Psychological, Inflammatory, and Blood-Brain Interface Biomarker Levels at Rest Between Untrained and Resistance Trained Groups and in Response to a Single Bout of Resistance Exercise in Healthy Adult Females

by

Michael David Diggs

(Under the Direction of Patrick O'Connor)

Abstract

Purpose: This research (i) investigated the acute responses of mood, cognitive inhibitory control, a blood-brain interface biomarker (S100 calcium-binding protein β; S100β), and an inflammation biomarker (c-reactive protein; CRP) to a single bout of high intensity resistance exercise in trained (TR) and untrained (UT) females, and (ii) cross-sectionally compared the TR and UT groups on these outcomes at rest to examine potential training adaptations. **Methods:** Thirty-seven young adult females (18=TR and 19=UT) participated in a randomized crossover design experiment, completing two sessions: one resistance exercise and one resting control. The full-body exercise protocol consisted of eight exercises and the rest protocol entailed watching a 50-minute National Geographic video on whales. Saliva samples and mood states were obtained before as well as immediately, 30-minutes, and 24-hours after the conditions. Cognitive inhibitory control was assessed before and 15 minutes after each condition using the Stroop Color-Word Test. Fingertip blood lactate was obtained before as well as immediately, 5-, and 15-minutes post-exercise. Heart rate and ratings of perceived effort and activated muscle pain intensity were obtained during exercise. **Results:** Cross-sectionally, S100β and inhibitory control did not differ between TR and UT. Vigor was moderately higher for TR than UT except the effect prior to rest was large (d=0.81) and significant (p=.019). CRP was moderately lower for TR than UT prior to rest (d=.65, p=.056) and 24-hours after (d=.65, p=.03). Acutely, TR and UT had psychological and physiological responses to high intensity acute exercise that did not differ. For the combined groups, the acute exercise increased feelings of vigor immediately and 30-minutes post-exercise (df=2, 72, F=7.455, p=0.001, $\eta^2 = 0.172$) and did not significantly change inhibitory control, CRP or S100β. **Conclusion:** In a sample of young adult females when compared cross-sectionally to the UT, the TR have higher vigor, lower CRP and do not differ on inhibitory control or S100β. The TR and UT respond similarly to an acute bout of high intensity whole body resistance exercise which increases vigor and does not change inhibitory control or salivary CRP and S100β.

Key words: Blood-Brain Barrier, Cognition, c-reactive protein, MoTrPAC, S100β, vigor

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by

Michael David Diggs

B.S., University of Alabama (2010)

M.S., University of Alabama at Birmingham (2018)

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by

Michael David Diggs

Major Professor: Patrick J. O'Connor

Committee: Jarrod Call

Chris D. Mojock

Electronic Version Approved:

Ron Walcott

Dean of the Graduate School

The University of Georgia

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DEDICATION

This is dedicated to Rachel, my wife. Rachel is a beautiful, mellifluous, supportive, hard-working, terpsichorean wife and mother. She is an all-American, a mighty host, and an army with its banners flown. This work is also dedicated to Rhyken, Quinlan, Zoie, and the little one on the way. Each of them is a unique delight and a joy to be around.

My parents, Mike and Leah Diggs, have been steadfast and diligent through all of life's hardships. I am thankful for their example of loyalty, work ethic, and determination. The same is true of my brother, Jonathan, and my sister, Lydia, both of whom I appreciate very much and am thankful for their love and support.

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Chapter I.

Introduction

1.1 Psychological and Physiological Significance

This dissertation research examined selected physiological and psychological responses to an acute bout of high intensity resistance exercise (also known as weight lifting) in samples of females who were either resistance exercise trained or untrained (not reporting any physical activity). Thus, there are two separate studies in this one research project; a cross-sectional study comparing training adaptations from at least three months of resistance exercise training as well as an acute exercise experiment. The experiment used a high intensity resistance exercise bout as a stimulus aimed at eliciting changes in indicators of inflammation, blood-brain interface permeability, mood, and cognition. The resistance exercise stimulus used in this study is identical to what is being used in a large ongoing NIH funded study titled Molecular Transducers of Physical Activity Consortium (MoTrPAC). This research design choice was made purposefully so that the dissertation results in the future could be compared as directly as possible to MoTrPAC results summarizing responses to resistance exercise in their sample of ~840 healthy adults.

This study fills several gaps in the literature. There is a need for research into resistance exercise because the preponderance of exercise research is conducted with aerobic exercise as the stimulus. There is a need for research conducted with females because the preponderance of resistance exercise research is conducted with male participants. There is a need for research aimed at integrating psychological and biological variables. In this dissertation psychological responses to acute resistance exercise are being examined in parallel with biomarkers of astrocyte perturbation and systemic inflammation to better understand plausible physiological mechanisms that might be impacting psychological outcomes of mood and cognitive inhibitory control.

Few exercise research studies have been completed examining blood-brain interface biomarker responses and no well-designed research study has examined the effects of resistance exercise on any aspect of the blood-brain interface (BBI) to date. Examination of exercise-related aspects of the BBI, which serves a host of neurological functions - chief of which is as neurometabolic intermediary and neuroprotective gateway - may be particularly important for females.

Females engage in relatively low rates of participation in resistance exercise; compared with males, females had 34% lower odds of meeting U.S. national recommendations for muscle strengthening exercise (Bennie, 2018). Hence, many females fail to accrue acute or chronic psychological and physical health benefits of resistance exercise.

While not a primary focus of the present dissertation it is worth pointing out that repeated acute bouts of resistance exercise cause adaptations that are thought to result in chronic health benefits including positive cognitive and mood changes. Some age-related biological changes, such as losses in lean muscle mass and bone density as well onset of dementia, are more pronounced in females. Overall compared to males, there appears to be a greater need for resistance exercise research in females to better understand the influences on various health outcomes.

By investigating the acute effects of resistance exercise on indicators of inflammation, the blood-brain interface, mood, and cognitive inhibitory control in both trained and untrained women we can start to better understand selected neuropsychological responses as well as the potential influence of chronic adaptations to resistance exercise (Figure 1.1). This study also may lay the foundation for future explorations to understand potential physiological mechanisms that interface between resistance exercise, mood, and cognition.

1.2 Limitations

Research on biomarkers response to exercise, while pivotal for understanding how our bodies respond to physical activity, encounters several challenges that researchers must navigate. One significant hurdle is the variability in biomarker responses among individuals. This variability stems from factors like age, sex, genetics, and overall health. For instance, biomarker levels can differ widely between a young athlete and a sedentary older adult or between males and females. This diversity makes it difficult to establish universally applicable biomarker thresholds or responses that are meaningful for most people.

Another complexity lies in the temporal dynamics of biomarker responses. When we exercise, biomarkers can change rapidly and potentially unpredictably based on the type, intensity, and duration of the activity. For researchers, this means carefully timing sample collection and the exercise stimulus to both capture time-based fluctuations accurately and minimize time-based error variance. Moreover, understanding the extent to which exercise affects biomarkers over time—both immediately after a session and in the long term— is complicated because changes are based on release, transport in tissues and circulation and metabolism which adds another layer of complexity to interpreting results, especially regarding novel biomarkers.

Physiologically, exercise engages multiple systems simultaneously. This intricate interaction among biomarkers can make it challenging to isolate the effects of exercise on any single marker. For instance, a biomarker linked to muscle damage may respond differently depending on whether someone is engaged in endurance training or resistance exercises. Moreover, standardizing measurement techniques and protocols across studies remains a persistent challenge. Variations in sample collection methods, assay procedures, and laboratory techniques also can introduce inconsistencies in biomarker data, complicating comparisons across different research studies.

Lastly, the generalizability of findings from exercise biomarker studies can be limited. Many studies, including the present investigation, focus on relatively small convenience samples, often with young healthy adults. Compellingly, extending these findings to other groups, such as older adults or individuals with chronic diseases, requires additional research efforts with substantial financial support.

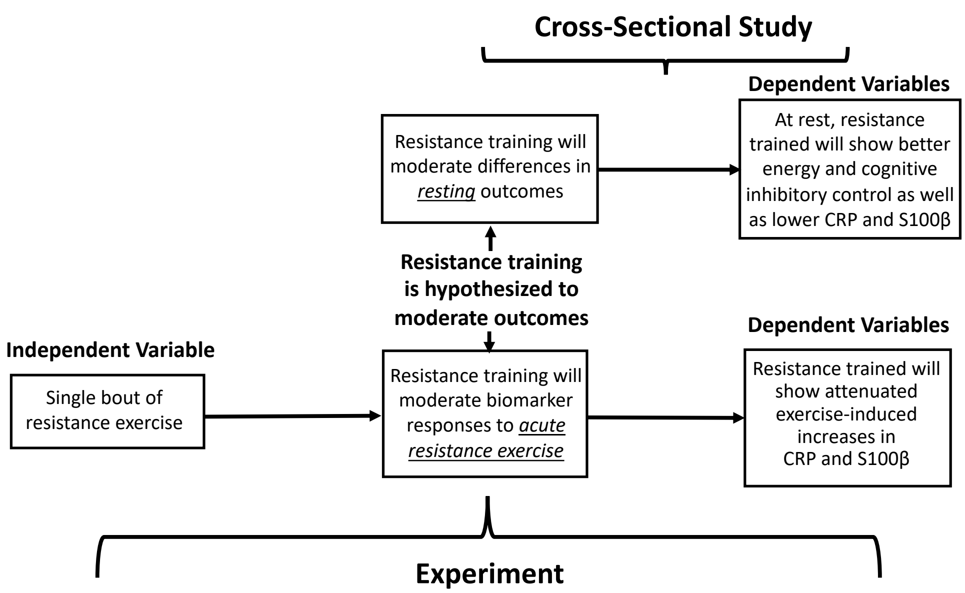
Despite these challenges, ongoing advancements in interdisciplinary collaboration, rigorous study design, and standardized methodologies hold promise for overcoming these hurdles. By addressing these limitations to the extent possible, researchers can deepen our understanding of how exercise influences biomarkers as well as the extent to which they have broader implications for mental and physical health as well as disease prevention.

1.3 References

Bennie, J. A., Lee, D. C., Khan, A., Wiesner, G. H., Bauman, A. E., Stamatakis, E., & Biddle, S. J. H. (2018). Muscle-Strengthening Exercise Among 397,423 U.S. Adults: Prevalence, Correlates, and Associations with Health Conditions. *Am J Prev Med*, *55*(6), 864-874. https://doi.org/10.1016/j.amepre.2018.07.022

1.4 Figures

Figure 1.1 Hypothesized moderating effects of resistance exercise training on resting outcomes and biomarkers of inflammation (CRP) and blood-brain interface integrity (S100β) in response to a single bout of resistance exercise in the two studies in this dissertation.



Chapter II.

Selected Neurophysiological and Psychological Effects of Acute Resistance Exercise

2.1 Blood-Brain Interface Structure and Function

The BBI is a specialized structure that separates peripheral blood circulation from the brain tissue, thereby helping to maintain the homeostasis of the central nervous system. It consists of tightly packed endothelial cells, surrounded by pericytes, astrocyte end-feet, and an extracellular matrix. The BBI selectively regulates the transport of substances into and out of the brain, protecting it from potentially harmful molecules entering the brain and maintaining a stable environment by allowing unneeded substances to exit the brain.

In this document the phrase "blood-brain interface" will be used as opposed to "blood-brain barrier" because it more clearly indicates the two-way nature of this neural interface. This is highlighted when the blood-brain interface and the neurovascular unit become altered or damaged. The functional unit of the blood-brain interface is not a barrier per se but the neurovascular unit. This neurovascular unit is composed of neurons, glia (astrocytes, pericytes, microglia), endothelial cells, and extracellular matrix components which function as metabolic intermediaries between neurons and the neurovasculature.

Neurons are the fundamental units of the central nervous system and are indirectly involved in metabolic exchange across the BBI. For instance, the neuron-astrocyte lactate shuttle functions to supply lactate from the periphery and ultimately provide a fuel to neurons. Astrocytes, with closer proximity to the cerebrovascular vessels, function as nutrient intermediaries for neurons while also contributing to the structure and function of the BBI. Pericytes, another type of glia, also act to aid in the structure and function of the BBI. The extracellular matrix, or the basement membrane, is a matrix of molecules and proteins adding structure and function. Endothelial cells form the lining of cerebrovascular vessels in the BBI. Healthy adjacent endothelial cells have tight junctions that prevent large molecules from passing through the interface. Figure 2.1 illustrates the blood-brain interface. The area indicated by the red arrow in Figure 2.1 shows the general area of the cells of the blood-brain interface that together constitute a neurovascular unit with the blue arrow indicating brain parenchyma (Sharif, 2018).

While many of the mechanisms of action of the BBI have not been fully elucidated, there does seem to be a multifunctional, tiered immunometabolic communication that occurs across each of these layers. Dysfunction in immunometabolic communications can alter receptor and transporter expression, affecting signaling of neurotransmitters and neuromodulators as well as transport of nutrients and metabolites to the brain. Gradual progressive deterioration through chronic inflammation leads to a disruption of the BBI which, given the multiple layers and dependent on the severity of degradation, appears to produce a subtle "loosening" of the interface. This process has been hypothesized to initially result in the paracellular passage of molecules that would not pass during a healthier state. Sustained chronic inflammation, or an acute severer traumatic injury can lead to an insurmountably large loss of integrity in the BBI. The diminished loss of integrity can disrupt the tight junctions between endothelial cells which allows for the passage of the cytokines and chemokines which promote brain responses (e.g., increased concentration of metalloproteinases) that can create positive feedback loops leading to further localized inflammation called neuroinflammation and potentially contributing to short-term, small changes in neural circuit activity involving mood and cognitive function.

Human research into the blood-brain interface has limitations due constrained and expensive techniques and tools such as invasive surgery and neuroimaging. Because advances are needed before BBI neuroimaging is readily available at a low-cost, a current alternative to learning about the BBI is by measuring changes in biomarkers of BBI integrity in response to standardized stimuli. A frequently used diagnostic and research biomarker to indicate deviations in blood-brain interface integrity is peripheral levels of S100β –a calcium-binding protein released from astrocytic end-feet when astrocytes are perturbed. Repeated perturbations of the BBI, specifically of astrocytes which are a part of the BBI, over time can lead to chronic neuroinflammation. Chronic neuroinflammation is an assault on the front lines of neural regulation that can be caused by chronic, systemic inflammation brought on by multiple factors such as obesity, metabolic disease, exposure to environmental toxins, traumatic brain injury, or ischemia/hypoxia (Rothermundt, 2003; Block, 2009). These conditions can have deleterious synergistic effects on the BBI, especially with aging. For instance, in the case of someone who has persistent high blood pressure and unregulated caloric intake leading to insulin resistance, these characteristics can contribute to the development of obesity and metabolic dysfunction. Metabolic dysfunction can lead to increased baseline levels of cytokines, such as interleukin-1β and tumor necrosis factor-alpha (each having NF-κB as a transcription factor), which can disrupt the neuroendothelial cells and loosen tight junctions of the BBI (reducing BBI integrity) precipitating the creation of a neuroinflammatory environment within the brain (DiSabato, 2016; Sun, 2022). Other insults like transient ischemia can result in the propagation of the inflammatory factors, in association with reactive oxygen species and matrix metalloproteinases, that can further degrade the integrity of the blood-brain interface as has been illustrated through contrast-enhanced imaging (Leigh, 2021). Traumatic brain injuries (TBI) are also known to produce adverse effects on the BBI, thus S100β is a commonly used biomarker to assess TBI severity in addition to being considered a biomarker of a chronic neuroinflammation in the absence of a TBI.

2.2 Inflammation and the Impact on the Blood-Brain Interface

Chronic inflammation can have a significant impact on the BBI and its integrity. The blood-brain interface is located between the brain parenchyma and blood vessels. Persistent systemic, chronic inflammation can result in alterations of the BBI and associated neurovasculature which can lead to both transient structural damage and more subtle dysfunction which allows the passage of larger than normal molecules into the brain as well as immune cells such as monocytes and lymphocytes which perpetuate the inflammatory response in the brain. Furthermore, glial cells such as microglia and astrocytes become activated and release pro-inflammatory cytokines, chemokines, and reactive oxygen species. The chronic perturbation of glia can create a positive feedback loop leading to dysregulation of the fundamental BBI structural element, the neurovascular unit, and the propagation of the neurodegeneration over time. Specific immune functions of glial cells are in Table 1.1 (Leiter, 2016).

BBI dysfunction indicate a decrease in interface tightness and a loss of integrity. The BBI disruption exposes the brain to peripheral cytokines and immune cells, which subsequently activates microglial cells and changes the extracellular environment promoting neurotoxicity. Decreased integrity increases the probability for the entry of plasma proteins, toxins, and leukocytes, which may compromise different brain regions, resulting in motor and cognitive impairment (Klein, 2017). This process further increases the activation of the immune system creating a vicious cycle. In this context, the anti-inflammatory effect of regular exercise training could either reduce peripheral inflammation, decrease the entry of inflammatory cells in the brain, or maintain the density of tight junctions of the BBI (Malkiewicz, 2019).

