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The BDNF Val66Met polymorphism does not moderate the effect of self-reported physical activity on depressive symptoms in midlife

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ABSTRACT

The brain-derived neurotrophic factor (BDNF) Val66Met single nucleotide polymorphism may be associated with clinical and subsyndromal depression, but physical activity improves mood and increases BDNF expression. The aim of the study was to examine whether the *BDNF* polymorphism moderates an effect of physical activity on depressive symptoms. *BDNF* genotype, physical activity measured by the Paffenbarger Questionnaire, and depressive symptoms using the Center for Epidemiology Depression Scale (CES-D) were collected on 1072 participants (mean age=44). Multiple linear regression was used to examine the association between *BDNF* genotype, physical activity, and depressive symptoms. After adjusting for family income, age, and education, depressive symptoms were higher in Met carriers compared to Val homozygotes ($p=0.03$), but this was only significant in men. Physical activity was associated with fewer depressive symptoms, but only in women ($p=0.01$). *BDNF* genotype did not moderate the effect of physical activity on depressive symptoms ($p=0.94$). In midlife, the *BDNF* Val66Met polymorphism neither attenuates nor magnifies the effect of physical activity on depressive symptoms.

1. Introduction

Depression is the most common psychiatric disorder, estimated to afflict more than 121 million adults worldwide (Kessler et al., 2003; Mathers et al., 2008; Ustun et al., 2004). Antidepressants are generally an effective treatment for depression, but because of variation in compliance, latency in the therapeutic effects, and continued risk of relapse, alternative methods for preventing or treating depressive symptoms has become an increasingly important avenue of research.

Physical activity is one promising method of reducing risk for depression. For example, greater amounts of self-reported physical activity are associated with fewer depressive symptoms in epidemiological studies (Galper et al., 2006; Goodwin, 2003; Hassmen et al., 2000; Paffenbarger et al., 1994; Teychenne et al., 2008) and randomized interventions find that physical activity enhances mood in depressed populations (Barbour et al., 2007; Blumenthal et al., 2007; Bridle et al., 2012; DiLorenzo et al., 1999; Rimer et al., 2012). Nonetheless, the evidence for therapeutic effects of physical activity on depressive symptoms is far from conclusive (Bailey and McLaren, 2005; Brown et al., 1995; Cramer et al., 1991; King et al., 1989). Variation in dose of physical activity, age, or unmeasured genetic variation could be contributing to discrepant findings.

Although Genome Wide Association Studies (GWAS) have not found a significant association between any particular gene and major depression (Shyn et al., 2011), several candidate-gene studies have reported that a single nucleotide polymorphism (Val66Met; rs6265) in the gene encoding brain-derived neurotrophic factor (BDNF) may be a risk factor for depression, although the results have not been consistent. A recent meta-analysis did not find a significant association between *BDNF* variants and major depression (Gyekis et al., 2013); however, they found significant heterogeneity among studies. This heterogeneity is consistent with evidence suggesting that the association between the *BDNF* Val66Met polymorphism and depression may be stronger in males (Verhagen et al., 2010) and geriatric populations (Hwang et al., 2006). Significant heterogeneity among studies suggests that there

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may be unexamined factors that moderate the influence of *BDNF* on risk for depression.

Physical activity is one such factor that may moderate the influence of *BDNF* on risk for depression. Increased expression of BDNF is considered one of the primary pathways by which physical activity affects brain function (Griffin et al., 2009). For example, running increases BDNF levels in the hippocampus, cerebellum, and cortex (Li et al., 2008; Vaynman et al., 2004). Physical activity also increases BDNF expression in rodent models of depression (Garza et al., 2004) and normalizes BDNF levels in women with remitted major depression (Laske et al., 2010). In addition, physical activity increases BDNF levels in humans (Erickson et al., 2012) and the combination of pharmaceutical antidepressant treatment (tranylcypromine) and physical activity increases BDNF levels in the hippocampus more than either treatment by itself (Garza et al., 2004).

