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Role of Brain Derived Neurotrophic Factor (BDNF) In Stimulating Strength Improvements Induced by Short-Term Resistance Training

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ROLE OF BRAIN DERIVED NEUROTROPHIC FACTOR (BDNF) IN STIMULATING STRENGTH IMPROVEMENTS INDUCED BY SHORT-TERM RESISTANCE TRAINING

by

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ABSTRACT

Strength adaptations from short-term resistance training are thought to be related primarily to neurological adaptations. Considering brain-derived neurotrophic factor (BDNF) role in the nervous system, it is possible that BDNF has a role in these adaptations. Fourteen untrained males were randomized into either a resistance training (RT; n =8) or control (CON; n=6) group. Motor unit (MU) recruitment at 50% and 80% of each participant's maximal voluntary isometric contraction (MVIC), muscle cross sectional area (CSA) and thickness (MT), as well as one-repetition maximum (1RM) of the squat (SQT), leg press (LP), and leg extension (LE) were performed before (PRE) and after (POST) the training period. Following the MU assessment, the recruitment threshold (RT; % MVIC) and mean firing rate (MFR; pulse per second [pps]) of each MU were determined. Linear regression was used to quantify the slope (pps/% MVIC) and y-intercept (pps) of the MFR versus RT relationship for each participant and time point. Participants completed an acute resistance exercise bout at PRE and POST consisting of 3 sets of 8 – 10 repetitions with 90 seconds of rest between each set of SQT, LP, and LE. Blood samples were obtained following a 4-hour fast before (BL), immediately-(IP), and one-(1H) hour post resistance exercise. RT subjects performed the same resistance exercise protocol at PRE twice a week for 3-weeks. CON subjects were instructed to not perform any resistance exercise. Area under the curve (AUC) analysis was determined by the trapezoidal method. Pearson product-moment correlations were used to examine selected bivariate relationships. The ΔBDNF AUC was significantly correlated to the relative 80% Δy-intercept (r=-0.626, p=0.030), and trended to be correlated to the relative 80% Δslope (r=0.551, p=0.063). Our results indicate that Δ in plasma BDNF concentrations appear to be related to Δ's MU recruitment at high intensities (80% of MVIC) of exercise.

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CHAPTER ONE: INTRODUCTION

Brain-derived neurotrophic factor (BDNF) is a neurotrophin that exerts pleiotropic effects and is regulated by a variety of stimuli (Marosi and Mattson, 2014). BDNF serves as a mediator of synaptic plasticity and neuronal survival (Sasi et al., 2017). Dysregulated BDNF signaling/action has been associated with a variety of neurological pathologies such as posttraumatic stress disorder (PTSD), attention-deficit hyperactive disorder (ADHD), and Parkinson's disease (Liu et al., 2015; McEwen et al., 2007; McEwen et al., 2015). BDNF acts as both a neuro- and metabotropic protein, and links energy utilization to neurogenesis, playing an important role in the adaptive response of neurons to activity (Mattson et al., 2018).

BDNF expression and regulated secretion are under control of neuronal activity and is dependent on an increase in intracellular calcium (Rothman and Mattson, 2013). BDNF exerts its function through its high-affinity receptor, tropomyosin receptor kinase B (TrkB), and is involved in synaptic structure and function (Lu et al., 2008), neurogenesis (Bergami et al., 2008), and neuronal survival (Marosi and Mattson, 2014). The synthesis and release of BDNF has been shown to be activity-dependent, and the magnitude of the increase appears to be dependent upon acute program changes (e.g. volume and intensity of exercise) (Dinoff et al., 2017). Previous research has demonstrated circulating BDNF to increase following both aerobic and resistance exercise (Marston et al., 2017; Rasmussen et al., 2009; Matthews et al., 2009; Seifert et al., 2010), and the BDNF response to an acute bout of resistance exercise is enhanced by 5-7 weeks of training (Yarrow et al., 2010, Church et al., 2016).

It is well documented that increases in strength in the early phases (initial 2 – 4 weeks) of a resistance training program occur without changes in muscle cross-sectional area (Griffin and

Cafarelli, 2006; Moratani and DeVries, 1978; Sale, 1988). These initial increases in strength have been primarily attributed to neurological adaptation such as increased neural drive (Aagaard et al., 2002), enhanced motor unit firing rate (Vila-Cha et al., 2010), and decreased recruitment thresholds (Keen et al., 1994). Due to technological constraints, the ability to investigate activity of a large number of motor units (MU's) has been limited. However, recent advances in signal processing have alleviated the complex challenges associated with decomposing the surface electromyographic (EMG) signal that is detected non-invasively from the surface of the skin (Nawab et al, 2010). The use of non-invasive surface EMG sensors, as opposed to intramuscular, has led to an increased amount of MU's that can be studied during a contraction (De Luca et al., 2006) allowing researchers to noninvasively quantify the slope and y-intercept of the relationship between recruitment threshold (RT), and firing statistics (e.g. firing rates, action potential size, common drive) of MU's. Previous research has shown these relationships to be sensitive to resistance training (Pope et al., 2016) and training status (Herda et al., 2015).

Previous investigations examining the response of circulating BDNF concentrations to exercise have noted positive correlations between the change in BDNF concentrations and the change in maximal voluntary contraction torque ($r = 0.76$) as well as central activation ratio ($r = 0.81$) following 12 x 5-s maximal effort cycling sprints with 3 min of rest between each sprint (Skurvydas et al., 2017). Tsai and colleagues (2015) reported a significant correlation ($r = 0.54$) between changes in knee extensor strength and changes in serum BDNF concentrations following 12-weeks of low intensity, cycling exercise. However, to the best of our knowledge no study has been previously conducted investigating initial improvements are strength, associated with short-term resistance training induced neural adaptation is associated with changes in circulating BDNF concentrations. Thus, the purpose of this study was to see if short-term

resistance training (8 workouts over the course of 4 weeks) is able to increases circulating BDNF concentrations and decrease the mean firing rate (MFR) or slope of the MFR by RT relationship. Secondly, if so were these changes in motor unit behavior and/or strength related to changes in BDNF resulting from short-term resistance training.

CHAPTER TWO: REVIEW OF LITERATURE

Introduction

The brain plays an integral part in the physical and mental health of an organism. Brain derived neurotrophic factor (BDNF) has an important role in maintaining neuronal health through its role in synaptic plasticity, neurogenesis, and neuronal stress resistance (Marosi & Mattson, 2014). Although the majority of research on BDNF has focused on neurological health, recent investigations have demonstrated a role for BDNF in promoting physical health as well. The finding by Neeper and colleagues (1995) that BDNF mRNA expression is activity-dependent inspired over 20 years of research on the effects of exercise to improve brain health. The main site of BDNF production appears to be the brain (Klein et al., 2011; Pan et al., 1998), however, whether or not it is the primary source of circulating BDNF may be debatable. BDNF has been detected in brain, muscle, immune, platelets, epithelial, satellite, and motor neuron cell types (Brunelli et al., 2012; Fujimura et al., 2002; Garcia et al., 2010; Matthews et al., 2009; Mousavi and Jasmin, 2009). Previous research has demonstrated circulating BDNF concentrations to increase following both aerobic and resistance exercise (Marston et al., 2017; Rasmussen et al., 2009; Matthews et al., 2009; Seifert et al., 2010), and the BDNF response to an acute bout of resistance exercise is enhanced by 5-7 weeks of training (Yarrow et al., 2010; Church et al., 2016).

Mechanism of Exercise-Induced Production of BDNF

It has been well demonstrated that BDNF production is increased in response to bioenergetic challenges (i.e., exercise and fasting). Activation of signaling cascades leading to BDNF synthesis in neurons are initiated by membrane depolarization. The subsequent increase in synaptic activity increases intracellular calcium concentrations resulting in activation of

calcium/calmodulin sensitive kinases (Mattson et al., 2018), such as cyclical adenosine monophosphate (cAMP) response element-binding protein (CREB). BDNF transcription is dependent on CREB activation, as mice with repressed CREB activity do not significantly increase BDNF mRNA or protein content in response to exercise (Chen and Russo-Neustadt, 2009; Aguiar et al., 2011).

Although the exact mechanisms behind how exercise upregulates BDNF are ambiguous, it does appear that a switch from liver glycogen-derived glucose to adipose cell-derived fatty acids and their ketone metabolites during exercise and fasting is necessary (Mattson et al., 2018). Beta-hydroxybutyrate (BHB), a ketone produced during exercise, has been demonstrated to act directly on neurons to induce transcription of the *bdnf* gene (Marosi et al., 2016). BHB inhibits class 1 histone deacetylases (HDACs), specifically HDAC2 and HDAC3, which stimulates histone acetylation at the *bdnf* promoters; resulting in an increase in *bdnf* gene transcription (Sleiman et al., 2016). Therefore, BHB is thought to act as a signal to neurons that the major cellular fuel source has switched from carbohydrates and glucose to fatty acids and ketones (Mattson et al., 2018).

In addition to BHB, research supports the idea of muscle contraction playing a role for upregulation of BDNF in the hippocampus, the part of the brain implicated in learning, memory and emotion (Cotman et al., 2007). In a mouse model of progressive resistance exercise, phosphorylated mTOR and 70-kDa ribosomal protein S6 kinase (p70S6K) in the soleus were correlated with hippocampal BDNF and CREB levels (Suijo et al., 2013). Although BDNF is produced by muscle cells in response to contraction, it does not appear to be released into the

circulation (Matthews et al., 2009). Therefore, another factor produced by skeletal muscle contraction is likely responsible for the increased expression of BDNF in the hippocampus.

Previous research has observed increased *bdnf* gene expression in the hippocampus following adenoviral overexpression of fibronectin type III domain-containing protein 5 (FNDC5), in the liver (Wrann et al., 2013). This is an important consideration, as this occurred without any viral mediated expression of *Fndc5* in the brain, suggesting that the secreted form of FNDC5 mediates this effect. Peroxisome proliferator-activated receptor-gamma coactivator (PGC-1α), which is upregulated in skeletal muscle in response to exercise, regulates FNDC5 (Bostrom et al., 2012). Taken together one potential mechanism of exercise-induced upregulation of BDNF in the brain appears to be upregulation of PGC-1α in skeletal muscle, leading to production and secretion of FNDC5, which can regulate *bdnf* in the hippocampus. However, as FNDC5 can be processed into irisin, a myokine secreted in response to muscle contraction, it is unknown whether FNDC5, the full length irisin protein, or a further modified form is crossing the blood brain barrier (BBB) to induce *bdnf* gene expression.

Physiological Role of BDNF in the Nervous System

BDNF's primary known role is inducing synaptic plasticity via axonal and dendritic remodeling, synaptogenesis, and synaptic efficacy (Park and Poo, 2013; Raefsky and Mattson, 2017). Furthermore, BDNF acts to counter the deleterious effects of neuronal apoptosis and oxidative stress (Rothman and Mattson, 2013). Lastly, recent research indicates increased mitochondrial biogenesis (Raefsky and Mattson, 2017) and inhibition of autophagy (Nikoletopoulou et al., 2017) as important cellular processes involved in synaptic plasticity that are regulated by BDNF signaling. In addition to BDNF's role in mediating adaptive responses of

the central and peripheral nervous systems to exercise (Skurvydas et al., 2017), it is also involved in regulating energy metabolism (Pedersen et al., 2009).

Gomez-Padilla and colleagues (2008) laid the ground work for BDNF to be thought of as a "metabotrophin," as it acts at the interface between neural plasticity and metabolism. They reported exercise-induced increased gene expression of BDNF, Insulin like growth factor-1 (IGF-1), and ghrelin, as well as in the metabolic markers of AMP-activated protein kinase (AMPK), ubiquitous mitochondrial creatine kinase (uMtCk), and uncoupling protein 2 (UCP2). In addition to these genes, memory and learning as assessed by the Morris water maze was improved compared to sedentary control animals. Interestingly, exercise-induced improvements in memory and learning were correlated with exercise-induced increases in synaptic and metabolic markers. In further support, when the action of BDNF was blocked the exercise-induced increase in AMPK, uMtCk, ghrelin, IGF-1, and spatial memory were absent. These results suggest that BDNF mediates or is involved in crosstalk of the energy state of the neuronal cell and neurogenesis.

BDNF primarily works through its high-affinity receptor tropomyosin-kinase receptor B (TrkB). Following binding of BDNF, TrkB undergoes autophosphorylation, which internalizes the receptor within a cell (Marosi and Mattson 2014). Subsequently, protein kinase B (Akt), mitogen activated protein kinase (MAPK), and phospholipase C-γ (PLC) pathways are activated (Kowianski et al., 2017). Activation of Akt will increase protein synthesis, via activation of the mammalian target of rapamycin (mTOR), and suppress autophagy, promoting synaptic plasticity (Gonzalez et al., 2016; Nikoletopoulou et al., 2017). Induction of MAPK and extracellular signaling kinase ½ (ERK1/2) leads to increased anti-apoptotic markers promoting neuronal

survival, increase phosphorylation of synapsin-1 which mediates the release of synaptic vesicles, and the activation of CREB (Sasi et al., 2017). Interestingly, BDNF transcription is dependent on CREB activation (Chen et al., 2009), therefore, BDNF signaling can induce the production and secretion of itself.

In addition to the processes mentioned above, evidence supports a role for BDNF in mitochondrial biogenesis through a Calcium-CREB- PGC-1α pathway (Mattson et al., 2018). BDNF has been demonstrated to increase mitochondrial biogenesis in embryonic hippocampal neurons (Cheng et al., 2012), and inhibits mitochondria motility in mature neurons (Su et al., 2014). In addition, when PGC-1α knockdown in developing hippocampal neurons basal synapse formation is reduced, and BDNF's ability to induce synaptogenesis is abolished (Cheng et al., 2012). As a result of these processes an increased number of mitochondria at pre-synaptic terminals occurs. Local increases in neuronal mitochondria activity of excited neurons leads to increased BDNF production, supplying the "active" area of the neuron with trophic support from BDNF, which is essential for the strengthening of synapses (Raefsky and Mattson, 2017). Further support for increased mitochondrial biogenesis being the major physiological process responsible for BDNF neuronal health effects is that neurons have a limited glycolytic capacity, as only approximately 10% of their adenosine triphosphate (ATP) is produced through glycolysis (Rolfe et al., 1997). Therefore, regulation of mitochondrial biogenesis is crucial for ATP-dependent processes, i.e., protein synthesis, that are required for synaptic plasticity (Raefsky and Mattson, 2017).

The BDNF System in Circulation; Serum, Plasma, and Platelets

Circulating BDNF is present in both a free, unbound, form in the plasma and a bounded form in platelets. Platelets in serum sequester free BDNF from the plasma (Fujimura et al., 2002). Serum BDNF represents the total amount of circulating BDNF from both of these compartments. The BDNF concentration in plasma is significantly lower than that seen in serum or platelets, indicating that the majority of circulating BDNF is stored within the serum (Fujimura et al., 2012; Gilder et al., 2014; Yoshimura et al., 2010). BDNF concentrations in human serum, 25.3 ± 15.0 ng·mL^{-1}, was reported to be similar to that of the BDNF content in washed platelets, 25.2 ± 21.0 ng/4 X 10^8 platelets (Fujimura et al., 2002) indicating that serum BDNF is primarily BDFN stored in platelets. In addition, although serum concentrations are significantly greater that plasma previous research has reported the two pools to be significantly correlated, $r = 0.731$, $p < 0.0001$ (Yoshimura et al., 2010).

The time course of the increase in serum BDNF and platelets following exercise into circulation parallel each other (Matthews et al., 2009). This provides a plausible explanation of why serum BDNF concentrations are routinely observed to be significantly elevated from resting levels immediately after exercise, but return to resting levels quickly (Yarrow et al., 2010). The increase in serum BDNF concentrations immediately after exercise is likely the result of exercise-induced thrombocytosis caused by an increase in sympathetic nerve activity (Walsh et al., 2017). BDNF can move between the bound form in platelets and unbound form in plasma in response to low PO_2 and high shear stress (Helan et al., 2014; Prigent-Tessier et al., 2013). In support of this notion, previous research has demonstrated low and high shear stress to release 16% and 32%, respectively, of the BDNF from platelets (Fujimura et al., 2002). This provides evidence for platelets being a major source of circulating BDNF that can be released into the

plasma as a result of exercise-induced sheer stress. Therefore, thinking of serum BDNF as an "inert" pool is incorrect, as the BDNF protein can move between pools depending on conditions of the circulatory environment.

In contrast to serum, which is thought to contain stored BDNF, plasma concentrations are thought to be indicative of the BDNF content that is actively produced by a cellular source. This is because platelets turn over every 10 days whereas turnover of plasma BDNF is completed in about 6 minutes (Yoshimura et al., 2010). If BDNF is able to cross the BBB in humans only the plasma pool would be able to do so as BDNF in serum is stored in platelets (Pan et al., 1998). This combined with a quick turnover time suggests that plasma BDNF is more likely to be an indicator of acute changes in BDNF production by a cellular source, whereas serum is more indicative of chronic BDNF production. Therefore, acute exercise studies would benefit from the measurement of plasma BDNF, as it likely represents the increase in BDNF concentrations resulting from cellular translation and/or release. In contrast, exercise training interventions are not only interested in how BDNF production by cellular sources are effected, hence in plasma, but also how the training intervention altered stored BDNF concentrations (i.e., what is seen in serum).

