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The influence of high intensity exercise and the Val66Met polymorphism on circulating BDNF and locomotor learning

Erin E. Helm², Kathleen S. Matt⁴, Kenneth F. Kirschner⁴, Ryan T. Pohlig³, Dave Kohl⁵, and Darcy S. Reisman^{1,2}

¹Department of Physical Therapy, University of Delaware, Newark, Delaware

²Biomechanics and Movement Science Program, University of Delaware, Newark Delaware

³Biostatistics Core Facility, University of Delaware, Newark Delaware

⁴College of Health Sciences, University of Delaware, Newark Delaware

⁵Christiana Care, Newark Delaware

Abstract

Brain-derived neurotrophic factor (BDNF) has been directly related to exercise-enhanced motor performance in the neurologically injured animal model; however literature concerning the role of BDNF in the enhancement of motor learning in the human population is limited. Previous studies in healthy subjects have examined the relationship between intensity of an acute bout of exercise, increases in peripheral BDNF and motor learning of a simple isometric upper extremity task. The current study examined the role of high intensity exercise on upregulation of peripheral BDNF levels as well as the role of high intensity exercise in mediation of motor skill performance and retention of a novel locomotor task in neurologically intact adults. In addition, the impact of a single nucleotide polymorphism in the BDNF gene (Val66Met) in moderating the relationship between exercise and motor learning was explored. It was hypothesized that participation in high intensity exercise prior to practicing a novel walking task (split-belt treadmill walking) would elicit increases in peripheral BDNF as well as promote an increased rate and magnitude of within session learning and retention on a second day of exposure to the walking task. Within session learning and retention would be moderated by the presence or absence of Val66Met polymorphism. Fifty-four neurologically intact participants participated in two sessions of split-belt treadmill walking. Step length and limb phase were measured to assess learning of spatial and temporal parameters of walking. Serum BDNF was collected prior to and immediately following either high intensity exercise or 5 minutes of quiet rest. The results demonstrated that high intensity exercise provides limited additional benefit to learning of a novel locomotor pattern in neurologically intact adults, despite increases in circulating BDNF. In addition, presence of a

Corresponding author: Darcy Reisman, PT, PhD, University of Delaware, 540 South College Ave, Newark, DE 19713, PH: 302-831-0508, FAX: 302-831-4291, dreisman@udel.edu.

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single nucleotide polymorphism on the BDNF gene did not moderate the magnitude of serum BDNF increases with high intensity exercise, nor did it moderate the relationship between high intensity exercise and locomotor learning.

Keywords

Brain-derived neurotrophic factor; Val66Met polymorphism; Locomotor learning; Motor Learning; Split-belt treadmill

1. Introduction

Animal models suggest that exercise may promote a nurturing environment for the formation of functionally appropriate synaptic connections during learning (Black, Isaacs, Anderson, Alcantara, & Greenough, 1990; Cotman, Berchtold, & Christie, 2007; Klintsova, Dickson, Yoshida, & Greenough, 2004; Xu et al., 2009). Through upregulation of molecular mediators of neural plasticity, exercise strengthens synaptic transmission, thus “priming” the nervous system for encoding of pertinent information (Cotman et al., 2007; Intlekofer et al., 2013; Ploughman et al., 2007). Experiments within animal models corroborate the molecular influences of exercise on enhanced cognitive and motor performance and learning and indicate brain derived neurotrophic factor (BDNF) as a key mediator of these enhancements (Griesbach, Hovda, & Gomez-Pinilla, 2009; Intlekofer et al., 2013; Klintsova et al., 2004; Vaynman, Ying, & Gomez-Pinilla, 2004; Ying et al., 2008).

Brain derived neurotrophic factor has been identified as a requisite for induction of neural plasticity with motor learning and has been evidenced to mediate functional recovery following neurologic insult in the animal model (Ploughman et al., 2009; Wolf-Rüdiger Schäbitz et al., 2007; W-R Schäbitz et al., 2004). In addition, animal models have shown that BDNF mediates the beneficial effects of exercise in facilitation of spatial learning (Intlekofer et al., 2013) and recovery of motor skill function (Griesbach et al., 2009; Ploughman et al., 2007, 2009; Ying et al., 2008). Blockade of BDNF mRNA, via an antisense BDNF oligonucleotide, negates the ability of exercise and rehabilitation to upregulate BDNF gene expression as well as limit recovery of skilled reaching with rehabilitation in the ischemic animal (Ploughman et al., 2009).