Despite these independent literatures, few studies have explored whether the *BDNF* Val66Met polymorphism moderates the association between physical activity and depressive symptoms. In adolescents, one study ($N=75$) reported that physical activity mitigated depressive symptoms in *BDNF* Met carriers but not in Val homozygotes (Mata et al., 2010); however, this effect was not replicated in a larger sample of adolescents ($N=1196$; (Stavrakakis et al., 2012). Nonetheless, given the biological plausibility of BDNF pathways in both the etiology of depression and the therapeutic effects of physical activity, we predicted that the *BDNF* genotype would moderate the association between self-reported physical activity and depressive symptoms in a large sample ($N=1072$) of middle-aged adults.

2. Methods

2.1. Subjects

The data employed here include measurements obtained on 1295 middle-aged adults who participated in the University of Pittsburgh Adult Health and Behavior (AHAB) project between 2001 and 2005. Data was collected over several sessions spanning several weeks, and informed consent was obtained in accordance with approved protocol and guidelines of the University of Pittsburgh Institutional Review Board.

To mitigate potential for confounding by ethnic differences in *BDNF* val66met allele frequencies, we selected the 1072 non-Hispanic Caucasian participants from this sample. The AHAB project provides a registry of behavioral and biological measurements on midlife community volunteers. Registry data include socio-demographic measurements; indices of personality and temperament; psychiatric history and symptomatology; aspects of social and cognitive functioning (e.g., social and cognitive abilities); health-impairing attributes of habit and lifestyle; physiological measurements germane to cardiovascular, autonomic, metabolic, immune, and central nervous system functioning; and DNA extracted for the study of genetic variation associated with registry phenotypes (cf. Bleil et al., 2008; Hall et al., 2008; Manuck et al., 2010, 2011;).

2.2. Procedures

2.2.1. 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 and Yeh (2005) and detection by fluorescence polarization as described by Chen et al. (1999). Genotypes were assigned by comparison to individuals of known BDNF genotype run in parallel. We used a dominant model to group individuals based on genotype, which conforms to conventions from prior studies (Chen et al., 2008; Hariri et al., 2003; Ho et al., 2006; Krueger et al., 2011). Therefore, heterozygotes and Met homozygotes were combined into a single group. This resulted in 378 Met carriers and 694 Val homozygotes for analysis. Allelic frequencies were in conformity with Hardy–Weinberg equilibrium ($\chi^2=0.04$; $P>0.05$). Prior studies using the AHAB sample have not found any discernible population substructure, so stratification or population-level adjustments were not conducted (Erickson et al., 2013).

2.2.2. Physical activity assessments

Participants completed the Paffenbarger Physical Activity Questionnaire (Paffenbarger et al., 1978). This questionnaire is a widely used instrument to estimate weekly kilocalories expended 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. This instrument has high test-retest reliability after 1-month ($r=0.72$) (Ainsworth et al., 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). From this questionnaire, an estimate of average weekly energy expenditure, in kilocalories, was calculated (Paffenbarger et al., 1978).

2.2.3. Depression measures

Participants completed the Center for Epidemiology Scale for Depression (CES-D) (Radloff, 1977). This is a 20-item self-report questionnaire used to assess current depressive symptoms. A cutoff score of 16 has been used by several studies to determine clinically significant depressive symptoms (Myers and Weissman, 1980; Radloff, 1977; Weissman et al., 1977). We used the CES-D score as both a continuous and dichotomous variable with a cut-off of 16 (see below). There is evidence for high internal consistency (Cronbach $\alpha=0.85$–0.90) on the CES-D across studies, as well as evidence for construct validity and concurrent validity with clinical and self-report criteria (Radloff, 1977).

2.2.4. Analytic approach

Associations between *BDNF* genotype, self-reported physical activity, and depressive symptoms were modeled using multiple linear regression. All variables were assessed for normality; kilocalories of energy expenditure and the CES-D total score were significantly skewed and subsequently log transformed. Family income, age, and years of education were associated with depressive symptoms (see Section 3), and were therefore included as covariates in the model.