Inflammation literature is awash with many biomarkers to examine and many studies have conflicting evidence. Since this study aimed to elicit the differences between those who were resistance trained compared to an untrained sample across each outcome measure, a measure of systemic inflammatory response was needed. C-reactive protein is commonly used as a marker for systemic inflammation. A meta-analysis analyzed different modes of exercise and the corresponding CRP response. Across 75 articles and 4048 participants, resistance training was the most recommended mode of exercise to decrease CRP levels (Tan, 2024). More than that, a recent prospective, cohort study across 18 years linked moderate and high CRP to decreases in cognitive performance including aspects of executive functioning (Bahorik, 2024).

2.3 Resistance exercise effects on inflammatory status

Resistance exercise involves intentional, structured, repetitive movement against gravity or an external resistance, often using a band or a weighted device such as barbells, dumbbells, kettlebells, or machines design for strength training. Typical resistance exercise training programs use at least one of the aforementioned methods to perform concentric, eccentric, and/or isometric muscle actions.

Resistance exercise has been shown to have various benefits for overall health and well-being, include mood and cognitive functioning. One area of interest with implications for health is the potential impact of resistance exercise on reducing chronic inflammation. Acute resistance exercise generally induces mild acute inflammation responses which when repeated are thought to promote adaptations that reduce chronic inflammation. Skeletal muscle adaptations are typically triggered when the repeated resistance exercise stimuli are sufficient to invoke cardiovascular, skeletal, inflammatory, and immune responses that can, among other things, restructure the activated muscles and ultimately restore homeostasis.

Chronic inflammation is a sustained or overactive inflammatory response that is characterized by elevated levels of pro-inflammatory biomarkers and/or reduced levels of anti-inflammatory cells, the combination of which can contribute to the development and progression of several chronic conditions, including cardiovascular disease, type 2 diabetes, and certain types of cancer. Multiple stimuli are thought to contribute to chronic inflammation such as aging, infections and other diseases and conditions such as smoking and diet.

A low-to-moderate dose of regular resistance exercise might offer a nonpharmaceutical, beneficial therapy for chronic inflammation via an attenuation of upstream responses. Regular resistance exercise, for example, can improve insulin sensitivity as an aid against type 2 diabetes and increase skeletal muscle mass which can help reduce excess adipose tissue, especially abdominal and visceral adipose tissue. Resistance exercise also can decrease pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha), while simultaneously boosting anti-inflammatory cytokines, such as interleukin-10 (IL-10). Resistance exercise also can aid in management of oxidative stress (the balance between reactive oxygen species and antioxidants) by influencing a common transcription factor (NF-κB) to both IL-6 and TNF-alpha thereby mitigating effects of reactive oxygen species through antioxidant responses to exercise.

Exercise-induced neurological, endocrine, and inflammatory responses are key processes contributing to skeletal muscles adapting to overload stimuli. Experts on the topic of exercise and the immune system have argued that myokines could be a means to help maintain immune homeostasis when threatened by disease processes involving systemic inflammation such as obesity, cardiovascular disease, atherosclerosis, neurodegenerative diseases, insulin resistance, and type 2 diabetes (Rohm, 2022). Myokines are cytokine proteins which act on immune cells after being released by muscle cells in response to muscle actions. Topic experts also hypothesize that exercise-induced increases in proteins that influence the immune system, such as myokines, can be an effective means to redress chronic low-grade inflammation commonly found in chronic diseases (Mee-Inta, 2019; Severinsen, 2020). Moreover, inflammatory cytokines, which act on the brain, also have been associated with cognitive impairments (Geng, 2018) and worsened mood such as elevated symptoms of anxiety and depression (Costello, 2019; Hunt, 2020). While resistance exercise potentially can be beneficial for reducing chronic inflammation, it’s important to note that the effects vary among individuals, and likely are influenced by factors such as absolute and relative exercise intensity, duration, frequency, and overall lifestyle variables that moderate inflammatory status (e.g., diet, sleep quantity and quality).

2.4 Lactate: A Byproduct of Vigorous Exercise with Blood-Brain Interface Interactions

Since the stimulus in this study is an acute resistance exercise designed to initiate a robust inflammatory response, it is potentially useful to consider typical products of the metabolic pathways of vigorous resistance exercise such as lactate. Lactate is a product of glycolysis, a significant metabolic pathway that contributes to the performance of resistance exercise. While lactate has traditionally been considered a metabolic waste product, much of the recent research has demonstrated that lactate is recycled for the continued use in anaerobic glycolysis as well as in the tricarboxylic (TCA) cycle within mitochondria. Normally, glucose is processed into pyruvate, which enters the TCA cycle to produce ATP through the mitochondrial electron transport chain. However, under hypoxic or anoxic conditions, only 2 ATP molecules are produced per glucose molecule, and pyruvate is converted into lactate by lactate dehydrogenase a process called anaerobic glycolysis. Anerobic glycolysis is a primary metabolic pathway leveraged to support resistance exercise and high intensity, powerful movements. In aerobic glycolysis, lactate is formed despite the presence of normal oxygen levels. This metabolic pathway promotes the conversion of pyruvate into lactate rather than its entry into the TCA cycle. The role of lactate is in the brain has become better understood in recent years. In addition to evidence of the astrocyte-neuron lactate shuttle hypothesis (ANLSH), lactate is a metabolic and signaling factor of considerable importance to brain function (Ferguson, 2018). For instance, research indicates that through the ANLSH, neurons under some conditions prefer lactate as an energy substrate over glucose (Bonvento, 2021). In addition to being an energy substrate, lactate might also function as a signaling molecule in areas of the brain such as hippocampus and amygdala with implications for decision making, memory consolidation, and emotion regulation (Magistretti, 2018). Astrocytic function in the ANLSH implicates astrocytes as essential metabolic thoroughfares for neurons allowing for sustained function during states of high neuronal activity and decreased glucose through lactate as the chief energy substrates. The interplay between energy supply and demand is crucial in determining overall neurological outcomes, and the metabolic contributions of astrocytes play a significant role in this process.

The production of lactate by astrocytes, despite having abundant mitochondria, raises questions about their preference for lactate production instead of using pyruvate for energy generation. The enzyme pyruvate dehydrogenase is less active in astrocytes due to phosphorylation, favoring aerobic glycolysis. Astrocytes also have a unique organization of mitochondrial respiratory chain complexes, resulting in poor mitochondrial respiration compared to neurons. Lactate may play a role in signaling structural changes to the blood-brain interface through vascular endothelial growth factor stimulation, promoting angiogenesis, and fortifying the integrity of the BBI (Morland, 2017). This dual function of lactate as an energy substrate and signaling molecule may have implications for understanding the effects of resistance exercise on the brain. Hence, lactate will be measured in the present study to help confirm exercise intensity and as an exploratory variable in relation to mood and cognition,

In traumatic brain injury (TBI), elevated lactate and S100β levels in the brain are generally associated with TBI severity. Elevated lactate levels with normal oxygen levels indicate better clinical outcomes, while high lactate levels with low oxygen levels indicate poorer outcomes. Brain oxygen levels and blood lactate levels have been identified as reliable predictors of TBI outcomes. One study using magnetic resonance spectroscopy and peripherally administered labeled lactate showed that increased lactate uptake and oxidation in the brain are associated with improved clinical outcomes in TBI patients (Gallagher, 2009). These findings have prompted the exploration of intravenous administration of lactate solutions as a potential therapeutic intervention for TBI patients. If more evidence supports these findings, then it may be useful to determine if skeletal muscle activity could be leveraged as a lactate factory to promote lactate as an alternative energy substrate for the brain health and recovery from insults.

Another study highlighted the importance of neurometabolism in TBI focusing on individuals with head injuries and aiming to predict neurological outcomes based on glucose, lactate, and oxygen metabolism (Glenn, 2003). Patients with favorable outcomes had higher cerebral metabolic rate of oxygen (CMRO2), lower blood-brain interface damage, and lower systemic lactate and glucose levels, suggesting that they can effectively use lactate as an additional fuel source. On the other hand, patients with more severe injuries and higher systemic lactate levels appear to be less able to use lactate effectively, leading to poorer outcomes. The study concluded that CMRO2 and arterial lactate levels are strong predictors of neurological outcome during the first 6 days after moderate or severe TBI. The ability to use alternative fuel sources in lieu of glucose, such as keytones or lactate, might be a factor in determining patient outcomes. Lactate metabolism in the brain, particularly in astrocytes, plays a complex role in energy generation and signaling, and it has significant implications for neurological outcomes after traumatic brain injury. Further studies are needed to explore the molecular mechanisms underlying lactate metabolism and its effects on the blood-brain interface, and how resistance exercise training might serve as a non-pharmaceutical therapy for neurological insults and neurodegenerative diseases associated with diminished blood-brain interface integrity.

Therefore, the ability to meet energy demands through various means, including the use of alternative fuel sources like lactate, may distinguish patients with favorable recovery from those with unfavorable outcomes. Since lactate is not, as historically thought, solely a waste product but instead a vital energy substrate and molecular signal, further understanding of lactate metabolism within the brain could be a critical factor in predicting the diverse health timelines in response to acute insults to the BBI such as traumatic brain injury, ischemia, and downstream neurodegenerative diseases and adverse psychological responses.

In summary, one logical place to start a line of research is to examine the influence of single, standardized stimuli on measurable outcomes relevant to both brain function and the BBI and examine their inter-relationships.

2.5 Resistance exercise effects on mood

While there is limited evidence testing hypothesized brain-related mechanisms for effects of exercise on mood, dozens of experiments have investigated the influence of a single bout of exercise on mood states. The primary consistent findings from this research are that a single bout of low-to-moderate intensity exercise results in transient increased feelings of energy and calmness. Most of the research has examined aerobic exercise modes such as running, cycling, and swimming; nevertheless, similar observations have been reported for resistance exercise. For example, a sample of 26 pregnant females who performed low-to-moderate intensity resistance exercise twice weekly for 12 weeks on average reported increased feelings of energy after 22 of the 24 workouts (Herring, 2009).

One previous experiment with college students examined energy and fatigue responses to an acute bout of resistance exercise in sedentary females(Ward-Ritacco, 2016). It was found that young, sedentary females reported below-average feelings of energy at baseline while measures evaluating energy using the Profile of Mood States questionnaire were higher during and after the acute bout of resistance exercise (70% 1RM), with medium-to-large effect sizes (d=0.37-0.73), when compared to the no exercise control group. Two prior studies investigating mood and acute resistance exercise (Bartholomew, 2001; Focht, 1999) showed smaller effect sizes (d=0.30-0.36). These studies used workloads of 50% 1RM and 80% 1RM, for low and high workloads, respectively, alongside a no exercise control.

The mechanisms by which acute exercise causes improved mood are poorly understood. An early hypothesis that exercise-induced increases in blood lactate caused increased symptoms of anxiety in anxiety-prone patients has been shown to be incorrect (O'Connor, 2000). However, worse mood states have been associated with poorer BBI function (Wang, 2022), including after a TBI that injured the BBI (Hubbard, 2022). And it has been known for decades that effective medical therapies for mood disorders influence the blood-brain interface (Preskorn, 1981). The field of exercise psychology would be moved forward if science-based evidence were generated regarding biomarkers of BBI function and relationships with acute exercise-induced changes in mood and cognition.

2.6 Resistance exercise effects on inhibitory control

Positive effects of aerobic exercise on cognition have been hypothesized to result, in part, from increased cerebral blood flow due to neurocognitive demand and increased cardiac output. Additionally, increases in lactate (Xue, 2022) and peripheral neurotrophic factors such as brain-derived neurotrophic factor (BDNF) have been suggested as mediators of increased cognitive performance following exercise. It is important to note that biomarkers collected from the periphery may not be representative of central nervous system responses or those present in the cerebrospinal fluid. Whether or not a neurotrophic factor or biomarker is able to act centrally is likely gated by the BBI based on factors such as the size of a molecule and the tightness of the BBI. There is a need to better understand the influence of a single bout of resistance exercise on the BBI and related phenomena, such as biomarkers of BBI integrity, and the extent to which such phenomena are related to changes in cognitive function after exercise.

Over the past several decades there has been a growing body of research investigating the relationships between exercise and cognition. However, fewer investigations have explored whether a single bout of resistance exercise has an impact on cognitive function. A prominent meta-analytic review identified 12 experiments with at least fair methodological quality (Wilke, 2019). It was found that acute resistance exercise had a positive mean effect on measures of inhibitory control (Standardize mean difference [SMD]: 0.73, 95% CI 0.21–1.26, $p = 0.01$) and cognitive flexibility (SMD: 0.36, 95% CI 0.17–0.55, $p = 0.004$) when compared to no exercise controls (Chang, 2012). For instance, this analysis showed positive results after acute resistance exercise bouts on cognitive function using the Stroop Color-Word Test (SCWT) as their measure of inhibitory control. In this analysis a dose-response relationship was established between differing resistive loads – control, 40%, 70%, 100% - and cognition. Specifically, performance on the SCWT was most improved between 60-80% 10RM centering on the 70% 10RM condition.

2.7 Exercise and S100β

Studies have investigated sport and physical activity effects on the BBI using S100β as a biomarker indicative of decreased BBI integrity. Many field investigations have shown increases in S100β post-exercise (Bailey, 2011; Dietrich, 2003; Graham, 2011; Hasselblatt, 2004; Michetti, 2011; Neselius, 2012; Otto, 2000; Schulpis, 2007; Stalnacke, 2003, 2004, 2006; Straume-Naesheim, 2008; Tyler, 2010; Watson, 2005, 2006) while some have not shown this relationship (Cheuvront, 2008; Mussack, 2003; Saenz, 2006; Schulte, 2011; Stalnacke, 2008; Stavrinou, 2011; Zetterberg, 2007). The intensity, modality, and duration are variable across this small literature. In most of these studies confounding variables were not accounted for making it uncertain if exercise is the true sole cause of any pre- to post- activity changes in S100β reported. Examples of the confounding variables include training status, environmental heat, hydration status, sleep, circadian rhythm, nutrition, caffeine intake, alcohol intake, marijuana intake, sleep, neurologically ill sample, acute head trauma (e.g. boxing, football, soccer), chronic hypoxic conditions in diving (Andersson, 2009), decompression after scuba diving some of which have been summarized in a systematic review and visually in Figure 2.2 (Koh, 2014) . Another broad confounding variable are extracerebral sources of S100β (Arrais, 2022; Pham, 2010).

In the landscape of exercise research, resistance exercise is under-researched for multiple reasons including access, feasibility, interest, and requisite expertise. This void in exercise research may be particularly detrimental to females as sixty-one percent of females in the United States do not engage in resistance exercise, with participation rates decreasing with age (Bennie, 2018). Since resistance training is associated with improved physical function and reduced risk of cardiovascular disease and all-cause mortality (Garber, 2011), increasing engagement in muscle strengthening activity should be a priority for everyone.

There appears to be only one investigation of the effects of acute resistance exercise on S100β in a small mixed gender sample that included males and a few females (Rogatzki, 2018). Each participant's one-repetition maximum (1RM) was obtained for the following free weight exercises: dumbbell squat, dumbbell flat bench press, dumbbell bicep curl to shoulder press, leg press, and kneeling overhead triceps extension. Participants were then placed into one of three different intensities: low intensity (30% 1RM, n=2 females), moderate intensity (60% 1RM, n=2 females), or high intensity (90% 1RM, n=4 females). All three groups completed the same workout in the same order but with a resistance corresponding to the different percentages of their 1RM. Each exercise was performed for 30 seconds followed by 30 seconds of rest, with this cycle being repeated for four sets totaling 2 minutes of exercise and 2 minutes of rest. After four sets, the participant was given 1 minute of rest to transition to the next exercise. Blood was drawn immediately before and within 30 minutes after the resistance exercise protocol. The female-specific responses were not reported separately. The changes in S100β pre-to-post according to exercise intensity were: 0.0003pg/mL (30% 1RM), 0.01 pg/mL (60% 1RM), and 0.006 (90% 1RM). Neither low resistance exercise ($p = 0.348$, $d = 0.283$) nor high resistance exercise ($p = 0.308$, $d = 0.362$) caused a significant increase in S100β. The moderate resistance exercise protocol ($p = 0.029$, $d = 0.548$) did cause a significant increase in S100β. This study had low power for finding statistically significant differences. Thus, the best of the available, very weak, evidence suggests that acute resistance exercise may increase S100β levels in females. Clearly, better research is needed to accept or reject this possibility.