Species Differences in BDNF Physiology

There are some important species differences in the BDNF system that are worth noting in order to translate research from animal models to humans. BDNF has been demonstrated to cross the BBB of mice and rats (Poduslo and Curran, 1996; Pan et al., 1998), however; the human BBB is structurally and functionally different from those in animals (Dinoff et al., 2017). Previous research has been unable to detect BDNF in whole blood and plasma of mice but have

reported positive correlations between BDNF concentration in the plasma and hippocampus in a porcine model, as well as BDNF concentrations in whole blood and the hippocampus of rats (Klein et al., 2011). Furthermore, plasma and cerebrospinal fluid BDFN concentrations have been shown to be significantly positively correlated ($r = 0.509$, $p = 0.03$) with each other in humans (Pillai et al., 2010).

Acute BDNF Response to Exercise

Exercise induces a robust response in circulating BDNF concentrations, with concentrations in the serum and plasma consistently demonstrated to be significantly increased following exercise (Church et al., 2016; Ferris et al., 2007; Gilder et al., 2014; Marston et al., 2017; Marquez et al., 2015; Matthews et al., 2009; Rasmussen et al., 2009; Seifert et al., 2010; Skurvydas et al., 2017; Walsh et al., 2016; Zoldaz et al., 2008). BNDF concentrations in human skeletal muscle, endothelial, and peripheral blood mononuclear cells have also been shown to be increased following exercise (Brunelli et al., 2012; Mathews et al., 2009; Prigent-Tessier et al., 2013). In animals, transcription and translation of BDNF has been shown to be upregulated by exercise in the brain (Cotman et al., 2007; Gomez-Pinilla et al., 2008; Hoffman et al., 2015; Neeper et al., 1995; Rasmussen et al., 2009). Furthermore, the average reported increase in circulating BDNF concentrations in humans following an acute exercise bout has been reported to be 60% (Dinoff et al., 2017). Although there is general agreement that increases in BDNF concentrations are seen following exercise (Dinoff et al., 2017; Huang et al., 2014; Knaepen et al., 2010), how the magnitude of the BDNF response is affected by BDNF pool measured (i.e., plasma or serum), exercise mode, intensity, volume, training status, gender, and age is still an active area of research. Previous meta-analyses have observed exercise induced increases in circulating BDNF concentrations to be both intensity- (Szuhany et al., 2015) and volume-

dependent (Dinoff et al., 2017). However, comparison of BDNF concentrations across studies is complicated by differences in blood processing methods which can affect the measured BDNF concentration (Pareja-Galeano et al., 2015; Polyakova et al., 2017) and the high variability of BDNF concentrations in healthy populations (Knaepen et al., 2010).

Acute Plasma versus Serum BDNF Response to Exercise

As previously mentioned, BDNF is detectable in both the serum (total BDNF), plasma (free BDNF), and platelets (bound BDNF) in circulation. However, the response of each compartment differ, and to date, only one study has simultaneously measured all three pools at once. Cho and colleagues (2012) demonstrated that BDNF concentrations were increased in all three pools immediately after a VO_{2Max} test suggesting that both bound and free BDNF is upregulated. In addition, it was reported that the increase in serum BDNF was 108% whereas plasma was 28% (Cho et al., 2012). This contrasts with Gilder and colleagues (2014) who observed a 48% increase in serum and a 99% increase in plasma BDNF concentrations. However, plasma BDNF concentrations were 100 times lower than serum. This result is in agreement with a meta-analysis that included 13 and 46 studies that measured BDNF in the plasma and serum, respectively, and reported a significantly greater increase in plasma as compared to serum (Dinoff et al., 2017). Although absolute BDNF concentrations are greater in the serum, a greater relative increase in plasma is relative to resting concentrations, consequent to exercise.

In addition to the magnitude of both absolute and relative increases, the serum and plasma pools display different temporal responses to exercise. To date, only two studies have directly compared the temporal response of both BDNF pools to exercise beyond an immediately

post-exercise time point. Gilder and colleagues (2014) reported serum BDNF concentration to be significantly elevated immediately after exercise only, whereas plasma BDNF concentrations were still significantly elevated at 30- and 60-minutes post exercise, returning to resting levels at 90-minutes post. These results were supported by Pareja-Galeano et al (2015) who observed a significant increase in serum BDNF concentrations immediately following a cycle ergometer VO_{2Max} test, which returned to resting levels by 30 minutes post-exercise.

Effect of Exercise Mode on the Acute BDNF Response

Although direct comparison between modes of exercise have not been made, the increase in circulating BDNF does not appear to be sensitive to the mode of exercise. Previous reports have demonstrated significant increases in circulating BDNF concentrations from resistance exercise (Church et al., 2016; Marston et al., 2017; Yarrow et al., 2010), endurance exercise (Cho et al., 2012; Ferris et al., 2007), sprinting (Winter et al., 2007), high-intensity interval training [HIIT (Marquez et al., 2015)], and yoga (Pal et al., 2014). The first evidence for increases in circulating BDNF concentrations from exercise in humans was observed following 30 minutes of bicycle ergometry at 60% of VO_{2Max} (Gold et al., 2003). Since then, multiple studies have shown BDNF to be elevated in serum (Marston et al., 2017; Walsh et al., 2016; Yarrow et al., 2010) and plasma (Church et al., 2016) following resistance exercise. In a comparison of 47 aerobic and eight resistance exercise studies Dinoff and colleagues (2017) reported no significant differences in the BDNF response between the two modes of exercise. It does appear that all modes of exercise of sufficient volume and intensity are able to increase circulating BDNF concentrations, however, additional studies using multiple modes of exercise are needed to fully characterize the BDNF response to exercise.

Effect of Exercise Intensity and Volume on the Acute BDNF Response

Both aerobic and resistance exercise models have been utilized to investigate how exercise intensity effects the acute BDNF response. Previous research supports the notion of a threshold intensity of approximately 75% of VO_{2Max} or a 14 on the RPE scale to observe a significant elevation from baseline BDNF concentrations (Ferris et al., 2007; Gilder et al., 2014). Neeper and colleagues (1995) provided the first link between exercise and BDNF using an animal model. They reported that BDNF mRNA expression in the hippocampus and caudal neocortex was associated with distance run per night in rats. Additional investigations have provided additional evidence that elevations in circulating BDNF concentrations during exercise are related to the total volume or duration of activity (Dinoff et al., 2017; Cho et al., 2012; Marston et al., 2017).

In addition to volume and duration of activity, circulating BDNF concentrations are regulated by the intensity of activity (Ferris et al., 2007; Marques et al., 2015; Walsh et al., 2017). Ferris and colleagues (2007) had participants perform a 30-minute cycling exercise at either 10% above or 20% below their ventilatory threshold. BDNF concentrations were only significantly elevated from resting levels following the 10% above ventilatory threshold trial. Similarly, Marquez and colleagues (2015) observed greater serum BDNF concentrations following high-intensity interval training (HIIT) as compared to a time-matched trial set at 70% of maximal work rate. These results are in agreement with Schmolesky and colleagues (2013) who investigated the serum BDNF response to 6 different conditions on a cycle ergometer: 80% heart rate reserve (HRR) for 20 minutes, 80% HRR for 40 minutes, 60% HRR for 20 minutes, 60% HRR for 40 minutes, control condition for 40 minutes, and control condition for 20 minutes. They observed that individuals in the 80% HRR groups were most likely to have a

significant (≥ 10%) BDNF rise during exercise, but that individuals in the 40 minute group had a greater increase in the volume of BDNF circulated during exercise.

In comparison to aerobic exercise the BDNF response to resistance exercise, has not been as well characterized. A recent study examining different resistance training paradigms found greater increases in serum BDNF following a bout of hypertrophy style (3 sets of 10-repetitions with 60 seconds of rest) bout of exercise as compared to a strength (5 sets of 5 repetitions with 180 seconds of rest) based bout when matched for mechanical work, (strength = 45.2 ± 12.0 joules; hypertrophy = 46.0 ± 7.5 joules) (Marston et al., 2017). The strength training paradigm consisted of longer rest periods, which the authors speculated reduced the BDNF response. This idea was expanded upon by Walsh and colleagues (2017) who a utilized handgrip exercise to investigate the effects of maximal and submaximal effort exercise on the BDNF response. Despite the maximal effort bout being shorter in duration (10 minutes) as compared to the submaximal effort exercise (30 minutes), the BDNF response was still greater during the maximal effort bout. Therefore, it appears that BDNF is dependent on intensity, however, the rest period has to be taken into account as well, indicating that exercise density, mechanical work or volume load of a training session reported relative to the summed inter-set recovery periods (Marston et al., 2017) regulates the BDNF response. These studies all measured serum BDNF concentrations. Only one study utilizing resistance exercise compare a high-volume, low intensity (70% 1RM, 4 set of 10 – 12 repetitions, 1 minute rest periods) to a high-intensity, low volume (90% 1RM, 4 sets of 3 – 5 repetitions, 3 minute rest periods) training program on the plasma BDNF response (Church et al., 2016). No group differences were seen before or after training, however, the high-volume protocol did elicit greater (non-significant) BDNF concentrations before and after training. Similar to the serum BDNF response this was probably

a result or a greater density of work performed by the high volume group as compared to the high intensity group. This makes sense as BDNF is increased during bioenergetics challenges. Furthermore, recent research has demonstrated exercise density to be significantly different even when work and volume are matched (Marston et al., 2017b). Therefore, it appears that a sufficient magnitude and duration of peripheral stimuli like shear stress or deoxygenation are required for endothelial or brain BDNF production (Fujimura et al., 2002; Rasmussen et al., 2009; Prigent-Tessier et al., 2013).

Sex and Age Differences for the BDNF Response to Acute Exercise

Previous research had observed significantly lower platelet (Lommatzch et al., 2005) and serum (Ozan et al., 2010) BDNF concentrations in females as compared to males. However, Trajkovska and colleagues (2007) reported resting whole blood BDNF concentrations to be higher in females as compared to males. Two recent meta-analyses have reported a significant negative correlation between effect size and percentage of females in studies (Dinoff et al., 2017; Szuhany et al., 2015). These results suggest that females tend to have lower BDNF concentrations after exercise. In support of this notion, recent research reported a trend ($p = 0.06$) for BDNF concentrations to be lower in females, compared to males, immediately after 10-minutes of running at 85 – 90% of an individual's VO_{2Max} (Hwang et al., 2016).

Effect of Training Status on Resting and the Acute BDNF Response to Exercise

Despite the increased interest in BDNF within exercise science the last 20 years, the understanding of how chronic exercise training alters circulating BDNF concentrations is still not well-understood. Cross-sectional studies have reported significantly decreased resting serum and increased resting plasma BDNF concentrations in trained athletes compared to untrained individuals (Babaei et al., 2014; Belviranli et al., 2016; Correia et al., 2011; Nofuji et al., 2008;

Silveira et al., 2016). A meta-analysis of 29 studies reported that resting peripheral blood BDNF concentrations were increased following exercise interventions. When studies were separated into aerobic and resistance exercise interventions, only aerobic interventions caused a significant increase in resting BDNF concentrations (Dinoff et al., 2016). These results are in agreement with previous meta-analyses (Huang et al., 2014; Knaepen et al., 2010). Furthermore, not all studies measure the same BDNF pool (serum vs plasma), which may be an important factor to be considered as these two pools are regulated by different mechanisms.

There have been a limited number of studies examining the BDNF response to exercise, thus limiting our understanding. Both endurance (Griffin et al., 2011; Seifert et al., 2010; Zoladz et al., 2008) and resistance (Church et al., 2016; Yarrow et al., 2010) training paradigms have been demonstrated to enhance the BDNF response to an acute bout of exercise in young healthy adults. Szuhany and colleagues (2015), reported that regular exercise, durations ranging from 3 to 24 weeks, can increase the acute BDNF response to exercise. Interestingly, an analysis of 24 studies observed a significant positive association between cardiorespiratory fitness (VO_{2Peak}) and increases in circulating BDNF after acute exercise (Dinoff et al., 2017). Individuals who are more trained appear to have an enhanced circulating BDNF response to exercise.

It seems contradictory that trained individuals have a lower resting BDNF concentrations, but a greater response to exercise. However, this may be an evolutionary adaptation to activity (i.e., locomotion) that occurred in animals millions of years ago. As previously mentioned transcription of the *bdnf* gene is dependent on CREB activity. This pathway is highly conserved, as previous research has shown that fasting increased CREB activation and improved long-term memory formation in *Drosophila melanogaster* (Chen et al., 2009). Considering the *homo*

sapiens and *Drosophila melanogaster* diverged from a common ancestor approximately 782.7 million years ago (Shih et al., 2015), and activity is required for animal species to obtain calories, it would be beneficial for to have a greater BDNF response to activity. This greater response during activity could serve two purposes. First, an increase in memory and spatial learning would help an organism recall details about its local area (topography, water sources, etc.) and track its prey. Secondly, it would ensure trophic support of repetitively stimulated synapses used during movement, which may help reduce neuromuscular fatigue. Support for BDNF playing a role in neuromuscular fatigue is provided by Skurvydas and colleagues (2017), who observed basal serum BDNF concentrations predicted central motor fatigue following 12 "all out" 5-second sprints on a cycle ergometer. Furthermore, they reported significant correlations between the percent change in serum BDNF concentrations from pre to 24-hours post exercise were positively correlated to change in central motor fatigue. These results indicate individuals with lower serum BDNF concentrations and a greater response of BDNF to exercise have smaller decrements in neuromuscular fatigue following exercise, which is in agreement with decreased serum BDNF concentrations (Babaei et al., 2014; Nofuji et al., 2008), but a greater response in trained individuals (Dinoff et al., 2017). Therefore, it is plausible the enhanced BDNF response to may be an adaptation from when food resources were not as plentiful, allowing the brain and body to function well.

Potential Role of BDNF in Resistance Training-Induced Neural Adaptations

It is apparent that BDNF has an important role in maintaining and promoting the health of both the peripheral and central nervous system. Previous research indicates that strength gains resulting from short term resistance training are primarily the result of neural adaptations (Moritani and deVries, 1979). These adaptations are thought to include improved motor unit

(MU) efficiency, where a MU's firing rate is decreased at the same maximum force level that could be produced prior to training. In addition, neurological adaptations also include a greater MU firing rate, generating a higher force level than could be produced prior to training. However, evidence of these changes in MU's occurring in response to resistance training is limited. It is currently unknown if circulating BDNF concentrations are related to resistance training induced alterations in MU characteristics.

Although not well studied, there is evidence to suggest that alterations in circulating BDNF concentrations play a role in resistance training induced strength adaptations. For example, Tsai and colleagues (2015) observed a significant increase in serum BDNF concentrations following a 12-weeks of aerobic bicycle ergometer exercise. Interestingly, this significant increase in serum BDNF concentrations were significantly correlated ($r = 0.54$, $p = 0.001$) to the percent change in quadriceps extensor torque. These results were supported by a subsequent investigation that observed a significant ($r = 0.460$, $p = 0.048$) correlation between changes in 1RM back squat and the change in resting plasma BDNF (Church et al., 2016). Furthermore, changes in the plasma BDNF AUC with respect to increase (AUCi), a measure of how much BDNF is increased above basal concentrations in response to a stimuli, was significantly correlated to the change in absolute ($r = 0.594$, $p= 0.006$) and relative ($r = 0.600$, $p = 0.005$) peak power produced during performance of a maximal bench press (Church et al., 2016). As BDNF is consistently shown to be upregulated by exercise, each bout of exercise is thought to provide a "dose" of BDNF. It appears individuals who had a greater change in the "dose" of BDNF from an acute bout of exercise are able to produce more power during maximal lifts.

The physiological role that circulating BDNF has on strength expression is not understood. Some potential explanations may be provided by two of BDNF's known cellular roles which help regulate neurogenesis. Nikoletopoulou and colleagues (2017) demonstrated that BDNF signaling suppresses autophagy in the brain, which is required for synaptic plasticity. They observed that fasting induced increases in BDNF signaling resulting in a significantly greater number of dendritic spines in the hippocampus of mice. It is possible that the greater amount of BDNF released during a bioenergetic stress such as exercise would lead to a greater amount of dendritic spines. Whether this is a mechanism that occurs within the neuromuscular junction is not known. But, this may also be a plausible explanation for the previously mentioned correlation between the change in serum BDNF concentrations and central motor fatigue (Skurvydas et al., 2017). However, BDNF also plays a role in promoting anabolic processes in the brain such as protein synthesis, via activation of the Akt/mTOR pathway (Kowianski et al., 2017). Previous research has demonstrated a significantly greater protein synthesis rates in the brain (3 – 4% turnover a day), compared to muscle (1 – 2% turnover a day) (Smeets et al., 2018). This implies that complete renewal of brain tissue protein occurs well within 4 – 5 weeks, which fits into the time line of muscle strength improvements occurring within 2 – 5 weeks of training without an increase in muscle size (DeFreitas et al., 2011; Moritani and deVries, 1979; Nuzzo et al., 2017; Weier et al., 2012). Therefore, the highly plastic nature of neural brain tissue coupled with a suppression in autophagy, would strengthen existing synapses and help form new ones in repetitively stimulated neural pathways. As previously mentioned BDNF appears to play a role in mitochondrial dynamics and biogenesis, which would generate a greater amount of ATP for energy costly processes, such as protein synthesis. Taken together, an increase in BDNF signaling causes a myriad of downstream effects that strengthen

existing synapses and help form new ones. These processes which are upregulated by exercise-induced BDNF signaling provide a plausible theoretical basis for BDNF promoting strength gains through its role in synaptic plasticity.

