

The Brain Derived Neurotrophic Factor (BDNF) val66met Polymorphism Moderates the Effect
of Subjective Experience on Long-Term Exercise Maintenance

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Abstract

Seventy-five to 95 percent of Americans do not meet recommended levels of physical activity. It is of critical importance that we uncover individual differences regarding long-term adherence to exercise to prevent detrimental health outcomes related to chronic inactivity. This study aimed to identify the influence that the brain derived neurotrophic factor (BDNF) val66met polymorphism has on the effect of subjective experience on long-term exercise maintenance. Subjective response to exercise was measured by self-reports of positive affect and perceived pain. Exercise maintenance was measured through self-reported 7-day minutes of voluntary exercise 12 months following intervention. Data were collected from 219 participants and genotypes for the val66met polymorphism were obtained from DNA extracted from saliva. The multivariate regression analysis obtained a significant variance in exercise adherence associated with perceived pain measures accounted for by BDNF genotype. The multivariate regression analyses for positive affect were not statistically significant. The implications of the study suggest a heritable difference in the influence of subjective experience on long-term health behavior outcomes and stress the importance of individually tailored exercise interventions.

The Brain Derived Neurotrophic Factor (BDNF) val66met Polymorphism Moderates the Effect of Subjective Experience on Long-Term Exercise Maintenance

Regular physical activity has been implicated as a key measure of reduced risk of chronic diseases such as cancer, heart disease, and Type II diabetes (De Schutter, Lavie, & Milani, 2014, Gilbert & Sligerland, 2013, Vucenik & Stains, 2012). Additionally, lack of physical activity accounts for one-third of all heart disease and type-II diabetes mortality (Volgari, Pagoni, Vinik, & Poirier, 2013). Despite the widespread and well-known benefits of regular activity, 75 to 95 percent of Americans fail to meet the World Health Organization's (2010) recommended levels of regular physical activity (at least 150 minutes of moderate-level physical activity per week, with some amount of that activity performed five or more days within that week) (Reilly et al., 2008, Troiano et al., 2008). Moreover, Prince et al. (2008) have found that self-report measures of physical activity vastly overestimate actual objective measures of physical activity by accelerometer. While self-report measures allow for accurate representations of trends of exercise frequency across groups and across time, it is most likely that the majority of participants are engaging in even less exercise than they report (Ainsworth et al., 2012).

Given the health risk factors listed above, it is of paramount importance that underlying factors influencing health and exercise interventions are uncovered. Long-term physical activity interventions of sedentary adults are almost always unsuccessful in creating any sort of lasting change in exercise behavior (Marcus et al., 2000, Schwarzer et al., 2007, Woodward & Berry, 2001). One potential reason for this is the interventions' lack of consideration for individual differences within their participant populations (Sherwood & Jeffery, 2000). These individual factors can include demographic differences (gender, ethnicity, race, and socio-economic status),

physiological differences (body mass index, VO2 Max, body temperature, and blood pressure), genetic differences (BDNF, rs6265; FTO, rs9941349, rs8044769, rs37751812; OPRMI, rs1799971), and subjective measures of response to physical activity (perceived pain or positive/negative affect) (Bryan et al., 2007, 2011). It is possible that consideration of certain individual differences that account for variance within participant populations on long-term exercise adherence can tailor interventions to individuals, thus increasing the likelihood of intervention success.

Several studies have assessed the success of trans-disciplinary methods of exercise intervention and cross-sectional measurement. Bryan et al. (2007) have proposed a possible methodology for organizing these mechanistic variables of exercise behavior. The framework suggests that certain variables lead to variation in others that ultimately influence an individual's long-term outcome of exercise adherence variation. It has been found that certain genetic factors can influence an individual's subjective experience to exercise, and that subjective experience can have long-term effects on exercise behavior (Kwan & Bryan, 2012, McBride et al., 2012, Williams, 2008). Conversely, Ekkekakis, Parfitt, and Petruzzello (2011) and Karoly et al. (2012) propose a theory suggesting that genetic factors can moderate the effects of participants' similar subjective experiences on long-term exercise behavior.

Determining cause and effect relationships between moderating factors of exercise intervention outcome can lead to sophisticated understanding of physiological or neurological mechanisms underlying response to physical activity and physical activity motivation. However, these mechanisms can be difficult to measure in a clinical population in a non-invasive manner, particularly when desired mechanisms are neurologic (Dishman et al., 2006, Viss, Vivar, & Kramer, 2013). This is particularly true in the case of *brain-derived neurotropic factor (BDNF)*

(Rasmussen et al., 2009). BDNF is a common growth factor in the brain that is known to influence neuronal plasticity (synaptic pathway mediation), synaptic strength and efficiency, and overall brain and neuronal growth (Eker et al., 2005, Toro et al., 2009). Increases in BDNF are known to be activity-dependent in that their levels increase within synapses that are more frequently activated, leading to upstream synaptic strength and even increased neurogenesis (neuron formation) within the hippocampus and the occipital lobe (Cheeran et al., 2008, Vaynman, Ying, & Gomez-Pinilla, 2003).

Fortunately, there is a well-known single nucleotide polymorphism (SNP) within the BDNF gene that is present in at least one allele in approximately 30 percent of the population (Bian, Zhang, Zhang, & Zhao, 2005, Egan et al., 2003, Hariri et al., 2003). This polymorphism (BDNF val66met) results in abnormal BDNF function because it codes for a methionine amino acid (polar) in place of the wild type valine amino acid (nonpolar) (Egan et al., 2003, Hariri et al., 2003). The SNP's alteration of polarity leads to impairment of nonpolar membrane crossing of the transcribed BDNF protein within the brain (Egan et al., 2003). As a result, lowered levels of BDNF protein are found within neurons at baseline activity levels amongst those individuals exhibiting the methionine-coding allele compared to wild type (Egan et al., 2003, Eker et al., 2005). The val66met SNP leads to significant differences in downstream effects on motor learning (exhibited through motor map area decreases upon motor training), PAS induced plasticity, and reduced retention of vasomotor skill (Cheeran et al., 2008, Joundi et al., 2012, Kleim et al., 2006). Additionally, it has been hypothesized that this polymorphism is associated with a vast array of neurological and mood disorders such as depression, schizophrenia, Parkinson's, and Alzheimer's disease (Altmann et al., 2016, Housang et al., 2014, Lim et al., 2015, Zhang et al., 2016).