2.8 References

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2.9 Figures

Figure 2.1 Anatomy of the blood-brain interface

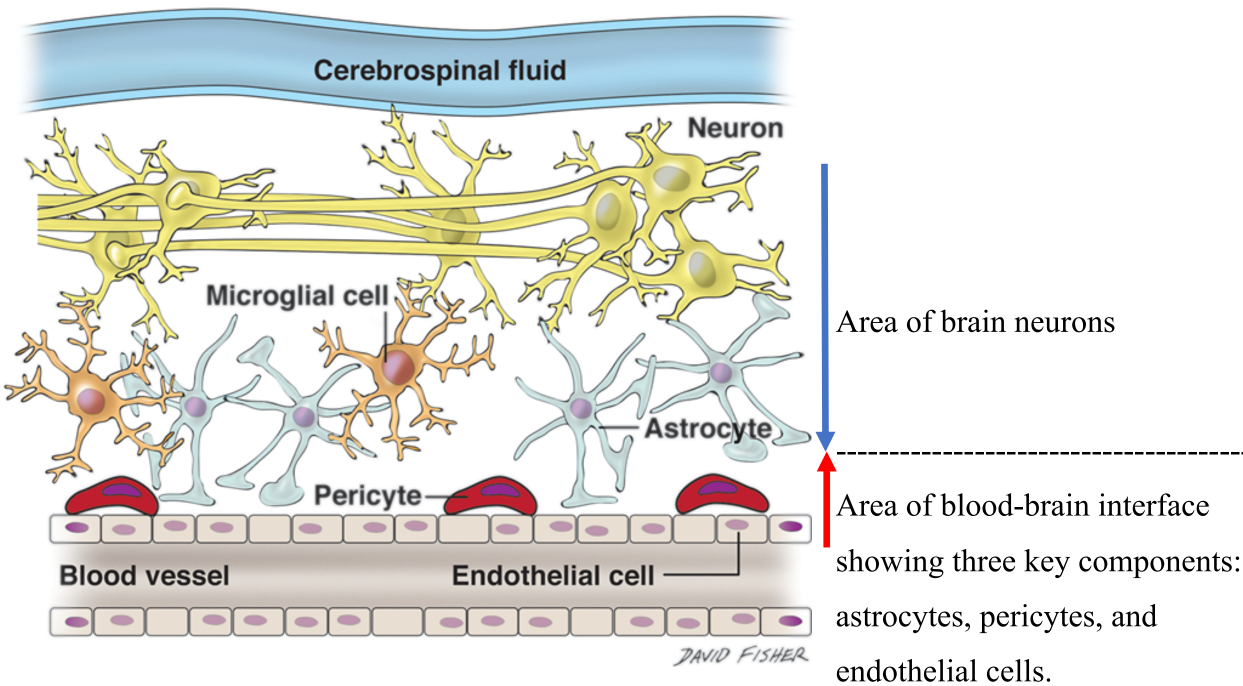


Figure 2.2 Cross-sectional layering of blood-brain interface (Abbott, 2010)

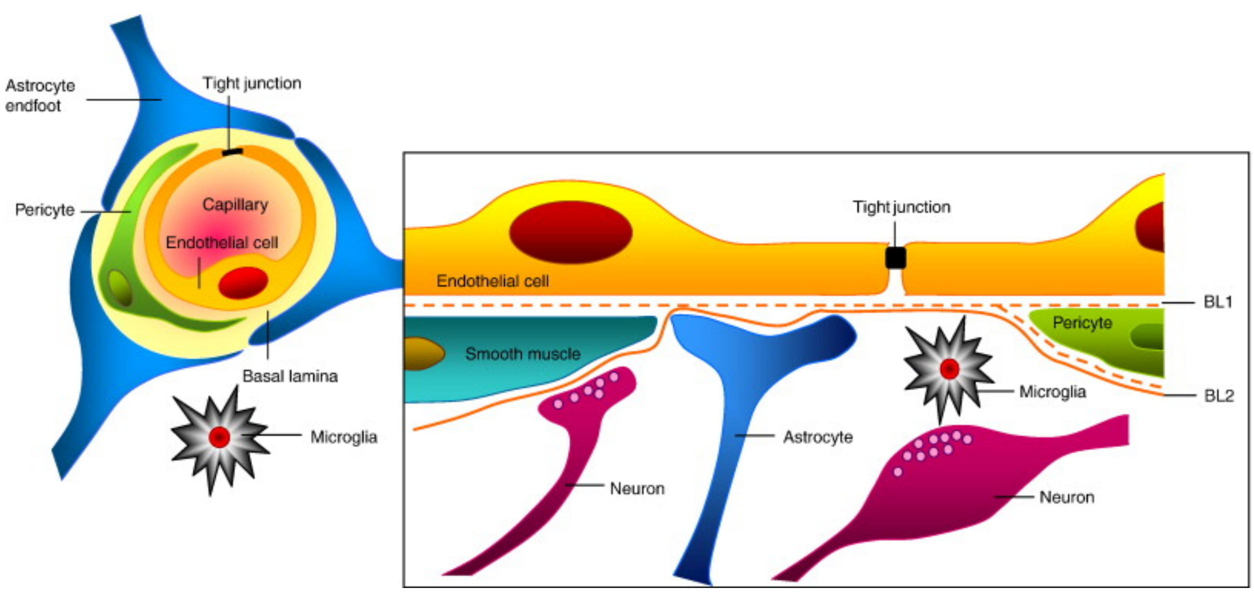
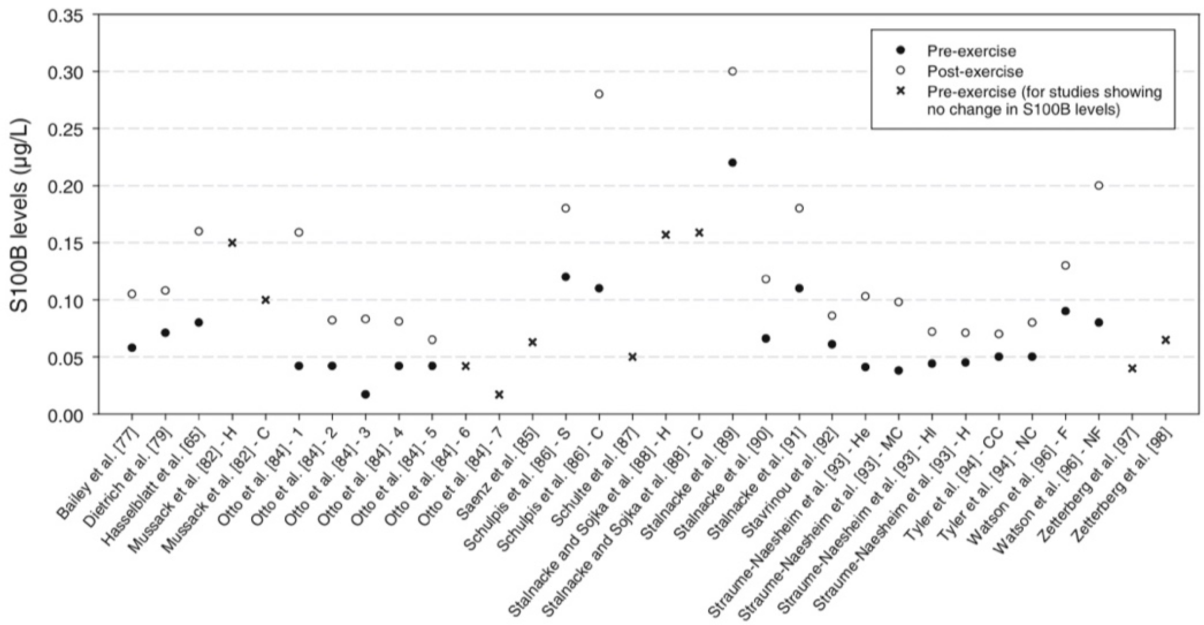


Figure 2.2 Summary of S100β responses to conditions involving exercise presented in a systematic review (Koh, 2014).



2.10 Tables

Table 2.1 Immune function of glial cells (Leiter, 2016)

Glial Cell Type	Hypothesized structural and physiological functions of glial cells
Astrocytes	Help form the physical structure of the brain and performs several active roles, including the secretion or absorption of neurotransmitters and maintenance of the BBI
Microglia	Surveils the local microenvironment to respond to injuries by releasing pro-inflammatory molecules; phagocytize clearance of apoptotic cells
Pericytes	Regulate BBI integrity; clear and phagocytize cellular debris; neurogenic potential to differentiate into neurons
Perivascular macrophages	Phagocytize cellular and pathogenic debris; maintain brain homeostasis; maintain tight junctions; initiate CNS acute phase response via the production of prostaglandins

Chapter III.

Psychological, Inflammatory, and Blood-Brain Interface Biomarker Levels at Rest Between Untrained and Resistance Trained Groups and in Response to a Single Bout of Resistance Exercise in Healthy Adult Females

Michael David Diggs[1], Alison R.Bamford[2], Elizabeth A.Thomas[2] & Patrick J. O'Connor[1]

[1]Department of Kinesiology, University of Georgia, Athens, GA 30601

[2]Institute for Interdisciplinary Salivary Bioscience Research, UC Irvine, Irvine, CA 92697

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3.1 Abstract

Purpose: This research (i) investigated the acute responses of mood, cognitive inhibitory control, a blood-brain interface biomarker (S100 calcium-binding protein β; S100β), and an inflammation biomarker (c-reactive protein; CRP) to a single bout of high intensity resistance exercise in trained (TR) and untrained (UT) females, and (ii) cross-sectionally compared the TR and UT groups on these outcomes at rest to examine potential training adaptations. **Methods:** Thirty-seven young adult females (18=TR and 19=UT) participated in a randomized crossover design experiment, completing two sessions: one resistance exercise and one resting control. The full-body exercise protocol consisted of eight exercises and the rest protocol entailed watching a 50-minute National Geographic video on whales. Saliva samples and mood states were obtained before as well as immediately, 30-minutes, and 24-hours after the conditions. Cognitive inhibitory control was assessed before and 15 minutes after each condition using the Stroop Color-Word Test. Fingertip blood lactate was obtained before as well as immediately, 5-, and 15-minutes post-exercise. Heart rate and ratings of perceived effort and activated muscle pain intensity were obtained during exercise. **Results:** Cross-sectionally, S100β and inhibitory control did not differ between TR and UT. Vigor was moderately higher for TR than UT except the effect prior to rest was large (d=0.81) and significant (p=.019). CRP was moderately lower for TR than UT prior to rest (d=.65, p=.056) and 24-hours after (d=.65, p=.03). Acutely, TR and UT had psychological and physiological responses to high intensity acute exercise that did not differ. For the combined groups, the acute exercise increased feelings of vigor immediately and 30-minutes post-exercise (df=2, 72, F=7.455, p=0.001, $\eta^2 = 0.172$) and did not significantly change inhibitory control, CRP or S100β. **Conclusion:** In a sample of young adult females when compared cross-sectionally to the UT, the TR have higher vigor, lower CRP and do not differ on inhibitory control or S100β. The TR and UT respond similarly to an acute bout of high intensity whole body resistance exercise which increases vigor and does not change inhibitory control or salivary CRP and S100β.

Key words: Blood-Brain Barrier, Cognition, c-reactive protein, MoTrPAC, S100β, vigor

3.2 Introduction

A myriad of psychobiological responses to an acute bout of exercise have been documented and these literatures are biased toward studies of men performing aerobic type exercise such as running and cycling (Cowley, 2021). Prominent psychological changes in response to acute exercise in laboratory experiments, which typically have involved moderate intensity aerobic exercise of 20 to 45 minutes, include consistent moderate-sized transient improvements in feelings of energy/vigor (Loy, 2013) and small reductions in feelings of tension/anxiety (Ensari, 2015) as well as improvement in some aspects of cognitive functioning (Chang, 2012) for up to about one hour post-exercise. A smaller literature focused on the effects of acute resistance exercise shows enhanced feelings of energy post-exercise and inconsistent anxiety reductions (Ensari, 2015; Herring, 2009) while the largest mean change has been for inhibitory control (standardized mean difference = 0.73) (Wilke, 2019), one index of executive function (Baggetta, 2016). Most of these studies have used moderate intensity resistance exercise and reviewers have pointed out that more data from low and high intensity resistance exercise bouts are needed (Chang, 2012; Wilke, 2019).

Few investigations have examined co-occurring biological changes that could potentially help to account for the psychological changes observed in response to acute exercise. In rodents the potential role of acute exercise-induced changes in brain norepinephrine and galanin in relation to signs of anxiety has been explored (Sciolino, 2012). In humans, a few studies have indirectly indexed exercise-induced brain function in relation to changes in anxiety by measuring startle responses (Smith, 2013). Regarding feelings of energy/fatigue, one study has implicated central nervous system neurotransmitter histamine in feelings of fatigue but not energy in response to acute aerobic cycling exercise. The investigation used pre-exercise administration of a placebo or doxepin, a histamine receptor (H1) antagonist, which blocked post-exercise changes in feelings of fatigue but not changes in feelings of energy. Regarding cognition, the results have been mixed that cognitive changes following acute exercise can be accounted for by changes in serum levels of brain derived neurotrophic factor, the most commonly tested potential biological correlate of cognitive changes, and methodological inelegancies have been suggested as possibly explaining the varied findings (Piepmeier, 2015).

The potential role of the blood brain interface (BBI), measured directly or indirectly via biomarkers, in relation to psychological responses to an acute bout of resistance exercise has yet to receive any research attention. For example, there are no studies that have used low intensity pulsed ultrasound or magnetic resonance imaging (diffusion prepared arterial spin labeling) techniques to directly examine BBI changes in response to acute exercise (Carpentier, 2016; Pappas, 2024). Rodent research showed that compared to resting controls, 30-minutes of forced swimming increased BBI permeability to infused radiolabeled albumin in several brain regions in 8-9 week-old rats 30-minutes, but not 15-minutes, after the swim (Sharma, 1991). It is unclear if this increased BBI permeability was caused primarily by the exercise stimulus or the stress associated with forcing rats to swim.

Numerous studies have examined acute exercise effects on blood biomarkers thought to reflect BBI permeability. Most of these investigations have included S100β, a calcium-binding protein primarily found in the central nervous system in astrocytes and glial cells but also present peripherally in cardiac and skeletal muscle as well as fat tissue (Arrais, 2022). The extent to which peripheral sources of S100β contribute to serum levels is uncertain but one study of 200 individuals found no correlation between body mass index and S100β levels suggesting that S100β from peripheral adipose did not contribute significantly to the serum levels (Pham, 2010).

At least 23 studies have examined acute exercise and S100β. Most of these studies measured serum S100β while one study measured salivary S100β (Michetti, 2011). Most of these studies (65%) found a mean increase in S100β following exercise (Koh, 2014). While these increases were small, typically less than 0.07 μg/L, the results potentially suggest that acute exercise causes a potentially unhealthy disruption in the BBI. One interpretive challenge stems from the fact that most of these investigations also involved exercise with concomitant environmental stimuli that could confound the results. Changes in S100β reported in studies of boxing (Graham, 2011), scuba diving (Stavrinou, 2011), hiking to high altitude (Bjursten, 2010), and competitive soccer which involves heading (Straume-Naesheim, 2008), for example, could be attributed in part to confounding non-exercise variables such as forces applied to the brain from hits to the head or the influence of pressure changes on the BBI.

There appears to be only one study of the effect of a single bout of resistance exercise alone on S100β (Rogatzki, 2018). College students (n=18) were placed into low (30% 1 RM, n=6, 2 females), moderate (60% 1 RM, n=6, 2 females) or high (90% 1 RM, n=6, 4 females) intensity resistance exercise groups. Four sets of six exercises (squat, bench press, biceps curl, shoulder press, leg press, and triceps extension) were performed for 30 seconds followed by 30 seconds of rest for a total of 2 minutes of exercise and 2 minutes of rest with an additional minute of rest between exercises. Moderate, but not low or high intensity exercise significantly increased serum S100β. However, the mean values of S100β did increase for all three intensities and the statistical power for detecting an increase was low. Hence, whether there is truly a dose-dependent effect of exercise intensity on S100β is uncertain. If the data for females had been reported separately, the small sample sizes would have rendered the data difficult to interpret in a scientifically meaningful way. One review of exercise and sport studies involving S100β found a bias toward studying males; in the studies describing the sex of the samples, the total number of females and males included were 14 (2%) and 655 (98%), respectively. The National Health Interview Survey found that 35% of men and 27% of women met the muscle-strengthening federal guidelines. In sum, there clearly is a need for rigorous laboratory research investigating the influence of a single bout of resistance exercise *per se* on S100β, especially in female samples (MMWR, 2022).

The BBI and its functions are influenced by inflammation and several aspects of inflammation are influenced by exercise. Chronic, systemic inflammation disrupts the integrity of the BBI resulting in increased permeability (Galea, 2021). Regular physical activity is consistently negatively associated with levels of inflammatory biomarkers in population-based cohort studies (Beavers, 2010). Randomized controlled trials of resistance exercise training (n=19) showed that C-reactive protein (CRP), a widely used index of chronic inflammation, is consistently reduced post-training, with a mean standardized effect size of −0.542 (Costa, 2019). There are few studies of the influence of acute resistance exercise on CRP and the findings are mixed. One study of 19 men found no change in CRP after 8 sets of 10 reps of isokinetic leg exercise (Gordon, 2017). A separate study of 14 mid-aged men found that serum CRP increased by 25% immediately after the completion of 10 low intensity (35% of MVC) resistance exercises while CRP values decreased by 7% in a non-exercise control condition (Bizheh, 2011). Animal research has linked CRP to BBI disruptions. Using both a cell culture model of the BBI and isolated whole guinea pig brain preparation, both approaches showed that CRP directly influenced BBI integrity and these effects were observable from 15 to 60 minutes post treatment

(Librizzi, 2001). There is a gap in our understanding of the potential effect of acute resistance exercise on CRP in humans as well as how any changes might relate to BBI integrity especially among understudied females (Rose, 2021).