The log-transformed CES-D total score was regressed onto sex, log-transformed kilocalories, and *BDNF* genotype along with a log-transformed kilocalories × *BDNF* genotype interaction term. Given that women tend to have higher rates of depression (Weissman et al., 1996) and the *BDNF* val66met polymorphism increases the risk for depression primarily in males (Verhagen et al., 2010), we also examined effect moderation by sex by adding an interaction term of the product between sex and *BDNF* genotype and an interaction term between sex and log-transformed kilocalories to the regression model. Additional secondary analyses were conducted on significant interactions to decompose effects of *BDNF* genotype, physical activity, and sex on depressive symptoms. Standardized regression coefficients and *p*-values are reported for all comparisons.

We also conducted an exploratory analysis to examine whether physical activity and *BDNF* genotype were associated with clinically significant levels of depressive symptoms. This was done using a two-predictor logistic regression model testing the relationship between the likelihood of a participant scoring 16 or higher on the CES-D, indicative of subclinical depression (Myers and Weissman, 1980; Radloff, 1977; Weissman et al., 1977), level of physical activity and *BDNF* genotype. We also tested whether the relationship between self-reported physical activity and the likelihood of having subclinical depression varies according to *BDNF* genotype by adding a *BDNF* genotype × kilocalories interaction term to the logistic model. All analyses were run using IBM SPSS 20.

3. Results

3.1. Sample characteristics

Out of 1072 participants, there were 525 males and 547 females, with an average age of 44.7 years (S.D.=6.78). Forty-one participants had the Met/Met genotype (22 males, 19 females), 337 had the Val/Met genotype (154 males, 183 females), and 694 had the Val/Val genotype (349 males, 345 females). As described above, *BDNF* genotypes were grouped according to a dominant model such that Met carriers were collapsed into a single group for all analyses. Higher levels of depressive symptoms on the CES-D were associated with lower family income ($r=-0.26$, $P<0.001$) and younger ages ($r=-0.09$, $P<0.001$). Physical activity was associated with higher family income ($r=0.14$, $P=0.001$) and more years of education ($r=0.07$, $P=0.01$), but not associated with age ($r=-0.03$, $P=0.37$). Val homozygotes had slightly lower family income compared to Met carriers (Val/Val Mean=5.22; Met carrier mean=5.87; $t=5.14$, $P=0.004$). Age did not differ between Val homozygotes and Met carriers ($t=0.06$, $P=0.77$), but Val homozygotes had slightly fewer years of education compared to

Table 1
Demographic and clinical characteristics of participants.

Characteristic	Total sample mean (S.D.) $N=1072$	Men mean (S.D.) $N=525$	Women mean (S.D.) $N=547$
% Men	49%	–	–
Age (years)	44.7 (6.78)	44.5 (6.91)	44.87 (6.66)
Education (years)	16.03 (2.78)	16.24 (2.6)	15.82 (2.93)
SES (Family Income scale 0-8)	5.7 (1.98)	5.67 (1.98)	5.72 (1.97)
Exercise (kilocalories expended)	2504.24 (1812. 02)	2590.24 (1800.86)	2421.68 (1820.48)
% Met carriers	35.2%	33.5%	36.9%
% Lifetime diagnosis MDD	15.7%	14.3%	16.7%
% CES-D score 16+	11.9%	13.7%	10.3 %
CES-D total score	7.38 (7.45)	7.93 (7.63)	6.86 (7.23)

Table 2
Linear and logistic regression models showing the contributions of the BDNF Val66Met polymorphism, Physical Activity, and Sex to the prediction of log transformed CES-D score and a CES-D score of 16+, respectively, in the overall sample.

	Ln (CES-D total) $N=1072$			CES-D 16+ $N=1072$	
	β	P-value	R^2	OR	P-value
BDNF	0.07*	0.04	0.003	1.26	0.02
Physical activity	−0.05	0.15	0.002	0.80	0.06
Physical activity × *BDNF*	−0.01	0.94	0.00	1.10	0.42
Physical activity × Sex	−0.10*	0.03	0.005	0.84	0.44
BDNF × Sex	−0.04	0.20	0.005	0.79	0.03
Physical activity × *BDNF* × Sex	−0.02	0.64	0.001	0.94	0.58

* Indicates significant associations.