It has been suggested that exercise can influence these effects of the val66met polymorphism, or visa versa (Pilc, 2010). Exercise has been found to increase BDNF populations within areas of the brain such as the hippocampus, leading to increased neuronal health and neurogenesis (Rossi et al., 2006). There is a discrepancy in the field though as to whether or not exercise can induce a greater effect on mutant populations due to a greater increase of BDNF protein from baseline compared to those already experiencing wild type BDNF levels (Erickson et al., 2013, Hopkins et al., 2012). Erickson et al. (2013) have found that the methionine-coding polymorphism can positively moderate exercise's effects on motor learning and working memory, while Hopkins et al. (2012) conclude that the BDNF val66met SNP attenuates the positive effects of exercise on motor learning. Hopkins et al. (2012) argue that only wild type individuals are able to cross the threshold of exercise-induced functional improvement of BDNF levels due to their higher levels at baseline compared to the mutant allele.

Similar discrepancy is found in the field relating to the val66met polymorphism's association with subjective experience of exercise and how that association can lead to long-term effects of physical activity increases upon intervention. Bryan et al. (2007) have found significant variation in affective response to exercise accounted for by the BDNF val66met SNP. Participants with the mutant allele have shown to exhibit decreased scores of perceived exertion, heart rate, and body temperature both during and upon completion of exercise (Bryan et al., 2007). Because in-task affective response has been found to be the greatest predictor of long-term exercise adherence, it is very probable that the mutant allele can actually advantage sedentary individuals in terms of long-term exercise intervention success (Kwan & Bryan, 2012). However, Hooper, Bryan, and Hagger (2014) found no significant correlation between genotype and affective response, but did find a significant variance in an in-task measure of exercise

motivation. It is possible that while participants may experience in-task levels of affect that are similar, the val66met polymorphism can influence the relationship between affective response to physical activity and motivation to be physically active. Hooper et al. (2014) hypothesize that increased levels of BDNF in the brain induced by exercise can have a greater effect on individuals due to an increase from a lower baseline level. It is possible that increased levels of BDNF compared to a lower baseline can have a reward effect of exercise as a result of increased neuronal health or synaptic strength in individuals with the methionine-coding allele.

While there is still a discrepancy regarding cause and effect relationships and underlying neural mechanisms of the BDNF val66met polymorphism, their moderation effects on the relationship between exercise and learning or motivation effects in both animal and human populations are significant when it comes to acute or in-task measures (Erickson et al., 2013, Hooper et al., 2014, Novkovic, Mittmann, & Manahan-Vaughan, 2015). There are significant exercise-related effects of the val66met polymorphism during and immediately following a bout of moderate-level exercise (Bryan et al., 2007, Hooper et al., 2014). However, little research has been done to determine if this acute effect can be translated to a long-term effect of exercise motivation or habituation. We are unsure if the improved learning and motivation effect related to exercise truly impacts a sedentary individual's chances for permanently increased exercise. Knowledge of a genotype's long-term effect on exercise motivation and adherence can be an important factor in determining a useful framework for exercise intervention individualization, possibly leading to greater intervention success on sedentary populations at risk of detrimental health outcomes related to their inactivity. Additionally, a more sophisticated knowledge of the BDNF genotype difference and its cause and effect relationships with subjective experience

(affective response) to exercise is also important for future individualized tailoring of exercise interventions of sedentary individuals.

We addressed these questions by taking a longitudinal approach to an exercise intervention targeting sedentary individuals that lasted up to twelve months and consisted of both genotyping (through saliva collection) and collection of several measures of subjective experience resulting from exercise. The study below aimed to uncover associations between BDNF genotype, affective response to exercise (including overall positive affect and perceived pain levels) during and upon completion of exercise, and minutes of voluntary physical activity within a week one year following the exercise intervention's baseline. We hypothesize that the val66met single nucleotide polymorphism will moderate the effect of participants' measures of affective response (overall positive affect and perceived pain) to exercise on self-reported minutes of voluntary physical activity at twelve months following the intervention's baseline. We predict that positive affect will have a greater positive effect on exercise adherence in methionine allele participants, and that pain measures will have less of a negative effect on exercise adherence for methionine allele participants. Additionally, we also predict that pain will account for a greater percentage of the variance in exercise adherence than overall positive affect in participants, and that both affective response measures in-task (and averaged) will account for more of the variance in exercise adherence at the 12 month mark than affective response measures taken upon completion of exercise for both wild type and mutant alleles.

Method

Participants

The study was conducted on a sample of 219 individuals between the ages of 18 and 45. Participants were recruited from the University of Colorado community and the Denver metro

area. Initial recruitment criteria consisted of an average of 90 minutes or less of voluntary vigorous or moderate-level physical activity per week for at least three months. Recruited participants were screened for eligibility, and those who smoked cigarettes, were on a restricted diet, receiving treatment for a psychiatric disorder, taking psychiatric medications, Type I or Type II diabetic, had any cardiovascular or respiratory diseases, had the flu or illness in the last month, or were pregnant or planning to become pregnant in the next 12 months (if female) were excluded. Required criteria for study eligibility were a body mass index (BMI) between 18 and 37.5, being physically capable of participating in moderate-level intensity physical activity, and having a regular menstrual cycle (if female). All participants had to consent to random assignment to one of the study's two exercise intervention types. Upon completion of this baseline assessment, 238 eligible participants were selected and randomized from the initially recruited 338. 219 of those participants completed all baseline sessions and were included in the sample.

