The BDNF val66met polymorphism moderates an effect of physical activity on working memory performance

Journal:	*Psychological Science*
Manuscript ID:	PSCI-12-1728.R1
Manuscript Type:	Research article
Date Submitted by the Author:	n/a
Complete List of Authors:	
Keywords:	Genetics, Visual Memory, Episodic Memory

BDNF and Physical Activity

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, Met carriers 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 moderates an association of physical activity with cognitive functioning among 1032 midlife volunteers (mean age = 44.59), we evaluated performance on a battery of tests assessing memory, learning and executive processes and physical activity with the Paffenbarger 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

Introduction

Physical activity enhances cognitive function in both healthy and impaired populations (Hillman, Erickson, & Kramer, 2008). For instance, randomized clinical trials demonstrate that increasing 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 to enhance 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, meta-analyses and critical reviews suggest 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 factors moderate 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 *APOE* ε4 allele are at a greater risk for amyloid plaque deposition than 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 non-synonymous 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 is associated with decreased levels of BDNF protein secretion and distribution, as compared to the alternate, valine-specifying (Val) allele (Egan et al., 2003), with corresponding deficits in episodic and working memory function among Met carriers (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 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).

Since 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 otherwise seen in individuals homozygous for the Val allele. Such an interaction would suggest that cognitive deficits associated with the Met allele might be overcome by participating 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 cognitive-enhancing effects of physical activity.

Methods

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 measurements on midlife community volunteers (30 to 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, nightshift workers and non-native English speakers were excluded from participation.

AHAB data employed here include measurements obtained on 1295 participants having estimated IQ scores >80. To reduce the possibility of admixture, we selected the 1081 non-Hispanic Caucasian participants from this sample. A standard score below 80 on an index in the Wechsler suite of cognitive assessment (see below) 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 1032 participants (mean age = 44.59; 52.13% female) – 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. (Cheng et al., 2005), and detection by fluorescence polarization as described by Chen et al. (X. Chen, Levine, & Kwok, 1999). Genotypes were assigned by comparison to the genotypes of individuals of known *BDNF* genotype run in parallel. Participants were grouped according to whether they were homozygous or heterozygous for the *BDNF* val66met functional polymorphism. Using conventions from prior studies (Krueger et al., 2011), heterozygotes and Met homozygotes were combined into a single group because of the low frequency of Met homozygotes (n=40). This resulted in 361 Met carriers and 671 Val homozygotes for analysis. Allelic frequencies were in conformity with Hardy-Weinberg equilibrium (χ^2=.04; p>.05).

To test for possible genetic substructure in this sample, we genotyped an additional 15 genome-spanning SNPs for analysis using the program STRUCTURE (Falush, Stephens, & Pritchard, 2003). A model with admixture, uncorrelated allele frequencies, individual alpha parameters, and independent F statistic (fixation index) was run assuming one, two, or three subpopulations. For each model, we used a burn-in of 40K simulations, followed by 80K repetitions, and compared the likelihoods of models fitting the data. Because the likelihood of data fitting a model with ≥2 subpopulations did not exceed that of a model with 1 population (log probabilities for k = 1, 2, and 3 subpopulations were -15904, -16846, and -16846), 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 – 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 can be compared to Part A to control for baseline differences in processing speed. Time taken in seconds to complete each test was used as the primary outcome variable. Longer durations indicate worse performance.

Logical Memory I and II: In these subtests of the WMS-III (Wechsler, 1997), participants were read two 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 after a 25- 35 minute delay from initial presentation. Following free recall, the participants were then asked Yes or No questions about both stories. Memory performance was defined as the following three scores: 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 memory components for nonverbal stimuli. Five different line drawings were each

presented sequentially for 10 seconds. 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 25-35 minute delay. In the recognition component, the participant chose the presented drawings, one at a time, from an array of drawings. In each condition, the scores from 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 500ms with an inter-trial interval of 2000ms. Participants performed 1-back and 3-back conditions with 56 trials presented for each. There were match and non-match trials for both conditions with 50% as match trials. In the 1-back, 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. Instructions were similar for the 3-back, but in this condition participants responded according to whether the currently presented letter was the same or different to the letter presented 3 trials previously. The outcome measures were number of correct responses for each condition.