CHAPTER THREE: METHODOLOGY

Participants

Seventeen males between the ages of 18 and 35 volunteered to participate in this study. However, one participant in the training group did not complete this study due to injuries sustained outside of the study. Therefore, only data from 16 men (mean ± SD; age = 23.8 ± 2.5 years; height = 177.5 ± 6.3 cm; mass = 84.9 ± 13.7 kg; body fat = 21.5 ± 10.2 %) were analyzed and reported on. This study was approved by the University of Central Florida Institutional Review Board (ID#: SBE-17-13299) prior to participant enrollment. Following an explanation of all procedures, risks, and benefits, each participant provided his informed consent prior to completing any testing. For inclusion in the study, participants had to be untrained in the squat exercise (≤6 months of training), be free of physical limitations, and be willing to maintain a habitual diet while abstaining from dietary supplements. Following determination of the squat one repetition maximum participants were counterbalanced into either a control group (n = 6) or a resistance training group (n = 10). Participants placed in the control group were asked to refrain from lower-body strength training throughout the duration of the study. Participants placed in the resistance training group completed a two-day per week, 3-week resistance training program that was focused primarily on stimulating the vastus lateralis (VL) muscle.

Study Design

A randomized, repeated-measures (RM), between-group, parallel design was used to investigate if alterations in circulating BDNF were related to short-term resistance training adaptations (Figure #1). Following the informed consent, we took ample time to thoroughly explain how the barbell back squat was to be performed throughout the study. Participants were given the opportunity to watch demonstrations of the exercises being performed correctly, and

also learned of mental cues to concentrate on. Participants were taught to perform the barbell back squat with their feet approximately shoulder width apart, with their toes pointed slightly outward (Hoffman and Ratamess, 2008). The participants were instructed to keep the musculature of the upper-back contracted throughout the entire range of motion. Weight belts were not used, however, participants were taught how to correctly execute the Valsalva maneuver to increase intra-abdominal pressure, and its use was encouraged. During this visit participants were allowed to practice the barbell back squat during this time, however, they were limited to just the bar (20.5 kg). After this participants were familiarized with the leg press and leg extension machines that were used throughout the study. Participants performed an acute resistance exercise bout twice; before (Visit 4 [PRE]) and after (Visit 12 [POST]) the 3-week resistance training program with blood samples being collected prior to (BL), immediately (IP), and 60 minutes (1H) after the acute resistance exercise bout. Prior to all assessments participants were asked to avoid caffeine and alcohol use for 24 hours. In addition, participants performed all assessments at the same time of day at POST (± 1 hour) as they did at PRE.

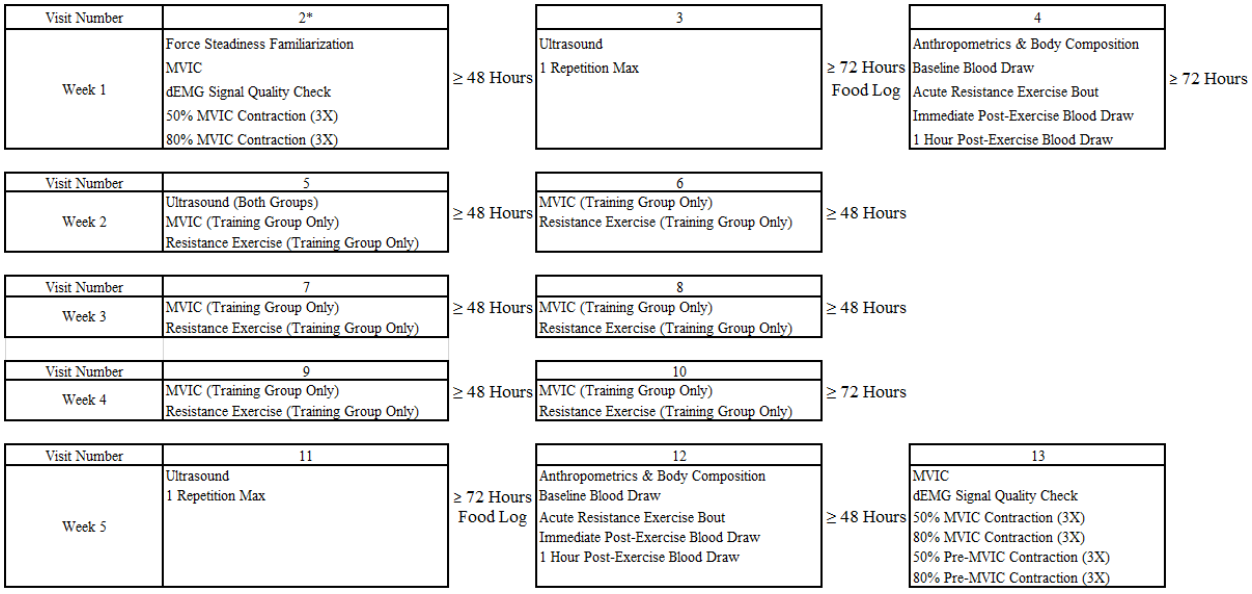


Figure 1. Illustration of study design.

Isometric Torque Assessment

Participants were seated in an isokinetic dynamometer (System 4, Biodex Medical System, Inc., New York, NY, USA) strapped to the chair at the waist, shoulders, and across the thigh, with their hip at an angle of 110°, to evaluate isometric strength during a maximal voluntary isometric contraction (MVIC) of the VL. Chair and dynamometer settings were adjusted for each participant to properly align the axis of rotation with the lateral condyle of the femur. These settings were used at both PRE and POST assessments. All maximal and submaximal torque testing occurred at a knee joint angle of 70° below the horizontal plane. Before performing any testing, participants were asked to warm-up by contracting their VL three times using 50% of their self-perceived maximal effort for 10 seconds with 10 seconds of rest between each contraction. Following the warm-up, each participant performed three 5-second MVIC's at 70° of knee flexion with 3-minutes of rest between each attempt. The highest value from the three trials was chosen as the MVIC and was used to standardize the submaximal

testing among participants. Test-retest reliability analysis for our laboratory's MVIC torque values in ten participants demonstrated an intraclass correlation coefficient (model 3,1) of 0.90 (Church et al., 2017).

Submaximal Muscle Actions

Prior to testing, each participant was familiarized with both the 50% and 80% submaximal isometric trapezoidal contractions (≤3 contractions for each). Following determination of the MVIC and familiarization, the participants performed trapezoidal isometric contractions at 50% and 80% of MVIC in accordance with a visual template on a computer monitor. Each participant performed 3 contractions at 50% and 80% of their MVIC with 3 minutes of rest between each contraction. Isometric trapezoidal contractions involved the participants increasing isometric torque in a controlled manner from 0 – 50% MVIC in five seconds ($10\%\cdot second^{-1}$), holding this contraction for 10-seconds, and then decreasing isometric torque in a controlled manner from 50 – 0% MVIC in five seconds ($10\%\cdot second^{-1}$). The total time for each contraction was 20-seconds. Subsequently, participants then performed a similar isometric contraction using 80% of MVIC. Participants increased isometric torque from 0% – 80% of MVIC in six seconds ($13.3\%\cdot second^{-1}$), held 80% constant for four seconds, and decreased isometric torque from 80% – 0% in six seconds ($13.3\%\cdot second^{-1}$). The total time per contraction at 80% MVIC was 14-seconds. Visual feedback of the real-time torque level was provided with a target template of the trapezoid. Participants were instructed to maintain their torque output as close as possible to the target torque. At POST, the participants performed the trapezoidal isometric contractions at the absolute torque level corresponding to 50% and 80% of the PRE-test and POST-test MVIC's. For example, if a participant in the strength training group demonstrated MVICs of 500 N and 750 N for the PRE-test and POST-test the constant torque

levels at 50% corresponded to 250 N and 375 N. Torque steadiness was defined as the smallest coefficient of variation ([CV]; [SD/mean] ×100) during a two second period during the constant torque portion. The average CV of all three contractions at each respective torque level was used for statistical analysis. For each participant, the PRE- and POST-test isometric torque assessment sessions occurred at approximately the same time of day (± 1 hour).

Surface EMG Signal Recording

Surface EMG signals were recorded from the VL during each of the submaximal contractions with a Bagnoli 16-channel Desktop system (Delsys, Inc., Boston, MA). Prior to detecting EMG signals, the skin over the muscles and patella was shaved and cleansed with rubbing alcohol. Oil, debris, and dead skin cells were removed with hypo-allergenic tape. The sensor was placed over the muscles in accordance with the recommendations described by Zaheer, Roy, and De Luca (2012). A reference electrode was placed over the patella. The signals were detected with a surface array EMG sensor (Delsys, Inc., Boston, MA) that consisted of five pin electrodes (Nawab, Chang, and De Luca, 2010). Four of the five electrodes are arranged in a square, with the fifth electrode in the center of the square and at a fixed distance of 3.6 mm from all other electrodes. Pairwise subtraction of the five electrodes was used to derive four single differential EMG channels. These signals were differentially amplified, filtered with a bandwidth of 20 Hz to 450 Hz, and sampled at 20 kHz. Surface EMG signal quality (i.e., signal-to-noise ratio >3.0 [PRE = 5.96 ± 2.11; POST = 5.69 ± 1.87], baseline noise value ≤2.0 μV RMS [PRE = 1.94 ± 0.60; POST = 2.53 ± 0.20] and line interference <1.0 [PRE = 0.44 ± 0.29; POST = 1.05 ± 0.22]) was verified for a 20% MVIC assessment prior to data acquisition. The mean ± SD for PRE-test and POST-test SubQ were 0.58 ± 0.67 and 0.56 ± 0.66 cm, respectively, POST-test did not change ($p = 0.93$).

Surface EMG Signal Decomposition

The four separate filtered EMG signals from the VL served as the input to the Precision Decomposition III algorithm (see Nawab, Chang, and De Luca, 2010 for more detail). The surface EMG signals were decomposed into their constituent motor unit (MU) action potential trains. These trains were then used to calculate a time varying firing rate curve for each detected MU. All firing rate curves were smoothed with a 1-second Hanning filter, and selected from the 2-second portion of the constant-torque contraction with the lowest torque CV. High threshold MU's that were recruited or derecruited during the constant-torque portion of the protocol and therefore not active throughout the entire 2-second portion of the firing rate curve were not considered for data analysis. Custom-written software (Labview 2017; National Instruments, Austin, TX, USA) were used to calculate the following properties for each validated MU; 1) recruitment threshold (RT) defined as the relative torque (%MVIC) at which the MU first discharged; 2) mean firing rate (MFR) defined as the average firing rate (pulses·second^{-1} [pps]) during the 2-second portion in each individual MU's firing curve. Linear regression was used for each participant's PRE and POST MU data to calculate the slope coefficient and y-intercept for their MFR vs RT relationship (MFR-RT$_{Slope}$ and MFR-RT$_{Y}$, respectively).

Motor Unit Decomposition Accuracy

Once all of the signals were successfully decomposed, the Decompose-Synthesize-Decompose-Compare test was used to determine the accuracy of each MU (De Luca and Contessa, 2012). Except for one participant, MU's with accuracy levels less than 91.0% (mean ± SD = 93.2 ± 1.4%) were removed from further statistical analyses. The one instance in which this did not occur was a MU from participant 13 during the POST-80% contraction, which had an accuracy of 90.8%, however, this exception was made so that a total of 5 MU's were detected

for this contraction. Two additional steps were taken to increase the validity of our procedures. First, contractions that yielded less than five MU's were removed from consideration. Furthermore, contractions that yielded MU's with a recruitment threshold range of less than 8.6% were also removed from consideration. For a few contractions, very low threshold MU's were detected just prior to the onset of measurable torque (i.e., recruitment thresholds at 0% MVIC). These MU's were not considered for further statistical analysis.

Ultrasonography

Ultrasound measurements of the VL were made using a 12MHz linear probe (General Electric LOGIQe, Wauwatosa, Wisconsin) using previously described standardized procedures and settings (frequency: 12 MHz; gain: 50 dB; dynamic range: 72; and depth: 5 cm) to ensure consistency (Bartolomei et al., 2016). ImageJ software (National Institute of Health, USA, v1.48) was used for image analysis. Participants reported limb dominance (kicking leg) and were positioned on their non-dominant leg side, with legs stacked together allowing for a 10° bend at the knee. Sagittal still and transverse panoramic images were taken at the same site as the placement of the surface EMG sensor. Muscle Thickness (MT) was determined from the sagittal still image as the distance between the inferior border of the superficial aponeurosis and the superior border of the deep aponeurosis. Cross-sectional area (CSA) was measured by tracing the outline of the muscle from the transverse panoramic image (Arroyo et al., 2016). Subcutaneous adipose tissue (SubQ) was determined from the sagittal still image and defined as the distance between the inferior border of the epithelium and the superior border of the superficial aponeurosis. Images were taken at three time-points during the study: 1) prior to the PRE 1-RM (Visit 3, PRE); 2) prior to the first workout of the training period (Visit 5) which was standardized to 72-hours after Visit 3; and 3) prior to the POST 1-RM (Visit 11, POST). Three

images were taken at each time-point, and the mean of the two closest values for each measurement was recorded. Intraclass correlation coefficients (ICC; model 3,1) and standard error of measurements (SEM) for the ultrasound technician were determined from a repeated-measures analysis of 9 individuals (CSA: ICC3,1 = 0.98, SEM = 0.88 cm^2 [3.44%]; MT: ICC3,1 = 0.92, SEM = 0.21 cm [0.80%]; SubQ: ICC3,1 = 0.95, SEM = 0.12 cm [0.47%]) (Weir, 2005).

1-Repetition Maximum Testing

Direct measurement of one repetition maximal strength (1-RM) was completed on the barbell squat and leg press exercises, while a predicted 1-RM was performed on the leg extension exercise. PRE and POST 1-RM testing took place prior to the acute resistance exercise bouts at in order to properly assign training loads. All participants completed a standardized warm-up, consisting of 5 minutes on a cycle ergometer against a self-selected resistance, 10 body weight squats, 10 walking lunges, 10 dynamic hamstring stretches and 10 dynamic quadriceps stretches. All 1-RM testing was completed as previously described (Hoffman, 2006). Briefly, each participant performed two warm-up sets consisting of 5-10 repetitions and 3-5 repetitions at approximately 40 – 60% and 60 – 80% of his perceived maximum, respectively. Each participant then performed up to five subsequent trials to determine his 1-RM with 3-5 minutes of rest between each set.

During the squat exercise, participants descended to the parallel position, where the greater trochanter of the femur reached the same level as the knee. Participants ascended to a complete knee extension. Leg press was completed with the participant sitting in a reclined position, with their legs extended. Participants were asked to lower the weight until the lower leg and femur created a 90° angle, and then press the weight up. Participants that were unable to complete the repetition or maintain proper range of motion were given one additional

opportunity. If they were still unable to perform the exercise correctly, the last completed weight was recorded as the 1-RM.

For the leg extension exercise, participants were placed in a seated position, and asked to extend their legs straight out in front of them. Participants were asked to perform as many repetitions as possible, and the resulting repetitions and weight were applied to a prediction equation (Brzycki, 1993). If more than 10 repetitions were performed, the weight was increased and the participant repeated the measure 3 – 5 minutes later. All testing was observed by a Certified Strength and Conditioning Specialist to monitor adherence to form.

Body Composition Assessment

Anthropometric measurements were assessed during the acute resistance exercise bout at PRE and POST for each participant during their visit to the laboratory. Upon arrival to the laboratory, participants were instructed to void their bladder in order to properly assess body composition. Height (±0.1 cm) and body mass (±0.1 kg) were determined using a Health-O-Meter Professional scale (Model 500 KL, Pelstar, Alsip, IL, USA). Body composition was assessed via air displacement plethysmography (BodPod®, COSMED, Chicago, IL, USA).

Acute Resistance Exercise Protocol

Both groups reported to the University of Central Florida Human Performance Lab on a four hour fast to complete the acute resistance exercise protocol. After the BL blood draw was obtained, participants performed the same warm-up they did prior to the 1-RM assessments plus one set of ten squats at 50% of their 1-RM. The acute resistance exercise bout consisted of three sets of 8 – 10 repetitions of the squat, leg press, and leg extension exercises with 90 seconds of rest between each set and 120 seconds between each exercise. The training load was adjusted on

a set-by-set basis to assure that the participant was able to complete 8 – 10 repetitions per set (i.e., if the subject was only able to complete 6 repetitions, the load was decreased accordingly before the next set). Total volume load was calculated for each participant at PRE and POST as the sum of the product of the number of repetitions completed and the load lifted and expressed as kilograms (kgs) for each set across all sets. All testing was supervised by a Certified Strength and Conditioning Specialist to monitor adherence to form.