In humans, aerobic and anaerobic exercise are thought to promote increases in systemic BDNF (Ferris, Williams, & Shen, 2007; Knaepen, Goekint, Heyman, & Meeusen, 2010; Rojas Vega et al., 2006; Skriver et al., 2014; Winter et al., 2007). However, direct causal evidence of BDNF's moderating role in the relationship between exercise and learning, demonstrated in the animal literature, has not been demonstrated in humans. Converging evidence has linked exercise with improved cognitive function in healthy individuals as well as those post stroke (Colcombe & Kramer, 2003; Kluding, Tseng, & Billinger, 2011; Quaney et al., 2009; Rand, Eng, Liu-Ambrose, & Tawashy, 2010; Winter et al., 2007). Evidence citing the effects of aerobic exercise on *motor* learning, however, is sparse in comparison to studies of cognitive performance and learning (Roig, Skriver, Lundbye-Jensen, Kiens, & Nielsen, 2012; Skriver et al., 2014; Statton, Encarnacion, Celnik, & Bastian, 2015).

Roughly thirty percent of humans (Shimizu, Hashimoto, & Iyo, 2004) possess a single nucleotide polymorphism (SNP) on the BDNF gene (Val66Met) (Egan et al., 2003). This polymorphism has been linked to decreased activity dependent release (Chen et al., 2004; Egan et al., 2003) of BDNF within the animal model. In healthy humans, presence of the polymorphism has been associated with altered cortical activation and short term plasticity (Beste et al., 2010; Cheeran et al., 2008; McHughen et al., 2010) as well as altered skill acquisition and learning (Beste et al., 2010; Joundi et al., 2012; Kleim et al., 2006; McHughen et al., 2010). In addition, presence of the polymorphism has recently been shown to influence the rate of motor learning in individuals post-stroke (Helm, Tyrell, Pohlig, Brady, & Reisman, 2015). It is currently unknown whether presence of the Val66Met polymorphism would attenuate release of BDNF in response to exercise in humans and if this attenuation would impact motor learning.

Although theorized to moderate the influence of exercise on learning in humans, no studies have concurrently assessed the relationship between exercise induced changes in BDNF, the BDNF Val66Met polymorphism and motor learning. In the current study we utilized the split-belt treadmill paradigm (Reisman, Bastian, & Morton, 2010; Reisman, Block, & Bastian, 2005; Reisman, McLean, Keller, Danks, & Bastian, 2013; Reisman, Wityk, Silver, & Bastian, 2007) to examine the role of BDNF in mediating within session learning and retention of a novel locomotor task following high intensity exercise. We hypothesized that participation in a single session of high intensity upper extremity cycling would elicit increases in peripheral BDNF levels relative to quiet rest. In addition, we hypothesized that high intensity exercise prior to a novel walking task (split-belt treadmill walking) would enhance the rate and magnitude of within-session learning as well as retention on a second day of exposure to split-belt walking. We postulated the benefits of high intensity exercise on motor learning would be greater for subjects without the Val66Met polymorphism.

2. Materials and Methods

2.1 Participants

Neurologically intact subjects between the ages of 21 and 35 were recruited as a sample of convenience for participation. All subjects provided written informed consent, with the study protocol approved by the University of Delaware Human Subjects Review Board. To be included, subjects must have demonstrated the ability to walk without assistance and without assistive devices, the ability to understand spoken instruction and communicate with investigators, a resting heart rate between 40–100 beats per minute and a resting blood pressure between 90/60 to 170/90. In addition, to be included participants provided written informed consent to supply a saliva sample for genetic testing for the BDNF Val66Met polymorphism. Exclusion criteria included any neurologic condition, intermittent claudication, total joint replacement and orthopedic problems in the lower limbs or spine that limited walking.

2.2 Instrumentation and Procedures

Subjects were randomly assigned to an Exercise + Learning or Learning condition. Subjects assigned to the Exercise + Learning condition participated in a short bout of high intensity

exercise on an upper body ergometer (UBE) (SCIFIT Systems, Inc., Tulsa, OK) prior to split-belt walking on Day 1. The high intensity exercise consisted of pedaling for 1 minute with high resistance immediately followed by 1 minute with resistance decreased by half, at speeds sufficient to achieve 80% of the subject's age predicted heart rate maximum. Subjects were provided a timed 1-minute rest break, and then repeated the upper-body cycling protocol. Subjects in the Learning group were asked to quietly rest for 5 minutes prior to treadmill walking to account for time differences between groups (Figure 1).