Spatial N back: The spatial N-back was analogous to the Letter N-back except that spatial locations were to-be-remembered rather than letters. In the spatial N-back, participants viewed a series of dot patterns sequentially for 500ms with an inter-trial interval of 2000ms. Again, there were 56 trials per condition, 50% of which were target matches. In the 1-back, 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 they differed. Instructions were similar for the 2-back, but participants were instructed to respond when the

dot pattern matched or did not match the dot pattern presented 2 trials previously. The outcome measures were number of correct responses for each condition. Spatial working memory tasks are usually more difficult than verbal working memory tasks, so 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.

Spatial Span Backward: 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 this same sequence in reverse order. The outcome for this task was the span length, or total number of correctly tapped cubes in a single sequence.

Physical Activity Assessment

The Paffenbarger Physical Activity Questionnaire is a widely used instrument to estimate weekly kilocalories expended (Paffenbarger, Wing, & Hyde, 1978) from self-reported activities of daily living (stairs climbed, blocks walked) and leisure time 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 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/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, the 12 cognitive tests were first subjected to an exploratory factor analysis, with varimax rotation (SPSS v.20). Four factors were identified having eigenvalues >1 and corroborated by Scree test. These accounted, respectively, for 30.94, 16.79, 10.25 and 9.03 percent 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) included the Trails A and B and 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 due to their modest association with physical activity and several of the cognitive variables. Also entered were *BDNF* genotype (any Met allele vs. Val/Val homozygous genotype, coded 1 and 0 respectively), physical activity (kilocalories/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 statistical threshold of $p<.05$) were run on individual cognitive tests comprising any factor that revealed a significant *BDNF* x physical activity interaction. To decompose significant *BDNF* by

physical activity interactions, the kilocalories variable was re-centered at 1.5 standard deviations (SD) below the mean (i.e., at 6.38) and the linear regression analyses were recomputed. This analysis examined if main effects of *BDNF* appeared at lower physical activity levels.

Results

There were no significant associations between *BDNF* and any demographic measures (all p>.20), but there were modest correlations between kilocalories and sex (r=-.06; p<.03) and education (r=.07; p<.02) such that males and those with higher education levels had 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) and therefore was not included as a covariate in the regression models. All analyses reported below 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 (β = 0.107; t = 3.413; p<.001), but were not significantly associated with either the episodic memory factor (β = 0.025; t = 0.835; p<.404), the visuo-spatial memory factor (β = -0.034; t = -1.067; p<.286) or the switching factor (β = -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 (β= .135; t = 4.352; p< .001) and the spatial 2-back (β= .088; t = 2.815; p< .005), but were not significantly associated with the letter 1-back (β= .046; t=1.468; p<.142), and were only trending for the letter 3-back (β= .053; t=1.686; p<.092) tasks.

In contrast, there were no significant main effects of the *BDNF* polymorphism on any of the factors, including working memory (β= -0.038; t=-1.215; p<.225), visuo-spatial memory

(β= .020.; t= .631; p<.528), episodic memory (β= .040; t=1.316; p<.189), and switching (β= -.008; t= -.251; p<.802).

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

Consistent with our hypothesis, we found that the *BDNF* gene moderated the effect of physical activity on cognitive performance, but the effect was specific to working memory. Specifically, the *BDNF* x physical activity interaction was significant for the working memory factor (β= 1.154; t=3.768; p<.001; partial r^2 = .014), but not significant for the episodic memory factor (β= .260; t=0.872; p<.384; partial r^2 = .000), the visuo-spatial memory factor (β= .18; t=.578; p<.563; partial r^2 = .000) , or the switching factor (β= -.123; t= -.399; p<.690; partial r^2 = .000) (Figure 1). When decomposing this interaction, we confirmed that Met carriers performed worse than Val homozygotes at 1.5 SD below the sample mean of physical activity (β=-.114; t=-2.056; p<.05; partial r^2=.004). As described above, the main effect of *BDNF* was not significant in the regression model using mean-centered physical activity, indicating that the physical activity by *BDNF* interaction emerges from the diminution of genotype differences at higher physical activity levels.