At least one large cross-sectional study (n=2,523) found that plasma lactate was positively associated with systemic inflammation as measured by CRP (Pan, 2019). High intensity exercise increases blood lactate which crosses the BBI and has been hypothesized to have multiple long term (e.g., synaptic plasticity, memory formation) and short term (e.g., a fuel source, contribution to calcium signaling) impacts on the brain. Accordingly, it is of potential exploratory interest to examine associations between exercise-induced increases in blood lactate and biomarker and psychological outcomes in an experiment examining potential BBI related psychobiological responses to high intensity acute resistance exercise (Brown, 2015; Costa, 2019; Kuhlmann, 2009).

3.3 Aims & Hypotheses

One key aim of this study was to quantify the influence of an acute bout of high intensity resistance exercise on CRP and S100β and to assess the magnitude of these responses in relation to changes in feelings of energy, cognitive inhibitory control, and blood lactate. Another aim was to test whether untrained (UT) individuals respond to a high intensity bout of resistance exercise differently compared to those who have psycho-biologically adapted to regular resistance training (TR). Another aim was to test cross-sectionally if the biological or psychological outcomes measured at rest differed between TR and UT groups, presumably reflecting the effects of exercise training adaptations.

Based on the existing literature briefly outlined above it was hypothesized that:

H1: At rest (i.e., both the pre-condition baseline testing [T1] and the 24-hour post-condition testing [T4]), the TR group will be characterized by higher feelings of energy and lower resting values of S100β and CRP compared to the UT group.

H2: Immediately (T2) and 30-minutes (T3) after completing a single bout of resistance exercise the TR and UT groups combined will have increased feelings of energy compared to no changes from baseline (T1) in the rest condition.

H3: Fifteen minutes (T2.5) after completing a single bout of resistance exercise the TR and UT groups combined will have improved cognitive inhibitory control performance compared to no changes from baseline (T1).

H4: Immediately (T2) and 30-minutes (T3) after resistance exercise the TR and UT groups combined will have increased CRP compared to no changes from baseline (T1).

H5: Thirty-minutes (T3) after a single bout of resistance exercise S100β will be increased in the TR and UT groups combined compared to baseline.

H6: Thirty-minutes after a single bout of resistance exercise the increases in S100β and CRP will be lower for the TR compared to the UT group.

H7: The changes in CRP and S100β 30-minutes after exercise, for the two groups combined, will be significantly inversely associated with the changes in both feelings of energy and cognitive inhibitory control performance.

H8: The increases in lactate immediately after exercise, for the two groups combined, will be significantly associated with the changes S100β, CRP, feelings of energy, and inhibitory control.

Study Design

A cross-sequential research design was used. This design involves both cross-sectional comparisons between groups and the testing of those groups prospectively. Cross-sectional comparisons were made between a resistance trained (RT) and an untrained (UT) group at both a pre-condition baseline (T1) and 24-hours later at a post-condition testing time (T4). After baseline, all participants were randomly assigned in blocks of four to the order in which the acute exercise or resting control conditions were completed using the Research Randomizer website. Half the sample completed exercise first and the other half completed rest first. Participants subsequently crossed over to the other condition. In both conditions, the prospective component of the research involved repeated measures made at baseline (T1), immediately following exercise or passage of the equivalent amount of rest time (T2), and 30-minutes post-condition(T3).

3.4 Methods

Participants

Flyers, emails, visits to local gyms, and snowball sampling were used to identify potential study participants who were directed to complete an online screening for the purpose of applying the inclusion and exclusion criteria.

The exclusion criteria were: males, females using hormonal birth control, pregnant individuals, those with a concussion in the past year or a neurological illness, individuals meeting United States federal guidelines for aerobic exercise (>150 minutes of exercise per week or >75 minutes of moderate to vigorous exercise per week during either of the prior two weeks), those with medical or health-related contraindications for vigorous intensity resistance exercise, individuals over 45 years or under 18 years old, and those with elevated resting systolic (>140 mmHg) or diastolic (>90 mmHg) blood pressure. Additional exclusion criteria included individuals characterized by a color vision deficiency, regular users of anti-inflammatory over-the-counter medications, anti-inflammatory prescriptions, antioxidant medications, those consuming more than six servings of dark fruits or vegetables per day in the past week, and individuals with chronic illnesses such as COPD, cancer, inflammatory bowel diseases, cardiovascular disease, hypertension, chronic active or latent infections, or active or latent infections requiring chronic antibiotic or antiviral treatment. Also excluded were individuals with HIV or active hepatitis B or C. Users of any amount or type of tobacco and marijuana users who used ≥3 days/week in any form were also excluded.

Those included in the resistance trained (TR) group were required to report having completed regular resistance training sessions involving ≥3 upper and ≥3 lower body muscle groups at least twice a week for more than three months, using a set/rep/load regimen associated with increases in muscle strength or mass. Those included in the untrained (UT) group did not report engaging in any type of regular physical activity. A total of 37 participants completed the study, 18 TR and 19 UT. The flow of study participants is summarized in Figure 3.1. A statistical power analysis using G*Power, with alpha error of 0.05, beta error of 0.20 and an assumed correlation between repeated measures of 0.70 and a desire to detect a moderate effect size (i.e., f effect size = 0.17), it was found that a total sample size of 36 was required given the 2 groups x 3 times mixed model design.

Protocol

Participants were instructed to abstain from exercise for at least 24 hours before each visit, with visits separated by a minimum of 48 hours. All testing sessions were begun in the morning prior to 12pm. Collection timepoints for both rest and exercise conditions were as follows: at baseline (T1), immediately post-condition (T2), 30-minutes post-condition (T3), and 24-hours post-condition. Participants arrived at the laboratory for their first visit, sat and read an informed consent document that had been approved by the University of Georgia IRB, had any questions answered and signed the document.

A heart rate monitor was affixed to the chest then heart rate and blood pressure measures were made. A finger-prick blood sample (50µl) was obtained to measure lactate (lactate was obtained only during the exercise session). Next, a saliva sample (1 ml) was obtained using the passive drool method using standard instructions (cf. https://iisbr.uci.edu/sample-collection-andshipping); the process took about 5 minutes. Saliva collection was used as it provided a less invasive and less stressful method than venipuncture. Next, the Profile of Mood States questionnaire was completed, followed by the Stroop task. Next, participants were assigned to and then completed a rest or exercise condition. In both conditions, the participants were allowed to drink water ad libitum except for 10 minutes prior to the saliva collections. Participants were asked to arrive after a minimum 10-hour fast and did not eat until the testing session was completed; thus, most testing was in the morning. Participants were instructed to not exercise until after the 24-hour follow-up testing and to arrive fasted following the same protocol regarding caffeine, alcohol, marijuana, anti-inflammatory medications, and nutrition.

Non-Exercise Control Condition

After T1 testing the participants in the control condition then walked about 10 meters into a laboratory room and sat alone and watched a National Geographic video about humpback whales for ~50 minutes. No measurements were made during this time. Participants were asked to not use their phone. Immediately (T2) and 30 minutes post-condition (T3) saliva samples were obtained and then mood was assessed. The Stroop was completed once after the T2 mood assessment but before the T3 saliva collection and mood assessment. This is labelled as T2.5.

Resistance Exercise

After T1 testing the participants in the exercise condition walked about 40 meters to an adjacent fitness room and completed a standardized warm-up consisting of a 5-minute treadmill walk. The walk started at 0 grade and about 3.0 mph and increased to a self-selected speed and grade perceived as brisk. Resistance exercise mode specific warm-ups were completed immediately before each exercise. This warmup also was used to provide an estimated 10 repetition maximum (10RM) based on corresponding ratings of perceived exertion (RPE) and using an established method (Eston, 2009).

The high intensity resistance exercise protocol used was selected to fill a gap in the prior research which often involved moderate intensity exercise. The protocol was based on a near identical protocol being used in a large ongoing multi-center trial funded by the National Institutes of Health titled “Molecular Transducers of Physical Activity Consortium” (MoTrPAC). This approach was taken to allow for the current study results to be compared in the future to numerous findings expected from MoTrPAC; an initial MoTrPAC study has been published (Chambers, 2023).

The exercise protocol, in order, consisted of 5 upper body exercises (chest press, seated row, military press, bicep curl, triceps press) and 3 lower limb exercises (leg press, leg extension, leg curl). All of these exercises were completed using commercial Selectorized Cybex Fitness strength training equipment. The weight used for the exercise protocol was set at 70% of the participant's estimated 10RM for each exercise. Participants completed 3 to 4 sets of 10 repetitions depending on the exercise (3 sets of 10 repetitions: military press, bicep curl, and triceps press; 4 sets of 10 repetitions: chest press, seated row, leg press, leg extension, and leg curl). The exercise was supervised by trained research assistants and participants were asked to complete the prescribed number of repetitions in each set at a 1:1 concentric:eccentric ratio with prescribed 30-second rest periods between sets and a 1-minute rest period between exercises. The total exercise time was 49.5 minutes. If a participant was unable to maintain the prescribed number of repetitions at 70% of 10RM, or demonstrated unsafe lifting technique, the weight was decreased by 5% of 10RM on the subsequent set. Ratings of perceived exertion (RPE, 6-20) and muscle pain intensity rating (0-10) were obtained after each set using well-validated scales and standardized instructions (Borg, 1998; Cook, 1997). Immediately after completing the final rep of the exercise session, which was performed in a seated position, a finger prick blood sample was obtained then the second saliva collection (T2) was made followed by a 5-minute lactate analysis. Participants then walked back to the lab and mood measurement was collected. At 15-minutes post-exercise another finger prick blood sample was obtained, the Stroop was completed (T2.5), and at 30 minutes post-exercise a third saliva sample was obtained followed by a mood assessment (T3). Details of the exercise protocol are provided in Table 3.1.

Saliva Collection and Analyses

Saliva was collected at each time point (T1-T4) using commercially available collection devices from Salimetrics. Participants drooled into test tubes until 1 ml of saliva was obtained. The saliva was immediately stored on ice and then shortly thereafter placed into a −80°C freezer until shipped. Samples were shipped on dry ice following International Air Transport Association guidelines to the Institute for Interdisciplinary Salivary Bioscience Research at the University of California, Irvine for analysis of S100β and CRP.

S100β levels in saliva were measured using the R-PLEX Human S100β immunoassay (Cat # K1512ER; Meso Scale Discovery [MSD], Gaithersburg, MD) and CRP using the validated V-PLEX Human CRP Kit (Cat #K151STD; MSD, Gaithersburg, MD). For S100β, saliva samples were diluted 1:2 with Diluent 12 and for CRP, saliva was diluted 1:4 with Diluent 101. Plasma internal controls were included on each plate and were diluted 1:1,000 with Diluent 101. All assays were run in duplicate according to MSD manufacturer's protocol. The human S100β and CRP calibrators provided with the kit were used for generating the standard curve, and sample concentrations (pg/ml) were determined with MSD Discovery Workbench Software using curve fit models. Lower limits of detection (LLoD) and intra-assay CVs were as follows: S100β (0.82 pg/ml, 5.95%) and CRP (3.82 pg/ml, 7.39%). No intra-assay CVs were greater than 20%. Inter-assay CVs were determined using plasma internal control samples and were 9.4% for S100β and 11.8% for CRP.

Lactate

Blood samples were analyzed the day of collection for lactate using a portable lactate analyzer (Lactate Plus; Nova Biomedical) which has well established reliability and validity (Tanner, 2010). The Lactate Plus analyzer uses an electrochemical lactate oxidase biosensor to measure lactate concentrations using a 0.7 µl fingertip blood sample.

Cognitive Testing

Paper versions of the Stroop Color and Word Test (SCWT) were administered at baseline (T1) and 15 minutes post-conditions (T2.5). Participants were asked to complete three related tasks, all presenting stimuli on an 8" x 11" piece of paper. For each task a time limit of 45 seconds was enforced. Participants were asked to complete each task as quickly as possible, reading by stating aloud as many words or colors as possible in the allotted time. The first task required the participants to read aloud words describing colors printed in black ink (e.g., red, green, blue). The second task required the participants to state the color of a series x only characters (printed in red, green, or blue). The third task required the participants to state the color of the ink that the word was printed in which in each case did not match the word (e.g., the word "blue" printed in green ink). In this incongruent condition, the task requires participants to inhibit the interference from the more automated congruent task of word reading (Nyenhuis, 1999; Scarpina, 2017; Strauss, 2006; Stroop 1935). The criterion measure used for hypothesis testing was the interference score which was calculated as the number of correct items read aloud in 45 seconds.

Profile of Mood States Questionnaire

The Profile of Mood States (POMS) questionnaire measured six mood states: tension, depression, anger, vigor, fatigue, and confusion. The POMS contains 65 adjectives (e.g., relaxed, sad, annoyed, energetic, weary, muddled) that describe feelings people experience. The intensity of feelings is scaled across five categories: not at all (scored as 0), a little (1), moderately (2), quite a bit (3), and extremely (4). Participants indicated how they felt in the current moment for each timepoint. There is a large body of evidence supporting that the POMS reliably and accurately measures these six mood states (O'Connor, 2004). Total mood scores were calculated by summing the five negative mood scores, subtracting vigor and adding 100 to avoid negative numbers. Thus, the higher the total mood score the worse the overall mood state.

Data Analysis

Data were analyzed using IBM SPSS (Version 29.0.1.0). Data were entered into the associated spreadsheet and double checked for accuracy. Missing data (< 1%) were imputed using the mean of the respective training status group. Data distributions were checked to determine if assumptions underlying the primary statistics were met. Extreme outliers were identified as data points that were more extreme than either the lowest quartile (Q1) minus three times the interquartile range (IQR) or the upper quartile (Q3) plus three times the IQR.

Winsorization was used to manage extreme outliers, this involves giving lower (or higher) values immediately adjacent to the next highest non-outlier (or lowest) while maintaining the same rank within the data. In instances of non-normal distributions (i.e., S100β and CRP), the data were log transformed prior to the final analysis.

Hypothesis 1 was analyzed using independent t-tests. The hypothesis was that at rest, both prior to the exercise and control conditions and 24-hours later, the resistance exercise trained group would be characterized by higher feelings of energy, better inhibitory control (more correct words said aloud), and lower resting values of S100β and CRP compared to the untrained group.

Hypothesis 2 was tested using ANOVAs and post hoc tests. The hypothesis was that immediately and 30-minutes (T2 & T3) after a single bout of resistance exercise (vs. T1 baseline), both the untrained and the resistance exercise trained groups combined would be characterized by improved feelings of energy. Specifically, a doubly-repeated measures two-way ANOVA (Rest and Exercise Conditions x Times T1, T2, and T3) tested the hypothesis. A significant interaction was followed up with separate one-way repeated measures ANOVAs to detect if there was a significant change across time in either condition separately. The location of differences was determined from simple contrasts. Partial eta square statistics from the ANOVA as well as Cohen's d (standardized mean difference or SMD) between groups at specific time points provided effect size estimates. Here and elsewhere when the assumption of sphericity in an ANOVA was not met the degrees of freedom were adjusted using the Greenhouse-Geisser correction. This same approach was used for hypotheses 4 and 5.

Because the cognitive measure was made only once post-exercise a 2 x 2 ANOVA and post-hoc tests for hypothesis 3.

For hypothesis 6 regarding potential training group differences, Group (RT vs UT) x Condition (Rest vs Exercise) x Time (T1, T2, T3) interaction effects were quantified using mixed model 3-way ANOVAs with Group as the between factor and Condition and Time as the repeated factors. The hypothesis was that 30-minutes (T3) after a single bout of resistance exercise the changes in S100β and CRP will be lower for the trained group compared to the untrained group.

For hypotheses 7, Pearson correlations were used to analyze the relationships between changes among the variables of interest. Hypothesis 7 predicted that the changes in S100β and CRP 30-minutes after exercise, for the trained and untrained groups combined, will be significantly inversely associated with the changes in both feelings of energy and inhibitory control.

For hypotheses 8, Pearson correlations were used to analyze the relationships between changes among the variables of interest. Hypothesis 8 predicted that the changes in lactate immediately after exercise, for the TR and UT groups combined, would be significantly inversely associated with the changes S100β, CRP, feelings of energy, and inhibitory control.