The sample's gender proportion was 19.6% male ($N = 43$) and 80.4% female ($N = 176$). The average age of the participant sample was 28 years ($SD = 7.95$). The majority of the participants identified as white ($N = 147$) while 3.7% identified as black ($N = 8$), 11.9% as Asian ($N = 26$), 11.9% as Latino or Latina ($N = 26$), 2.3% as Native American ($N = 5$), and the remaining 2.8% of participants either identified with an unlisted race or were multicultural ($N = 7$). A significant difference in genotype was found between racial groups when racial categories were analyzed both separately and when grouped as white and non-white (see Table 1). This however was most likely due to our sample's homogeneous nature. 52.1% of participants ($N = 114$) were assigned to the COSTRIDE intervention condition and 47.9% ($N = 105$) were assigned to the Health and Wellness (HW) control condition. Detailed descriptions of the

intervention conditions are provided below in the study's design. Participants possessing the more common genotype (that codes for the amino acid valine) of the BDNF allele (G/G) made up 62.6% of the sample ($N = 137$) and 36.5% ($N = 80$) of the participant population possessed at least one A allele coding for methionine (A/G and A/A). Genotypes of two participants could not be determined. Previous studies suggest that the frequency of the A allele occurs between 18% to 45% across samples taken and populations of ethnic groups (Bian, Zhang, Zhang, & Zhao, 2005, Egan et al., 2003, Hariri et al., 2003).

Study Design

The study was designed as a twelve-month randomized control trial in which participants were assigned to two versions of an exercise intervention (random assignment outcomes described above). The COSTRIDE condition provided participants with specific goal-setting measures (to increase moderate-level intensity physical activity to at least five days a week for 30 or more minutes per session) and individually tailored messages regarding their progress at various time points throughout the study. The control condition (HW) only provided participants with a general goal of increasing overall health and well-being. HW participants received non-tailored uniform printed mailing throughout the study at the same time points as the corresponding COSTRIDE participants.

The data were analyzed using several multivariate regression analyses where the independent variables were affective response and the BDNF allele, and the dependent variable was minutes of voluntary physical activity to assess whether the effect of subjective response to exercise on long-term exercise maintenance depended upon BDNF allele. The affective response measures were of *perceived pain* and the *positive affect subscale* of the Physical Activity Affect Scale (PAAS; Lox, Jackson, Tuholski, Wasley, & Treasure, 2000). The

participants' perceived pain was assessed using a single-item 12-point Borg CR10 scale ranging from 0 (*no pain at all*) to 10 (*extremely intense pain*) (Hardy & Rejeski, 1989). The participants' positive affect was assessed using the *Physical Activity Subscale* of the PAAS. The scale measures four categories of affect resulting in four subscales (positive affect, negative affect, tranquility, and physical exhaustion) on 15 5-point Likert scales ranging from 0 (*do not feel*) to 4 (*feel very strongly*). The three "positive affect" measures ("enthusiastic," "energetic," and "upbeat") were averaged ($\alpha = 0.90$) to obtain each participant's measure of overall positive affect.

Exercise maintenance at the 12-month time point was assessed using the *7-Day Physical Activity Recall* (PAR) interview to collect the number of minutes of physical activity each participant had engaged in in the past 7 days (Blair et al., 1985). The physical activity was categorized by intensity (mild, moderate, or high) and type (voluntary, work-related, leisure, and walking).

Measures

Participants' maximal oxygen capacity (VO₂ max) was obtained via a Balke protocol (a maximal exercised test on a motorized treadmill where the participant is initially brought to a comfortable speed corresponding to 70% of age-predicted maximal heart rate and then the grade is increased in 2.5% increments every two minutes until maximal VO₂ is reached) (Christou, Gentile, DeSouza, Seals, & Gates, 2005). VO₂ max was assessed using an online computer-assisted open-circuit spirometry with the Medgraphics CardiO₂/CP system (St. Paul, MN) during treadmill exercise (Trackmaster 425 treadmill, Newton, KS).

DNA was obtained from saliva using an Oragene self-collection kit. Commercially available kits described in previously published procedures were used to manually extract DNA

(Freemen et al., 1997, Hutchison, McGeary, Smolen, Brayn, Swift, 2002; Walker et al., 1999).

The BDNF SNP (rs6265) was assayed using a commercially available 5'-nuclease (TaqMan, Roche Molecular Systems, Pleasanton, CA) PCR assay in conjunction with the 7500 thermocycler (Applied Biosystems, Foster City, CA) protocol outlined by Livak, 1999.

Procedures

Following recruitment, participants were brought in for three baseline sessions (orientation, fitness test, and submaximal test). In addition to obtaining informed consent during the orientation appointment, physical activity levels were measured via self-report conducted by a trained interviewer. Interviewers filled out the 7-day PAR for participants, reviewing each day from the participant's last week in detail. Minutes of voluntary exercise for the week were added and recorded for each participant. Following the orientation visit, participants completed a VO₂ Max test during a separate visit. On that same day but prior to the maximal fitness test, participants' DNA was collected through saliva collection using an Oragene kit and an intravenous blood draw performed by clinical staff. Blood and saliva samples were stored at approximately 5 degrees Celsius until DNA could be extracted and incubated.