Met carriers (Val/Val mean=15.61; Met carrier mean=15.96; $t=2.05$, $P=0.04$). See Table 1 for detailed demographic and clinical characteristics of the sample. Because of these associations, we used family income, age, and years of education as covariates, and further examined effect moderation of sex.

3.2. Main effects of self-reported physical activity on depressive symptoms

Physical activity was unrelated to depressive symptoms on the CES-D in this midlife sample when accounting for variance explained by family income, age, and education ($\beta=-0.05$; $P=0.15$) (See Tables 2 and 3). However, the association between physical activity and depressive symptoms was moderated by sex (Physical activity × Sex: $\beta=-0.09$; $P=0.046$). Given this significant interaction, we stratified the sample by sex to decompose the interaction and found that self-reported physical activity was associated with fewer depressive symptoms in females ($\beta=-0.11$; $P=0.01$), but not in males ($\beta=0.02$; $P=0.59$). Also, using logistic regression we found that physical activity was marginally associated with a reduced risk of clinically significant depressive symptoms determined by a score of 16 or above on the CES-D ($OR=0.83$; $P=0.06$). After stratifying by sex, this association was significant in females ($OR=0.77$; $P=0.03$) but not in males ($OR=0.99$; $P=0.90$).

3.3. Main effects of BDNF on depressive symptoms

Met carriers reported higher levels of depressive symptoms compared to Val homozygotes after accounting for variance explained by family income, age, and education ($\beta=0.07$; $P=0.04$). Although the interaction between sex and *BDNF* genotype was not significant ($\beta=-0.06$; $P=0.37$), previous studies have reported sex differences in the association between *BDNF* genotype and depressive symptoms (Verhagen et al., 2010). Thus, we conducted additional sex stratified linear regression analyses and found that male Met carriers reported higher levels of depressive symptoms compared to male Val homozygotes ($\beta=0.10$; $P=0.03$), but this association was not significant in females ($\beta=0.03$; $P=0.51$). Similarly, logistic regression indicated that male Met carriers were at a significantly higher risk for having clinically significant depressive symptoms ($OR=2.63$; $P=0.02$), while the effect in females was not significant.

3.4. The BDNF polymorphism does not moderate the effect of physical activity on depressive symptoms

Inconsistent with our predictions, *BDNF* genotype did not moderate the effect of kilocalories on depressive symptoms in the linear or logistic regression analyses ($\beta=-0.002$ $P=0.94$) ($OR=1.10$, $P=0.42$) (See Table 2). Furthermore, these interaction terms were not significant for either males or females in sex-stratified analyses (Males: $P=0.34$, Women: $P=0.88$; see Table 2).

4. Discussion

We predicted that Val66met variation in the *BDNF* gene would moderate the association between physical activity and depressive symptoms such that physical activity would be associated with reduced depressive symptoms more for Met carriers than Val homozygotes. Inconsistent with this prediction, we failed to find a significant interaction between *BDNF* genotype and self-reported measures of physical activity on depressive symptoms in either males or females.

There are several possible explanations for the non-significant interaction. For example, one might argue that we were underpowered to detect such an effect. The likelihood of this explanation is weakened by the fact that we had 1072 adults with no evidence of population admixture. We conducted an *a posteriori* power analysis, which indicated that a sample of 199 would be needed to explain 3% variance; thus it seems unlikely that we were underpowered to detect such an effect. Furthermore, another study of 1196 adolescents also failed to find a significant interaction between *BDNF* and physical activity on depression (Stavrakakis et al., 2012). Nonetheless, insufficient power is difficult to eliminate as a potential explanation. It remains possible that a larger sample with a greater contingency of subjects with clinical depression might find a different outcome from that observed here.

Despite the non-significant interaction between *BDNF* and self-reported physical activity on depressive symptoms, the *BDNF* Met allele was associated with a greater number of depressive symptoms on the CES-D. Interestingly, this effect was only found in males. A meta-analysis of 14 studies reported similar sex-specific effects of *BDNF* genotype on major depression such that the Met allele conferred a greater risk for major depression only in males (Verhagen et al., 2010). There are a number of possible explanations for the sex differences as described by Verhagen et al. (2010)

Table 3
Multiple linear regression models and binary logistic regression models showing the contributions of the BDNF Val66Met polymorphism and physical activity to the prediction of a CES-D score of 16 or above in sex-stratified samples.