3.5 Results

1. Sample characteristics

The mean (±SD) age, height, weight, and body mass index for the UT group was 24.47 (±6.7yrs), 166.74 (±5.7cm), 74.11 (±17.5kg) and 26.66 (±6.1 BMI units). The associated values for the TR group were 20.61 (±1.6yrs), 164.29 (±9.95cm), 62.15 (±9.8kg) and 23.0 (±2.98). The UT group were significantly older ($t = 2.382$, $df=35$, $p=0.023$), heavier ($t = 2.566$, $df=35$, $p=0.015$), and with a higher body mass index ($t = 2.268$, $df=35$, $p=0.03$). The four oldest participants in the study (ages 32, 34, 36, and 43) were in the UT group and they were among heaviest participants (84-115kg).

There were no significant differences in quantity of sleep in minutes between groups or ratings of quality of sleep (Likert scale 0-4; ‘Very Poor’, ‘Poor’, ‘Fair’, ‘Good’, ‘Very Good’). The UT group averaged more sleep than the TR group prior to both rest (411±112min, 396±93min) and exercise (422 ±132min, 414 ±86min), respectively. The groups reported similar ratings of quality of sleep prior to rest (UT 3.68±1.1; TR 3.39±1.0) and exercise (UT 3.67 ±1.2; TR 3.61 ±0.85).

The TR group reported resistance training two times per week or more for at least the past three months or longer. Resistance training was defined as performing at least three upper body and three lower body exercises during each training session and each exercise followed a set/repetition scheme of 3-4 sets of 8-12 repetitions.

The TR group was significantly stronger than the UT group relative to body weight in each of the eight exercises. Significance values ranged from $p<0.001$to $p = 0.019$. The differences between groups were large ($d = 0.81$-1.44). Data are presented in Table 3.6.

2. Exercise Intensity Manipulation Checks

Mean ratings of perceived exertion for both groups ranged from an average of “somewhat hard” on the first set of chest press which was the first exercise (UT 13.7±2.4.9, TR 13.1±1.1) to “very hard” (UT 17.7±1.9, TR 18.3±1.5) on the final set of leg press which was the last exercise. Mean ratings of muscle pain intensity for both groups ranged from “weak pain” on the first set of chest press (UT 1.8±2.2, TR 1.4±1.5) to “strong pain” (UT 5.0±2.5, TR 4.8±2.4) on the final set of leg curl which was the last exercise. Mean heart rate across all exercises for both groups ranged from ~53% of estimated heart rate maximum on the first set of chest press which was the first exercise (UT 103±17.8 bpm, TR 105±15.6 bpm) to ~70% of estimated heart rate maximum on the final set of leg press (UT 136±20.9 bpm, TR 145±21.0 bpm). The perceived exertion, pain, and heart rate descriptive data are provided in Tables 3.2, 3.3, and 3.4, respectively.

Blood lactate values for the UT and TR groups, respectively were 1.45±0.77 and 1.81±1.07 mmol/L prior to exercise and the immediate post-exercise values were 6.94±0.79, 7.68±0.69 mmol/L, respectively. Thus, the resistance exercise caused similarly large increases in blood lactate in both the UT (mean increase = 5.49 mmol/L) and TR (mean increase = 5.87 mmol/L) groups. The descriptive lactate results are presented in Table 3.5.

The lactate, heart rate, RPE, and pain responses all confirmed that the exercise bout was high intensity for both groups. The combination of the objective and subjective evidence indicates that a high level of exercise intensity was achieved (Fry, 2004; Lea, 2022).

3. Mood Differences Between Training Groups at the Pre-Condition Baselines (T1)

The RT group had significantly higher feelings of energy/vigor compared to the UT group prior to the control condition (13.9±6.7 vs. 9.1±5.1; t = -2.470, df=35, p=.019) and the size of the effect was large (d=0.81). Prior to exercise this group difference was moderate sized (d=0.60) and did not reach statistical significance (13.1±6.2 vs. 9.9±4.5; t = -1.752, df=35, p=.088). Otherwise, as summarized in Table 3.6, there were non-significant small sized differences in most of the other mood states measured which favored the RT group (i.e., score reflected a more positive mood state) at both the control and exercise pre-condition baselines.

4. Mood Differences Between Training Groups at the Post-Condition Timepoint (T4)

As shown in Table 3.6, there were non-significant small sized differences in all the mood states that predominantly favored the RT group at both the control and exercise post-condition timepoints (T4). The RT group had higher feelings of energy/vigor compared to the UT group after both the control and exercise conditions that were small and moderate in size, respectively (d=0.42 and d=0.58).

5. Acute Resistance Exercise Effects on Mood

Descriptive mood data in response to acute resistance exercise for the two training groups are provided in Table 3.7. Figure 3.2 illustrates the vigor response to exercise in the TR and UT groups separately. In the 3-way ANOVA, there were no significant interactions with training status for any of the mood variables.

For the training groups combined, there were large significant Condition x Time interaction effects for vigor (df=2, 72, F=7.455, p=0.001, $\eta^2 = 0.172$). Post-hoc tests revealed significant large increases in vigor immediately and 30 minutes after exercise and no change in vigor after rest as illustrated in Figure 3.3.

Descriptive data for the other mood states for the two groups combined are provided in Table 3.8. For the training groups combined, there were significant Condition x Time interaction effects for tension-anxiety symptoms (df=1.706, 61.406, F=10.239, p<0.001, $\eta^2 = 0.221$), feelings of anger (df=1.651, 59.453, F=21.788, p=0.003, $\eta^2 = 0.164$) and symptoms of fatigue (df=1.499, 53.976, F=34.886, p=0.023, $\eta^2 = 0.112$). Tension scores were increased immediately but not 30 minutes after exercise while tension steadily decreased immediately and 30-minutes after rest. Anger scores steadily decreased immediately and 30 minutes after exercise while immediately after rest anger decreased and then return to baseline at 30 minutes. Fatigue scores were increased immediately after exercise and returned to baseline after 30 minutes while fatigue steadily decreased during rest.

6. Inhibitory Control Differences Between Training Groups at Pre-Condition Baselines (T1)

The RT and UT groups did not differ significantly on the Stroop interference task prior to the exercise or rest condition. The descriptive data for the interference task as well as the component color and word variables at the pre-condition baselines (T1) are provided in Table 3.9.

7. Acute Resistance Exercise Effects on Inhibitory Control

Descriptive Stroop task data in response to acute resistance exercise for the two training groups separately are provided in Table 3.9. In the 3-way ANOVA, there were no significant interactions with training status for the inhibitory control scores. For the training groups combined, there was no significant condition x time (2 x 2) interaction effect for inhibitory control scores. There was no significant main effect of time and there were small increases in mean inhibitory control scores 15 minutes following both the exercise and rest conditions at the single post-condition testing trial (T2.5).

8. CRP Differences Between Training Groups at the Pre-Condition (T1) and Post-Condition (T4) Time Points

At T1, the mean value for CRP was lower for the RT compared to the UT group prior to both the control and exercise conditions and these differences were moderately sized (d = 0.65 to

0.46, respectively) and approached statistical significance for the control condition (TR: 1.72±0.65 vs. UT: 2.16±0.71; t = 1.975, df=35, p=0.056) but not the exercise condition (p=0.18). Descriptive CRP data at T1 is provided in Table 3.10.

At T4, the mean value for CRP was lower for the RT compared to the UT group. These differences were moderately sized and significantly different in the control condition (d=0.65; p = 0.03) and small and insignificant (d=0.46; p=0.16) in the exercise condition. Descriptive CRP data at T4 is provided in Table 3.10.

9. S100β Differences Between Training Groups at Pre-Condition (T1) and Post-Condition (T4) Time Points

The mean value for S100β was insignificantly lower for the RT compared to the UT group prior to the control and exercise conditions and 24-hours later. The magnitude of the difference was small at both T1 (d = 0.13) and T4 (d = 0.14). Descriptive S100β data at T1 and T4 are provided in Table 3.10.

10. Acute Resistance Exercise Effects on S100β

In the 3-way ANOVA, there were no significant interactions with training status for S100β. For the training groups combined, there was no significant condition x time interaction effect for S100β. There was a significant time effect (df=2, 70, F=7.288, p=0.001, $\eta^2 = 0.172$). S100β was reduced significantly in both groups at 30 minutes post-exercise (T3) compared to both the T1 and T2 time periods. These S100β data are summarized in Table 3.11 and Figure 3.4.

11. Acute Resistance Exercise Effects on CRP

In the 3-way ANOVA, there were no significant interactions with training status for CRP, thus the data for the two groups were combined for the primary analysis. For the training groups combined, there was no significant 2 x 3 interaction effect for CRP (df=1.58, 56.95, F=1.22, p=0.29, $\eta^2 = 0.033$). There was a small (d=.22) non-significant increase in CRP immediately following exercise. These CRP data are summarized in Table 3.11 and Figure 3.5.

12. Correlations between S100β and CRP in the exercise condition

Pearson correlations between S100β and C-reactive protein levels in the exercise condition were statistically significant at each time point whether the data for the two groups were combined or if the data were analyzed separately for the TR and UT groups. The magnitude of the correlations ranged from r = 0.56 to 0.81. These data as shown in Table 3.12.

The correlation between the change in CRP at T2 and the change in S100β at T2 was statistically significant (r=0.51, p=0.002). The correlation between the change in CRP at T2 and the change in S100β at T3 was insignificant as was the correlation between the change in CRP at T3 and S100β at T3.

13. Correlations between the change in inhibitory control and changes in S100β and CRP

For the TR and UT groups combined, or when analyzed separately by group, there were no significant correlations between the changes in the biomarkers and changes in cognitive inhibitory control.

14. Correlations between changes in S100β and changes in mood states in the exercise condition

For the TR and UT groups combined (n=37), there were no statistically significant correlations between the exercise-induced changes in any mood variable and the S100β change scores for the T2-T1 delta time period. For the T3-T1 delta time period, there were significant positive relationships between changes in S100β and changes in total mood disturbance (r=0.51, p=0.001), fatigue (r=0.49, p=0.002), and anger (r=0.48, p=0.002).

15. Correlations between changes in lactate and psychobiological changes post-exercise

The peak increases in lactate immediately post exercise (T2) were not significantly correlated with any post-exercise changes in CRP, S100β, feelings of energy, or cognitive inhibitory control.

3.6 Discussion

Summary of Key Findings

In a sample of young adult females when compared cross-sectionally to the UT, the TR have higher vigor, lower CRP and do not differ on inhibitory control or S100β. The TR and UT respond similarly to an acute bout of high intensity whole body resistance exercise which increases vigor and does not change inhibitory control or salivary CRP and S100β. The most notable acute finding was the null response for S100β, a biomarker of blood-brain interface integrity, because a prior review concluded that S100β increases with acute exercise (Koh, 2014). This discrepancy can be accounted for by the better control over confounding factors in the present study.

Acute effects

A primary finding of the present experiment was that an acute bout of high intensity resistance exercise had no meaningful effect on salivary S100β immediately and 30 minutes post-exercise in a sample of young healthy resistance trained and untrained adult women. This finding is generally inconsistent with prior research. A systematic review of a small body of prior research investigating acute exercise effects on S100β predominately found that S100β was increased post-exercise (Koh, 2014). There are several plausible explanations why the current findings for S100β were in contrast with most of the prior studies. One plausible reason is that the present investigation avoided potential non-exercise confounding factors, such as occurs in boxing (Graham, 2011) and soccer (Straume-Naesheim, 2008), in order to examine the influence of high intensity resistance exercise *per se*.

One possible reason that S100β did not increase post-exercise in this experiment is that high intensity resistance exercise truly has no effect on S100β. The lactate, heart rate, RPE, and pain responses all confirmed that the exercise bout was high intensity for both groups. The combination of the objective and subjective evidence indicates that a high level of exercise intensity was achieved (Fry, 2004; Lea, 2022).

Another possible reason that S100β did not increase after exercise is that the immediate exercise-induced inflammation responses were inadequate to alter BBI permeability in time to show an effect 30-minutes post-exercise. The present experiment had one measure of inflammation, salivary CRP. CRP did increase immediately following exercise but by only a small, nonsignificant magnitude and the mean values returned to baseline at 30-minutes post-exercise. If a larger immediate post-exercise CRP response had been observed, it potentially could have contributed to greater BBI permeability and resulted in higher S100β levels at 30-

minutes post-exercise. It is potentially noteworthy that there were positive correlations between the changes in S100β and the changes in CRP immediately ($r=.31$) and 30-minutes ($r=.80$) post-exercise. This indirectly supports a potential effect of CRP on S100β.

Regardless, the CRP results contribute to the very small body of research that has quantified the effect of acute resistance exercise on CRP and found mixed results. Other pro- or anti-inflammatory molecules, such as TNF-alpha or interleukin-6 or interleukin-10, may have acted on the BBI of the current study participants but those immune system variables were not measured. It also cannot be ruled out that significant exercise-induced changes in salivary CRP occurred later during recover from exercise when measurements were not made such as from 1 to 3 hours post-exercise.

We hypothesized that the CRP and S100β responses to the high intensity acute resistance exercise would be different between the TR and UT groups. This assumed that resistance exercise training would produce biological adaptations that would have contributed to the TR group having attenuated responses compared to the UT group. This difference could potential occur via metabolic effects such as reduced sympathetic nervous system activation or increased relative lactate shuttling. While the lactate responses were higher in absolute amount for the TR compared to the UT group, the relative (%) increase from pre-exercise was similar. Regardless, there were not significant differences between the TR and UT groups in the acute physiological or psychological responses to exercise measured in the present investigation.

Another possible reason that S100β did not increase post-exercise in this experiment is that increases in lactate during exercise did not have pro-inflammatory effects on CRP or other unmeasured immune biomarkers that could influence S100β. This was an exploratory element of the present investigation and therefore appears to be the first acute resistance exercise study to examine potential relationships between exercise-induced changes in blood lactate immediately post-exercise and subsequent changes in S100β up to 30-minutes post-exercise. This null effect was not moderated by training status.

Another potential reason that S100β was not significantly altered by vigorous resistance exercise is that participants were young, healthy females with no chronic inflammatory or neurological conditions. Chronic inflammation which can contribute to neuroinflammation likely predisposes the human body to greater sensitivity to physiological challenges whether from exercise or a disease course.

Acute high intensity resistance exercise did increase feelings of energy immediately and 30-minutes following exercise for the combined sample of UT and TR participants. This observation is consistent with prior investigations reporting improved feelings of energy post-exercise. In one study of pregnant women, for example, 90% of the participants reported post-work improvements in feelings of energy after 90% of 24 workouts performed twice weekly for 12 weeks (Ward-Ritacco, 2016). The present sample had pre-exercise vigor/energy levels that were somewhat lower than is typical for female college students and this starting point may have contributed to the increased feelings of energy. The changes in feelings of energy were unrelated to changes in lactate, CRP and S100β thereby providing the first evidence of these null observations.

Acute high resistance exercise in the present study did not cause a significant change in cognitive inhibitory control scores. This is inconsistent with the extant literature. Indeed, an inhibitory control task was selected for use in the present study because a meta-analysis of the effects of acute resistance exercise on cognition found this task as changing the most post-exercise. One potential explanation is that the study participants on average performed well on the task prior to exercise and therefore there was a ceiling effect. This is likely the case as a large study that established normative data among females with a high level of education had average interference scores of 31.34 (±9.82) for 25yo (±1) (Van der Elst, 2006). The baseline interference score for the groups combined prior to rest (50.54 ±8.4) and exercise (52.47 ±8.9) are around the 90th percentile (51.2) relative to the normative data. Post-condition interference scores for rest (53.76 ±9.4) and exercise (56.41 ±7.7) were around the 95th percentile (55.7). Ceiling effects likely contributed to an absence of significant change in inhibitory control task scores and is therefore the most likely reason for there to be no significant correlation between changes in the scores and changes in either lactate, CRP, or S100β.

Chronic (Cross-sectional) Differences at Rest between RT and UT groups

Consistent with prior literature, this study showed elevated vigor/energy for participants who had been engaged in resistance exercise for at least 3 months when compared to sedentary controls (Herring, 2009). The psychobiological mechanisms for this difference are incompletely understood but no evidence was provided here that group differences in blood brain interface permeability, as indexed by S100β, contributed to the difference in feelings of energy.

The cognitive task for this study was the Stroop Task and the criterion measure was the interference score. Prior literature has shown small, positive effects on executive function scores after exercise (d=0.19) with cognitive effects being pronounced in those with high fitness levels (d=0.22) (Chang, 2012). However, the same meta-analysis showed small, negative effects are reported for those exercising at very hard or maximal levels (d=-0.16, -0.04) and when using resistance exercise (d=-0.33). The current study showed no significant effects on interference scores for the groups combined or when separated by training status.

There were no cross-sectional differences in S100β between the TR and UT groups. This observation is potentially consistent with the acute exercise findings because presumably training adaptations result in part from an accumulation of effects of responses to acute exercise bouts. Thus, if acute resistance exercise truly does not increase S100β then no cross-sectional difference between the TR and UT groups would be expected. Nevertheless, it cannot be ruled out that group differences in biomarkers would have occurred if the TR group had been training regularly for many years months and the UT group had continued to refrain from resistance exercise for many months longer.