Participants returned to the clinic one week following the fitness test for a submaximal exercise session lasting 30 minutes (with allotted times for warm up and cool down). During this session, participants were brought to 65% of their maximal VO₂ value derived from their fitness test one week earlier. A target heart rate range was determined during this test for the participant to adhere to for the remainder of the study. Several measures were taken during the submaximal assessment. Prior to activity, resting heart rate, blood pressure, and affective response measures (described above) were taken, and an intravenous catheter was inserted so blood samples could be taken at each checkpoint of the bout. There were three checkpoints during the 30-minute bout

(taken at 8-10, 18-20, and 28-30 minutes) where blood samples were collected and affective response measures were taken and recorded. Heart rate, blood pressure, blood samples, and affective response measures were taken again at the end of the bout while the participant was resting. Average measures of positive affect and perceived pain were taken from the three checkpoints listed above and endpoint measures were taken from the 28-30 minute checkpoint.

For the remainder of the 12-month study, participants were sent either tailored (COSTRIDE condition) or non-tailored (control condition) printed health and wellness mailings weekly during month 1, biweekly during months 2 and 3, monthly during months 4 through 6, and bimonthly during months 7 through 12. Follow up assessments were taken at months 3, 6, 9, and 12 where participants received increments of their final \$300 compensation for completing each phase of the study. 7-Day PAR minutes of exercise were recorded at this time, and a follow up VO₂ maximal fitness test was completed at the 12-month follow up session to assess changes in fitness levels. The correlation between minutes of exercise reported at 12 months and VO₂ Max calculated at 12 months was significant, $r(164) = 0.29$, $p < 0.001$. The correlation between minutes of exercise reported at 12 months and change in VO₂ max from baseline was also significant, $r(164) = 0.20$, $p < 0.05$. Because these correlations were significant, and because preliminary objective measures of exercise taken via pedometer during the first month of the study were consistent with participant self-report exercise data, 7-Day PAR measures were used to assess exercise minutes for the remainder of the study.

Following clinical trial completion, DNA was extracted and the well-established Taqman assay was used to assay the BDNF SNP (rs6265) following previously published procedures (Bryan et al., 2007). Samples were not assayed until DNA was collected and extracted from all participants for all time points to avoid batching errors.

Using the BDNF SNP assays, participants were either coded as G/G = 0 (for having both valine genotypes) or G/A or A/A = 1 (for having at least one methionine-coding genotype at the val66met polymorphism site). Four multivariate regression analyses were performed using SPSS statistical programming to determine if the selected subjective measure, BDNF genotype, and/or the interaction between the two variables predicted minutes of exercise during the participants' last week of exercise collected at the 12-month follow up session. Four separate regression models were made for each of the four subjective measures (average and endpoint positive affective response and average and endpoint perceived pain) that included the selected subjective measure, genotype, and an interaction term between subjective measure and genotype.

Results

Due to participant attrition, only 166 participants were accounted for in the study's 12-month follow up assessment, making the study's retention rate of participants 75.8% (see Table 2). 7-day PAR minutes of exercise reported at 12 months differed marginally between the COSTRIDE condition ($M = 103.01$) and the control condition ($M = 68.42$), $t(164) = -2.34$, $p = 0.021$. There were no statistically significant differences between BDNF genotypes observed for 7-Day PAR minutes of exercise reported at 12 months, or for positive affective response recorded at the end of the exercise bout or averaged throughout (see Table 3). There was however a statistically significant difference observed for perceived pain recorded at the end of the exercise bout between the wild type ($M = 1.30$) and methionine-coding allele ($M = 1.04$), $t(213) = 1.30$, $p = <0.01$. There was also a statistically significant difference observed for perceived pain averaged between the three recorded time points (8-10 minutes, 18-20 minutes, and 28-30 minutes) between the wild type ($M = 1.43$) and the mutant allele ($M = 1.07$), $t(214) =$

2.02, $p = 0.001$. The differences observed for perceived pain between BDNF genotypes are consistent with the work of Bryan et al. (2007).

Endpoint Perceived Pain Model

A multiple regression analysis was conducted to determine whether BDNF genotype and/or pain level assessed at the end of the exercise bout (between 28 and 30 minutes of the 30-minute session) predicted exercise behavior twelve months following intervention, and if there was a significant interaction between BDNF genotype and perceived pain level reported at the end of a submaximal exercise bout that influenced exercise maintenance at 12 months.

Results indicated that the overall regression model was significant, $R^2 = 0.08$, $F(3, 161) = 4.68$, $p = <.01$, with approximately 8% of the variance in exercise at 12 months explained by the interaction between BDNF genotype and pain level assessed at end of exercise session. The main effect of BDNF genotype on exercise maintenance at 12 months was also significant, $b = -0.25$, $t(162) = -2.38$, $p = <0.05$, such that those with the mutant allele engaged in less physical activity at 12 months, as was the main effect of pain assessed at end of exercise bout, $b = -0.33$, $t(162) = -3.59$, $p < 0.001$, such that participants who experienced more pain during the bout of exercise at baseline were engaging in less voluntary physical activity at 12 months. The effect of the interaction between BDNF genotype and pain assessed was also significant, $b = 0.31$, $t(162) = 2.69$, $p = <0.01$. For those with the wild type allele, increased levels of perceived pain resulted in fewer minutes of exercise, while those with the mutant allele actually displayed a positive influence of perceived pain during the baseline session on minutes of exercise at 12 months (see Figure 1).

Average Perceived Pain Model

A second multiple regression analysis was conducted to determine if BDNF genotype and/or average pain levels recorded and averaged during exercise bout predicted exercise behavior twelve months following intervention, and if there was a significant interaction between BDNF genotype and average perceived pain that influenced exercise maintenance at 12 months following intervention.

