.107$, $t(1002) = 3.413$, $p < .001$, but were not significantly associated with the episodic memory factor ($\beta = 0.025$, $t = 0.835$, $p < .404$), the visuo-spatial memory factor ($\beta = -0.034$, $t = -1.067$, $p < .286$), or the switching factor ($\beta = -0.035$, $t = -1.109$, $p < .268$). Secondary analyses were conducted on the individual tests of the working memory factor. We found that greater amounts of physical activity were associated with higher accuracy rates on the spatial working memory tasks, including the spatial 1-back, $\beta = 0.135$, $t(1010) = 4.352$, $p < .001$, and the spatial 2-back, $\beta = 0.088$, $t(1010) = 2.815$, $p < .005$; however, greater amounts of physical activity were not significantly associated with the letter 1-back task, $\beta = 0.046$, $t(1008) = 1.468$, $p < .142$, and were only trending for the letter 3-back task, $\beta = 0.053$, $t(1008) = 1.686$, $p < .092$.

In contrast, there were no significant main effects of the *BDNF* polymorphism on any of the factors, including working memory ($\beta = -0.038$, $t = -1.215$, $p < .225$), visuospatial memory ($\beta = 0.020$, $t = 0.631$, $p < .528$), episodic memory ($\beta = 0.040$, $t = 1.316$, $p < .189$), and switching ($\beta = -0.008$, $t = -0.251$, $p < .802$).

The BDNF *polymorphism moderates the effect of physical activity on working memory*

Consistent with our hypothesis, results revealed that the *BDNF* gene moderated the effect of physical activity on cognitive performance, but the effect was specific to working memory. Specifically, the *BDNF* × Physical Activity interaction was significant for the working memory factor, $\beta = 1.154$, $t(1000) = 3.768$, $p < .001$, partial $r^2 = .014$, but was not significant for the episodic memory factor ($\beta = 0.260$, $t = 0.872$, $p < .384$, partial $r^2 = .000$), the visuo-spatial memory factor ($\beta = 0.18$, $t = 0.578$, $p < .563$, partial $r^2 = .000$), or the switching factor ($\beta = -0.123$, $t = -0.399$, $p < .690$, partial $r^2 = .000$; see Fig. 1). When decomposing this interaction, we confirmed that Met carriers performed worse than Val homozygotes at 1.5 standard deviations below the sample mean of physical activity, $\beta = -0.114$, $t(1002) = -2.056$, $p < .05$, partial $r^2 = .004$. As described earlier, the main effect of *BDNF* was not significant in the regression model using mean-centered physical activity, which indicates that the physical-activity-by-*BDNF* interaction emerged from the diminution of genotype-dependent differences at higher levels of physical activity.

Again, secondary analyses were conducted for each of the working memory tasks that generated the working

Table 2. Participant Demographics

Demographic	Full sample (N = 1,032)	Met-allele carriers (n = 361)	Val-allele homozygotes (n = 671)
Age (*M*)	44.59 (6.78)	44.40 (6.74)	44.67 (6.80)
Sex (percentage of female participants)	52.1	54.8	50.2
Education (mean number of years)	16.07 (2.79)	16.06 (2.73)	16.08 (2.82)
Weekly kilocalorie count (*M*)	2,502.17 (1,816.44)	2,383.87 (1,675.16)	2,568.03 (1,894.07)

Note: Standard deviations are shown in parentheses. The two columns on the right show results separately for individuals carrying the methionine-specifying (Met) allele of the brain-derived neurotrophic factor (*BDNF*) gene and for individuals homozygous for the valine-specifying (Val) allele.