The present CRP findings support that resistance training appears to reduce chronic inflammation in young women. The RT group had CRP values that were lower than the UT group (effect size d ranged from 0.46 to 0.71). These observations are consistent with a meta-analysis of randomized controlled trials revealed that resistance training can reduce CRP ($d = -0.72$, $p < 0.001$) in older adults (n=539, mean age = 70.2 years, 76.7% female) (Kim, 2022).

Correlations between the biomarkers and mood.

Hypothesized correlations between changes in feelings of energy and changes in CRP and S100β 30-minutes after exercise were not supported. These results suggest that mood responses to exercise in this study were not influenced by immune or BBI biomarker changes. It is plausible that the correlations that were hypothesized were not significant due to the small insignificant changes in biomarkers in response to resistance exercise.

The POMS measure used includes mood states beyond our *a priori* focus on vigor and some discussion of the other mood states is warranted. Consistent with prior research the TR participants tended to be characterized by better mood states compared to UT and the size of the effects were small. In response to acute high intensity resistance exercise for the TR and UT groups combined, feelings of anger decreased steadily in the post-exercise period while feelings of anxiety and fatigue were increased immediately post-exercise and decreased to baseline levels by 30-minutes post-exercise. It is not surprising that high intensity exercise transiently increased feelings of fatigue as has been shown before (Martínez-Díaz, 2021). In contrast to acute aerobic exercise in which anxiety scores are typically lower immediately after exercise, following resistance exercise this effect can be delayed with anxiety symptoms elevated immediately post-exercise as was found in the present study. There is a much smaller literature regarding the influence of acute exercise on anger and the finding can depend on multiple factors including the intensity, the presence of other people, and the environmental setting such as exercise-based competition. Regardless, the small reduction in anger scores post-exercise is consistent with other investigations.

For the TR and UT groups combined, there were no statistically significant correlations between the exercise-induced changes in any mood variable and the S100β change scores for the immediately post-exercise delta time period. For the changes from pre-exercise to 30-minutes post-exercise, there were significant positive relationships between changes in S100β and changes in fatigue ($r=0.49$, $p=0.002$), anger ($r=0.48$, $p=0.002$), and total mood disturbance ($r=0.51$, $p=0.001$) which include both anger and fatigue. These unpredicted observations in apparently healthy young females were generally consistent with multiple studies showing elevated S100β in adult samples with mood disorders such as depression (Kozlowski, 2023).

All research has limitations, and this investigation is not different. A relatively small sample of young adult females performed highly controlled high intensity resistance exercise, so it is unknown the extent to which the present findings generalize to other samples or settings.

The sample's high performance on inhibitory control at baseline likely created a ceiling effect that limited exercise-induced changes. Also, limited exercise-induced changes in CRP and S100β likely attenuated correlations between these variables and inhibitory control and mood states. Lastly, compared to blood there are relatively few studies documenting salivary CRP and S100β changes in response to acute exercise. It is unknow if the choice of saliva for obtaining the biomarker samples influenced the outcome.

3.7 Conclusions

In a sample of young adult females when compared cross-sectionally to the UT, the TR have higher vigor, lower CRP and do not differ on inhibitory control or S100β. The TR and UT respond similarly to an acute bout of high intensity whole body resistance exercise which increases vigor and does not change inhibitory control or salivary CRP and S100β. The absence of change in S100β in response to the well-controlled resistance exercise bout in the present experiment is notable because it is in contrast with typical increases in S100β observed in numerous less well controlled prior exercise studies.

3.8 References

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3.9 Figures

Figure 3.1 – Consolidated Standards of Reporting Trials (CONSORT) diagram showing the flow of study participants into the experiment.

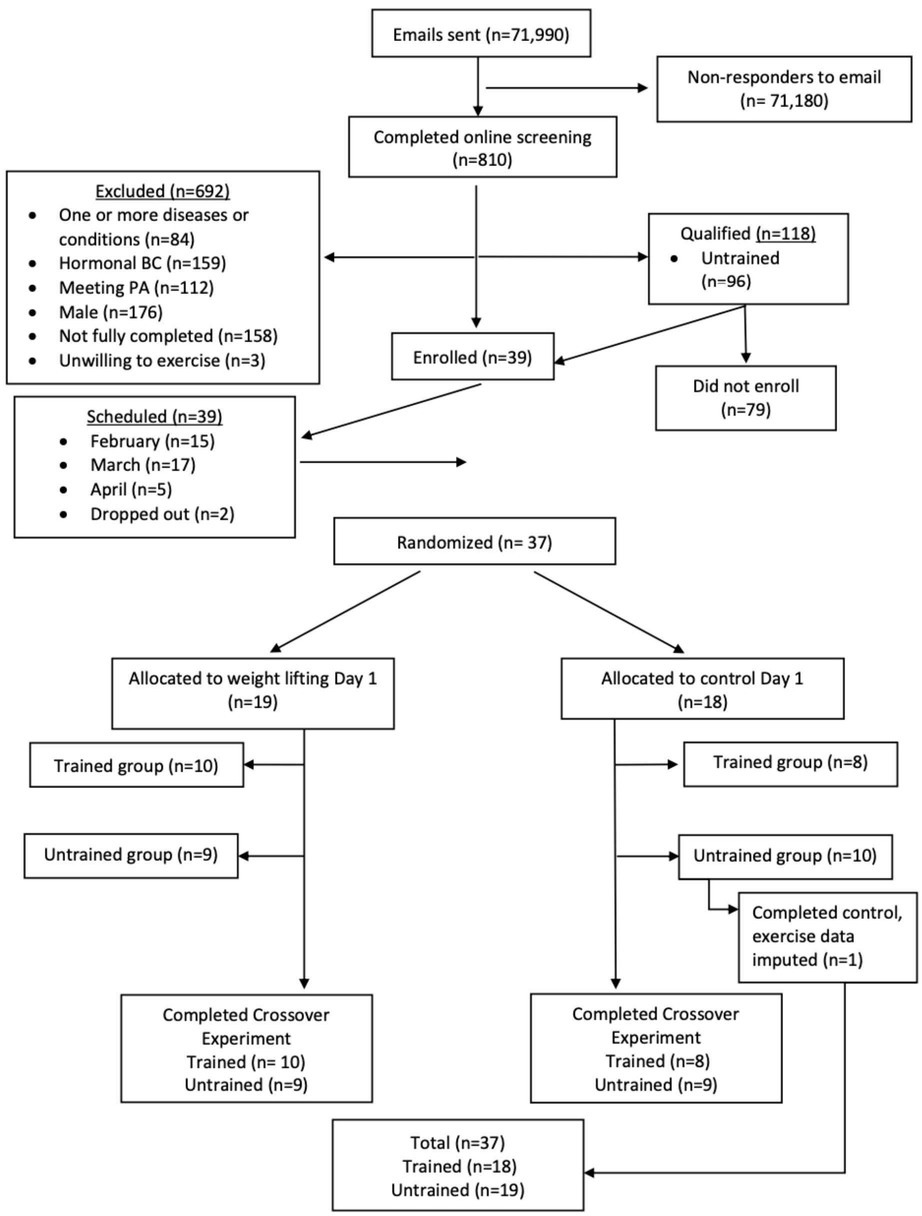


Figure 3.2 Mean lactate responses before and immediately post-exercise. There were no significant group differences at baseline (UT 1.45±0.77, TR 1.81±1.07) or immediately post-exercise (UT 6.94±0.79, TR 7.68±0.69).

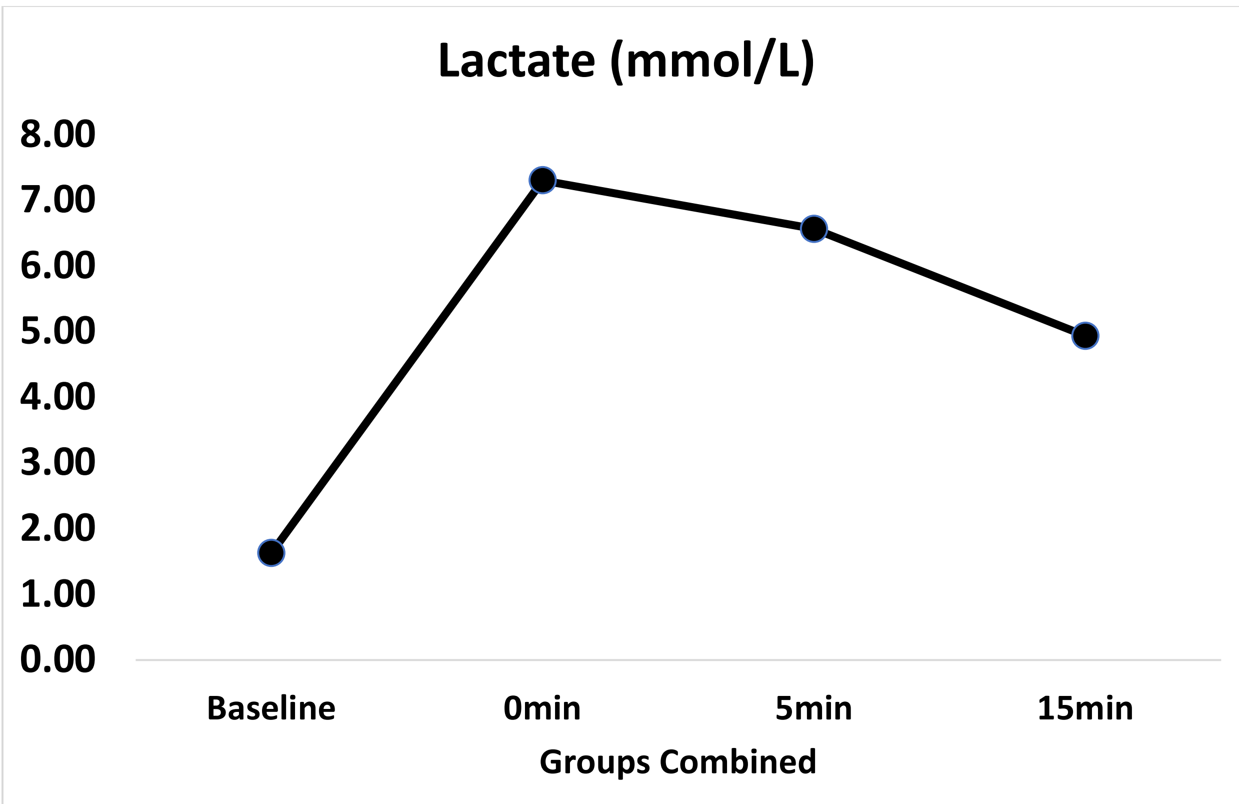


Figure 3.3 Changes in vigor in response to acute resistance exercise in the resistance trained (n=18) and untrained (n=19) groups. Testing was completed before exercise (T1), immediately after exercise (T2), 30 minutes after exercise (T3), and 24 hours after exercise. Vigor scores were higher at T1 and T4 in the TR versus the UT group and the Condition x Time interaction was statistically insignificant. Vigor scores have a maximum range from 0 to 32.

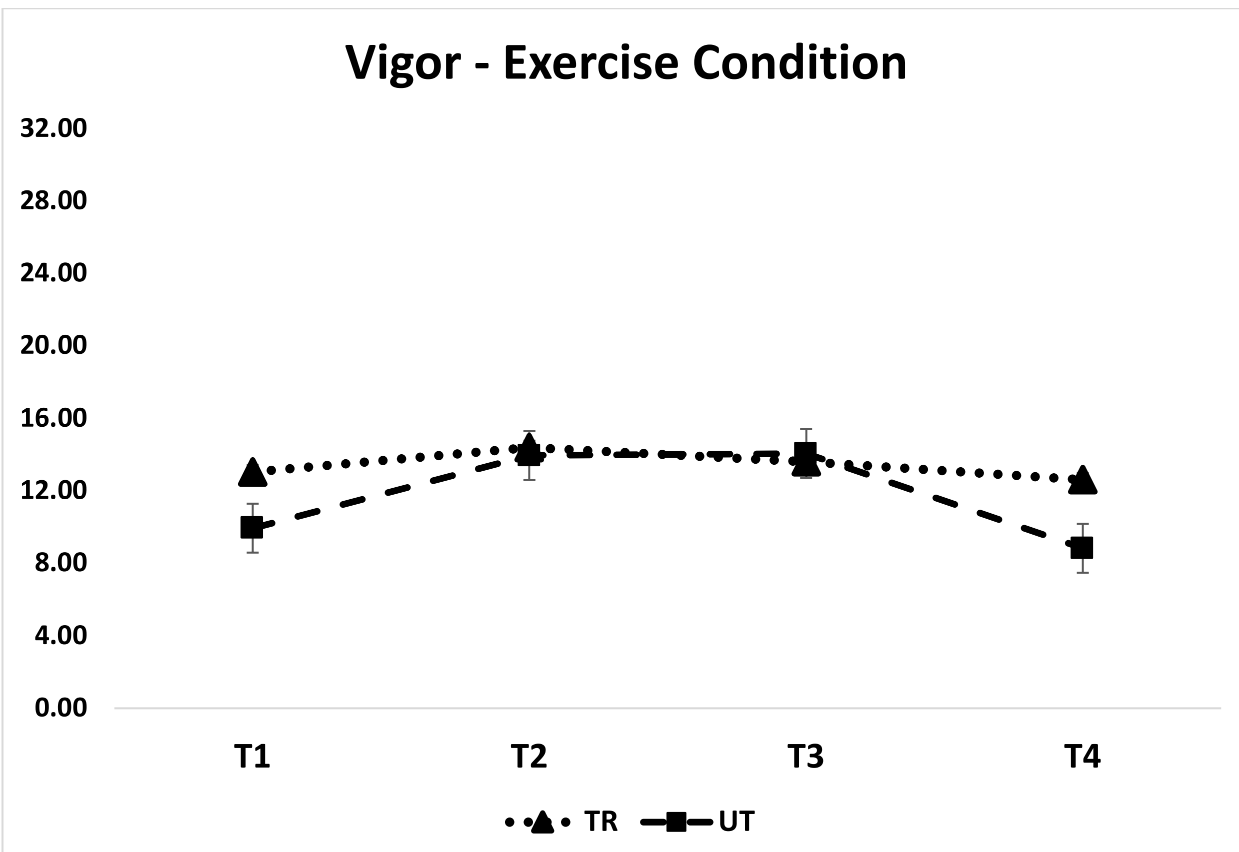


Figure 3.4 Vigor scores before (T1), immediately (T2) and 30 minutes after (T3) the exercise and rest conditions in the combined sample (n=37) with standard error. Vigor scores have a maximum range from 0 to 32.

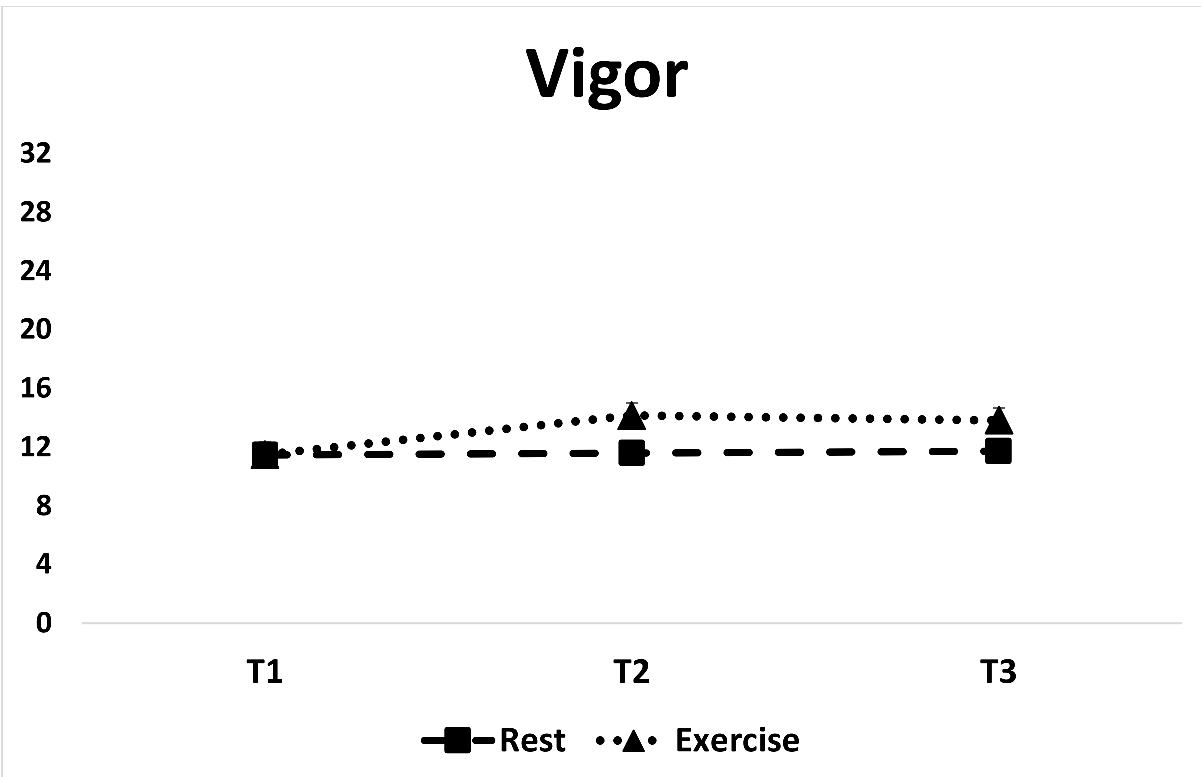


Figure 3.5 Acute S100β, a biomarker of blood brain interface permeability, responses to high intensity resistance exercise for UT and TR groups in log transformed units. Measurements were made prior to (T1) as well as immediately (T2), 30-minutes post-exercise (T3), and 24 hours post-exercise (T4) are in log pg/ml with standard error.