Results indicated that the overall regression model was significant, $R^2 = 0.055$, $F(3, 161) = 3.13$, $p = <.05$, with approximately 6% of the variance in exercise maintenance at 12 months explained by average perceived pain and BDNF genotype. The main effect of BDNF genotype on exercise maintenance at 12 months was not significant, $b = -0.23$, $t(162) = -1.95$, $p = 0.53$. However the main effect of average perceived pain was significant, $b = -0.26$, $t(162) = -2.97$, $p = <0.01$, such that participants displaying higher levels of perceived pain averaged throughout the exercise bout engaged in fewer minutes of exercise at 12 months. The effect of the interaction between BDNF genotype and average perceived pain was also not significant, $b = 0.22$, $t(162) = 1.81$, $p = 0.072$ (see Figure 2).

Endpoint Positive Affect Model

A third multiple regression analysis was conducted to determine if BDNF genotype and/or positive affect assessed at the end of the exercise bout (between 28-30 minutes of the 30-minute session) predicted exercise behavior twelve months following intervention, and if there was a significant interaction between BDNF genotype and positive affect reported at the end of a submaximal exercise bout that had an effect on exercise maintenance at 12 months.

Results indicated that the overall regression model was not significant, $R^2 = 0.022$, $F(3, 161) = 1.18$, $p = 0.32$, accounting for only 2% of the variance in exercise maintenance at 12 months. The main effect of BDNF genotype on exercise maintenance at 12 months was not

significant, $b = 0.21$, $t(162) = 1.25$, $p = 0.21$, and neither was the main effect of endpoint positive affect assessed at end of exercise bout, $b = 0.11$, $t(162) = 1.01$, $p = 0.31$. The effect of the interaction between BDNF genotype and endpoint positive affect was also not significant, $b = -0.32$, $t(162) = -1.76$, $p = 0.081$ (see Figure 3).

Average Positive Affect Model

A final multiple regression analysis was conducted to determine if BDNF genotype and/or average positive affect assessed during a submaximal exercise bout predicted exercise behavior twelve months following intervention, and if there was a significant interaction between BDNF genotype and average positive affect that influenced exercise maintenance 12 months following intervention.

Results indicated that the overall regression model was not significant, $R^2 = 0.015$, $F(3, 161) = 0.81$, $p = 0.42$, with approximately 2% of the variance in exercise maintenance at 12 months explained by BDNF genotype, average positive affect assessed during the exercise bout, and the interaction between the two variables. The main effects of BDNF genotype, average positive affect, and the interaction were all not significant, $b = 0.19$, $t(162) = 0.99$, $p = 0.32$, $b = 0.105$, $t(162) = 1.04$, $p = 0.30$, $b = -0.28$, $t(162) = -1.40$, $p = 0.16$ (see Figure 4).

Discussion

The goal of the study was to determine if the effect of subjective experience (measured by affective response to exercise) on exercise maintenance twelve months following intervention of sedentary individuals was moderated by the BDNF val66met single nucleotide polymorphism. We hypothesized that mutant BDNF-genotyped participants would experience a greater positive effect of positive affective response on minutes of exercise at twelve months compared to the wild type allele, and that there would be less of a negative effect of perceived pain on twelve-

month minutes of exercise for the mutant BDNF allele compared to wild type. We also hypothesized that the perceived pain regression models would account for more of the variance on twelve-month minutes of exercise than the overall positive affect regression models, and that averaged in-task measures for both perceived pain and overall positive affect would have a greater effect on minutes of exercise at 12 months than both subjective measures taken at the endpoint mark (28-30 minutes).

Our hypothesis that the BDNF SNP would moderate the effect of subjective experience on exercise minutes at twelve months was supported by our results for endpoint perceived pain measures and the overall average pain regression model, but not for either measure of overall positive affect. While all four of our regression models followed the pattern of our predictions, only the perceived pain models were statistically significant. Additionally, our prediction that averaged in-task measures of both perceived pain and positive affect would account for more of the variance in minutes of exercise at twelve months than endpoint measures of perceived pain and positive affect was not supported by our data. In fact, we found that the opposite was true for both perceived pain and positive affect models.

We can conclude from our results that the BDNF SNP more significantly moderates measures of perceived pain than measures of positive affect. This indicates that differences in BDNF protein levels in the brain brought on by the single nucleotide polymorphism may not result in a reward mechanism that is associated with increased exercise enjoyment like Hooper et al. (2014) suggest, but instead decreases the negative affect one feels while exercising. This could be particularly true for individuals who are beginning to exercise after being sedentary for an extended period of time. While previously sedentary participants with the mutant BDNF allele may not be enjoying the exercise or experiencing more positive affect than those with the

wild type allele, they may be experiencing less negative affect via lower measurements of perceived pain. This coincides with the lowered rates of perceived exertion observed in mutant BDNF allele-carriers reported by Bryan et al. (2007).

The intrinsically motivating reward mechanism of increased BDNF protein levels in areas of the brain involved in reward processing could possibly manifest itself as positive exercise enjoyment once participants are trained exercisers. This could explain why Petosa and Holtz (2013) suggest that those who enjoy exercise itself and are able to master their exercise skill are more likely to be intrinsically motivated to exercise and are thus more likely to maintain long-term exercise habits. Reed and Ones (2006) have shown however that exercisers who are untrained and are beginning to exercise after long sedentary periods are much less likely to enjoy themselves during the actual exercise period. In fact, mood levels don't improve in physically unfit participants until after they have completed their exercise bout (Reed & Ones, 2006).

While it is more likely that trained exercisers experience positive affect and mood elevations during an exercise bout, our results and the results of Bryan et al. (2007) and Hooper et al. (2014) indicate that the motivation or reward mechanism shown in individuals with the methionine-coding BDNF SNP is more likely to be associated with decreased negative effects in sedentary, unfit participants. It may be that before enjoyment of exercise becomes an individual's primary intrinsic motivator to be physically active, there is a training period that the unfit individual must first overcome. Our results indicate that there is a heritable tendency to more easily overcome that initial hurdle and that a reward and/or motivating mechanism for exercise is more likely present in the mutant allele. We can further support the work of Hooper et al. (2014) and their interpretation that higher exercise-induced BDNF levels from baseline in mutant allele-carriers can possibly override the negative effects that perceived pain have on long-

term exercise outcomes observed in the wild type carriers. Not only do individuals with the mutant BDNF allele experience lower measures of perceived pain both during and at the end of an exercise bout, but levels of perceived pain are also less likely to impede their long-term exercise adherence. In fact, our results indicate that higher levels of pain reported at the end of an exercise session predict greater exercise adherence at twelve months for mutant BDNF allele-carriers.