Resistance Training Program

Following the acute resistance exercise protocol the training group completed a two-day per week, 3-week resistance training program. The resistance training program was the same exact workout protocol the participants completed during the acute protocol with one exception. Each participant performed 3 MVIC's on the isokinetic dynamometer prior to each workout, which they performed twice a week for 3-weeks. Total exercise volume of the dynamic resistance training protocol was calculated for each participant as the sum of the product of the number of repetitions completed and the load lifted and expressed in kg for each set across all sets and exercise sessions. Participants had to complete all six training session to remain in the study. Participants in the control group were instructed to avoid resistance exercise during this 3-week period.

Blood Sampling

Blood samples were obtained at three-time points (BL, IP, and 1H) during each testing session (PRE and POST). Blood draws were obtained by a single use disposable needle with the participant in a supine position. IP blood samples were obtained within 5 minutes of cessation of exercise, whereas the remaining blood samples were obtained following a 15-minute equilibration period. Whole blood (20 ml) was collected into two Vacutainer® tubes (Becton

Dickinson, Franklin Lakes, NJ, USA), one containing heparin, and one containing no anti-clotting agents. The second tube clotted for a 30-minute period prior to being centrifuged at 4,000xg for 15 minutes, whereas the first tube was centrifuged immediately. The resulting plasma and serum was stored at -80°C for later analysis.

Plasma and Serum Brain Derived Neurotrophic Factor (BDNF)

Plasma and Serum concentrations of BDNF were obtained via enzyme-linked immunosorbent assay (ELISA) per the manufacturer's instructions. To remove any additional platelets from stored plasma samples, all samples were centrifuged at 10,000xg for 10 minutes at 4°C prior to being used for analysis. To limit the inter-assay variability, all samples were thawed once, and analyzed by the same technician using a BioTek spectrophotometer (BioTek, Winooski, VT, USA). The average intra- and inter-assay CV was 5.75% and 5.57%, respectively, for plasma BDNF concentrations. The average intra-assay CV was 5.98% for serum BDNF concentrations.

Nutrient Intake and Dietary Analysis

Participants were instructed to maintain their normal dietary intake habits throughout the investigation. Participants were required to record all food and beverage intake 72-hours prior to their acute resistance exercise bouts at PRE and POST on food logs provided to them with detailed instructions. Researchers reviewed the food logs prior to the participants leaving the laboratory to clear up any unknowns on the food log (e.g., food brand, serving size, etc.). In addition, participants were asked to refrain from caffeine and alcohol for 24-hours prior to all assessments being performed at PRE and POST. Total caloric, carbohydrate, fat, and protein intakes were calculated from the 72-hour food logs utilizing the MyFitnessPal® (MyFitnessPal Inc., Austin, TX., USA) database. The MyFitnessPal® database is comprised of over 5 million

foods that have been provided by users via entering data manually or by scanning the bar code on packaged goods. Thus, the data themselves are primarily derived from food labels (i.e., nutrition facts panel) derived from the USDA National Nutrient database.

Statistics

To identify differences in dependent variables an analysis of covariance (ANCOVA) was performed at all measures at POST. Associated values collected at PRE were used as the covariate to eliminate the possible influence of initial score variance on training outcomes. In the event of a significant F ratio, a paired sample *t*-test was used to determine whether a significant difference existed between measures collected prior to and immediately following 3 weeks of training. Area under the curve (AUC) was calculated for changes in plasma BDNF using a standard trapezoidal technique. Additionally, the change in plasma BDNF concentrations from BL to IP was calculated to investigate the amount of BDNF released from exercise. Linear regression was utilized to investigate the relationship between changes in BDNF to changes in the MFR-RT_{Slope}, MFR-RT_{Y}, isometric torque, and 1-RM's. For effect size, partial eta squared statistics were calculated, and according to Green et al., (2000), 0.01, 0.06, and 0.14 were interpreted as small, medium, and large effect sizes, respectively. Significance was accepted at an alpha level of $p \leq 0.05$ and data was reported as mean ± 95% confidence interval.

CHAPTER FOUR: RESULTS

Participant Characteristics

Participants were required to avoid any strenuous activity outside the study. As a result, one participant, who started wrestling, from the training group was removed from the investigation prior to analysis. In addition, one participant from the training group was removed as the change in his squat 1RM was 3 standard deviations above the group mean. Lastly, two participants in the control group had BDNF concentrations reading above the high standard, and therefore, had to be dropped from any blood analysis. As a result, changes in BDNF concentrations are presented on 12 participants (training = 8; control = 4), while performance results are presented on 14 participants (training = 8; control = 6).

Anthropometric and Morphological Changes

Changes in muscle size and anthropometrics following the training intervention are presented in Table 1. Body mass was significantly ($F = 6.345$, $p = 0.029$, $\eta^2 = 0.366$) greater in the control group compared to training at POST. No significant differences between groups were noted at POST for body fat percentage ($F = 2.383$, $p = 0.151$, $\eta^2 = 0.178$) or fat free mass ($F = 0.001$, $p = 0.974$, $\eta^2 \leq 0.001$). In addition, no significant group x time interaction was observed for muscle CSA ($F = 1.078$, $p = 0.322$, $\eta^2 = 0.089$), MT ($F = 0.369$, $p = 0.556$, $\eta^2 = 0.032$), or SubQ ($F = 0.474$, $p = 0.505$, $\eta^2 = 0.041$).

Nutrient Intake

Relative kilocaloric intake did not change significantly ($F = 0.807$, $p = 0.392$, $\eta^2 = 0.082$) over the course of the investigation for either training (PRE: 56.5 ± 25.4 $kCal \cdot kg^{-1}$; POST: 62.4 ± 22.3 $kCal \cdot kg^{-1}$) or control (PRE: 57.7 ± 25.4 $kCal \cdot kg^{-1}$; POST: 70.3 ± 30.8 $kCal \cdot kg^{-1}$) groups. Relative protein intake did not change significantly ($F = 0.001$, $p = 0.980$, $\eta^2 \leq 0.001$) over the

course of the investigation for training (PRE: 3.2 ± 1.2 g·kg^{-1}; POST: 3.2 ± 1.4 g·kg^{-1}) or control (PRE: 2.4 ± 0.9 g·kg^{-1}; POST: 2.3 ± 1.0 g·kg^{-1}) groups. In addition, relative carbohydrate intake did not change significantly ($F = 0.341$, $p = 0.574$, $\eta^2 = 0.036$) over the course of the investigation for training (PRE: 6.0 ± 3.7 g·kg^{-1}; POST: 6.0 ± 3.2 g·kg^{-1}) or control (PRE: 6.9 ± 3.5 g·kg^{-1}; POST: 7.7 ± 5.0 g·kg^{-1}) groups. Similarly, relative fat intake also did not change significantly ($F = 0.087$, $p = 0.774$, $\eta^2 = 0.010$) over the course of the investigation for training (PRE: 2.6 ± 1.1 g·kg^{-1}; POST: 2.8 ± 1.4 g·kg^{-1}) or control (PRE: 1.8 ± 0.6 g·kg^{-1}; POST: 2.1 ± 0.7 g·kg^{-1}) groups.

Strength Improvement

Changes in strength and workout volume can be seen in Figure 2. Significant improvements in 1RM Squat ($F = 6.266$, $p = 0.029$, $\eta^2 = 0.363$) and leg press ($F = 7.392$, $p = 0.020$, $\eta^2 = 0.402$) were noted in the training group compared to control at POST. No significant differences between groups were noted at POST for predicted leg extension 1RM ($F = 0.352$, $p = 0.565$, $\eta^2 = 0.031$), total acute workout volume ($F = 1.205$, $p = 0.296$, $\eta^2 = 0.099$), or MVIC ($F = 0.06$, $p = 0.811$, $\eta^2 = 0.005$).

Force Steadiness of Entire Contraction

Changes in absolute and relative force steadiness of the entire contraction can be seen in Figure 3. No significant differences between groups were noted at POST for the absolute ($F = 0.294$, $p = 0.598$, $\eta^2 = 0.026$) or relative ($F = 1.346$, $p = 0.271$, $\eta^2 = 0.109$) force steadiness for the duration of the 50% contraction. In addition, no significant differences between groups were noted at POST for the absolute ($F = 0.049$, $p = 0.829$, $\eta^2 = 0.004$) and relative ($F = 2.443$, $p = 0.146$, $\eta^2 = 0.182$) force steadiness for the duration of the 80% contraction.

Best Two Second Force Steadiness

Changes in the best 2-second absolute and relative force steadiness contraction can be seen in Figure 4. No significant differences between groups were noted at POST for the absolute ($F = 0.062$, $p = 0.808$, $\eta^2 = 0.006$ and $F = 0.223$, $p = 0.646$, $\eta 2 = 0.020$) or relative ($F = 0.050$, $p = 0.827$, $\eta^2 = 0.005$ and $F = 3.199$, $p = 0.101$, $\eta^2 = 0.225$) best 2-second force steadiness for either the 50% or 80% contractions, respectively.

$MFR\text{-}RT_{Slope}$ Relationship for the VL

Changes in the $MFR\text{-}RT_{Slope}$ can be seen in Figure 5. No significant differences between groups were noted at POST for the absolute ($F = 0.294$, $p = 0.598$, $\eta^2 = 0.026$ and $F = 0.145$, $p = 0.710$, $\eta^2 = 0.013$) or relative ($F = 1.346$, $p = 0.271$, $\eta^2 = 0.109$ and $F = 0.158$, $p = 0.699$, $\eta^2 = 0.014$) $MFR\text{-}RT_{Slope}$ in either the 50% or 80% contraction, respectively.

$MFR\text{-}RT_{Y}$ Relationship for the VL

Changes in the $MFR\text{-}RT_{Y}$ can be seen in Figure 6. No significant differences between groups were noted at POST for the absolute ($F = 0.096$, $p = 0.763$, $\eta^2 = 0.009$ and $F = 0.233$, $p = 0.639$, $\eta^2 = 0.021$) or relative ($F = 3.659$, $p = 0.082$, $\eta^2 = 0.250$ and $F = 0.376$, $p = 0.552$, $\eta^2 = 0.033$) $MFR\text{-}RT_{Y}$ in either the 50% or 80% contraction, respectively.

Resting BDNF Concentrations

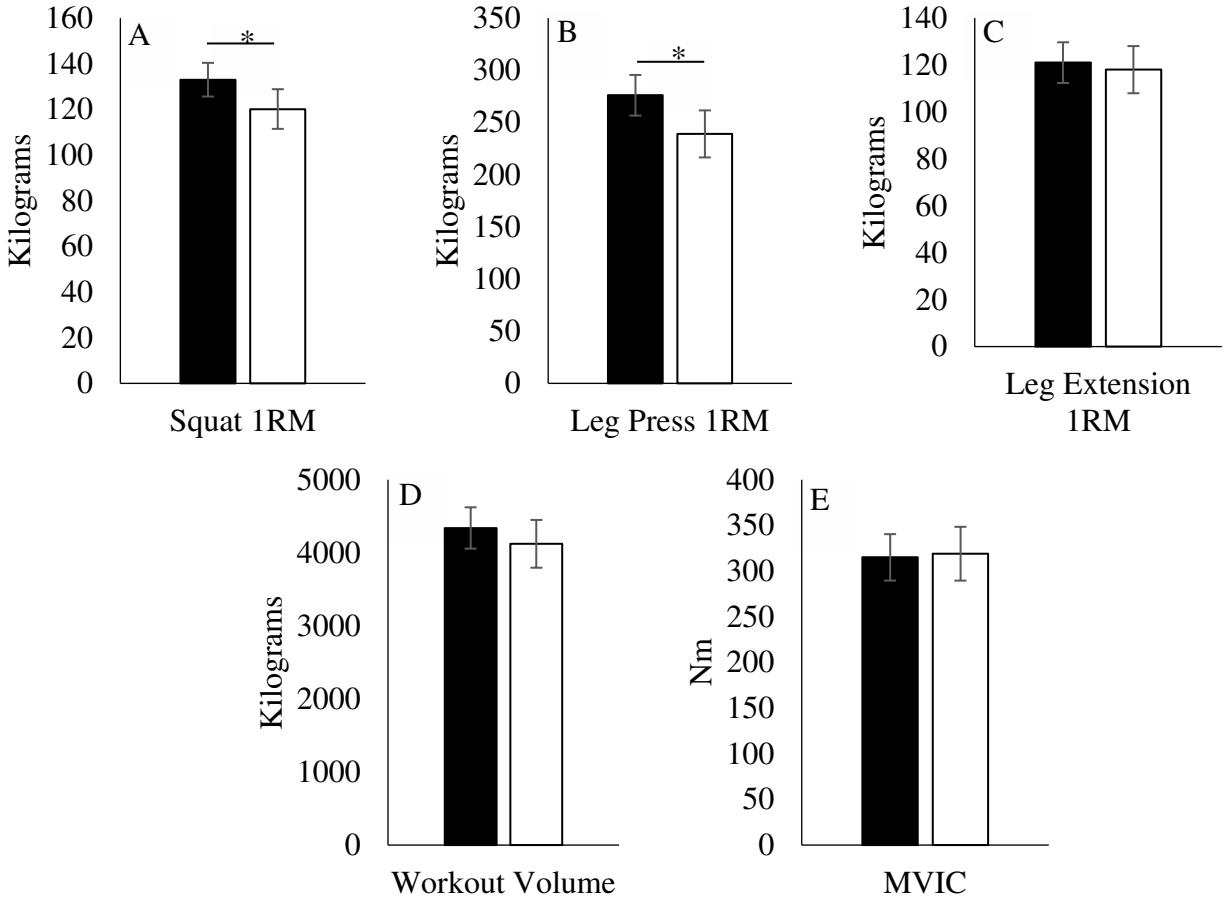
No significant differences ($F = 0.981$, $p = 0.348$, $\eta^2 = 0.098$) were noted at POST in resting plasma BDNF concentrations between the training (295.95 pg/mL; 95% confidence interval = 195.35 – 396.51 pg/mL) and control (374.31 pg/mL; 95% confidence interval = 230.11 – 518.51 pg/mL) groups.

BDNF Response to Resistance Exercise

Changes in the plasma BDNF response to resistance exercise at PRE and POST can be seen in Figure 7. A significant ($F = 5.875$, $p = 0.038$, $\eta^2 = 0.395$) group difference in the BL to IP BDNF change at POST was observed, with the training group (135.16 ± 111.03 pg·mL^{-1}) displaying a greater increase than the control group (-99.77 ± 229.12 pg·mL^{-1}). However, there were no group x time interactions observed at PRE ($F = 0.903$, $p = 0.367$, $\eta^2 = 0.395$) or POST ($F = 4.218$, $p = 0.070$, $\eta^2 = 0.319$) for the BDNF response to exercise. Similarly, no significant differences between groups were observed at POST for the BDNF AUC ($F = 1.082$, $p = 0.325$, $\eta^2 = 0.107$).

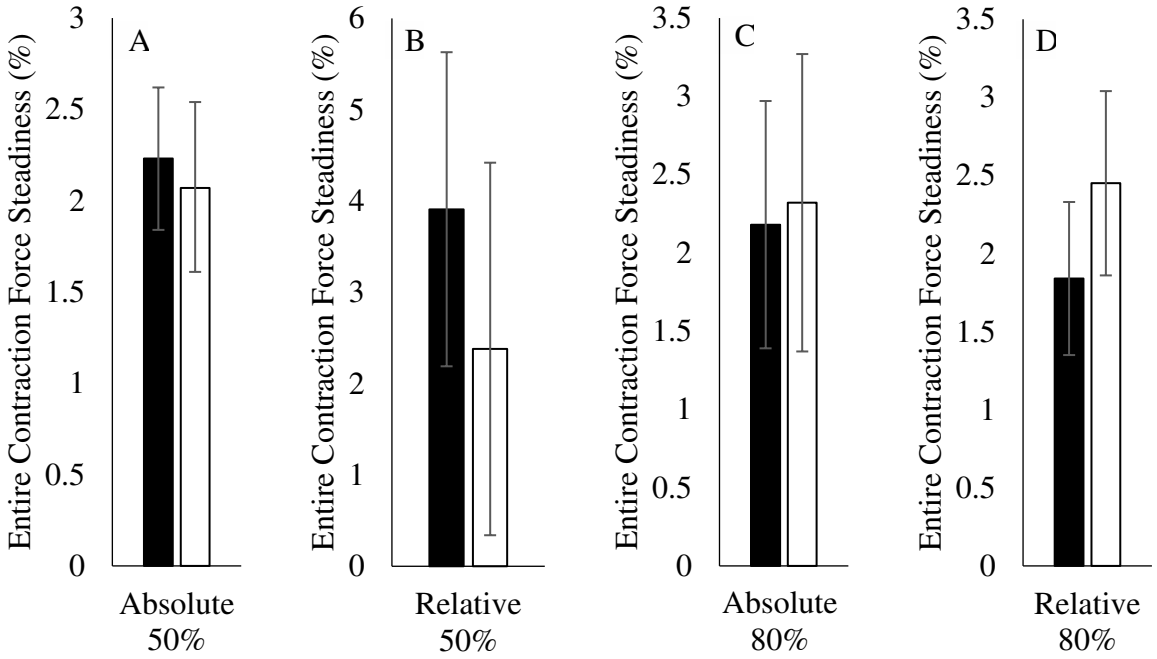
Correlations

Significant correlations were seen between changes in the BDNF response to resistance exercise and motor unit characteristics. The change in BDNF released during exercise was significantly correlated to the change in the relative MFR-RT$_{Slope}$ ($r = 0.779$, $p = 0.003$) and MFR-RT$_Y$ ($r = -0.715$, $p = 0.009$) of the 80% contraction. In addition, the change in the BDNF AUC was significantly correlated to the change in the relative MFR-RT$_{Slope}$ ($r = 0.551$, $p = 0.063$) and MFR-RT$_Y$ ($r = -0.626$, $p = 0.030$) of the 80% contraction. Lastly, the change in the BDNF AUC trended to be correlated to the absolute change in the best 2 second force steadiness ($r = 0.539$, $p = 0.070$) of the 50% contraction.