All subjects participated in two sessions of split-belt treadmill walking on two consecutive days. Prior to split-belt treadmill walking on Day 1 subjects were asked to walk on the treadmill with the belts tied at a 1:1 ratio at 0.5 m/s for 2 minutes in order to assess baseline step and limb phase symmetry. All subjects then participated in split-belt treadmill walking for 15 minutes, consisting of walking at a constant 3:1 speed ratio of 1.5:0.5 m/s. Subjects walked with this speed ratio throughout the entire session (Figure 1). Subjects returned for a second day of split-belt walking at the same 3:1 ratio for 15 minutes. Subjects did not participate in acute exercise or treadmill walking with the belts "tied" prior to the split-belt walking session on Day 2.

All participants walked on a split-belt treadmill instrumented with two independent six degree of freedom force platforms (Bertec, Columbus, OH) from which ground reaction force data was continuously collected at 1000Hz. Kinematic data was continuously collected using an 8-camera Vicon Motion Capture System (Vicon MX, Los Angeles, CA) at 100Hz. Retro-reflective markers (14-mm diameter) secured to rigid plastic shells were placed on the pelvis, bilateral thighs and bilateral shanks. Single markers were placed on the most prominent superior portion of the bilateral iliac crests, greater trochanters, medial and lateral knee joint lines, medial and lateral malleoli, bilateral heels, and the first and fifth metatarsal heads. During walking all subjects were instructed to gently rest fingertips on the treadmill handrail, and were given verbal cues, as necessary, to avoid excessive use of the handrail while walking.

All subjects wore a safety harness around their chest for fall prevention; however, the harness did not provide body weight support. Blood pressure, heart rate and rating of perceived exertion (RPE) (Borg, 1982) were monitored throughout the treadmill walking sessions.

2.2.1 Genotyping—Each subject provided a 2 mL saliva sample in a DNA Self-Collection Kit (DNA Genotek, Kanata, Canada) containing a DNA stabilizing buffer. The samples were sent to DNA Genotek (GenoFIND Services, Salt Lake City, UT) for processing. Genotek created a set of primers to amplify the region surrounding the SNP (Val66Met: rs6265) of the BDNF gene and then examined the sample for the presence (METs) or absence (VALs) of the Val66Met polymorphism. Extracted DNA results of genotyping were sent to the primary investigator with remaining saliva samples destroyed following analysis. Experimenters collecting the serum and behavioral data were blind to the Val66Met phenotype of the subject.

2.2.2 Serum BDNF and lactate collection—On Day 1, all subjects were asked to provide four blood samples to obtain levels of serum BDNF and lactate at specific time points throughout the session (Figure 1). To obtain blood samples, a venous catheter (IV) was inserted in the subject's arm prior to any activity by a registered nurse experienced in IV placement. Immediately before the intense exercise for subjects in the Exercise+Learning group or before 5 minutes of quiet sitting for subjects in the Learning group, a 7mL blood sample was collected to determine baseline levels of the above defined variables. A second and third 7mL sample was obtained immediately following the intense exercise or quiet sitting and immediately following treadmill walking. A final 7 mL sample was obtained 15 minutes after the end of treadmill walking. Serum samples were allowed to clot for 30 minutes at room temperature and then centrifuged at 3,000 rpm for 15 minutes. Samples were then divided into several aliquots in microcentrifuge tubes designated for lactate and serum BDNF and stored at -80°C until assayed.

Serum samples were analyzed for levels of circulating BDNF utilizing commercially available Enzyme Linked Immunosorbent Assay (ELISA) kits. To detect BDNF levels in serum across time points a Human BDNF Quantikine ELISA kit was utilized (R&D Systems; Minneapolis, MN). Utilizing the manufacturer's protocol, intra assay and inter assay coefficients of variation were 5.4% and 7.3% respectively.

To verify intensity of exercise, lactate levels were assessed utilizing a commercially available analysis kit (Lactate Colorimetric Assay Kit II, Bio Vision Incorporated, Milpitas, CA). Analysis was completed following the protocol established by the manufacturer (BioVision Incorporated). Optical density values derived from the microplate reader for serum samples were subtracted from a 0 lactate sample control. The levels of lactate present in each sample were determined through the use of a standard curve generated with the assay by measuring the optical density of a series of known concentrations of lactate. The experimenter analyzing the serum data was blinded to Val66Met phenotype and exercise condition.

2.3 Data Analysis

All kinematic and kinetic data were exported from Vicon-Nexus software, and further processed using Visual 3D (C-Motion, Inc, Germantown) and Matlab (MathWorks, Natick, MA). Gait events of foot strike and lift off were determined for each limb individually using an automatic algorithm in Visual 3D. Foot strike was identified when the vertical ground reaction force exceeded 20 Newtons for at least 8 frames, and lift-off identified when the vertical ground reaction force dropped below 20 Newtons for at least 8 frames. All gait events were visually checked for accuracy.