It is also important to note that for both of our positive affect and perceived pain measures, minutes of exercise at twelve months was better predicted by measures taken at the end of the bout as opposed to those averaged throughout. Kwan and Bryan (2012) have suggested that positive affect increases both during and upon completion of the exercise bout are indicators of long-term exercise maintenance. However, it is possible that this is only true for trained exercisers, while untrained exercisers are more greatly affected by how they feel once they have completed their exercise bout. It is also possible that increased levels of exercise-induced BDNF protein secreted into the neurons of reward-processing centers of the brain that mutant-allele carriers experience are only built-up to clinically significant and effective amounts 30 minutes after the exercise session has begun. This could explain why perceived pain measures averaged throughout a short exercise period of 30 minutes have less of an effect on exercise maintenance than measurements taken at the end of the 30-minute exercise period.

Limitations and Future Directions

One of our study's primary limitations is that in order to avoid overly invasive techniques for measuring BDNF levels in the brain, we are only able to infer the mechanistic difference exhibited between the two genotypes in our sample. While our study uses the work of previous experiments indicating that the BDNF val66met polymorphism results in differential BDNF

protein secretion induced by exercise in the brain in animal models, we are unable to directly detect the timing differentials between BDNF levels experienced throughout and at the end of our study's 30-minute bout (Egan et al., 2003, Erickson et al., 2013, Hopkins et al., 2013, Pilc et al., 2010, Rossi et al., 2006). It is possible that a longer exercise bout conducted with similar measures of subjective experience and long-term exercise maintenance could better indicate if perceived pain felt during the exercise bout can have a more lasting effect due to allotting more time for BDNF protein secretion in the brain during exercise.

It is also possible that we only observed significant results for measures of perceived pain because our measurement technique of positive affect was insufficient. It can be difficult for untrained exercisers to recognize and indicate a positive affect increase because negative effects of exercise such as perceived exertion, pain, and exhaustion override it. Asking participants to identify their own positive affect by way of subjective response (see Appendix A) may be too difficult of a request while the participant is in-task, and they could be unable to differentiate between the positive and negative affect they are experiencing. We suggest that more objective measures of positive affect be considered for measuring the untrained participant's positive exercise experience. These objective measures could be gained by measuring norepinephrine and other catecholamine levels in the blood both in-task and at the end of an exercise session through the administration of an intravenous catheter. Additionally, investigators could use fMRI to detect increased activation of excitatory dopamine receptors in reward centers of the brain upon completion of an exercise bout (Boecker et al., 2008). These and other objective measures of positive exercise experience could provide more sound evidence for an association between increased motivation for exercise adherence and increased exercise enjoyment.

Lastly, while our study originally used objective measures of exercise adherence for the first month, self-report measures were used for the majority of the study and our results were derived from self-report minutes of exercise. Even though our original objective measures seemed to correlate with participant self-report measures, and VO2 Max was significantly correlated with minutes of exercise reported at twelve months, the correlation was only mild. While there are many factors other than frequency of physical activity that contribute to an individual's change in fitness level indicated by VO2 Max, the mild correlation, along with the work of Prince et al. (2008), indicate that participants were most likely over-reporting their minutes of exercise. We can still make sound conclusions regarding minutes of exercise for one group relative to another (valine-coding alleles versus methionine-coding alleles in this case). However, we cannot be sure that our intervention truly resulted in the number of voluntary minutes of exercise that we report.

Conclusions

The brain derived neurotrophic factor val66met single nucleotide polymorphism moderates the effect of perceived pain on long-term exercise adherence. While other studies have indicated a heritable difference in exercise enjoyment expressed through the BDNF methionine-coding allele, our study is able to conclude that the allele also results in reduced negative feelings towards exercise that influence an individual's likelihood for long-term health behavior. This heritable difference stresses the importance for tailored exercise programs upon exercise intervention, particularly because those who experience both higher levels of perceived pain and more of a negative long-term effect of that perceive pain during exercise are the wild type and therefore are also the majority of the population. Our results call for more careful consideration of intensity and duration of exercise prescriptions given to those who have been

sedentary for six months or more, particularly if they carry the valine-coding allele or other genetic pre-dispositions for decreased exercise enjoyment.

It is of paramount importance that we continue to investigate genetic differences in exercise-induced experience across populations. These differences in experience can be subjective (perceived pain, increases or decreases in mood, etc.) or objective (higher increases in body temperature, lactic acid levels, etc.). With a better knowledge of what an individual experiences while they are transitioning from sedentary to being physically active, we will be able to better tailor our exercise programs to individuals. This could in turn not only increase the likelihood of exercise adherence and intervention success, but also create better health outcomes for individuals at risk of inactivity-related diseases such as heart disease, Type II diabetes, and even cancer. Recognizing that there are heritable differences that influence an individual's likelihood to engage in long-term exercise behaviors further justifies the need for a better understanding of the underlying motivational mechanisms for being physically active. This better understanding could allow us to tailor exercise programs to individuals, resulting in more positive long-term health outcomes.