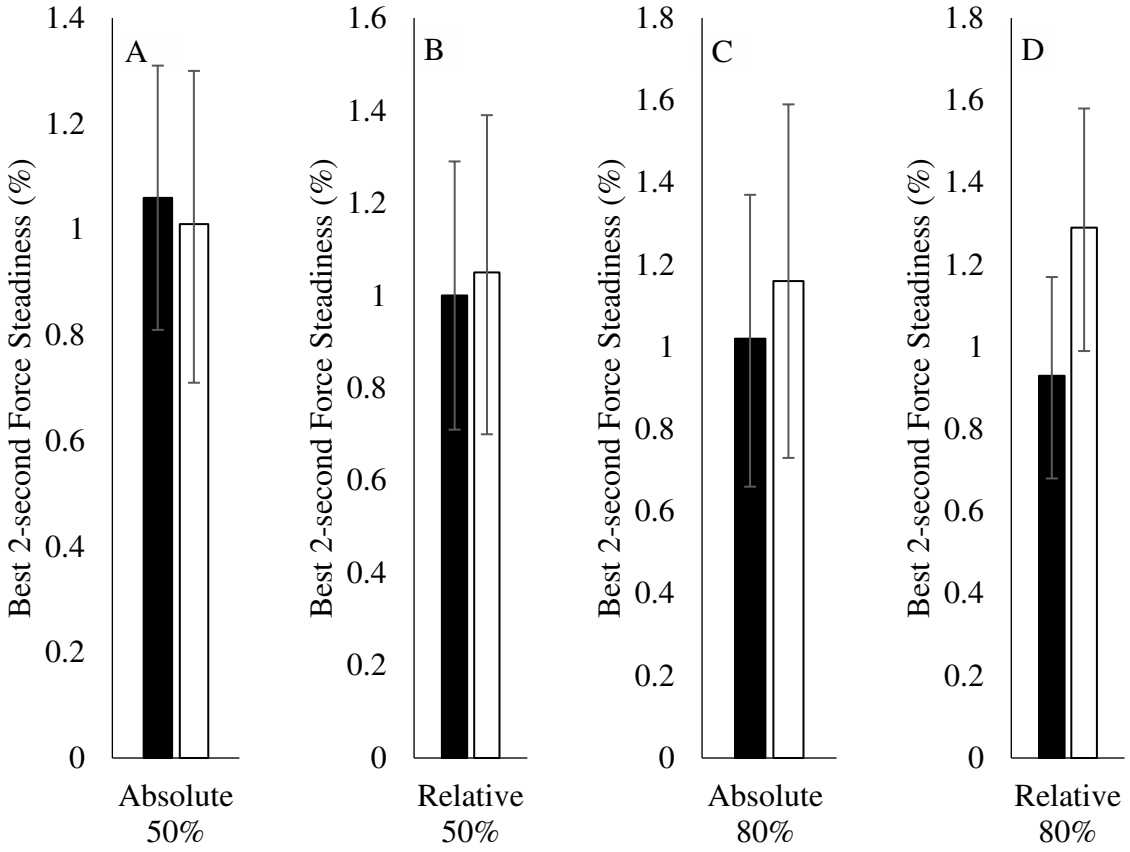
Note. Mean values (± 95% confidence interval) for posttest adjusted for initial differences in pretest for training (black bar) and control (white bar) groups: A. Squat 1RM (covariate: adjusted pretest mean = 117 kilograms); B. Leg Press 1RM (covariate: adjusted pretest mean = 217 kilograms); C. Leg Extension 1RM (covariate: adjusted pretest mean = 104 kilograms); D. Workout volume (covariate: adjusted pretest mean = 3364 kilograms); E. MVIC (covariate: adjusted pretest mean = 291 Nm). Indicates significant main effect of group.

Figure 2. Strength and workout volume at POST



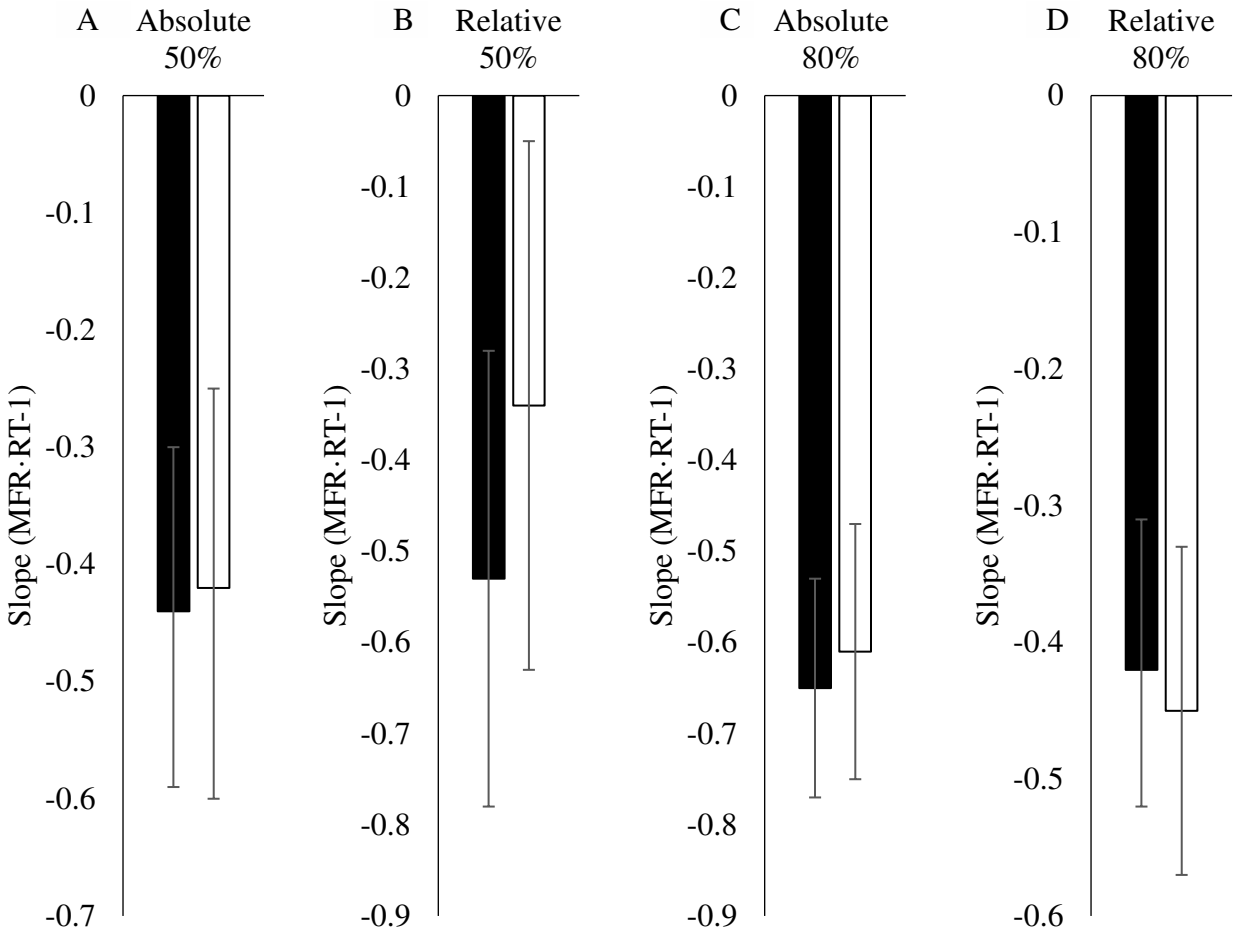
Note. Mean values (± 95% confidence interval) for posttest adjusted for initial differences in pretest for training (black bar) and control (white bar) groups: A. Absolute 50% force steadiness (covariate: adjusted pretest mean = 2.52%); B. Relative 50% force steadiness (covariate: adjusted pretest mean = 2.52%); C. Absolute 80% force steadiness (covariate: adjusted pretest mean = 2.66%); D. Relative 80% force steadiness (covariate: adjusted pretest mean = 2.66%).

Figure 3.Force steadiness for the entire 50% and 80% contraction at POST.



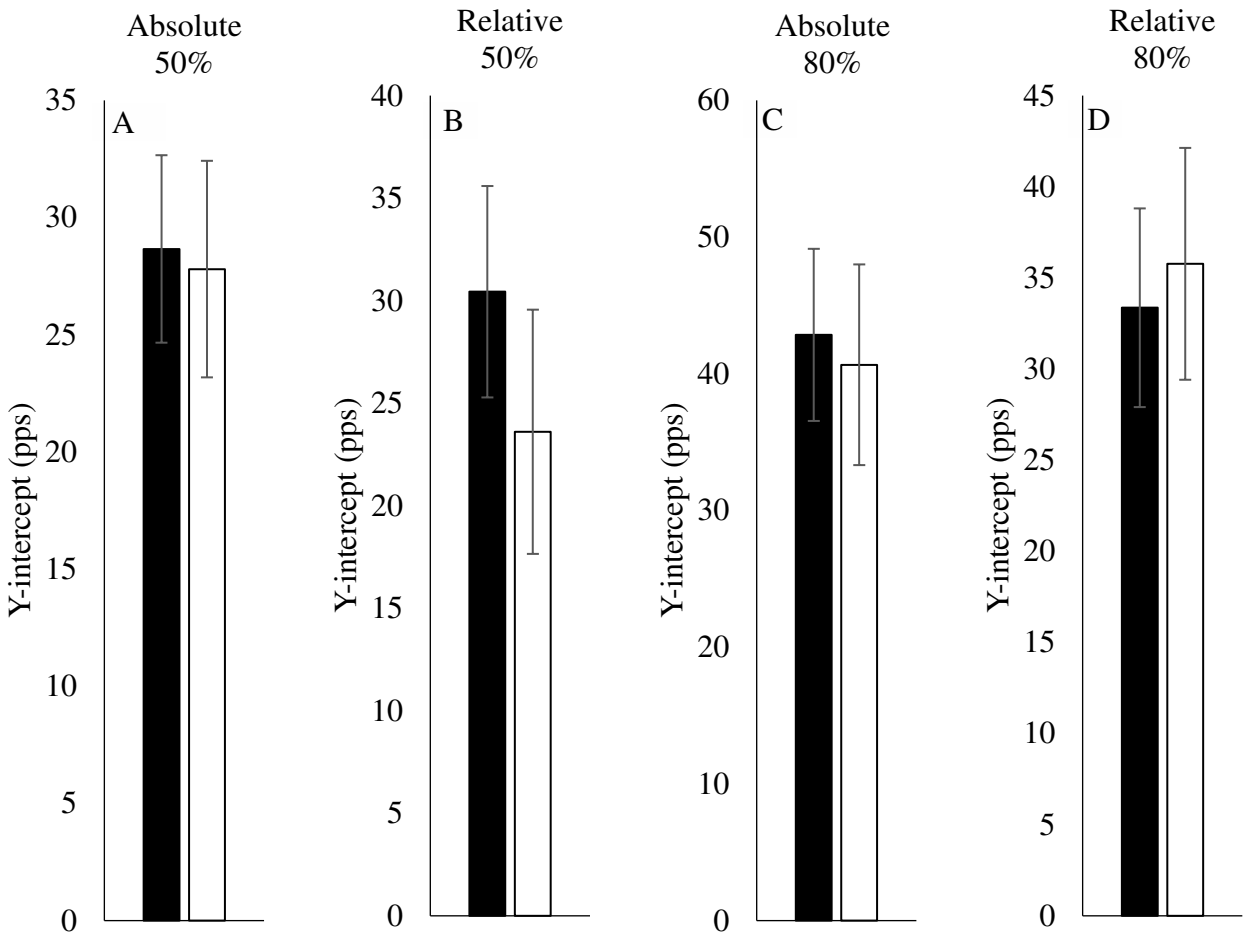
Note. Mean values (± 95% confidence interval) for posttest adjusted for initial differences in pretest for training (black bar) and control (white bar) groups: A. Absolute 50% force steadiness (covariate: adjusted pretest mean = 1.04%); B. Relative 50% force steadiness (covariate: adjusted pretest mean = 1.04%); C. Absolute 80% force steadiness (covariate: adjusted pretest mean = 1.28%); D. Absolute 80% force steadiness (covariate: adjusted pretest mean = 1.28%).

Figure 4. Best 2-second force steadiness for the entire 50% and 80% contraction at POST.



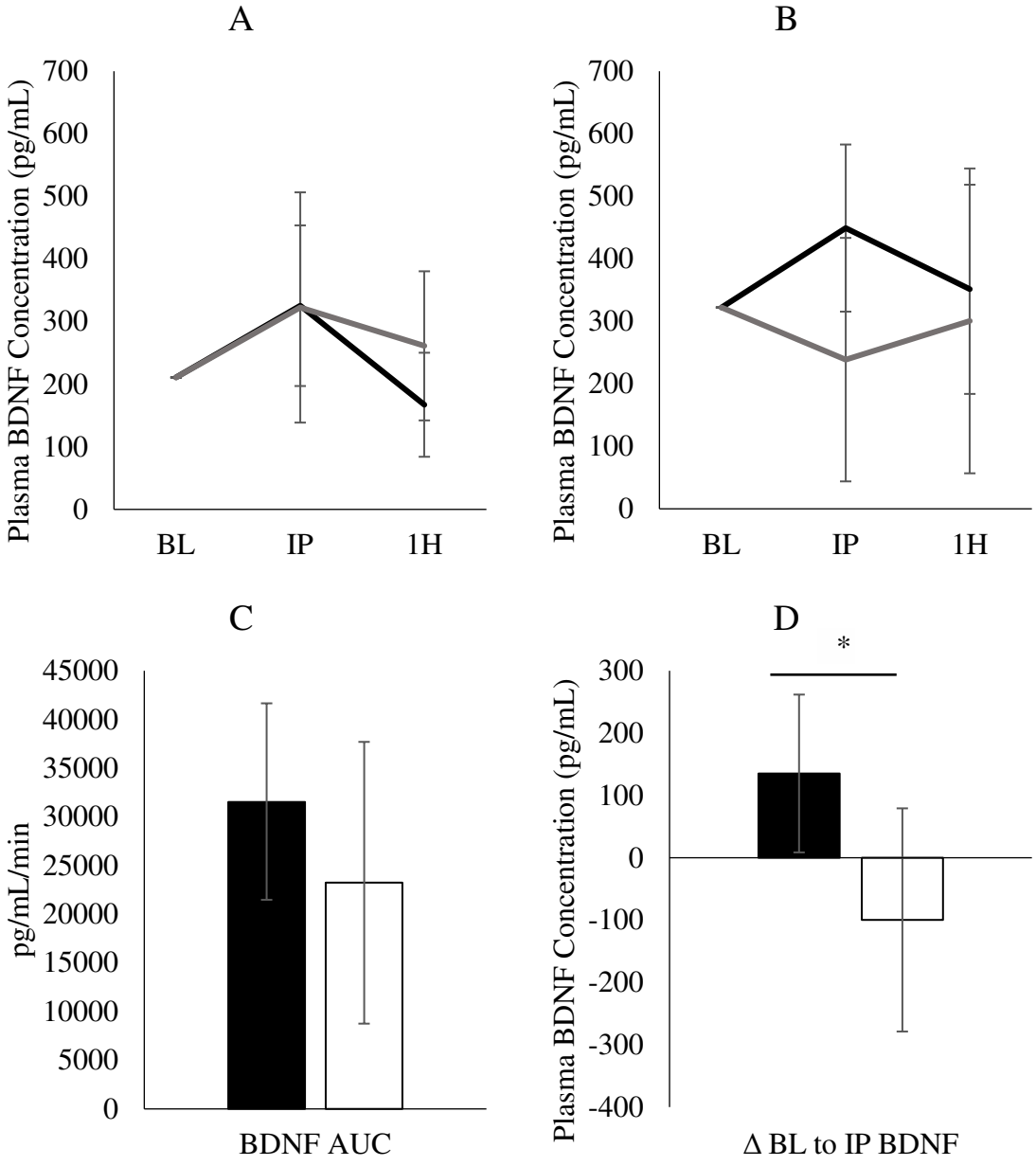
Note. Mean values (± 95% confidence interval) for posttest adjusted for initial differences in pretest for training (black bar) and control (white bar) groups: A. Absolute 50% MFR-RT_{Slope} (covariate: adjusted pretest mean = -0.36); B. Relative 50% MFR-RT_{Slope} (covariate: adjusted pretest mean = -0.36); C. Absolute 80% MFR-RT_{Slope} (covariate: adjusted pretest mean = -0.52); D. Relative 80% MFR-RT_{Slope} (covariate: adjusted pretest mean = -0.52).