2.3.1 Dependent variables

High Intensity Exercise and Serum BDNF: To evaluate the influence of high intensity exercise on peripheral BDNF and lactate we quantified the *Magnitude Change in BDNF* and the *Magnitude Change in Lactate* by subtracting the baseline concentration of BDNF and lactate from the concentration post-exercise (or quiet rest).

Spatial and Temporal parameters of Gait: Spatial and temporal parameters of gait have been found to respond differently during split-belt walking (Malone & Bastian, 2010; Malone, Vasudevan, & Bastian, 2011; Tyrell, Helm, & Reisman, 2014). Therefore, both spatial (step length) and temporal (limb phasing) variables were evaluated. Both variables were calculated for each leg continuously throughout treadmill walking. The spatiotemporal measure of step length was calculated as the sagittal distance between the right and left heel markers at foot strike. Step length was labeled as Left or Right based on leading leg. Stride by stride symmetry data for step length was calculated as:

$$\frac{(\text{StepLength of Leg on Slow Belt} - \text{SymmetricalStepLength})}{\text{SymmetricalStepLength}}$$

Where symmetrical step length = (Left step length + Right step length)/2 (Tyrell et al., 2014; Tyrell, Helm, & Reisman, 2015).

Based on the above calculations, a value of 0 would indicate that the subject has achieved perfect symmetry based on their individual stride length. A negative value denotes the leg on the slow belt has a decreased step length relative to perfect symmetry. This method is preferred over the calculation of a ratio (Leg on Slow Belt/Leg on Fast Belt) because it prevents extremely large values when the denominator of the ratio is small due to a “step to” gait pattern in which one leg does not pass the other leg (Patterson, Gage, Brooks, Black, & McIlroy, 2010).

The temporal measure of limb phasing was calculated as previously reported (Helm et al., 2015; Tyrell et al., 2014, 2015). Briefly, a calculation of limb phase for each leg provides a measure of the difference in time between the contralateral limb’s peak flexion and the ipsilateral limb’s peak extension, normalized by the ipsilateral limb’s stride duration. Stride-by-stride limb phase symmetry was calculated by dividing the limb phase value for the leg on the slow belt by the contralateral limb phase value.

The split-belt treadmill paradigm has previously been well-characterized as a tool to probe short-term locomotor learning in neurologically intact and individuals post-stroke (Reisman et al., 2010, 2005, 2013, 2007). Splitting the treadmill belts in a 2: 1 or 3:1 ratio elicits an asymmetry in subject’s locomotor pattern and requires subjects to utilize trial and error practice to return to their baseline walking pattern. The rate and magnitude of reduction of this asymmetry within-session, as well as across sessions has previously been utilized to explore differences in locomotor learning in various populations (Helm et al., 2015; Morton & Bastian, 2006; Reisman et al., 2010; Tyrell et al., 2014).

For both step length and limb phasing, each symmetry value was calculated to reflect deviation from an individual’s baseline (a)symmetry pattern. This was performed by subtracting the average of the last 30 strides of the baseline condition from each raw symmetry value (Tyrell et al., 2014, 2015; Vasudevan, Torres-Oviedo, Morton, Yang, & Bastian, 2011). Subtraction of the baseline symmetry pattern from each raw symmetry value allows for comparison of data across subjects who may demonstrate different levels of baseline (a)symmetry. A value of 0 therefore reflects a pattern identical to baseline

(a)symmetry. In order to account for individual differences in the initial (a)symmetry at the start of split-belt walking, individual stride data was normalized by initial perturbation (Helm et al., 2015; Vasudevan et al., 2011). Normalization was achieved by dividing each symmetry value by the initial perturbation value, where initial perturbation was defined as the average of the first 3 strides during adaptation (Vasudevan et al., 2011). This normalization allows individual subject data to be scaled to a proportion of the initial perturbation (Vasudevan et al., 2011). Changes in both step length and limb phasing (a)symmetry during the Adaptation period on Day 1 were determined to examine within session learning. Differences in the changes in step length and limb phasing (a)symmetry during the Adaptation periods of Day 1 and Day 2 were determined to examine retention of learning.

To evaluate differences between subjects participating in high intensity exercise or quiet rest prior to split-belt walking and the potential interaction of exercise and the presence of the Val66Met polymorphism, we examined locomotor adaptation in those with, METs, and without, VALs.

2.4 Statistical Analysis

Normality of the data distributions were assessed with the Kolmogorov-Smirnov test for normality. All statistical analyses were completed with SPSS v22 and performed for both step length and limb phasing symmetry. When normality assumptions were not met, Mann-Whitney U, Wilcoxin-Signed Ranks Assessment test or Kruskal-Wallis analysis of ranks were utilized instead of an Analysis of Variance (ANOVA).