Again, secondary analyses were conducted for each of the working memory tasks that generated the working memory factor. We found that accuracy rates on the letter 1-back (β= .905; t = 2.942; p< .003; partial r^2 = .008), the letter 3-back (β= .786; t = 2.547; p< .01; partial r^2 = .006), the spatial 1-back (β= .914; t = 2.998; p < .003; partial r^2 = .008), and spatial 2-back (β= 1.356; t = 4.498; p <.001; partial r^2 = .019) all showed significant *BDNF* x physical activity interactions. 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 physical activity levels (see Figure 2).

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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 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 benefits on cognition 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, we found 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 suggests that for working memory in this age range, Met carriers benefit more from physical activity than Val homozygotes (see (Mata, Thompson, & Gotlib, 2010) for a similar effect on depression symptoms).

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) (however see (Rockwood & Middleton, 2007)). In fact, *APOE* ε4 carriers who remain physically active show considerably attenuated levels of amyloid deposition compared to 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).

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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 greater amounts of physical activity. Although speculative, the effect we report here, in conjunction with 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 increased 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, compared 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 publications of more than 7000 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 amongst studies. Based on our results, studies with a greater number of less active individuals might show significant differences in memory function between Val homozygotes and Met carriers while 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

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BDNF as the only gene moderating the effects of physical activity on cognitive function. Moderating effects of *APOE* and physical activity have already been discussed above, 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 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, our index of physical activity is widely recognized and frequently used, yet as 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 well-validated instrument. Second, the cross-sectional nature of the study is an additional limitation that 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 increasing physical activity.

Despite these limitations, our sample size of more than 1000 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, we find 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.

Acknowledgements:

This research was partially supported by National Institutes of Health Grants PO1 HL040962 and RO1 HL065137 to SBM. KIE was supported by a Junior Scholar Award from the Pittsburgh Claude D Pepper Older Americans Independence Center (P30 AG024827) and the University of Pittsburgh Alzheimer's Disease Research Center (P50 AG005133). AMW was supported by Award Number T32GM081760 from the National Institute Of General Medical Sciences.

Table 1. Results from the factor analysis with varimax rotation resulted in 4 factors including 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 12 measures that generated the factors with respective loadings onto each. All values less than an absolute value of .40 are suppressed in this table.

Task	Component			
	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		
Trails A Time			.825	
Trails B Time			.766	
Spatial span			-.622	
Visual Reproduction Recall				.889
Visual Reproduction Recognition				.662

Table 2. Participant demographics split by *BDNF*. Numbers are Mean (Standard Deviation) unless otherwise indicated. There were no significant main effects of *BDNF* on any of these measures, but there were modest associations between physical activity (kilocalories) and sex (r=-.06; p<.03) and education (r=.07; p<.02).

	Overall (N=1032)	**Met Carriers (n=361)**	**Val/Val (n=664)**
Demographics:			
Age (SD)	44.59 (6.78)	44.40 (6.74)	44.67 (6.80)
Sex (# female)	538	198	337
Education	16.07 (2.79)	16.06 (2.73)	16.08 (2.82)
Weekly Kilocalorie Count	2502.17 (1816.44)	2383.87 (1675.16)	2568.03 (1894.07)

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Figure 1: Effects of physical activity and the BDNF polymorphism on cognitive performance. The effect of the BDNF polymorphism was only apparent for the working memory factor, such that higher physical activity levels offset the negative effects of the Met allele on working memory. The difference between BDNF genotypes was apparent at 1.5 standard deviations below the mean of physical activity (7.56). None of the other three factors (episodic memory, switching, and visuo-spatial memory) showed a significant *BDNF* x physical activity interaction. Beta and p-values are indicated in each plot. Physical activity was determined based on the energy expenditure metric from the Paffenbarger questionnaire.

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Figure 2: Effects of physical activity and the BDNF polymorphism on N-back working memory performance. The effect of the BDNF polymorphism was only apparent in people with lower physical activity levels. The difference between BDNF genotypes was apparent at 1.5 standard deviations below the mean of physical activity (7.56) for the spatial 2-back task. Higher physical activity levels offset the negative effects of the Met allele on performance and for letter 3-back and spatial 2-back magnified performance more for the Met carriers than the Val carriers at higher physical activity levels. All graphs show significant interactions at $p<.01$. Beta and p-values are indicated in each plot. Physical activity was determined based on the energy expenditure metric from the Paffenbarger questionnaire.