Figure 5. MFR-RTSlope of the 50% and 80% contraction at POST.



Note. Mean values (± 95% confidence interval) for posttest adjusted for initial differences in pretest for training (black bar) and control (white bar) groups: A. Absolute 50% MFR-RT_Y (covariate: adjusted pretest mean = 26.63 pps); B. Relative 50% MFR-RT_Y (covariate: adjusted pretest mean = 26.63 pps); C. Absolute 80% MFR-RT_Y (covariate: adjusted pretest mean = 39.86 pps); D. Relative 80% MFR-RT_Y (covariate: adjusted pretest mean = 39.86 pps).

Figure 6. MFR-RTY of the 50% and 80% contraction at POST.



Note. Mean values (± 95% confidence interval) for posttest adjusted for initial differences in pretest for training (black bar) and control (white bar) groups: A. Plasma BDNF concentrations at PRE (covariate: adjusted pretest mean = 210.73 pg/mL); B. Plasma BDNF concentrations at POST (covariate: adjusted pretest mean = 322.07 pg/mL); C. POST BDNF AUC (covariate: adjusted pretest mean = 21,309.2 pg/mL/min); D. Change (Δ) in plasma BDNF concentrations from BL to IP at POST (covariate: adjusted pretest mean = 113.73). * indicates main effect of group.

Figure 7. BDNF response to resistance exercise at PRE and POST.

Table 1. Anthropometric and morphological variables PRE and POST training.

									95% Confidence Interval	
		n	F	*P-value*	η2	Covariate	72H	POST	Lower	Upper
BM (kg)	Training	8	6.345	0.029	0.366	84.8	-	86.6	85.6	87.6
	Control	6					-	84.8	83.7	86.0
BF (%)	Training	8	2.383	0.151	0.178	21.5	-	22.4	21.2	23.7
	Control	6					-	21.0	19.6	22.5
FFM(kg)	Training	8	0.001	0.974	≤ 0.001	65.6	-	66.1	64.8	67.5
	Control	6					-	66.1	64.5	67.7
VL MT	Training	8	0.369	0.556	0.032	2.6	2.6	2.6	2.4	2.8
	Control	6					2.7	2.5	2.3	2.8
VL CSA	Training	8	1.078	0.322	0.089	23.9	25.4	26.3	24.1	28.2
	Control	6					24.4	25.0	22.3	27.1
VL SubQ	Training	8	0.474	0.505	0.041	0.6	0.6	0.6	0.5	0.7
	Control	6					0.6	0.6	0.5	0.6

Note. Data are posttest adjusted for initial difference in pretest for training and control groups measured at PRE and POST Training. *n = sample size;* η2 = eta squared; 72H = 72 hours after first acute resistance exercise protocol; BM = body mass; BF = body fat; FFM = fat free mass; VL = vastus lateralis; MT = muscle thickness; CSA = cross sectional area; SubQ = subcutaneous adipose tissue.

CHAPTER FIVE: DISUCSSION

The results of this study demonstrated significant relationships between the change in BDNF AUC and the change in appearance (change from BL to IP) of BDNF in circulation following an acute bout of resistance exercise to the changes in MFR-RT_Y and MFR-RT_{Slope} of the relative 80% contraction. Significant improvements were observed in 1RM squat and leg press exercises in the training group as compared to the control group, without any change in VL CSA and MT. These results are consistent with previous research indicating strength improvements can occur in the absence of significant hypertrophy during the early phases of resistance training (Blazevich et al., 2007; Damas et al., 2016; Moritani and deVries, 1979; Seynnes et al., 2007).

Results of this study also indicated no significant differences in measures of force steadiness (i.e., torque CV during the constant torque portion of the submaximal trapezoidal contractions) at POST between groups. These results appear to be consistent with previous investigation examining young, previously untrained adult men. Beck and colleagues (2011) observed no difference in force steadiness of the knee extensors at 80% of participants' MVIC following an 8-week, 3-day per week resistance training program in previously untrained men. This was further supported by others who observed no significant changes in the absolute or relative force steadiness of the knee extensors at 50% of participants' MVIC following 10-weeks of barbell deadlift training in previously, untrained men (Stock and Thompson, 2014). However, when using lower force levels significant changes have been noted. Vila-cha and Falla (2016) demonstrated improved force steadiness of the knee extensors at 20% and 30% of participants' MVIC following a 6-week resistance training program in previously untrained young adults. While study duration, exercises used, and the calculation of force steadiness differed between the

present study and the aforementioned studies, our results are in agreement with previous research on force steadiness of the knee extensors in untrained men.

It has been suggested that the MFR-RT_Y reflects the maximal sustainable firing rate of the lowest MUs in the motor neuron pool (Trevino et al., 2016). The classic work of Moritani and de Vries (1979) first demonstrated that strength improvements occurring within the first 2 – 4 weeks of initiating a resistance training protocol are largely the result of neural adaptation. One potential mechanism is an alternation in MU firing rates by either an increase in firing rates at higher absolute force levels, and/or a decrease in firing rates at the same absolute force level produced prior to training (Moritani and deVries, 1979; Patten et al., 2001). The present study does not support this assertion, nonetheless, our results are in line with previous resistance training studies that used comparable methods to measure MFR-RT_Y and MFR-RT_{Slope} (Beck et al., 2011a; Beck et al., 2011b; Pucci et al., 2006; Rich & Cafarelli, 2000; Stock and Thompson, 2014). In contrast to the results observed in this study, previous research has reported significant increases in firing rates following resistance training (Kamen & Knight, 2004; Patten et al., 2001; Vila-Cha and Falla., 2016; Vila-Cha et al., 2010). However, these investigations averaged individual MU firing rates, rather than analyzing individual motor units as a function of recruitment threshold, which provides significant insight into the overall control scheme regulating muscle force production (Contessa et al., 2016). Analyzing the slopes and y-intercepts of the MFR and RT relationship provides insight into the recorded and unrecorded lower- and higher-threshold MU's, allowing for comparisons of MU characteristics to be made across individuals (Herda et al., 2015; Stock et al., 2012; Trevino et al., 2016). These relationships appear to be sensitive to training stresses, however they are limited to exercise-induced muscle damage, fatigue, or cohort studies on chronically trained individuals (Herda et al., 2015; Hight et

al., 2017; Sterczala et al., 2018; Stock et al., 2012). In addition, all measures of MFR-RT_{Slope} were negative indicating an inverse relationship between MFRs of MU's and their RT's. This is consistent with the "onion skin" phenomenon described by De Luca and Hostage (2010) as an evolutionary means of optimizing force magnitude over time.

In the present study we did not observe any significant differences in resting BDNF concentrations at POST between groups. This is in agreement with previous studies showing little effect of short-term, resistance exercise (~5 - 12 weeks) on resting BDNF concentrations (Church et al,, 2017; Forti et al., 2014; Fragala et al., 2014; Goekint et al., 2010; Hvid et al., 2017; Yarrow et al., 2010). In a limited number of investigations, increases in basal BDNF concentrations appear to be more sensitive to aerobic training (Dinoff et al., 2017). Previous interventions have observed increased plasma BDNF concentrations resulting from resistance, but not aerobic training, however, the participants were older adults, and as such increases in basal BDNF concentrations resulting from resistance training may be limited to this population (Pereira et al., 2013). Although we did not observe significant elevation in resting BDNF concentrations in response to the 3-week resistance training program, the increase in BDNF concentrations from BL to IP was significantly greater in the training compared to the control group at POST. Further, results of the AUC for BDNF during exercise was not statistically different between groups. However, we did observe a large effect size, suggesting the potential training effect on the BDNF response. These results are in agreement with previous research demonstrating resistance training enhances the BDNF response to an acute bout of resistance exercise (Church et al., 2016; Yarrow et al., 2010).

Both the change in the appearance of BDNF in circulation and BDNF AUC were correlated to the change in the relative 80% MFR-RT_Y. To our knowledge this is the first investigation reporting a relationship between resistance training-induced changes in MU firing characteristics and the BDNF response to an acute bout of resistance exercise. These results indicate a greater increase in the BDNF response at POST, which was associated with a less negative MFR-RT_{Slope} and lower MFR-RT_Y. This is in agreement with previous research indicating resistance trained individuals have a less negative MFR-RT_{Slope}, lower MFR-RT_Y (Herda et al., 2015; Sterczala et al., 2018), and a greater BDNF response to resistance exercise (Church et al., 2016; Yarrow et al., 2010). Considering the release of BDNF is activity dependent (Egan et al., 2003), and participants were trained at 80% of their 1RM, the repeated release of BDNF from successive resistance exercise bouts may have provided trophic support for higher threshold MU's that were repeatedly stimulated during training. Alternatively, individuals that are able to more easily recruit type II fibers have a greater BDNF response. POST 1RM testing was completed prior to the POST acute blood response, during which the loads assigned were based off the POST 1RM. Individuals who can more easily recruit type II fibers (more negative MFR-RT_{Slope} and decreased MFR-RT_Y) will produce greater force, and are more likely to have a greater 1RM. Therefore, participants with a greater 1RM were trained at higher intensities and completed a greater workout volume. The greater workout volume and intensity may explain why these individuals had an augmented BDNF response. Previous investigations have demonstrated the BDNF response to exercise to be related to both training intensity and training volume (Dinoff et al., 2017; Ferris et al., 2007; Marquez et al., 2015; Marston et al., 2017). Despite the change in the circulating BDNF concentrations explaining 60.7% and 51.1% of the variance in the change of the MFR-RT_{Slope} and MFR-RT_Y, respectively, and the change in the

BDNF AUC explaining 30.4% and 39.2%% of the variance in the change of the MFR-RT_{Slope} and MFR-RT_{Y}, respectively.

In summary, the results of this investigation indicate that changes in the BDNF response to resistance exercise are related to changes in the relative 80% MFR-RT_{Slope} and MFR-RT_{Y}. In addition, this study appears to be the first to demonstrate that resistance training induces an enhanced BDNF release following an acute bout of resistance exercise. Future research is needed to investigate the potential role of BDNF in adaptations to exercise. Specifically, the role of circulating BDNF is not well known, nor are its origin or target tissues. Although investigations have been performed on the effects of training status on BDNF, MFR-RT_{Slope}, and MFR-RT_{Y}, no study has examined all measurements within the same pool of participants.

APPENDIX A:UCF IRB APPROVAL LETTER

University of Central Florida Institutional Review Board
Office of Research & Commercialization
12201 Research Parkway, Suite 501
Orlando, Florida 32826-3246
Telephone: 407-823-2901 or 407-882-2276
www.research.ucf.edu/compliance/irb.html

Approval of Human Research

From: **UCF Institutional Review Board #1**
FWA00000351, IRB00001138
To: **Jay R. Hoffman** and Co-PIs: **David Church, David Fukuda, Jeffrey Ray Stout, Matthew S. Stock**
Date: **September 29, 2017**

Dear Researcher:

On 09/29/2017 the IRB approved the following human participant research until 09/28/2018 inclusive:

Type of Review:	UCF Initial Review Submission Form Full Board Review
Project Title:	Role of Brain Derived Neurotrophic Factor (BDNF) in Stimulating both Strength and Cognitive Improvements Induced by Short Term Resistance Training
Investigator:	Jay R. Hoffman
IRB Number:	SBE-17-13299
Funding Agency:	
Grant Title:	
Research ID:	N/A

The scientific merit of the research was considered during the IRB review. The Continuing Review Application must be submitted 30days prior to the expiration date for studies that were previously expedited, and 60 days prior to the expiration date for research that was previously reviewed at a convened meeting. Do not make changes to the study (i.e., protocol, methodology, consent form, personnel, site, etc.) before obtaining IRB approval. A Modification Form **cannot** be used to extend the approval period of a study. All forms may be completed and submitted online at https://iris.research.ucf.edu .

If continuing review approval is not granted before the expiration date of 09/28/2018, approval of this research expires on that date. When you have completed your research, please submit a Study Closure request in iRIS so that IRB records will be accurate.

Use of the approved, stamped consent document(s) is required. The new form supersedes all previous versions, which are now invalid for further use. Only approved investigators (or other approved key study personnel) may solicit consent for research participation. Participants or their representatives must receive a signed and dated copy of the consent form(s).

All data, including signed consent forms if applicable, must be retained and secured per protocol for a minimum of five years (six if HIPAA applies) past the completion of this research. Any links to the identification of participants should be maintained and secured per protocol. Additional requirements may be imposed by your funding agency, your department, or other entities. Access to data is limited to authorized individuals listed as key study personnel.

In the conduct of this research, you are responsible to follow the requirements of the Investigator Manual.

IRB Chair

APPENDIX B: RECRUITMENT FLYER

You're invited to participate in a research study!!!!

Description of the project:
The University of Central Florida's Human Performance Lab is investigating the role of brain-derived neurotrophic factor in promoting strength and cognition performance resulting from resistance training.

Who is eligible to participate?
Men between the ages of 18-35 that **have not** performed resistance exercise in the last **6-months.**

What will you be asked to do?
Perform strength, body composition, and cognitive performance test before and after 3-weeks of resistance training. You will also be asked to provide blood samples during an exercise session before and after the 3 weeks of training.

Contact Information
To learn more, contact David Church, at David.Church@ucf.edu or call 407-823-2809.

This research is conducted under the direction of Jay R. Hoffman, PhD, Department of Educational and Human Sciences and has been reviewed and approved by the UCF Institutional Review Board.

APPENDIX C: INFORMED CONSENT

Role of Brain Derived Neurotrophic Factor (BDNF) in Stimulating both Strength and Cognitive Improvements Induced by Short Term Resistance Training

Informed Consent

Principal Investigator:	Jay R. Hoffman, PhD
Co-Investigator(s):	Jeffrey R. Stout, PhD David H. Fukuda, PhD Matt S. Stock, PhD David D. Church, MS
Sub-Investigator(s):	Nicholas A. Coker, MS Alyssa N. Varanoske, MS
Faculty Advisor:	Jay R. Hoffman, PhD
Investigational Site(s):	University of Central Florida Human Performance Lab

Introduction: Researchers at the University of Central Florida (UCF) study many topics. To do this we need the help of people who agree to take part in a research study. You are being asked to take part in a research study. This study will include about fifty males at UCF. You have been asked to take part in this research study because you are an adult male between the age of 18 and 35 years of age, that has not performed resistance exercise in the last 6 months. The personnel conducting this research are David D. Church, Nicholas A. Coker, and Alyssa N. Varanoske of UCF College of Education and Human Performance. Because they are graduate students, the study is being guided by Dr. Jay R. Hoffman, a UCF faculty supervisor in the Sport and Exercise Science Department, and the principal investigator of the study.

What you should know about a research study:

- Someone will explain this research study to you.
- A research study is something you volunteer for.
- Whether or not you take part is up to you.
- You should take part in this study only because you want to.
- You can choose not to take part in the research study.
- You can agree to take part now and later change your mind.
- Whatever you decide it will not be held against you.
- Feel free to ask all the questions you want before you decide.

Purpose of the research study: The purpose of this study is to examine if brain derived neurotrophic factor (BDNF) plays a role in the benefits associated with resistance exercise. BDNF is a protein that is involved in nervous system health.

What you will be asked to do in the study:

Screening Visit:

During the screening visit, we will review the inclusion/exclusion criteria with you. You will be asked to read and sign this consent form before any study-related test are performed. We will also inform you of the requirements of the study and determine whether you are able to do the exercise. This will be done by you filling out a physical activity readiness questionnaire (PAR-Q+) and a self-reported confidential medical and activity history questionnaire. If you do not qualify, any information you reported will not be kept. You will be thanked for your time and will not be further contacted. If you qualify and agree to participate in the study, you will be assigned a subject number. Your age, race, and gender will be collected. You will be randomly assigned (i.e., a coin flip) to either a resistance training or control group. Both groups will report for 13 total visits. The resistance-training group will be asked to perform six more resistance exercise visits than the control group. The control group will still come in for these visits to have an ultrasound image of their leg taken. The only difference between the two groups will be the six extra resistance exercise visits the resistance-training group will perform. In order to stay in the study you must agree to participate in the group that you are assigned to. In addition, we will ask that you not change your dietary habits while you are enrolled in the study, and that you do not consume any dietary supplements or performance enhancing drugs.