To test our hypothesis that participation in a single session of high intensity cycling would elicit increases in peripheral BDNF and lactate levels relative to quiet rest, group differences (Exercise + Learning vs. Learning) in the magnitude change for both serum BDNF and lactate were assessed utilizing the Kruskal-Wallis analysis of ranks.

2.4.1 Within session learning—We hypothesized that subjects participating in high intensity exercise prior to split-belt walking would demonstrate an increased amount of total adaptation during within session learning and a faster adjustment of their initial asymmetry, in comparison to subjects who did not participate in exercise immediately prior to split belt walking and that this effect would be greater in METs, those without the polymorphism. To test this hypothesis, a 2×2 ANOVA was utilized to compare the mean differences between exercise groups, Exercise + Learning vs. Learning, and between polymorphism groups, VALs vs. METs. The interaction between the presence or absence of the polymorphism and the effects of high intensity exercise were assessed through analysis of the interaction effect within the two-way ANOVA.

2.4.2 Retention—We hypothesized that following one day of practice (on Day 2), subjects in the Exercise + Learning condition would demonstrate an increased magnitude of retention of the split-belt walking pattern and a more rapid adjustment of their (a)symmetry relative to Day 1 (more rapid rate of relearning) compared to subjects in the Learning condition and that this effect would be greater for VALs. The interaction between the presence or absence

of the polymorphism and the effects of high intensity exercise were assessed through analysis of the interaction effect within the two-way ANOVA.

3. Results

A total of fifty-four subjects participated in the study with twenty-seven participants each in both the Exercise + Learning (24.51 $\pm$ 2.83 years) and Learning (23.88 $\pm$ 2.40 years) conditions. Within the Exercise + Learning condition, 16 subjects were METs, those identified to have the Val66Met polymorphism, while 11 subjects did not, VALs. Within the Learning condition, 10 subjects were identified in the MET group, and 17 subjects in the VAL group.

3.1 High Intensity Exercise and Serum BDNF

Serum BDNF and lactate levels for subjects participating in high intensity upper extremity cycling (Exercise + Learning) versus quiet rest (Learning) prior to split belt walking on Day 1 are shown in Figure 2 A and B. Secondary to technical issues, lactate was assessed in a total of 27 subjects in the Exercise + Learning and 22 subjects in the Learning group. Subjects in the Exercise + Learning group demonstrated a significant increase in peripheral serum BDNF levels compared to those in the Learning group (Exercise + Learning PRE = 24.54 $\pm$ 12.23, POST = 31.71 $\pm$ 8.07; Learning PRE = 28.75 $\pm$ 10.54, POST = 28.21 $\pm$ 9.58; $p < 0.001$). This was also true for lactate ($p < 0.001$). Subjects with (MET) and without (VAL) the polymorphism participating in exercise prior to split-belt treadmill walking demonstrated similar increases in serum BDNF from pre to post exercise (MET PRE = 23.68 $\pm$ 6.88, POST = 31.22 $\pm$ 11.59; VAL PRE = 25.63 $\pm$ 9.41, POST = 32.06 $\pm$ 11.94; $p = .577$; Figure 2C.).

3.2 Within session learning

Figure 3 illustrates the pattern of changes in step length asymmetry with exposure to the split-belt treadmill for subjects in the Exercise + Learning and Learning groups. At “baseline”, with both treadmill belts set to the same speed, subjects in both groups demonstrate a walking pattern near perfect symmetry (ratio = 0). With initial exposure to the 3:1 split belt speed ratio, participants demonstrate a large step length asymmetry. Utilizing trial and error practice, participants reduce this asymmetry to return to a walking pattern similar to baseline walking. This pattern of adaptation was similar for subjects participating in high intensity exercise prior to split belt walking (Exercise + Learning) and those participating in quiet rest prior to split belt walking (Learning) and was similar to previous studies utilizing the split-belt treadmill (Malone et al., 2011; Reisman et al., 2005).

This qualitative pattern is confirmed through analysis of the group data for both step length and limb phase (a)symmetry. The mean of the first 10 strides of the adaptation period - the mean of the last 10 strides of the adaptation period (Total Adaptation in Table 1) on Day 1 does not differ significantly for those participating in high intensity exercise prior to split belt walking vs. quiet rest (Exercise + Learning vs. Learning) nor does it differ for those with and without the polymorphism (VAL vs. MET) for step length or limb phase (Table 1; all p 's > 0.05). The interaction between exercise condition and presence vs. absence of the polymorphism was also non-significant (all p 's > 0.05). Similarly, there was no difference

between groups in the amount of (a)symmetry at the end of adaptation (mean of the last 10 strides of the adaptation period) relative to baseline (Return to Baseline in Table 1) for step length or limb phase (a)symmetry (Table 1; all p 's > 0.05). The interaction between exercise condition and presence vs. absence of the polymorphism for this measure was also non-significant for both step length and limb phase (a)symmetry (Table 1; all p 's > 0.05).