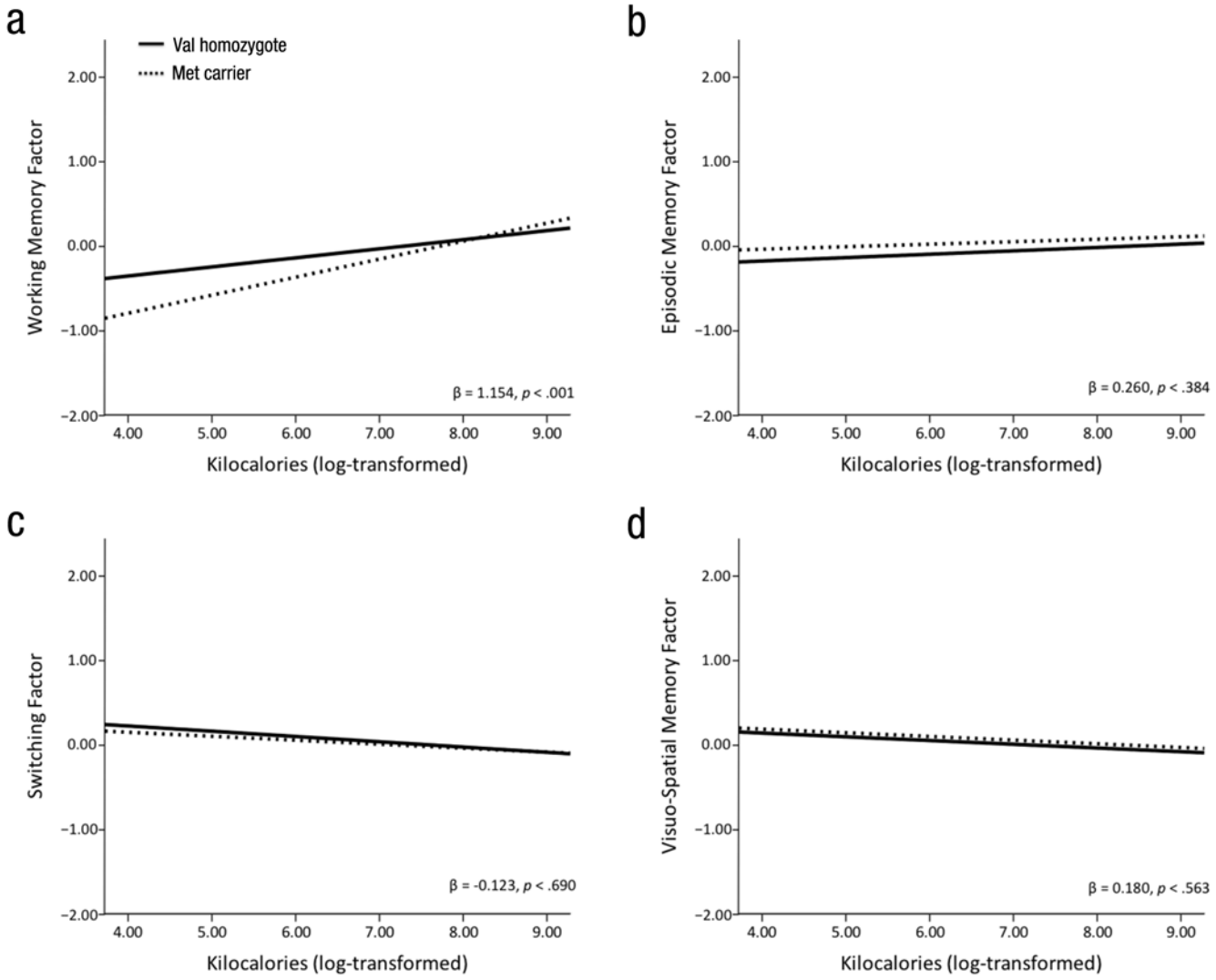

Fig. 1. Results showing the effects of physical activity (weekly kilocalories expended) and the brain-derived neurotrophic factor (*BDNF*) polymorphism on four factors of cognitive performance: (a) working memory, (b) episodic memory, (c) switching, and (d) visuo-spatial memory. Physical activity was determined using the energy-expenditure metric from the Paffenbarger Physical Activity Questionnaire (Paffenbarger, Wing, & Hyde, 1978). Val = valine-specifying allele; Met = methionine-specifying allele.

memory factor. We found significant *BDNF* × Physical Activity interactions for accuracy rates on the letter 1-back, $\beta = 0.905$, $t(1006) = 2.942$, $p < .003$, partial $r^2 = .008$; the letter 3-back, $\beta = 0.786$, $t(1006) = 2.547$, $p < .01$, partial $r^2 = .006$; the spatial 1-back, $\beta = 0.914$, $t(1008) = 2.998$, $p < .003$, partial $r^2 = .008$; and the spatial 2-back, $\beta = 1.356$, $t(1008) = 4.498$, $p < .001$, partial $r^2 = .019$. Plotting the regression lines from these interactions revealed that Met carriers performed more poorly than Val homozygotes at the lower end of the physical-activity spectrum, but this difference was eliminated at higher levels of physical activity (see Fig. 2).