	Ln (CES-D total) men $N=525$			Ln (CES-D total) women $N=547$			CES-D 16+men $N=525$		CES-D 16+women $N=547$	
	β	*P*-value	R^2	β	*P*-value	R^2	*OR*	*P*-value	*OR*	*P*-value
BDNF	0.10*	0.03	0.007	0.03	0.51	0.00	1.56*	0.00	0.96	0.79
Physical activity	0.02	0.59	0.00	−0.11*	0.01	0.01	0.87	0.40	0.71*	0.04
Physical activity × *BDNF*	0.02	0.65	0.00	−0.01	0.85	0.00	1.17	0.34	1.02	0.88

* Indicates significant associations.

including moderation by environmental factors (e.g. stress response), gender-related epistatic effects, or sexual dimorphic patterns in brain structures involved in the neurobiology of depression (e.g., hippocampus) or stress and reward (e.g., striatum).

Greater amounts of self-reported physical activity were associated with fewer depressive symptoms, but only for females. Such sexually dimorphic effects of physical activity are infrequently reported in humans since sex is often modeled as a covariate instead of in stratification or moderation analyses (Barbour et al., 2007; Blumenthal et al., 2007; Teychenne et al., 2008). Nonetheless, physical activity might be more effective at influencing brain and psychological outcomes in females compared to males (Baker et al., 2010; Colcombe and Kramer, 2003; Huang et al., 2013; Ma et al., 2012). For example, in the Health and Retirement study, physical activity was associated with reduced depressive symptoms in elderly women, not men (Carroll et al., 2010). In contrast, other studies have reported that males benefit more from physical activity than females (Brown et al., 2013; Herring et al., 2012; Rethorst et al., 2009). One potential explanation is that there might be interactions between estrogen and physical activity on *BDNF* gene expression (Berchtold et al., 2001), parahippocampal volume (Erickson et al., 2007), or hypothalamic–pituitary–adrenal (HPA) axis outcomes (Kokras et al., 2012).

Our original prediction was that *BDNF* genotype might moderate the effect of physical activity on depressive symptoms. This prediction was based on: (a) *BDNF* has been linked to depression and reduced levels of BDNF in brain regions associated with depression (i.e., hippocampus), (b) reduced levels of BDNF can be normalized by antidepressant treatment or exercise, (c) exercise is associated with elevated levels of BDNF, and (d) exercise is considered a propitious non-pharmaceutical treatment for depression. In line with this reasoning, one study reported a significant interaction between physical activity and the BDNF polymorphism in adolescents (Mata et al., 2010), but another showed a non-significant interaction (Stavrakakis et al., 2012). Our results are more consonant with the latter and suggest that *BDNF* genotype probably plays a negligible role in moderating the effect of physical activity on depressive symptoms.

There are several limitations to this study. First, both the CES-D and the Paffenbarger measures may be capturing state-based aspects of depressive symptoms and physical activity. Longitudinal assessments and objective measures of physical activity could be used to examine trait-based or long-term participation in physical activity and its links to depressive symptoms. Second, we used a global measure of energy expenditure and do not have information about particular types of activities. Third, this was an observational cross-sectional study, so it is impossible to determine whether reduced physical activity is simply a symptom among other depressive symptoms or whether it is a predictor of future depressive symptoms. Finally, we did not have blood data available in this study to provide us with an estimate of serum or plasma levels of BDNF, which prevents us from testing whether variation in BDNF protein expression are involved in these associations.

In sum, we do not find evidence in this study of midlife adults that *BDNF* genotype moderates the association between physical activity and depressive symptoms. Despite this null result, we find sex differences in the association between both *BDNF* and physical activity on depressive symptoms with the *BDNF* Met allele conferring risk for depressive symptoms in males, but not in females and lower amounts of physical activity associated with more depressive symptoms in females, not in males.

Conflict of interest

All authors declare no conflicts of interest.

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