To quantify the ability to rapidly reduce the amount of asymmetry initially produced on the split belt treadmill, we calculated the difference between the first and last 3 strides within early adaptation (early adaptation = first 30 strides of the adaptation period). This difference was then divided by the first 3 strides to provide a percent change (Percent Change of Early Asymmetry in Table 1). This percent change on Day 1 was not significantly different between subjects participating in high intensity exercise prior to split belt treadmill walking versus subjects participating in quiet rest (Exercise + Learning vs. Learning), nor did it differ significantly for those with and without the polymorphism (VAL vs. MET) (Table 1; all p 's > 0.05). The interaction of exercise condition and presence vs. absence of the polymorphism for this percent change was also non-significant for step length and limb phase (a)symmetry (Table 1; all $p > 0.05$).

3.3 Retention

On a second day of practice, subjects in both exercise conditions (Exercise + Learning vs. Learning) participated in split belt walking at a 3:1 speed ratio. If participants learned something about how to walk on the split-belt treadmill, one would expect subjects to demonstrate a faster rate of re-adaptation and/or decreased magnitude of initial asymmetry upon re-exposure to the split-belt paradigm (Malone et al., 2011; Tyrell et al., 2014). Subjects in both the Exercise + Learning and Learning groups, with and without the Val66Met polymorphism demonstrated a reduction in the initial step length and limb phase asymmetry upon re-exposure to the split-belt treadmill on Day 2 (all p 's < 0.05). The magnitude of this reduction in early asymmetry (average of the first 10 strides in the adaptation period) from Day 1 to Day 2 did not differ between exercise conditions (Exercise + Learning) or polymorphism status (VAL vs. MET) for step and limb phase (a)symmetry, (Fig 4A and B; all p 's > 0.05 for all). The interaction of exercise condition and presence vs. absence of the polymorphism for this measure was also non-significant for step length ($p=0.475$) and limb phase (a)symmetry ($p=0.190$).

Subjects in both the Exercise + Learning and Learning groups demonstrated a faster rate of relearning on Day 2 as shown by significant differences in the Percent Change in Early Asymmetry from Day 1 to Day 2. With re-exposure to the split-belt paradigm on Day 2, subjects in both the Exercise + Learning and Learning groups, with and without the polymorphism, demonstrated a faster reduction in their initial asymmetry relative to Day 1 (all $p < 0.05$; Figure 5). While the amount of this change from Day 1 to Day 2, did not significantly differ between groups (Exercise + Learning vs. Learning), there was a trend toward an interaction between exercise condition and presence vs. absence of the polymorphism on the rate of relearning (Figure 5; step length ($p=0.165$) and limb phase (a)symmetry ($p=0.164$)).

4. Discussion

While studies of cognitive and motor learning have assessed the relationship between high intensity exercise, peripheral serum BDNF, and cognitive and motor learning (Skriver, Roig et al. 2014, Etnier, Wideman et al. 2016, Hotting, Schickert et al. 2016), to our knowledge, this is the first study to also include the BDNF Val66Met polymorphism. There are several novel findings of this study that can advance our understanding of the role of exercise and BDNF in motor learning. First, the results demonstrate that although high intensity exercise prior to a motor learning task results in an increase of peripheral serum BDNF, this exercise does not appear to provide significant additional benefit to learning of the novel locomotor pattern in neurologically intact adults. The results also demonstrate that presence of a single nucleotide polymorphism on the BDNF gene (Val66Met) does not influence the magnitude of upregulation of peripheral serum BDNF with high intensity exercise, nor does it interfere with learning of a novel locomotor pattern in neurologically intact subjects.