Study Protocol:

All procedures are being done solely for research purposes. Following enrollment into the study, you will report the Institute of Exercise Physiology and Wellness of the education complex at the University of Central Florida for thirteen visits. The visits are conducted in the following order:

1. The first visit will be a screening visit in which you will fill out a medical history form and PAR-Q+ to ensure that you are eligible to participate in the current resistance training study. If you meet eligibility, you will be asked to perform practice trials on upper body reaction, cave automatic virtual environment (CAVE), constant force, and exercise technique. The CAVE consists of a 7 ft. × 7 ft. × 7 ft. room that includes a canvas projection screen on the front wall.

A three-dimensional image of eight tennis balls will be projected onto the screen. You will be instructed to track 4 of the 8 balls that will move in three-dimensions. At the beginning of test, the balls appear frozen on the screen for 2 seconds, half of them will be grey. These are the balls you will track. After the 2 seconds, the balls will begin to move in three dimensions. At the conclusion of the trial (8 seconds), the balls will freeze and a number will appear on each ball. You will call out the numbers of the four balls you were tracking. The balls will move slow at first and will increase or decrease depending on your correct responses. The test will consist of 20 trials. During each trial, you will wear three-dimensional glasses. Your score will be the velocity of movement that was most successful.

Upper body reaction time will be tested on the Dynavision D2 Visuomotor Training Device, which is a 4 x 4 foot board with 64 lights in 5 circles. The height of the board is adjusted to each individual so they are able to reach every light on the board. Three separate tests will be performed with the Dynavision. The first test will measure your visual, motor, and physical reaction times to a stimulus with the dominant hand. The test will be initiated when you place and hold your hand on an illuminated "home" button. At this point, a stimulus (light) will be presented randomly in one of five locations, parallel to the home button. Visual reaction time will be measured as the amount of time it takes to identify the stimulus (light) and initiate a reaction by taking your hand off the home button. Motor response time will be measured as the amount of time it takes to physically touch the stimulus (light) with your hand following the initial visual reaction, and physical reaction time is a measurement of the total elapsed time from the introduction of the target stimulus to the physical completion of the task (returning to the home button after touching the stimulus with your hand). This will be repeated ten times. The second test will measure your ability to react to a stimulus (light) as it changes positions on the board. An initial stimulus (light) will present on the D2 in a random location. The stimulus will remain lit until you touch it. The stimulus (light) will then appear at another random location. You will be instructed to identify and touch as many stimuli as possible within 60 seconds. The number of "hits" and the average time per hit will be recorded as your score. The third test will be similar to the previous measure in that you will be required to react to a visual stimulus (light) as it changes positions on the board. However, during this test, you will be asked to verbally recite a 5-digit number that is presented on the center screen of the D2. A new 5-digit number will appear on the screen every 5 seconds. You will be asked to touch each stimulus before it changes position and verbally repeat the 5-digit numbers as they appear on the screen. Your score will be the number of successful hits during the 60 s trial. This visit should take at most an hour to complete.

2. The second visit occurs at least 3 hours after visit one. This visit will include practice trials for electromyography (EMG) procedures. You will be asked to perform a constant force contraction. The level of force you will be asked to maintain is 50% and 80% of your maximal force output. EMG is a technique for recording the electrical activity produced by the muscles. EMG activity of the upper leg muscle, specifically the vastus lateralis, of the dominant leg will be assessed. A surface electrode will be placed on the lower thigh of your dominant leg. The skin beneath the electrodes will be shaved and cleaned with alcohol to maintain a proper signal.

EMG does not cause any discomfort and will not interfere with your ability to perform the exercise routine. After the practice trials, participants will complete the test to obtain the EMG data. First you will be asked to contract your leg as hard as possible against an immovable object to obtain your maximal force level. The reading from this is your maximal voluntary isometric contraction (MVIC). Next, you will be asked to follow trapezoid tracings on a computer screen. These trapezoids start at 0% of your max force and will go up to 50% and 80% of your MVIC. Once at 50% and 80% you will be asked to continue to produce that amount of force, after which the tracing slowly returns to 0%. This visit should take at most 45 minutes to complete.

3. The third visit will occur at least 24-hours after second visit. During this visit, you will be asked to lie down on your back for 15 minutes. Afterwards you will have a water-based conduction gel over the area of interest. Next, an ultrasound image will be taken of your upper leg muscle. Then you will be asked to lift as much as you can (1RM) on the squat, leg press, and leg extension exercises. This allows us to use the appropriate load during the resistance-training period. This visit should take at most an hour to complete.

4. The fourth visit will occur at least 48-hours after the third visit. This visit will be the first resistance-training visit. We will ask you to refrain from eating or drinking (with the exception of water) for 4-hours prior to the visit. We will ask you to avoid any caffeine or alcohol consumption for 24-hours prior to this visit. You will be asked if you completed your online dietary log via the automated self-administered 24-hour dietary assessment tool for the previous 72-hours. If not we will ask you to complete this prior to any further participation in the study. Next, we will record your height. Then for the bioelectrical impedance (BIA) test, you will be asked to remove your footwear, including socks. The BIA requires you to wipe your hands and feet with an anti-bacterial tissue to enhance electrical conductivity and reduce surface bacteria. Next, you will be asked to stand on the BIA machine platform while holding two handles out to the side. You will hold this position for one minute as the device conducts an electrical current that cannot be felt, to determine your body composition. For the air displacement plethysmography (BodPod®), you will be asked to take your shirt off, and to either wear or bring tight compressive undergarments to wear during this test. You will also be asked to remove all jewelry, shoes, socks, shirt, and pants. You will be given a compression cap to wear to minimize the effect of hair on volume displacement inside the chamber. This is done because the BodPod® assesses your body composition through the amount of air that you remove from the machine. Baggy clothing will remove more air than tight clothing. If you wear baggy clothing for this test, the machine will not be able to give the right data. You will be asked to sit still inside the BodPod® for a period of about two minutes to obtain the data for fat mass and fat free mass. There are no risks or discomforts linked with the use of the BodPod®.

   Next, you will be asked to perform a baseline MVIC, upper body reaction, CAVE, and the Automated Neuropsychological Assessment Metrics (ANAM) General Neuropsychological Screen Test. The ANAM test system consists of seven computer-based tests that provide precise measurement of cognition. These test are as follows: code substitution – learning, code

substitution – immediate, matching grids, matching samples, pursuit tracking, Stroop, and the code substitution – delayed test. The code substitution – learning test involves comparing a number and symbol pair with a key. You will be asked to press a button to indicate whether the pair represents a correct or incorrect answer based on the key. The code substitution – immediate test involves being presented with a number and symbol pair. You will then decide whether or not this pair is correct based on the key presented during the code substitution – learning test. The matching grids test involves deciding whether or not two grid patterns presented side by side are identical except for possibly being rotated. The matching to sample test involves deciding which of the two grid patterns match to a previously shown grid pattern. The pursuit-tracking test involves moving your mouse so that the mouse pointer tracks a moving circle with a "+" inside. You will be asked to keep the pointer inside the circle and keep it as close to the "+" as possible. The Stroop test involves three blocks of test. In the first block you will be asked to read each word aloud and to press a corresponding key for each word (1 for red, 2 for green, 3 for blue). In the second block a series of XXXX's is presented to you on the display in one of three colors (XXXX, XXXX, XXXX). You will be instructed to press the corresponding key based on color. In the third block a series of individual words (RED, GREEN, BLUE) are presented to you in a color that does not match the name of the color depicted by the word. You will be asked to press the matching key assigned to that color. The code substitution – delayed test involves deciding if a number symbol pair is correct based on the key presented during the code substitution – learning test.

After the baseline tests, you will be asked to lie down in a flat position for a blood sample to be obtained. Personnel trained in phlebotomy with extensive experience in both research and clinical settings will obtain all blood samples. The blood samples collected will be drawn from a forearm vein using a cannula. A cannula is a hollow tube, which can be inserted into the opening of a vein and serve as a channel for the transport of fluid. The cannula prevents the need for multiple needle pricks from being performed. The cannula will be kept open following each blood draw with an infusion of a saline solution. This solution contains salt that is similar to the osmolality of the blood and acts to minimize potential blood clotting within the cannula that may occur with prolonged use. The cannula placement will not interfere with the ability to perform the exercise routine. The total volume of blood that will be obtained during each visit will not exceed 50 ml, and 100 ml for the study as a whole. This is less than 4 tablespoons per trial and 8 tablespoons for the entire study. To put the total volume of blood being drawn in proper perspective, one pint (475 ml) of blood is typically drawn when donating blood. All blood draws will be conducted under sterile conditions. As an additional safeguard in preventing contamination, new disposable gloves will be used for all blood draws. All blood samples collected will be frozen until analysis. The discomforts associated with the blood drawing procedures are minimal, but sometimes bruising and infection may occur, and the arm may become sore. This soreness usually resolves in a few days. If it persists, contact your doctor.

Following the blood sample, you will be asked to perform the resistance training protocol. The protocol will include 3 sets of 8-10 repetitions on the squat, leg press, and leg extension. This

resistance exercise visit should last no longer than 30 minutes. Then you will be asked to provide a blood sample as well as perform upper body reaction, MVIC, CAVE, and ANAM tests. These tests will occur immediately, 1-hour, 2-hours, 3-hours, and 4-hours after resistance exercise. During this 4-hour period following the resistance exercise, you will be asked to remain in the lab. During your time in the lab you can get up and walk around the lab, perform work, and any entertainment you bring with you. The entertainment can include watching television and browsing the internet. The visit is over after the last testing takes place at 4-hours following the resistance exercise. This visit should at most take 5 hours to complete, and the resistance exercise itself should take about 30 minutes.

5. The fifth visit will take place a minimum of 48 hours after the fourth visit. It will be a resistance training visit. You will be asked to perform 3 sets of 8-10 repetitions on the squat, leg press, and leg extension. Prior to the workout you will be asked to perform a MVIC and have a lying ultrasound image of your upper leg taken. This visit should take at most an hour to complete. If you are in the control group, you will come in only for the ultrasound image. The control group will not perform any resistance exercises including the MVIC. This visit will only take 15 minutes for the control group.

6. The sixth, seventh, eighth, ninth, and tenth visit will be identical to the sixth visit. With a minimum of 48 hours in between each one.

7. The eleventh visit will be at least 48 hours after the tenth visit and will be your last resistance exercise visit. This visit will be identical to the third visit.

8. The twelfth visit will take place a minimum of 72 hours after the eleventh visits. This visit will be identical to the fourth visit.

9. The thirteenth visit will be at least 48 hours after the twelfth visit. This will be your last visit and will be identical to your second visit.

Both Groups:	**Visit 1** 1. PAR-Q+ 2. Medical and activity questionnaire 3. Practice Dynavision 4. Practice CAVE	**Visit 2** 1. Practice Force Steadiness 2. MVIC 3. 50% Force Steadiness EMG 4. 80% Force Steadiness EMG	**Visit 3** 1. Ultrasound 2. 1 Repetition Max on: 1. Squat 2. Leg Press 3. Leg Extension	**Visit 4** 1. Body Composition 2. Baseline blood collection and cognition assessment 3. Resistance Exercise 4. Blood collected immediately, 1 hour, 2 hour, 3 hour, and 4 hour after the resistance exercise bout 5. Cognition assessments immediately, 1 hour, 2 hour, 3 hour, and 4 hour after the resistance exercise bout		
	Visit 5	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**
Both Groups:	1. Ultrasound	1. Ultrasound	1. Ultrasound	1. Ultrasound	1. Ultrasound	1. Ultrasound
Resistance Training Group only:	2. MVIC 3. Resistance Exercise	2. MVIC 3. Resistance Exercise	2. MVIC 3. Resistance Exercise	2. MVIC 3. Resistance Exercise	2. MVIC 3. Resistance Exercise	2. MVIC 3. Resistance Exercise
Both Groups:	**Visit 11** 1. Ultrasound 2. 1 Repetition Max on: 1. Squat 2. Leg Press 3. Leg Extension	**Visit 12** 1. Body Composition 2. Baseline blood collection and cognition assessment 3. Resistance Exercise 4. Blood collected immediately, 1 hour, 2 hour, 3 hour, and 4 hour after the resistance exercise bout 5. Cognition assessments immediately, 1 hour, 2 hour, 3 hour, and 4 hour after the resistance exercise bout		**Visit 13** 1. MVIC 2. 50% Force Steadiness EMG 3. 80% Force Steadiness EMG		

The figure above outlines the entire study protocol. You do not have to answer every question or complete every task. You will not lose any benefits if you skip questions or tasks.

Location: All testing will be conducted in the Institute of Exercise Physiology and Wellness at the University of Central Florida.

Time required: We expect that you will be in this research study for approximately 5weeks. This will consist of the initial screen visit, practice visits, and resistance training visits. Each visit will last approximately 45 to 60 minutes, with the exception of the visits 4 and 12. They will last 5 hours. Of this 5 hours, only 30 minutes of it will be spent exercising. If you feel uncomfortable at any point, you are free to discontinue the study. In total the individuals in the resistance training group will be asked for 21 hours of their time. In total the individuals in the control group will be asked for 15 and a half hours of their time.

Risks:

The exercise testing consists of movements that are simple, yet common to many exercise training programs. It is expected that you will experience the normal soreness that often accompanies these workouts. There are no risks associated with a 4-hour fast, other than feelings of hunger and tiredness.

The risks associated with the blood draw may include some momentary pain at the time the needle is inserted into the vein. It is also possible for a bruise to develop at the site that the needle entered the skin or for individuals to report dizziness and possibly faint after the blood is drawn. It is also rare, but possible, to develop minor infections and pain after the blood draw. To minimize the risks, the skin area where the needle or cannula is inserted will be cleaned and prepared with a disinfectant wipe before the needle or cannula is inserted. Needles and cannulas are sterile, and gloves are worn by the person trained in obtaining blood. During experimental trials, a cannula will be used. This is to minimize the number of needle sticks. Upon the removal of the cannula, the puncture site will be covered with a bandage. The total amount of blood drawn during each testing point will not exceed 4 tablespoon. The total amount of blood that will be obtained during the study will not exceed 8 tablespoons. To put the volume of blood being drawn in proper perspective, one pint (475 ml) of blood is typically drawn when donating blood. To reduce the risk of dizziness and fainting from the blood draws, the cannula will be inserted and all blood draws will occur while you are lying flat on your back.

Benefits:

We cannot promise any benefits to you or others from your taking part in this research. However, possible benefits include learning more about your muscular strength and body composition.

Compensation or payment:

There is no compensation or other payment to you for taking part in this study.

Cost:

There is no cost to you to be in the study other than your time.

Confidentiality:

Records of your participation in this study will be held confidential so far as permitted by law. The study investigator or its designee, and, under certain circumstances, UCF Institutional Review Board (UCFIRB), will be able to inspect and have access to confidential data that identifies you by name. Any publication or presentation of the data will not identify you. By signing this consent form, you authorize the study investigator to release your study records to the IRB.

The results of this study will be published as a group as part of a scientific publication. No individual results will be published or shared with any person or party. All information attained from the medical and activity questionnaire or performance tests will be held in strict confidence. Individual results will remain confidential and only be relayed to you upon request. All medical and activity questionnaires, as well as data collection sheets will be kept in a locked cabinet during and following the study. All de-identified data will be destroyed 5 years from the end of the study and not used for other research

purposes. Participant folders and blood storage tubes will be marked with an I.D. number to protect against a breach of confidentiality and the ID number will be removed upon disposal. Participant names and I.D. numbers will be stored apart from the blood samples. Once you have completed the study, your data will be de-identified. After all the blood analysis is complete the blood will be thrown out.

Study contact for questions about the study or to report a problem:
If you have questions, concerns, or complaints, or think the research has hurt you, talk to David D. Church, Human Performance Lab, College of Education and Human Performance at (407)-823-2809, or by email at david.church@ucf.edu. You may also contact Dr. Jay R. Hoffman, Institute of Exercise Physiology and Wellness, Sport and Exercise Science at (407) 823-1272 or by email at jay.hoffman@ucf.edu.

IRB contact about your rights in the study or to report a complaint: Research at the University of Central Florida involving human participants is carried out under the oversight of the Institutional Review Board (UCF IRB). This research has been reviewed and approved by the IRB. For information about the rights of people who take part in research, please contact: Institutional Review Board, University of Central Florida, Office of Research & Commercialization, 12201 Research Parkway, Suite 501, Orlando, FL 32826-3246 or by telephone at (407) 823-2901. You may also talk to them for any of the following:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You want to get information or provide input about this research.

If you are harmed because you take part in this study:

If you are injured or made sick from taking part in this research study, medical care will be provided. Depending on the circumstances, this care may be provided at no cost to you. Contact the investigator for more information. If you believe you have been injured during participation in this research project, you may file a claim with UCF Environmental Health & Safety, Risk and Insurance Office, P.O. Box 163500, Orlando, FL 32816-3500 (407) 823-6300. The University of Central Florida is an agency of the State of Florida for purposes of sovereign immunity and the university's and the state's liability for personal injury or property damage is extremely limited under Florida law. Accordingly, the university's and the state's ability to compensate you for any personal injury or property damage suffered during this research project is very limited.