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Table 1

Characteristic	M		Test Statistic	p
	G/G	G/A or A/A		
Age	28.75 (8.10)	27.13 (7.64)	$t(215) = 1.46$	0.251
BMI				
Male	25.14 (4.27)	24.7 (4.27)	$t(40) = .325$	0.9
Female	25.61 (4.99)	24.85 (4.93)	$t(170) = .954$	0.815
Race		N		
n Asian	8	17	$\chi^2(13, N = 217^{**}) = 16.62$	0.011
n Black	7	1		
n Latino or Latina	16	10		
n Native American	4	1		
n White	99	47		
n Multiracial	3	3		
n Other	0	1		
n White	99	47	$\chi^2(1, N = 217^{**}) = 4.19$	0.041
n Non-White	38	33		

Note. G/G = Valine allele, G/A or A/A = Methionine allele, BMI = body mass index, standard deviations (SD) for "age" and "BMI" are in parentheses. Two participants did not report their racial affiliation**

Table 2

<i>Genotype Descriptives Across Time</i>		<i>N</i>
Baseline		219
Participant number by genotype**	G/G	137
	G/A or A/A	80
Month 12		166
Participant number by genotype	G/G	106
	G/A or A/A	60

Note. G/G = Valine allele, G/A or A/A = Methionine allele. Genetic data was not collected for two participants at baseline**

Table 3

Outcome Differences Between Genotype

Outcome	M		Test Statistic	p
	G/G	G/A or A/A		
7-Day Par Minutes of Exercise Reported at Month 12	90.5 (104.85)	80.15 (79.6)	$t(164) = .664$	0.176
Average Positive Affect Reported Throughout Exercise Bout	1.81 (0.823)	1.84 (0.826)	$t(214) = -.263$	0.912
Positive Affect Reported at 28-30 Minutes into Exercise Bout	1.9 (0.923)	1.8 (0.970)	$t(213) = .776$	0.739
Average Perceived Pain Reported Throughout Exercise Bout	1.43 (1.42)	1.07 (0.938)	$t(214) = 2.02$	0.001
Perceived Pain Reported at 28-30 Minutes into Exercise Bout	1.3 (1.57)	1.04 (1.10)	$t(213) = 1.30$	0.009

Note. G/G = Valine allele, G/A or A/A = Methionine allele, standard deviations (*SD*) for outcomes are in parentheses

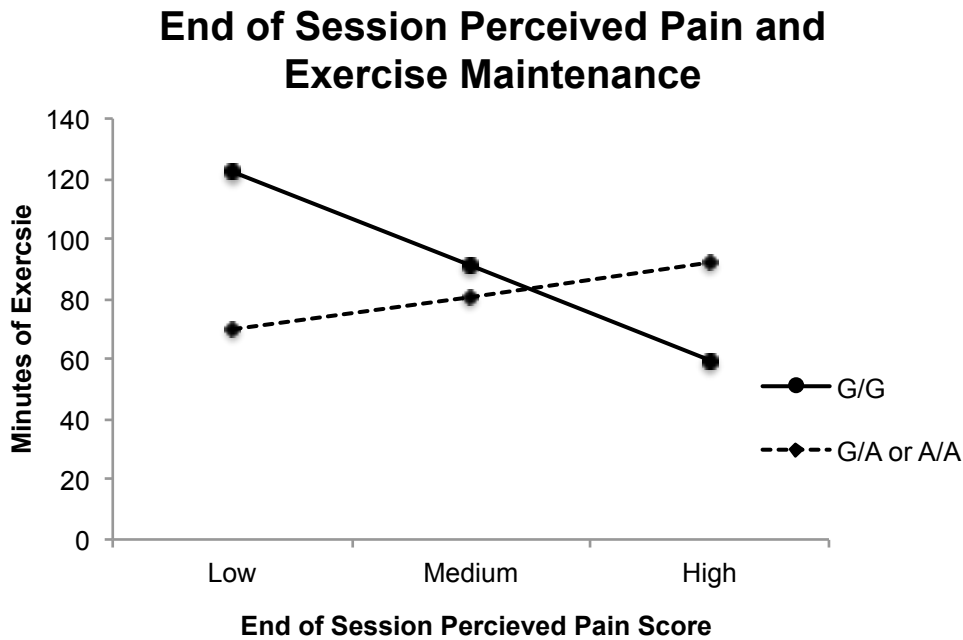


Figure 1. Predicted minutes of exercise as a function of end-of-session perceived pain score and BDNF genotype.

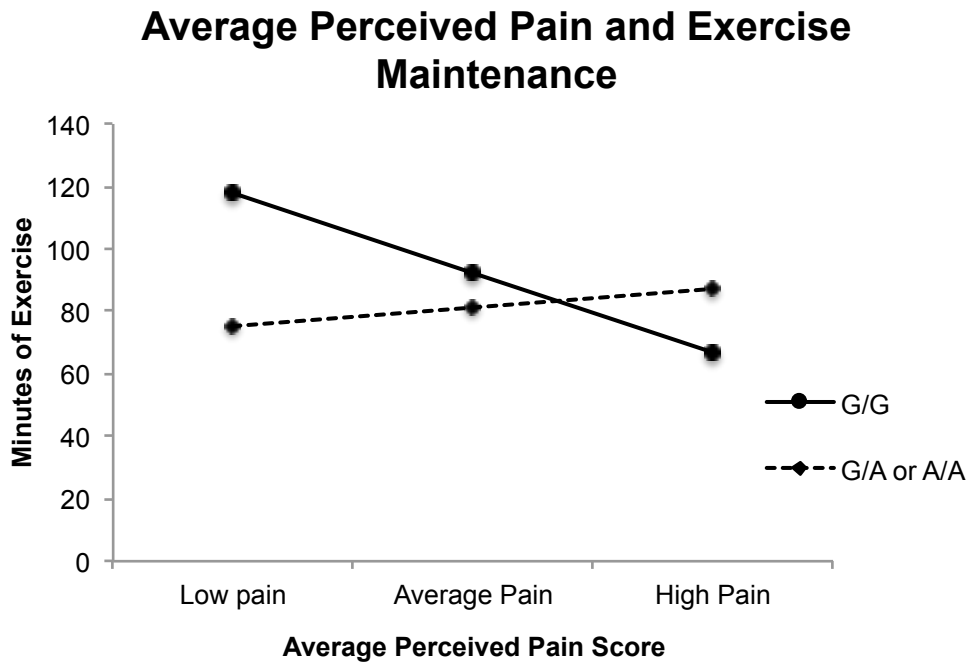


Figure 2. Predicted minutes of exercise as a function of average perceived pain score and BDNF genotype.