Similar to previous evidence in humans (Ferris et al., 2007; Knaepen et al., 2010; Rojas Vega et al., 2006; Winter et al., 2007), we found that a short bout of high intensity upper extremity cycling elicited a significant increase in serum BDNF relative to quiet rest. Surprisingly however, the magnitude of this increase did not differ between subjects with and without the Val66Met polymorphism. Previous evidence in the animal model indicates that presence of a gene mutation in the prodomain of BDNF results in decreased activity dependent secretion of the BDNF protein within neuronal cell populations (Chen et al., 2004; Egan et al., 2003). This has led many to suggest that the presence of the Val66Met polymorphism results in decreased secretion of activity dependent BDNF in the human (Mang, Campbell, Ross, & Boyd, 2013). Our results showing that the increase in serum BDNF with exercise was similar in those with and without the polymorphism, does not directly refute this hypothesis. Rather, it may simply be that serum BDNF, which reflects peripheral, circulating BDNF, does not provide an adequate reflection of BDNF within the central nervous system. Indeed, in the animal model described above, while the animals with the gene mutation show decreased activity dependent secretion of the BDNF protein within neuronal cell populations, this was not observed in endothelial or smooth muscle cell populations (Chen et al., 2004). This indicates that, in animals, the effects of the polymorphism may be isolated to the central nervous system. Our measures of serum BDNF suggest this may also be the case in humans. A lack of moderation in serum BDNF by the Val66Met polymorphism noted in the current study indicates that systemic increases in BDNF do not necessarily reflect central neural processes, as often hypothesized (Knaepen et al., 2010; Winter et al., 2007). As such, the utilization of serum BDNF as supplementary marker of intervention efficacy on cognitive and motor function should be approached with caution.

Our results suggest that high intensity exercise did not provide a significant additional benefit to learning of a novel locomotor pattern, conflicting with the results of previous studies examining the effects of exercise on motor learning in neurologically intact adults (Roig et al., 2012; Skriver et al., 2014; Statton et al., 2015). While non-significant, there were trends toward differences between the groups (Figure 5). It is possible that the weaker effects in the current study were related to the motor learning task examined. Previous

studies have examined the role of high intensity aerobic exercise on visuomotor accuracy in a variety of upper extremity tasks, demonstrating improvements in both acquisition (Mang, Snow, Campbell, Ross, & Boyd, 2014; Snow et al., 2016) and retention (Roig et al., 2012; Skriver et al., 2014; Statton et al., 2015). As eloquently stated by Snow (2016), “... exercise effects on motor behavior are not universal, and may be task-dependent, and/or reliant on the outcome measure used to assess motor performance (Snow et al., 2016).” Within the aforementioned studies each utilized a simple upper extremity learning task (Roig et al., 2012; Skriver et al., 2014; Statton et al., 2015). In the present study we examined a complex, whole body task requiring the coordination of both lower extremities to facilitate a new walking pattern. Given the differences in the neural control of the upper extremity and locomotion, it is plausible that the benefits of high intensity exercise for motor learning observed in simpler, upper extremity tasks may not generalize to locomotion. Another important difference between previous studies and the present study, is that here subjects were asked to learn a modification of a well-learned task (walking) as opposed to learning a task *de novo*. It is possible that there are more limited effects of exercise in this type of learning paradigm. It is also possible that greater effects on learning would have been observed at a time point more distant from practice. Recent studies in humans have found that the effects of a short bout of high intensity exercise on retention are present at 24 hours, but are greatest 7 days later (Thomas, Beck et al. 2016, Thomas, Johnsen et al. 2016). Finally, it is possible that the amount of time that the subjects exercised at high intensity could have limited the impact of exercise on learning. In previous studies, 3 bouts of 3 minutes of high intensity exercise on an exercise bike interspersed with 2 minutes of low intensity cycling were completed (Roig, Skriver et al. 2012, Skriver, Roig et al. 2014). The choice for a reduced high intensity exercise time in the present study was a practical one. Because our motor learning task involved treadmill walking, we wanted the high intensity exercise to avoid use of the legs. This resulted in our decision to use of the upper body ergometer for cycling. Our initial pilot testing of the protocol used in previous studies revealed that subjects could not tolerate this exercise protocol with the upper extremities. Thus, we modified the protocol to one that subjects could complete, resulting in the protocol described. It is possible that this reduced time of high intensity exercise could be a factor in the differing results compared to previous studies (Roig, Skriver et al. 2012, Skriver, Roig et al. 2014).

In a previous study by our group (Helm et al., 2015) we demonstrated that the Val66Met polymorphism impacts the rate of locomotor adaptation in subjects with chronic stroke, while in the current study, a main effect of polymorphism was not found in neurologically intact individuals. It is plausible that increases in BDNF in healthy, neurologically intact individuals, do not confer additional benefit to learning for our task, while in a population with a neurologic deficit, the influence of altered secretion of BDNF and/or the influence of the Val66Met polymorphism is more evident. The trends toward an interaction between exercise condition and the BDNF polymorphism on retention also leave open the possibility that the effects of exercise and/or the polymorphism are just quite small in a young, neurologically intact population. This is supported by the small effect sizes observed for the interaction (partial Eta squared = 0.012)