Discussion

Physical activity elevates cognitive performance (Erickson & Kramer, 2009; Etnier, Nowell, Landers, & Sibley, 2006), yet there is significant variability in the extent to which any individual's cognitive performance improves from activity. Such individual variation led to the hypothesis that genetic factors could be moderating the association by either attenuating or amplifying the benefits of physical activity on cognitive function (Kramer & Erickson, 2007). There has been considerable speculation that *BDNF* could be a candidate gene that moderates the

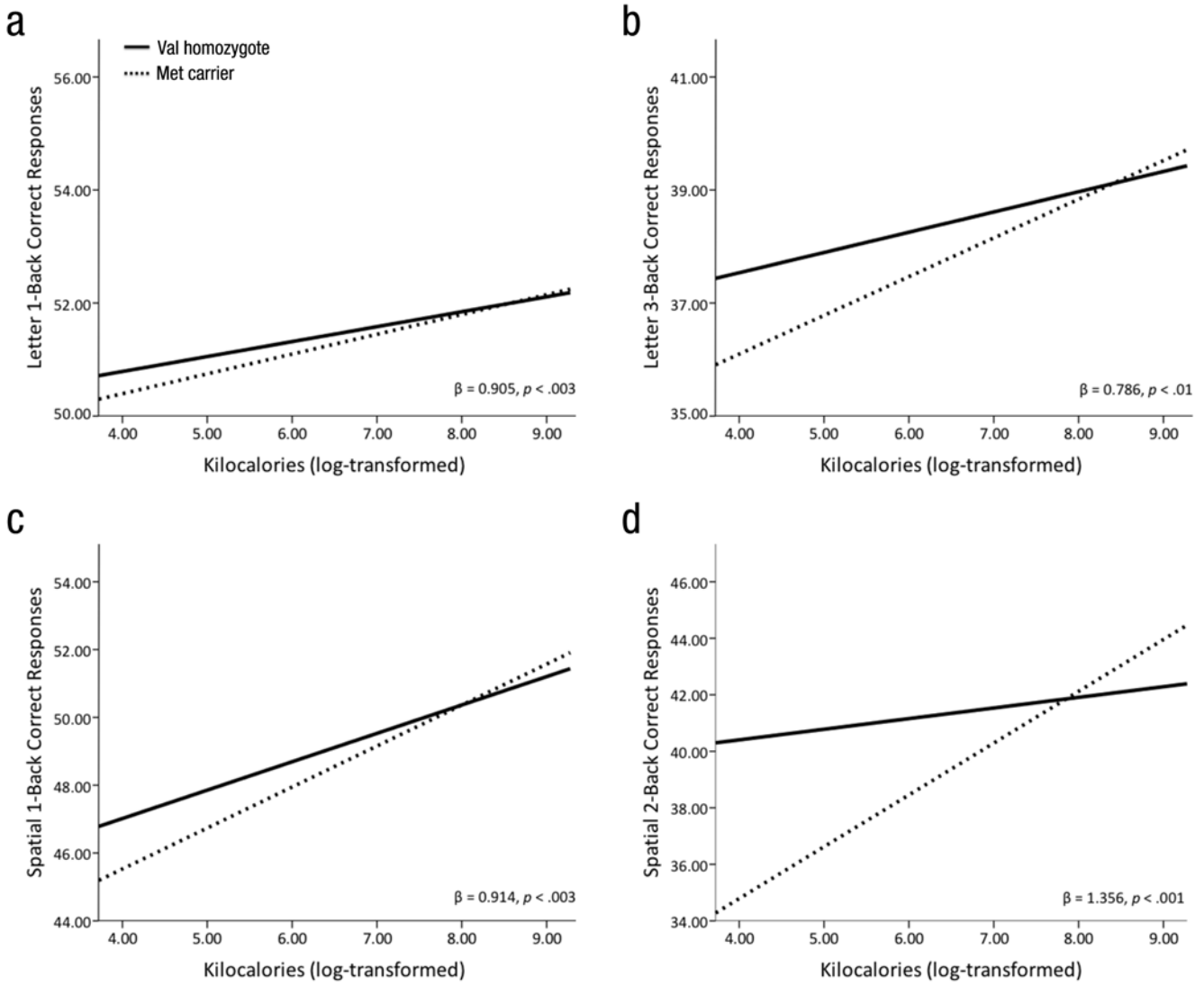

Fig. 2. Results showing the effects of physical activity (weekly kilocalories expended) and the brain-derived neurotrophic factor (*BDNF*) polymorphism on four factors of working memory performance: accuracy on (a) the letter 1-back test, (b) the letter 3-back test, (c) the spatial 1-back test, and (d) the spatial 2-back test. Each working memory test consisted of 56 trials (50% match, 50% nonmatch). Physical activity was determined using the energy-expenditure metric from the Paffenbarger Physical Activity questionnaire (Paffenbarger, Wing, & Hyde, 1978). Val = valine-specifying allele; Met = methionine-specifying allele.

cognitive benefits associated with physical activity. This speculation arises from the fact that the *BDNF* gene has common functional variation previously associated with brain integrity and memory and that physical activity might be exerting its effects on cognitive function by modifying the production and secretion of BDNF (Erickson et al., 2012; Erickson et al., 2011). Consistent with this prediction, our results showed that greater amounts of physical activity mitigated poorer working memory performance in Met carriers and had minimal effects on working memory function in Val homozygotes. This finding suggests that for working memory in the age range of our sample, Met carriers benefit more from physical activity than Val homozygotes do (see Mata, Thompson, & Gotlib, 2010, for a similar effect on symptoms of depression).

BDNF is not the only gene moderating the effects of physical activity. In late adulthood, greater amounts of physical activity mitigate the cognitive deficits associated with the *APOE* ε4 allele (Schuit, Feskens, Launer, & Kromhout, 2001; J. C. Smith et al., 2011; but see also Rockwood & Middleton, 2007). In fact, *APOE* ε4 carriers who remain physically active show considerably attenuated levels of amyloid deposition compared with their