Withdrawing from the study:
You have the right to discontinue participation without penalty, regardless of the status of the study. Your participation in the study may also be terminated at any time by the researchers in charge of the project. This could be based upon your refusal to follow study instructions or follow study protocol.

For Students and Employees of University of Central Florida:
Your participation in this study is voluntary. You are free to withdraw your consent and discontinue participation in this study at any time without prejudice or penalty. Your decision to participate or not participate in this study will in no way affect your continued enrollment, grades, employment, or your relationship with individuals who may have an interest in this study. _____ Initials

(Please note you will be participating in this study on your own time; not during regular working hours or class time.)

Your signature below indicates your permission to take part in this research.

DO NOT SIGN THIS FORM AFTER THE IRB EXPIRATION DATE BELOW

Name of participant	
Signature of participant	Date
Signature of person obtaining consent	Date
Printed name of person obtaining consent	

APPENDIX D: MEDICAL HISTORY QUESTIONNAIRE

Human Performance Laboratory
University of Central Florida

Confidential Medical and Activity History Questionnaire

When was your last physical examination?

1. List any medications, herbals or supplements you currently take or have taken the last month:

Medication	Reason for medication
_____	_____
_____	_____

2. Are you allergic to any medications? If yes,please list medications and reaction.

3. Please list any allergies, including food allergies that you may have?

4. Have you ever been hospitalized? If yes, please explain.

Year of hospitalization	Reason
_____	_____
_____	_____
_____	_____

5. Illnesses and other Health Issues

List any chronic (long-term) illnesses that have caused you to seek medical care.

6. Have you undergone major surgery within the previous 16 weeks? If yes, please explain.

7. Have you ever had (or do you have now) active malignant disease or cancer. If yes, please explain.

8. Have you ever had (or do you have scheduled) any procedure with Iodine, Barium, or Nuclear Medicine Isotopes? (CT and PET scans are examples) If yes, please specify the date of the procedure.

Human Performance Laboratory
University of Central Florida

Have you ever had (or do you have now) any of the following. Please circle questions that you do not know the answer to.

Cystic fibrosis	Yes	No
Water retention problems	Yes	No
Epilepsy	Yes	No
Convulsions	Yes	No
Dizziness/fainting/unconsciousness	Yes	No
Chronic headaches	Yes	No
Chronic cough	Yes	No
Chronic sinus problem	Yes	No
High cholesterol	Yes	No
Rheumatic fever	Yes	No
Bronchitis	Yes	No
Hepatitis	Yes	No
Bladder problems	Yes	No
Tuberculosis (positive skin test)	Yes	No
Yellow jaundice	Yes	No
Anemia	Yes	No
Endotoxemia	Yes	No
Hyperprolactinemia	Yes	No
Anorexia nervosa	Yes	No
Bulimia	Yes	No
Stomach/intestinal problems	Yes	No
Arthritis	Yes	No
Back pain	Yes	No
Gout	Yes	No
Dementia	Yes	No
Artificial limb	Yes	No
Alzheimer's	Yes	No

Human Performance Laboratory
University of Central Florida

Have you ever had (or do you have now) any of the following. Please circle questions that you do not know the answer to.

Cardiovascular Disease		
Peripheral vascular disease	Yes	No
Cerebrovascular disease	Yes	No
Coronary artery disease	Yes	No
Aortic stenosis	Yes	No
Congestive heart failure	Yes	No
Atrial fibrillation	Yes	No
"Heart block"	Yes	No
Myocardial infarction (Heart Attack)	Yes	No
Poorly controlled hypertension	Yes	No
Heart pacemaker	Yes	No
High blood pressure	Yes	No
Heart murmur	Yes	No
Pulmonary Disease		
Chronic obstructive pulmonary disease	Yes	No
Asthma	Yes	No
Interstitial lung disease	Yes	No
Emphysema	Yes	No
Chronic respiratory disorder	Yes	No
Metabolic Disease		
Diabetes mellitus (type 1, type 2)	Yes	No
Diabetes insipidus	Yes	No
Thyroid disorders	Yes	No
Renal disease	Yes	No
Liver disease	Yes	No
Immunodeficiency disorder	Yes	No

Any others (specify): _____

Human Performance Laboratory
University of Central Florida

Do you smoke cigarettes or use any other tobacco products?	Yes	No
Do you have a history of drug or alcohol dependency?	Yes	No
Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?	Yes	No
Do you feel pain in your chest when you do physical activity?	Yes	No
In the past month have you had chest pain when you were not doing physical activity?	Yes	No
Are you ever bothered by racing of your heart?	Yes	No
Do you ever notice abnormal or skipped heartbeats?	Yes	No
Do you ever have any arm or jaw discomfort, nausea, or vomiting associated with cardiac symptoms?	Yes	No
Do you ever have difficulty breathing?	Yes	No
Do you ever experience shortness of breath?	Yes	No
Do you lose your balance because of dizziness or do you ever lose consciousness?	Yes	No
Have you ever had any tingling or numbness in your arms or legs?	Yes	No
Has a member of your family or close relative died of heart problems or sudden death before the age of 50?	Yes	No
Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?	Yes	No
Do you have a bone or joint problem that could be made worse by a change in your physical activity?	Yes	No

Human Performance Laboratory
University of Central Florida

Has a health care practitioner ever denied or restricted your participation in sports for any problem. If yes, please explain:

_____

_____

Do you know of any other reason why you should not do physical activity? yes no

Are you presently taking any nutritional supplements or ergogenic aids? (if yes, please detail.)

_____

_____

I have answered these questions honestly and have provided all past and present health and exercise information to the best of my knowledge.

Signature Date

APPENDIX E: PHYSICAL ACTIVITY READINESS QUESTIONNAIRE

2017 PAR-Q+

The Physical Activity Readiness Questionnaire for Everyone

The health benefits of regular physical activity are clear; more people should engage in physical activity every day of the week. Participating in physical activity is very safe for MOST people. This questionnaire will tell you whether it is necessary for you to seek further advice from your doctor OR a qualified exercise professional before becoming more physically active.

GENERAL HEALTH QUESTIONS

Please read the 7 questions below carefully and answer each one honestly: check YES or NO.	YES	NO
1) Has your doctor ever said that you have a heart condition ☐ OR high blood pressure ☐?	☐	☐
2) Do you feel pain in your chest at rest, during your daily activities of living, **OR** when you do physical activity?	☐	☐
3) Do you lose balance because of dizziness **OR** have you lost consciousness in the last 12 months? Please answer **NO** if your dizziness was associated with over-breathing (including during vigorous exercise).	☐	☐
4) Have you ever been diagnosed with another chronic medical condition (other than heart disease or high blood pressure)? **PLEASE LIST CONDITION(S) HERE:** _____	☐	☐
5) Are you currently taking prescribed medications for a chronic medical condition? **PLEASE LIST CONDITION(S) AND MEDICATIONS HERE:** _____	☐	☐
6) Do you currently have (or have had within the past 12 months) a bone, joint, or soft tissue (muscle, ligament, or tendon) problem that could be made worse by becoming more physically active? Please answer **NO** if you had a problem in the past, but it ***does not limit your current ability*** to be physically active. **PLEASE LIST CONDITION(S) HERE:** _____	☐	☐
7) Has your doctor ever said that you should only do medically supervised physical activity?	☐	☐

☑ **If you answered NO to all of the questions above, you are cleared for physical activity.**
Go to Page 4 to sign the PARTICIPANT DECLARATION. You do not need to complete Pages 2 and 3.

- Start becoming much more physically active – start slowly and build up gradually.
- Follow International Physical Activity Guidelines for your age (www.who.int/dietphysicalactivity/en/).
- You may take part in a health and fitness appraisal.
- If you are over the age of 45 yr and **NOT** accustomed to regular vigorous to maximal effort exercise, consult a qualified exercise professional before engaging in this intensity of exercise.
- If you have any further questions, contact a qualified exercise professional.

🛑 **If you answered YES to one or more of the questions above, COMPLETE PAGES 2 AND 3.**

⚠ **Delay becoming more active if:**

- You have a temporary illness such as a cold or fever; it is best to wait until you feel better.
- You are pregnant - talk to your health care practitioner, your physician, a qualified exercise professional, and/or complete the ePARmed-X+ at **www.eparmedx.com** before becoming more physically active.
- Your health changes - answer the questions on Pages 2 and 3 of this document and/or talk to your doctor or a qualified exercise professional before continuing with any physical activity program.

2017 PAR-Q+

FOLLOW-UP QUESTIONS ABOUT YOUR MEDICAL CONDITION(S)

1. Do you have Arthritis, Osteoporosis, or Back Problems?

If the above condition(s) is/are present, answer questions 1a-1c — If **NO** ☐ go to question 2

1a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
1b.	Do you have joint problems causing pain, a recent fracture or fracture caused by osteoporosis or cancer, displaced vertebra (e.g., spondylolisthesis), and/or spondylolysis/pars defect (a crack in the bony ring on the back of the spinal column)?	YES ☐ NO ☐
1c.	Have you had steroid injections or taken steroid tablets regularly for more than 3 months?	YES ☐ NO ☐

2. Do you currently have Cancer of any kind?

If the above condition(s) is/are present, answer questions 2a-2b — If **NO** ☐ go to question 3

2a.	Does your cancer diagnosis include any of the following types: lung/bronchogenic, multiple myeloma (cancer of plasma cells), head, and/or neck?	YES ☐ NO ☐
2b.	Are you currently receiving cancer therapy (such as chemotheraphy or radiotherapy)?	YES ☐ NO ☐

3. Do you have a Heart or Cardiovascular Condition? *This includes Coronary Artery Disease, Heart Failure, Diagnosed Abnormality of Heart Rhythm*

If the above condition(s) is/are present, answer questions 3a-3d — If **NO** ☐ go to question 4

3a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
3b.	Do you have an irregular heart beat that requires medical management? (e.g., atrial fibrillation, premature ventricular contraction)	YES ☐ NO ☐
3c.	Do you have chronic heart failure?	YES ☐ NO ☐
3d.	Do you have diagnosed coronary artery (cardiovascular) disease and have not participated in regular physical activity in the last 2 months?	YES ☐ NO ☐

4. Do you have High Blood Pressure?

If the above condition(s) is/are present, answer questions 4a-4b — If **NO** ☐ go to question 5

4a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
4b.	Do you have a resting blood pressure equal to or greater than 160/90 mmHg with or without medication? (Answer **YES** if you do not know your resting blood pressure)	YES ☐ NO ☐

5. Do you have any Metabolic Conditions? *This includes Type 1 Diabetes, Type 2 Diabetes, Pre-Diabetes*

If the above condition(s) is/are present, answer questions 5a-5e — If **NO** ☐ go to question 6

5a.	Do you often have difficulty controlling your blood sugar levels with foods, medications, or other physician-prescribed therapies?	YES ☐ NO ☐
5b.	Do you often suffer from signs and symptoms of low blood sugar (hypoglycemia) following exercise and/or during activities of daily living? Signs of hypoglycemia may include shakiness, nervousness, unusual irritability, abnormal sweating, dizziness or light-headedness, mental confusion, difficulty speaking, weakness, or sleepiness.	YES ☐ NO ☐
5c.	Do you have any signs or symptoms of diabetes complications such as heart or vascular disease and/or complications affecting your eyes, kidneys, **OR** the sensation in your toes and feet?	YES ☐ NO ☐
5d.	Do you have other metabolic conditions (such as current pregnancy-related diabetes, chronic kidney disease, or liver problems)?	YES ☐ NO ☐
5e.	Are you planning to engage in what for you is unusually high (or vigorous) intensity exercise in the near future?	YES ☐ NO ☐

2017 PAR-Q+

6. Do you have any Mental Health Problems or Learning Difficulties? *This includes Alzheimer's, Dementia, Depression, Anxiety Disorder, Eating Disorder, Psychotic Disorder, Intellectual Disability, Down Syndrome*

If the above condition(s) is/are present, answer questions 6a-6b — If **NO** ☐ go to question 7

6a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
6b.	Do you have Down Syndrome **AND** back problems affecting nerves or muscles?	YES ☐ NO ☐

7. Do you have a Respiratory Disease? *This includes Chronic Obstructive Pulmonary Disease, Asthma, Pulmonary High Blood Pressure*

If the above condition(s) is/are present, answer questions 7a-7d — If **NO** ☐ go to question 8

7a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
7b.	Has your doctor ever said your blood oxygen level is low at rest or during exercise and/or that you require supplemental oxygen therapy?	YES ☐ NO ☐
7c.	If asthmatic, do you currently have symptoms of chest tightness, wheezing, laboured breathing, consistent cough (more than 2 days/week), or have you used your rescue medication more than twice in the last week?	YES ☐ NO ☐
7d.	Has your doctor ever said you have high blood pressure in the blood vessels of your lungs?	YES ☐ NO ☐

8. Do you have a Spinal Cord Injury? *This includes Tetraplegia and Paraplegia*

If the above condition(s) is/are present, answer questions 8a-8c — If **NO** ☐ go to question 9

8a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
8b.	Do you commonly exhibit low resting blood pressure significant enough to cause dizziness, light-headedness, and/or fainting?	YES ☐ NO ☐
8c.	Has your physician indicated that you exhibit sudden bouts of high blood pressure (known as Autonomic Dysreflexia)?	YES ☐ NO ☐

9. Have you had a Stroke? *This includes Transient Ischemic Attack (TIA) or Cerebrovascular Event*

If the above condition(s) is/are present, answer questions 9a-9c — If **NO** ☐ go to question 10

9a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
9b.	Do you have any impairment in walking or mobility?	YES ☐ NO ☐
9c.	Have you experienced a stroke or impairment in nerves or muscles in the past 6 months?	YES ☐ NO ☐

10. Do you have any other medical condition not listed above or do you have two or more medical conditions?

If you have other medical conditions, answer questions 10a-10c — If **NO** ☐ read the Page 4 recommendations

10a.	Have you experienced a blackout, fainted, or lost consciousness as a result of a head injury within the last 12 months **OR** have you had a diagnosed concussion within the last 12 months?	YES ☐ NO ☐
10b.	Do you have a medical condition that is not listed (such as epilepsy, neurological conditions, kidney problems)?	YES ☐ NO ☐
10c.	Do you currently live with two or more medical conditions?	YES ☐ NO ☐

PLEASE LIST YOUR MEDICAL CONDITION(S) AND ANY RELATED MEDICATIONS HERE: _____

_____

GO to Page 4 for recommendations about your current medical condition(s) and sign the PARTICIPANT DECLARATION.

2017 PAR-Q+

If you answered NO to all of the follow-up questions about your medical condition, you are ready to become more physically active - sign the PARTICIPANT DECLARATION below:

- It is advised that you consult a qualified exercise professional to help you develop a safe and effective physical activity plan to meet your health needs.
- You are encouraged to start slowly and build up gradually - 20 to 60 minutes of low to moderate intensity exercise, 3-5 days per week including aerobic and muscle strengthening exercises.
- As you progress, you should aim to accumulate 150 minutes or more of moderate intensity physical activity per week.
- If you are over the age of 45 yr and **NOT** accustomed to regular vigorous to maximal effort exercise, consult a qualified exercise professional before engaging in this intensity of exercise.

If you answered **YES** to **one or more of the follow-up questions** about your medical condition:

You should seek further information before becoming more physically active or engaging in a fitness appraisal. You should complete the specially designed online screening and exercise recommendations program - the **ePARmed-X+ at www.eparmedx.com** and/or visit a qualified exercise professional to work through the ePARmed-X+ and for further information.

Delay becoming more active if:

- You have a temporary illness such as a cold or fever; it is best to wait until you feel better.
- You are pregnant - talk to your health care practitioner, your physician, a qualified exercise professional, and/or complete the ePARmed-X+ **at www.eparmedx.com** before becoming more physically active.
- Your health changes - talk to your doctor or qualified exercise professional before continuing with any physical activity program.

- You are encouraged to photocopy the PAR-Q+. You must use the entire questionnaire and NO changes are permitted.
- The authors, the PAR-Q+ Collaboration, partner organizations, and their agents assume no liability for persons who undertake physical activity and/or make use of the PAR-Q+ or ePARmed-X+. If in doubt after completing the questionnaire, consult your doctor prior to physical activity.

PARTICIPANT DECLARATION

- All persons who have completed the PAR-Q+ please read and sign the declaration below.
- If you are less than the legal age required for consent or require the assent of a care provider, your parent, guardian or care provider must also sign this form.

I, the undersigned, have read, understood to my full satisfaction and completed this questionnaire. I acknowledge that this physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if my condition changes. I also acknowledge that a Trustee (such as my employer, community/fitness centre, health care provider, or other designate) may retain a copy of this form for their records. In these instances, the Trustee will be required to adhere to local, national, and international guidelines regarding the storage of personal health information ensuring that the Trustee maintains the privacy of the information and does not misuse or wrongfully disclose such information.

NAME _____ DATE _____

SIGNATURE _____ WITNESS _____

SIGNATURE OF PARENT/GUARDIAN/CARE PROVIDER _____

For more information, please contact

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