5. Conclusions

The goal of this study was to examine the relationship between high intensity exercise, peripheral BDNF, and locomotor learning. The current study also explored the influence of the BDNF Val66Met polymorphism in regulation of serum BDNF and locomotor learning in neurologically intact adults. The results of this study demonstrate that presence of a single nucleotide polymorphism on the BDNF gene (Val66Met) does not influence the magnitude of upregulation of serum BDNF with high intensity exercise, nor does it interfere significantly with learning of a novel locomotor pattern. In addition, the current results demonstrate that although high intensity exercise prior to a motor learning task resulted in increased peripheral BDNF, this exercise did not provide the substantial additional benefit to learning of a novel locomotor pattern that has been observed in previous studies of motor learning tasks performed with the upper extremity. These current findings suggest caution when interpreting peripheral BDNF levels as a marker of neural processes. The results also, however, may highlight the importance of task and neurologic status. It is possible that the influence of exercise and BDNF, although eliciting physiologic changes, was not captured behaviorally in a young, neurologically intact population during a locomotor learning task. Assessment of the effect of exercise on locomotor learning in those with neurologic deficit is warranted, as the current findings may be the result of the population tested, limiting the detection of a “priming” effect on locomotor learning.

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- High intensity exercise results in an increase of peripheral serum BDNF.
- Exercise does not provide increased learning of a novel locomotor pattern.
- Presence of the Val66Met polymorphism does not influence peripheral serum BDNF.
- Presence of the Val66Met polymorphism does not interfere with locomotor learning.

Fig. 1.
Experimental Protocol.

Fig. 2.

Magnitude change in peripheral serum BDNF (A) and Lactate (B) following high intensity upper extremity cycling (black) versus quiet sitting (gray). Data represents group averages. The magnitude change in peripheral serum BDNF following high intensity upper extremity cycling for those with (MET) (Gray) and without (VAL) (Black) the Val66Met BDNF polymorphism (C). Error bars = standard error. * $p=.000$; ** $p=.000$

Fig. 3.

Adaptation to Step Length Asymmetry. Group averaged stride by stride data for step length (a)symmetry during tied belt walking at a 1:1 speed ratio (Baseline) and during split belt walking (Adaptation) for Exercise + Learning (Black) and Learning (Gray) conditions on Day 1. The start of split-belt walking on Day 1 is depicted by double hash marks along the horizontal axis. A value of “0” represents perfect symmetry. Error bars = standard error.

Fig. 4. Reduction in early asymmetry between Day 1 and Day 2 for step length (**A**) and limb phase (**B**). A larger value indicates there was a greater reduction in early asymmetry on Day 2, suggesting greater retention. Error bars = standard error.

Fig. 5.

Magnitude of Percent Change for step length (A) and limb phase (B) for subjects participating in high intensity exercise (Black) or quiet rest (Gray) prior to split-belt walking on Day 1. A larger value indicates a greater rate of change of asymmetry (rate of relearning) on Day 2 relative to Day 1. Error bars= standard error.

Table 1

Within session learning variables for step length and limb phasing. Average and standard deviation for: *Total Adaptation* (average of first 10 symmetry values - last 10 symmetry values); *Return to Baseline* (average of last 10 symmetry values - baseline symmetry values); *Percent Change of Early Asymmetry* (average of initial 3 strides – last 3 strides of Early Adaptation/initial 3 strides).

STEP SYMMETRY							
	All Subjects		VAL		MET		
	Exercise + Learning	Learning	Exercise + Learning	Learning	Exercise + Learning	Learning	Learning
Total Adaptation	0.93±.29	0.81±.22	1.01±.29	0.85±.24	0.87±.29	0.74±.19	
Return to Baseline	-0.02±.21	-0.02±.20	-0.07±.23	-0.04±.22	0.00±.20	0.00±.17	
Percent Change of Early Asymmetry	49.29±26.2	53.07±24.4	39.60±36.9	54.25±27.9	55.95±12.9	51.06±18.3	
LIMB PHASE SYMMETRY							
	All Subjects		VAL		MET		
	Exercise + Learning	Learning	Exercise + Learning	Learning	Exercise + Learning	Learning	Learning
Total Adaptation	0.71±.32	0.69±0.40	0.63±.44	0.74±.09	0.77±.19	0.62±.63	
Return to Baseline	0.06±.30	0.10±.30	0.13±.40	0.09±0.23	0.02±.20	0.10±.41	
Percent Change of Early Asymmetry	18.24±11.9	16.69±14.8	20.0±13.8	19.39±15.6	17.32±10.8	12.19±12.8	