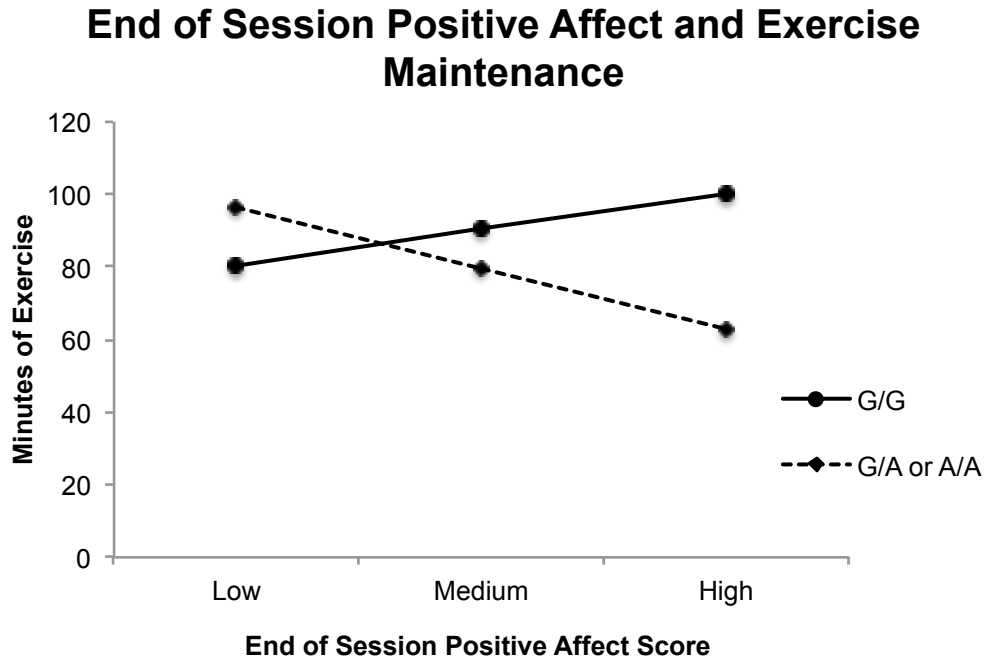


Figure 3. Predicted minutes of exercise as a function of end-of-session positive affect score and BDNF genotype.

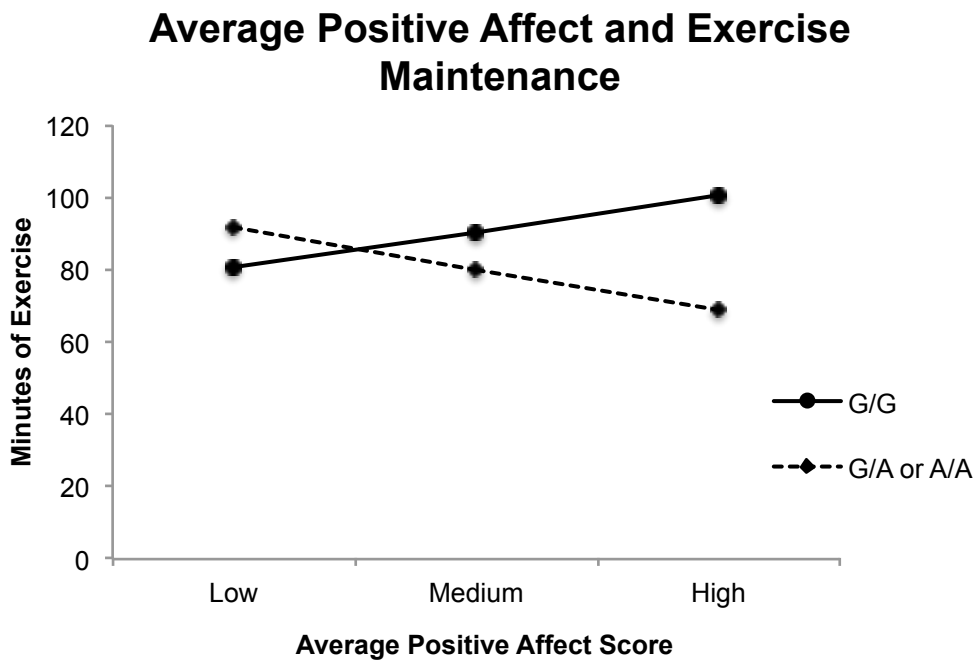


Figure 4. Predicted minutes of exercise as a function of average positive affect score and BDNF genotype.

Appendix A

(PAAS). Please use the following scale to indicate the extent to which each word below describes how you feel at this moment in time. Record your responses by circling the appropriate number.

	Do Not Feel	Feel Slightly	Feel Moderately	Feel Strongly	Feel Very Strongly
1. Enthusiastic	0	1	2	3	4
2. Energetic	0	1	2	3	4
3. Calm	0	1	2	3	4
4. Fatigued	0	1	2	3	4
5. Tired	0	1	2	3	4
6. Relaxed	0	1	2	3	4
7. Miserable	0	1	2	3	4
8. Upbeat	0	1	2	3	4
9. Discouraged	0	1	2	3	4
10. Crummy	0	1	2	3	4
11. Peaceful	0	1	2	3	4
12. Worn-out	0	1	2	3	4