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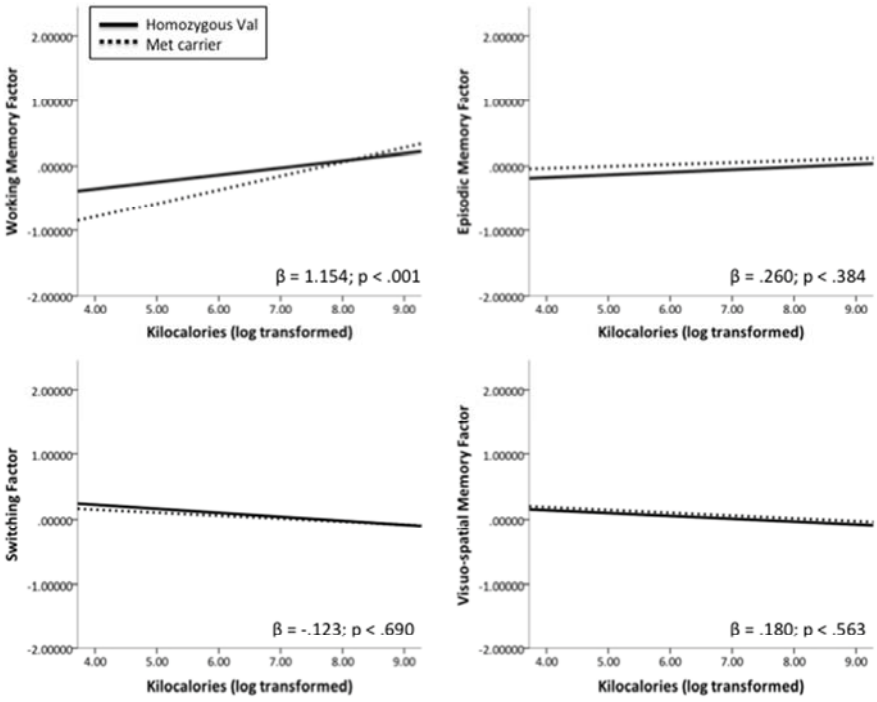

Figure 1.

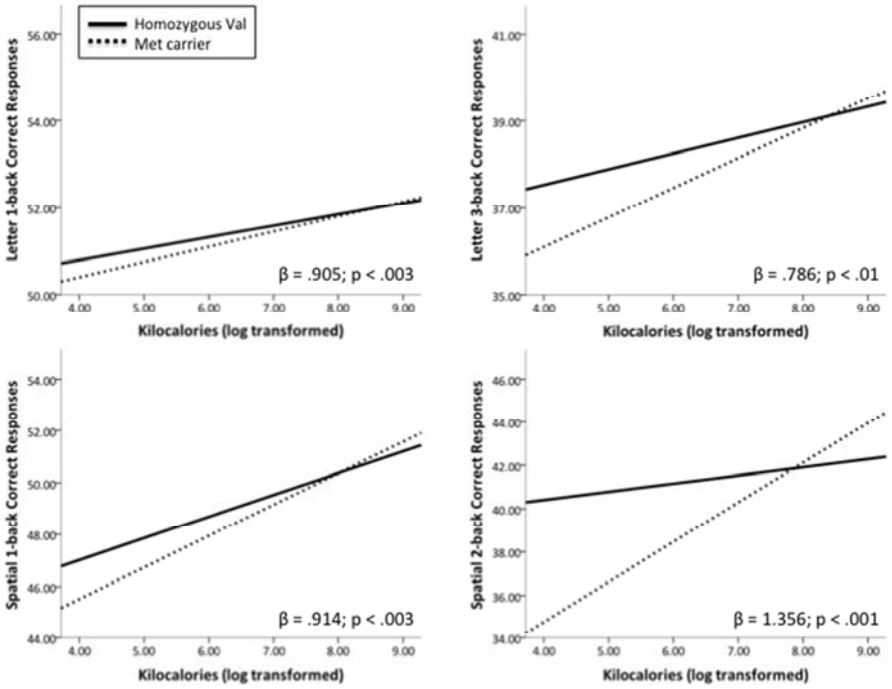

Figure 2.