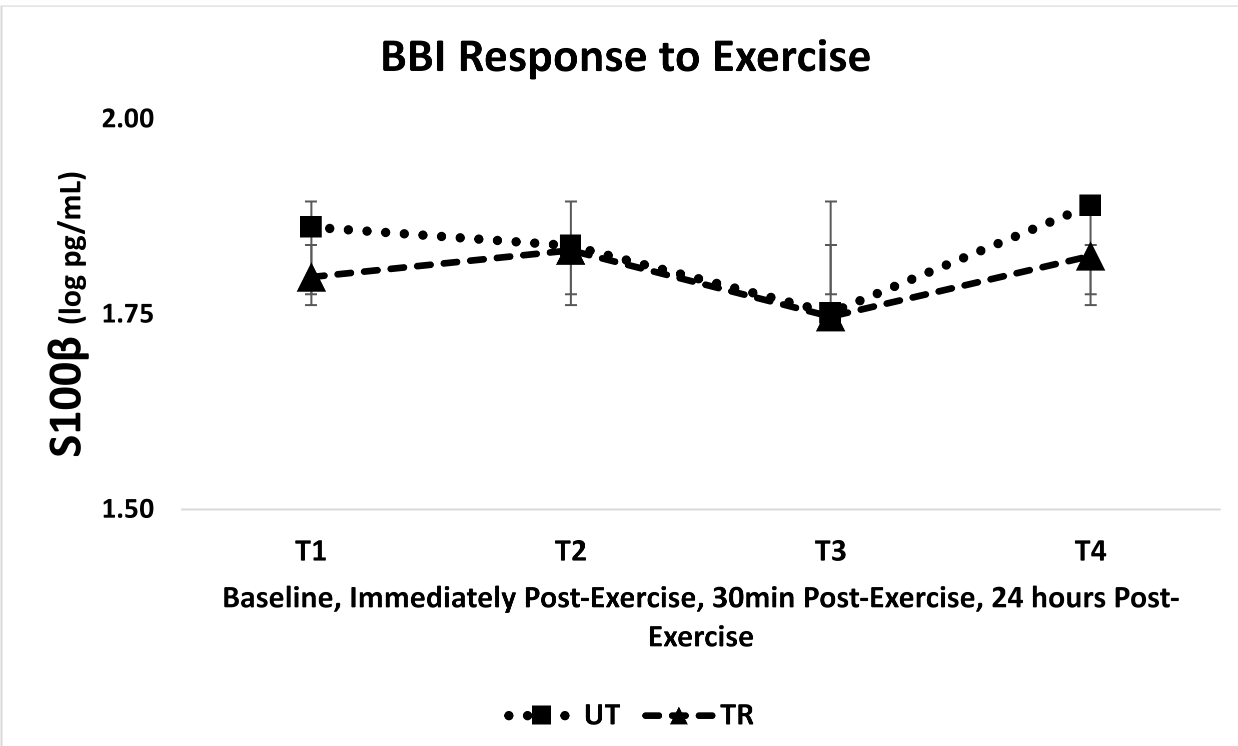


Figure 3.6 Acute CRP responses to exercise between UT and TR groups from baseline, immediately post-exercise, and 30-minutes post-exercise (T1-T3) in log pg/ml units with standard error.

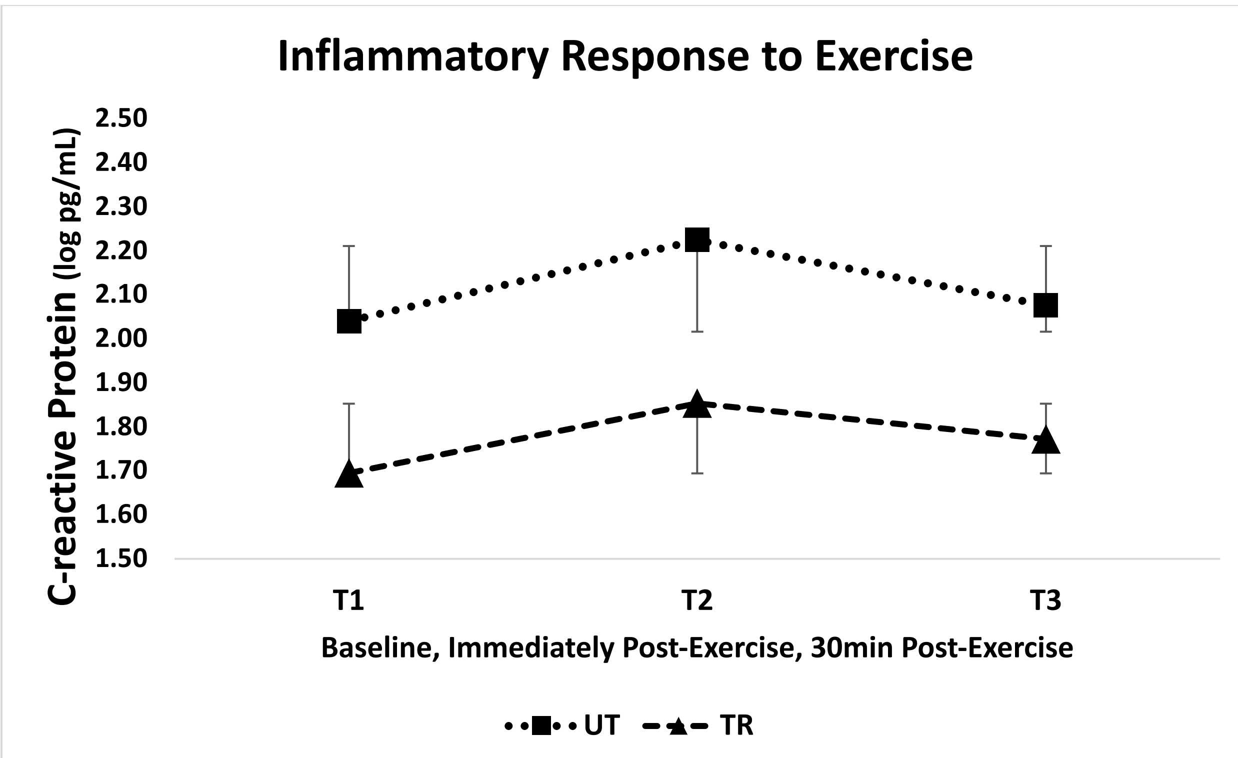


Figure 3.7 Acute CRP responses to exercise between UT and TR groups from baseline, immediately post-exercise, 30-minutes post-exercise, and 24 hours post-exercise (T1-T4) in log pg/ml units with standard error.

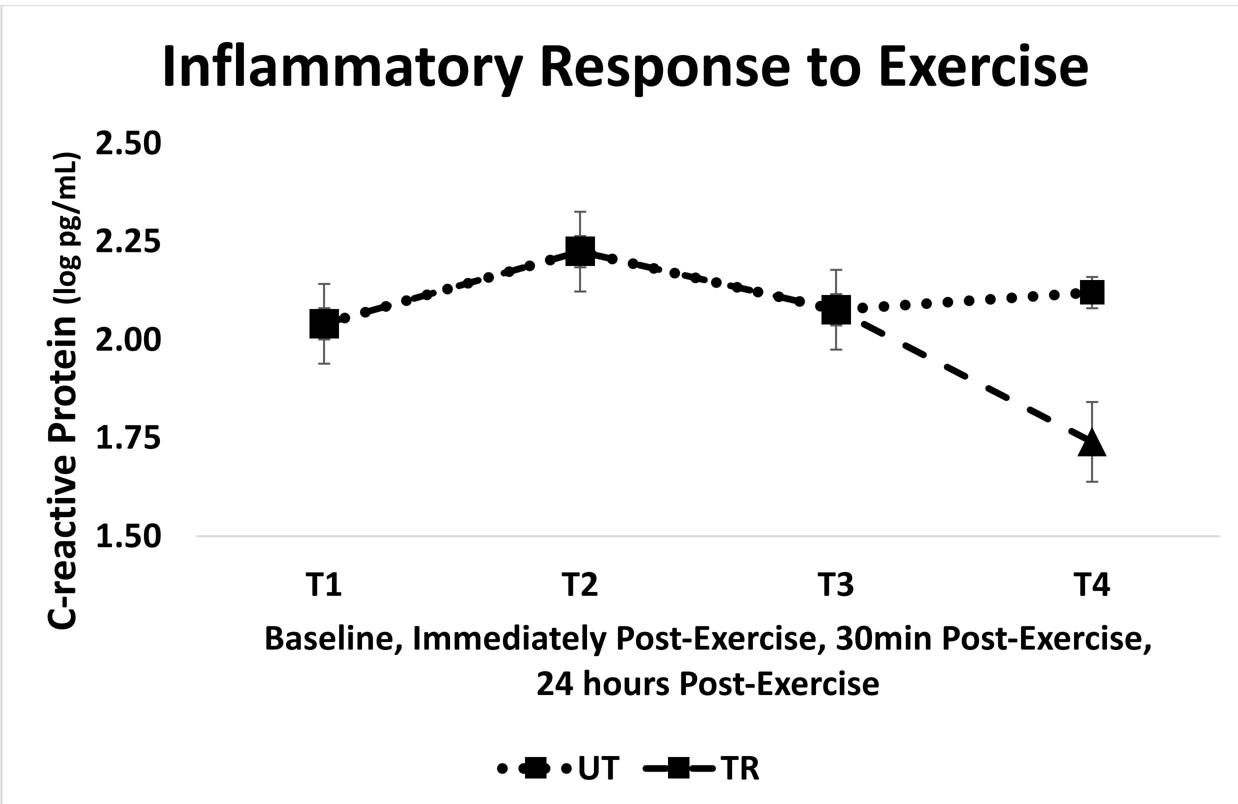
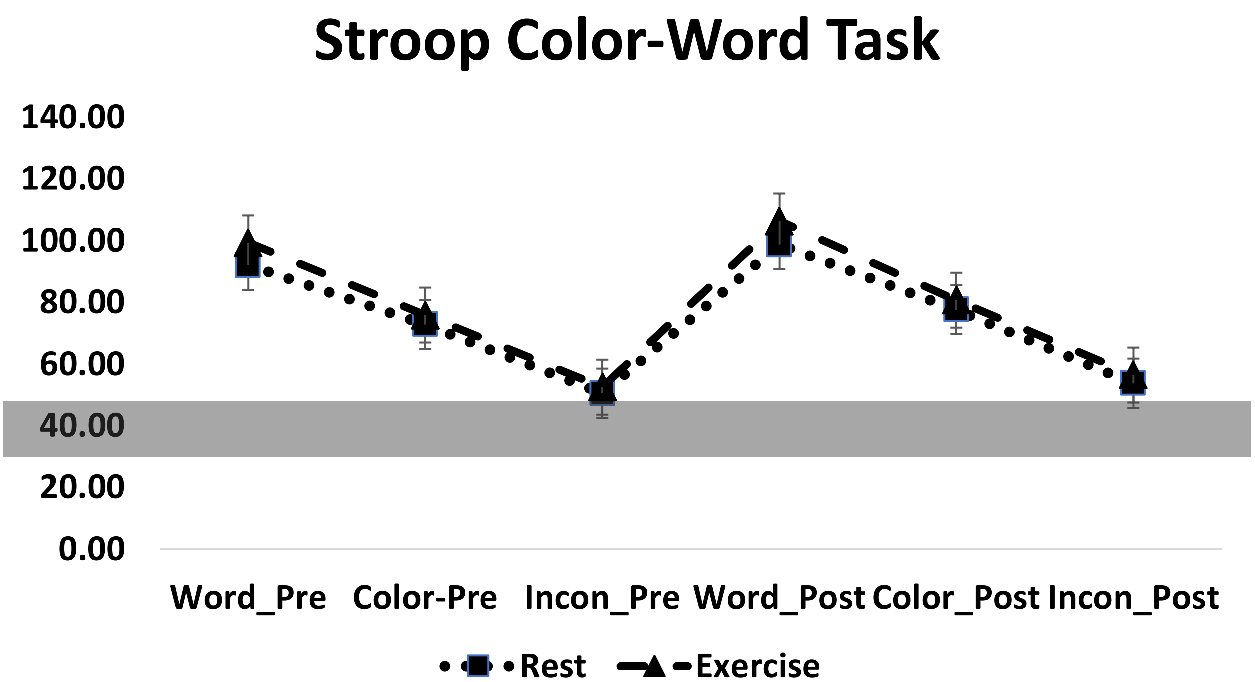


Figure 3.8 Combined group responses reflecting cognitive inhibitory control before and after rest and exercise with standard error. Shaded box represents normative data for highly educated 25 (±1) year old females. Both baseline and post-condition responses exceeded the mean normative data placing this group (n=37) at approximately the 90th percentile at each baseline and the 95th percentile at each post-condition.



3.10 Tables

Table 3.1 Resistance exercise protocol following 5-minute treadmill walk for general warm-up. Each exercise was preceded by a movement-specific warm-up involving 2 sets.

Exercises	**Sets x Reps**	**Ecc/Con Ratio**	**Rest Time**	**Total Time**
Upper Body				
Chest Press	4 x 10; 70% 10RM	1 sec/1 sec; 20 sec/set	30 secs/set	Warm-up 100sec Exercise 80 sec Rest 60 sec
Seated Row	4 x 10; 70% 10RM	1 sec/1 sec; 20 secs/set	30 secs/set	Warm-up 100sec Exercise 200 sec Rest 60 sec
Military Press	3 x 10; 70% 10RM	1 sec/1 sec; 20 secs/set	30 secs/set	Warm-up 100sec Exercise 150 sec Rest 60 sec
Biceps Curl	3 x 10; 70% 10RM	1 sec/1 sec; 20 secs/set	30 secs/set	Warm-up 100sec Exercise 150 sec Rest 60 sec
Triceps Press	3 x 10; 70% 10RM	1 sec/1 sec; 20 secs/set	30 secs/set	Warm-up 100sec Exercise 150 sec Rest 60 sec
Time between upper and lower	N/A	N/A	60 secs	Rest 60 sec
Lower Body				
Leg Press	4 x 10; 70% 10RM	1 sec/1 sec; 20secs/set	30 secs/set	Warm-up 100sec Exercise 200 sec

Leg Curl	4 x 10; 70% 10RM	1 sec/1 sec; 20secs/set	30 secs/set	Warm-up 100sec Exercise 200 sec
Leg Extension	4 x 10; 70% 10RM	1 sec/1 sec; 20secs/set	30 secs/set	Warm-up 100sec Exercise 200 sec
Summary				
8 exercises, 3 lower body	3 to 4 sets of 10 at 70% 10RM	Ecc/Con ratio of 1 sec/1 sec; 20 secs/set	Rest of 30 secs/set	Time at 70% of 49.5 minutes
			Total research time	~75min for testing + ~50min for exercise= ~125 min

Table 3.2 Mean rating of perceived exercise for the first and last set of each exercise in the untrained and trained groups.

RPE		Untrained (Mean ±SD)		Trained (Mean ±SD)	
Chest Press	*Set 1*	13.7	±2.4	13.1	±1.1
	Set 4	16.9	±2.4	18.3	±1.5
Seated Row	*Set 1*	13.4	±1.9	14.1	±2.5
	Set 4	17.5	±2.0	18.1	±1.4
Military Press	*Set 1*	16.3	±2.2	16.4	±2.6
	Set 3	17.7	±1.8	18.3	±2.1
Bicep Curl	*Set 1*	14.8	±1.9	14.2	±1.6
	Set 3	17.1	±2.5	17.6	±1.8
Triceps Press	*Set 1*	15.5	±2.9	15.8	±2.1
	Set 3	16.9	±2.5	18.2	±1.9
Leg Press	*Set 1*	13.6	±1.3	13.8	±1.7
	Set 4	17.3	±1.7	18.0	±1.5
Leg Extension	*Set 1*	14.6	±1.9	14.3	±1.6
	Set 4	17.7	±1.9	18.3	±1.2
Leg Curl	*Set 1*	14.8	±2.2	14.9	±1.4
	Set 4	17.7	±1.8	18.3	±1.5

Table 3.3 Mean pain intensity rating for the first and last set of each exercise by training status.