less active counterparts of the same *APOE* genotypes (Head et al., 2012). These and other results suggest that participating in greater amounts of physical activity reduces the genetic susceptibility to amyloid deposition and increased risk for dementia experienced by *APOE* ε4 carriers (Liang et al., 2010). The moderating effect of the *BDNF* polymorphism that we report here shares a striking resemblance to that observed in *APOE* ε4 carriers. That is, in both instances, one variant of the gene polymorphism is associated with reduced cognitive function, but this deficit is attenuated or even eliminated by increased amounts of physical activity. Although speculative, the effect we report here, in conjunction with results of prior studies on *APOE*, suggest that, at least in some instances, genetic risk factors for disease or cognitive impairment might be overcome by participation in regular physical activity.

In rodent models, exercise-induced improvements in learning and memory are mediated by BDNF (Vaynman et al., 2004). Wheel running increases both the production and secretion of BDNF, and blocking the binding of BDNF to its high-affinity receptor, TrkB, effectively abolishes the learning benefits associated with exercise (Li et al., 2008; Vaynman et al., 2004). Similarly, in humans, serum BDNF was found to increase after acute bouts of exercise (Knaepen, Goekint, Heyman, & Meeusen, 2010), and in a randomized controlled trial of exercise in older adults, increases in hippocampal volume were correlated with changes in serum BDNF (Erickson et al., 2011). Although it would be premature to directly link the association between physical activity and the *BDNF* polymorphism with disproportionately increased BDNF protein levels in Met carriers, it is plausible that physical activity moderates the rate of BDNF gene expression in a genotype-dependent manner. It will be important for future research to examine *BDNF* variants along with serum levels of BDNF protein and gene expression as a function of physical activity to more fully address this hypothesis.

Our results are also interesting in light of a meta-analysis of 29 randomized aerobic-exercise trials that concluded that exercise interventions were inconsistently associated with improved working memory performance (P. J. Smith et al., 2010). This inconsistency might be explained by the moderating influence of the *BDNF* polymorphism. That is, our results suggest that studies with a greater representation of *BDNF* Met carriers might show stronger effects of physical activity on working memory performance, relative to studies with fewer Met carriers. Given this possibility, it will be important for future randomized trials of exercise to consider genotyping participants to determine whether any effects on working memory are moderated by the *BDNF* polymorphism.

It is also interesting to consider our results within the context of studies examining the *BDNF* polymorphism and cognitive performance. Several studies have demonstrated that *BDNF* Val-allele homozygotes outperform Met carriers on both working and episodic memory paradigms (Z. Y. Chen et al., 2008; Egan et al., 2003). However, several other studies have failed to replicate this effect (Harris et al., 2006) or have found evidence that Met carriers outperform Val homozygotes. In fact, a recent meta-analysis of 23 published reports of studies with more than 7,000 subjects found no clear association between the *BDNF* Val66Met polymorphism and cognitive performance (Mandelman & Grigorenko, 2012). At the very least, this suggests that there is no clear consensus that the *BDNF* polymorphism unequivocally influences working or episodic memory. Yet, within the context of our results, it might be that interactions with previously unexplored variables—such as physical activity—could be driving variation among studies. Given our results, studies with a greater number of less active individuals might show significant differences in memory function between Val homozygotes and Met carriers, whereas studies with a greater number of more active individuals might report minimal differences in memory function between the variants. Hence, variation in the memory-*BDNF* association might be partially explained by the influence of physical activity, which has not been examined in previous studies.

We approached this study with a priori hypotheses about *BDNF*, given its putative role in both cognitive brain function and physical activity. However, it would be credulous to consider *BDNF* the only gene moderating the effects of physical activity on cognitive function. Moderating effects of *APOE* and physical activity have already been discussed here, but it is likely that many, perhaps thousands of other genetic variants, as well as interactions with other environmental factors (e.g., diet), also contribute to the association between physical activity and cognitive performance. In fact, despite significant effects, our effect sizes were not large, consistent with the results of many other candidate gene studies with similar cognitive phenotypes. Hence, it will be important for future studies to explore other measures of genomic variation, using haplotype- or genome-wide approaches, to replicate the effects we report here and extend them to other sources of genetic variation.

There are several limitations to this study. First, because our index of physical activity was a self-report measure, it is possible that biased reporting could have increased measurement error, reducing effect sizes. Objective measures of physical activity or cardiorespiratory fitness might produce more robust effects and interactions with *BDNF* genotype than those reported here. In any case, despite reliance on self-reported physical activity, we were able to reliably detect associations and interactions between this measure and working memory performance, and the

Paffenbarger questionnaire is a widely recognized, frequently used, and well-validated instrument. Second, the cross-sectional nature of the study precludes our ability to make any causal statements about physical activity and cognitive performance. It is possible that our physical-activity measure is a proxy for an unmeasured third variable. It will be necessary for randomized trials to stratify or randomize by *BDNF* to more conclusively determine whether Met carriers benefit more from increased physical activity.

Despite these limitations, our sample size of more than 1,000 participants vastly exceeds the sample sizes of most other studies in this area. Another strength of our study is that we used a battery of cognitive tasks that are well characterized and frequently employed to examine working memory, episodic memory, visuo-spatial memory, and switching. In sum, our results show that the association between physical activity and working memory was moderated by the *BDNF* Val66Met polymorphism, such that physical activity reduced the working memory deficits in Met carriers.

Author Contributions

All authors contributed to writing and editing the manuscript. K. I. Erickson, S. E. Banducci, and A. M. Weinstein analyzed the data. A. W. MacDonald, III, I. Halder, J. D. Flory, and S. B. Manuck were involved in study design and data collection. R. E. Ferrell, I. Halder, and S. B. Manuck were involved in genotyping.

Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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