Pain		Untrained (Mean ±SD)		Trained (Mean ±SD)	
Chest Press	*Set 1*	1.8	±2.2	1.4	±1.5
	Set 4	3.0	±2.5	3.0	±2.4
Seated Row	*Set 1*	1.6	±1.6	1.4	±1.4
	Set 4	3.2	±2.6	3.0	±2.0
Military Press	*Set 1*	3.3	±2.2	2.8	±2.0
	Set 3	4.3	±2.8	4.1	±2.7
Bicep Curl	*Set 1*	2.5	±2.0	1.6	±1.6
	Set 3	3.9	±3.0	2.6	±2.0
Triceps Press	*Set 1*	3.3	±2.9	2.2	±1.6
	Set 3	4.1	±3.1	3.5	±2.3
Leg Press	*Set 1*	2.0	±1.6	1.5	±1.3
	Set 4	3.9	±2.7	3.5	±2.3
Leg Extension	*Set 1*	3.1	±1.7	2.4	±1.7
	Set 4	4.9	±2.7	4.3	±2.6
Leg Curl	*Set 1*	3.3	±2.4	2.8	±2.0
	Set 4	5.0	±2.5	4.8	±2.4

Table 3.4 Mean heart rate for the first and last set of each exercise in the untrained and trained groups.

Heart Rate		Untrained (Mean ±SD)		Trained (Mean ±SD)	
Chest Press	*Set 1*	103.0	±17.8	105.0	±15.6
	Set 4	107.0	±15.3	124.0	±21.2
Seated Row	*Set 1*	106.0	±15.8	116.0	±15.1
	Set 4	122.0	±16.2	134.0	±22.3
Military Press	*Set 1*	121.0	±16.1	128.0	±22.7
	Set 3	126.0	±17.1	129.0	±23.4
Bicep Curl	*Set 1*	122.0	±16.8	125.0	±18.9
	Set 3	127.0	±16.8	138.6	±17.5
Triceps Press	*Set 1*	125.0	±15.8	125.0	±20.6
	Set 3	125.0	±18.2	130.0	±22.3
Leg Press	*Set 1*	119.0	±18.0	129.1	±19.2
	Set 4	136.0	±20.9	145.0	±21.0
Leg Extension	*Set 1*	124.0	±16.5	131.0	±19.8
	Set 4	128.0	±12.7	137.0	±22.5
Leg Curl	*Set 1*	118.0	±12.9	129.0	±19.1
	Set 4	129.0	±15.3	139.0	±18.0

Table 3.5 Blood lactate responses to a single bout of high intensity resistance exercise in untrained and trained groups

Lactate (mmol/L)	Pre-Exercise (T1)		Immediate Post (T2)		5-min Post (T3)		15-min Post (T4)		T2-T1	T3-T1	T4-T1
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	SMD	SMD	SMD
Untrained	1.45	0.8	6.94	0.8	6.15	1.7	4.86	1.6	7.1**	6.1**	2.98**
Trained	1.81	1.1	7.68	0.7	6.99	2.4	5.02	1.5	5.5**	4.8**	3.30**
SMD	*0.39**		*0.99**		*0.40**		*0.11**				

***Standard mean difference (SMD) between groups**

**** Standard mean difference within group across time**

Table 3.6 Relative strength results for each exercise between groups relativized to body weight

Strength Relative to Body Weight	Untrained (Mean±SD)		Trained (Mean±SD)		Cohen's d	p-value
Chest Press	26.30%	±12%	39.80%	±9%	1.27	*<0.001*
Seated Row	43%	±10.7%	56.30%	±8.7%	1.36	*<0.001*
Military Press	14%	±8.6%	20.60%	±5.8%	0.89	*0.01*
Bicep Curl	11.40%	±2.9%	15.10%	±4.1%	1.06	*0.003*
Triceps Press	11.10%	±2.7%	15.20%	±3.5%	1.31	*<0.001*
Leg Press	87.70%	±18.2%	115.30%	±20.1%	1.44	*<0.001*
Leg Extension	35.20%	±9.7%	46.10%	±7.2%	1.27	*<0.001*
Leg Curl	38.80%	±9.5%	46.80%	±10.4%	0.81	*0.019*

Table 3.7 Pre- and post-condition (T1 & T4) mood data for trained and untrained groups.

	PRE-CONDITION BASELINE (T1)									
	RESTING CONTROL DAY					***EXERCISE DAY***				
	Trained		**Untrained**			**Trained**		**Untrained**		
	Mean	SD	Mean	SD	P	Mean	SD	Mean	SD	P
Vig	13.9	6.7	9.1	5.1	0.019	13.1	6.2	9.9	4.5	0.088
Fat	5.9	5.8	7.8	7.1	0.5	4.7	4.8	6.7	7.0	0.32
Ang	1.8	2.9	3.3	4.5	0.22	1.2	2.1	1.8	3.3	0.47
Ten	6.0	5.2	7.7	7.2	0.41	4.8	4.0	4.8	4.3	1.0
Dep	2.3	5.7	6.6	8.8	0.9	1.3	2.4	3.2	4.1	0.095
Con	5.5	3.8	7.6	5.2	0.19	4.0	3.0	5.7	3.4	0.12
Tot	107.7	23.8	123.8	31.1	0.088	103.0	14.8	112.3	21.4	0.13
	POST CONDITION BASELINE (T4)									
	DAY AFTER RESTING CONTROL					***DAY AFTER EXERCISE***				
	Trained		**Untrained**			**Trained**		**Untrained**		
	Mean	SD	Mean	SD	P	Mean	SD	Mean	SD	P
Vig	11.4	7.2	8.6	6.0	0.21	12.6	7.1	8.8	6.0	0.088
Fat	5.7	6.8	6.9	6.0	0.58	5.2	5.1	7.2	6.3	0.3
Ang	2.1	4.4	2.5	3.8	0.73	0.7	1.1	1.7	2.5	0.14
Ten	4.9	5.9	6.3	5.6	0.47	4.0	3.7	5.9	6.8	0.31
Dep	2.1	4.7	4.1	5.6	0.24	0.9	1.8	1.7	2.5	0.29
Con	4.4	3.5	6.2	3.2	0.11	3.9	2.5	5.9	4.6	0.12
Tot	107.7	24.5	117.4	18.8	0.19	102.1	16.0	113.5	21.1	0.074

Table 3.8 Mood state means and standard deviations (SD) before (T1) and immediately (T2) and 30-minutes after (T3) the rest and exercise conditions for the untrained and trained groups. Total mood is the sum of the negative mood states minus vigor plus 100; thus, a higher total mood score indicates worse mood. SMD refers to Cohen's standardized mean difference (d). Moderate-sized (d=0.50) or larger SMDs are italicized.

CONDITION	**Before (T1)**		**Immediate Post (T2)**		**30-minutes Post (T3)**		**Effect T2-T1**	**Effect T3-T1**
REST	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**SMD**	**SMD**
Untrained (UT)								
Vigor	9.05	5.15	9.79	5.87	10.79	6.96	0.14	0.34
Anger	3.32	4.47	1.05	1.90	2.32	3.76	*-0.51*	-0.22
Confusion	7.58	5.23	6.16	4.06	5.47	3.79	-0.27	-0.40
Depression	6.63	8.75	2.11	2.60	2.00	3.18	*-0.52*	*-0.53*
Tension	7.74	7.22	5.53	5.57	4.89	4.67	-0.31	-0.40
Fatigue	7.58	7.11	5.90	5.56	5.47	6.21	-0.24	-0.30
Total Mood	123.79	31.10	110.95	18.66	109.37	21.47	-0.41	-0.46
REST								
Trained (TR)	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**SMD**	**SMD**
Vigor	13.89	6.70	13.89	6.71	12.67	6.74	0.00	-0.18
Anger	1.78	2.86	0.50	0.92	2.00	4.89	-0.45	0.08

Confusion	5.56	3.75	4.11	3.50	4.11	3.36	-0.39	-0.25
Depression	2.33	5.71	0.83	1.38	0.78	1.56	-0.26	-0.27
Tension	6.00	5.17	5.33	5.96	5.83	6.28	-0.13	-0.03
Fatigue	5.94	5.78	4.67	5.19	4.39	5.46	-0.22	-0.27
Total Mood	107.72	23.83	102.06	15.47	104.44	20.06	-0.24	-0.14
EXERCISE								
Untrained (UT)	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**SMD**	**SMD**
Vigor	9.94	4.49	13.94	6.49	14.06	6.75	*0.89*	*0.92*
Anger	1.83	3.25	1.50	2.67	0.94	1.75	-0.10	-0.27
Confusion	5.67	3.37	4.78	3.52	4.67	3.18	-0.29	-0.30
Depression	3.22	4.06	1.78	2.68	0.78	1.18	-0.36	*-0.60*
Tension	4.83	4.31	6.17	5.46	4.78	3.41	0.31	-0.01
Fatigue	6.72	6.98	7.50	5.97	6.56	5.52	0.11	-0.02
Total Mood	112.33	21.41	107.78	18.53	103.67	13.17	-0.21	-0.40
Trained (TR)	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**SMD**	**SMD**
Vigor	13.06	6.22	16.17	6.89	15.39	7.97	*0.50*	0.38
Anger	1.17	2.12	1.06	2.46	0.72	1.84	-0.05	-0.21
Confusion	4.00	2.97	3.83	2.98	3.06	2.21	-0.06	-0.32
Depression	1.33	2.35	0.56	1.29	0.39	0.78	-0.33	-0.4
Tension	4.83	3.97	6.00	4.96	5.50	5.34	0.30	0.17
Fatigue	4.72	4.82	5.61	4.26	4.44	3.24	0.19	-0.06
Total Mood	103.00	14.82	100.89	15.48	98.72	14.82	-0.14	-0.29

Table 3.9 Mood states means and standard deviations (SD) before and after the rest and exercise conditions for the untrained and trained participants combined. Total mood is the sum of the negative mood states minus vigor plus 100; thus, a higher total mood score indicates *worse* mood. SMD refers to Cohen's standardized mean difference (d). Moderate-sized (d=.50) or larger SMDs are italicized.

CONDITION	Pre-Condition (T1)		Immediate Post (T2)		30-min Post (T3)		T2-T1 Effect	T3-T1 Effect
REST	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**SMD**	**SMD**
Vigor	11.41	6.36	11.54	6.47	11.7	6.83	0.02	0.05
Anger	2.57	3.81	0.78	1.51	2.16	4.29	-0.47	-0.11
Confusion	6.6	4.62	5.16	3.88	4.81	3.6	-0.31	-0.39
Depression	4.54	7.64	1.49	2.17	1.41	2.57	-0.4	-0.41
Tension	6.89	6.28	5.43	5.68	5.35	5.45	-0.23	-0.25
Fatigue	6.78	6.46	5.3	5.34	4.95	5.8	-0.23	-0.28
Total Mood	115.97	28.6	106.62	17.53	106.97	20.66	-0.33	-0.31
EXERCISE								
Vigor	11.46	5.55	15.03	6.69	14.7	7.3	*0.64*	*0.58*
Anger	1.51	2.74	1.28	2.55	0.84	1.77	-0.08	-0.25
Confusion	4.86	3.25	4.32	3.26	3.88	2.83	-0.17	-0.3
Depression	2.83	4.43	1.18	2.18	0.59	1.01	-0.37	-0.51
Tension	4.83	4.09	6.09	5.15	5.13	4.41	0.31	0.07
Fatigue	5.75	6.03	6.58	5.22	5.53	4.62	0.14	-0.04
Total Mood	107.79	18.85	104.43	17.24	101.26	14.02	-0.18	-0.35

Table 3.10 Means, standard deviations (SD), and Cohen's (d) standardized mean differences (SMD) for the Stroop test variables in the trained and untrained groups prior to and after each condition.

Stroop Color-Word Task Inhibitory Control		**Pre-Condition Baseline** (T1)		**Post-Condition** (T2.5)	
REST		**Mean**	**SD**	**Mean**	**SD**
Word	**Untrained**	91.21	±20.17	100.47	±14.20
	Trained	92.78	±18.70	96.89	±17.56
	SMD	0.08		0.23	
Color	**Untrained**	73.68	±9.65	79.26	±7.46
	Trained	71.94	±11.63	75.94	±8.99
	SMD	0.16		0.40	
Interference	**Untrained**	51.00	±9.46	53.42	±11.63
	Trained	50.06	±7.37	54.11	±6.52
	SMD	0.11		0.07	
EXERCISE		**Mean**	**SD**	**Mean**	**SD**
Word	**Untrained**	102.83	±10.73	108.79	±11.81
	Trained	95.61	±15.92	103.89	±16.51
	SMD	0.50		0.30	
Color	**Untrained**	79.17	±8.86	82.37	±7.99
	Trained	72.56	±9.33	79.00	±9.00
	SMD	0.70		0.40	
Interference	**Untrained**	52.55	±8.88	56.58	±7.36
	Trained	52.39	±9.25	56.22	±8.17
	SMD	0.02		0.05	

Table 3.11 Pre-condition (T1) and post-condition (T4) S100β and CRP log-transformed data for the trained and untrained groups in relation to resting control and exercise conditions.

PRE-CONDITION BASELINE (T1)												
	RESTING CONTROL DAY						***EXERCISE DAY***					
	Trained		**Untrained**				**Trained**		**Untrained**			
	Mean	SD	Mean	SD	P	SMD	Mean	SD	Mean	SD	P	SMD
S100β	1.80	0.48	1.85	0.29	0.67	0.31	1.80	0.50	1.86	0.35	0.66	0.14
CRP	1.72	0.65	2.16	0.71	0.056	0.65	1.69	0.74	2.04	0.78	0.18	0.46
POST CONDITION BASELINE (T4)												
	24-HRS AFTER RESTING CONTROL						***24-HRS AFTER EXERCISE***					
	Trained		**Untrained**				**Trained**		**Untrained**			
	Mean	SD	Mean	SD	P	SMD	Mean	SD	Mean	SD	P	SMD
S100β	1.85	0.56	1.89	0.33	0.79	0.087	1.83	0.5	1.89	0.32	0.62	0.14
CRP	1.68	0.79	2.2	0.68	0.03	0.71	1.74	0.75	2.2	0.87	0.16	0.57

Table 3.12 Biomarker means and standard deviations (SD) before (T1) and immediately (T2) and 30-minutes after (T3) the rest and exercise conditions for the untrained and trained groups. The data are in log-transformed pg/mL units. SMD refers to Cohen's d standardized mean difference.

Biomarkers	**Pre-Condition (T1)**		**Immediate Post (T2)**		**30-min Post (T3)**		**T2-T1**	**T3-T1**
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**SMD**	**SMD**
S100β - Exercise								
Untrained	1.86	0.35	1.83	0.39	1.75	0.42	-3.48	-0.31
Trained	1.80	0.50	1.83	0.46	1.75	0.43	0.06	-0.01
SMD	*0.14*		*0.0*		*0.0*			
S100β - Rest								
Untrained	1.85	0.29	1.93	0.37	1.80	0.39	0.28	-0.17
Trained	1.80	0.48	1.78	0.50	1.69	0.43	-0.04	-0.23
SMD	*0.13*		*0.34*		*0.27*			
CRP - Exercise								
Untrained	2.04	0.78	2.22	0.83	2.08	0.80	0.23	0.05
Trained	1.69	0.74	1.85	0.74	1.77	0.62	0.22	0.11
SMD	*0.46*		*0.47*		*0.43*			
CRP - Rest								
Untrained	2.16	0.71	2.22	0.78	2.10	0.96	-0.82	-0.09
Trained	1.72	0.65	1.72	0.75	1.70	0.56	0.0	-0.03
SMD	*0.65*		*0.65*		*0.51*			

Table 3.13 Pearson correlations (r) between S100β and C-reactive protein at three time points during the exercise condition. 95% confidence intervals are shown in parentheses.

Trained and Untrained Groups Combined (n=37)			
S100β	**Timepoint**	**C-reactive Protein**	
	T1	**r=0.68, p<0.001**	**(0.45, 0.82)**
	T2	**r=0.72, p<0.001**	**(0.51, 0.85)**
	T3	**r=0.68, p<0.001**	**(0.46, 0.82)**

Trained Group (n=18)			
S100β	**Time**	**C-reactive Protein**	
	T1	**r=0.56, p=0.016**	**(0.12, 0.81)**
	T2	**r=0.62, p=0.007**	**(0.21, 0.84)**
	T3	**r=0.71, p<0.001**	**(0.37, 0.88)**

Untrained (n=19)			
S100β	**Timepoint**	**C-reactive Protein**	
	T1	**r=0.74, p<0.001**	**(0.44, 0.9)**
	T2	**r=0.81, p<0.001**	**(0.55, 0.92)**
	T3	**r=0.73, p<0.001**	**(0.41, 0.89)**

Chapter IV.

Future Research Directions

4.1 Other Variables to Consider

Future research should explore the long-term effects of resistance exercise training on S100β in the framework of a randomized controlled trial and include other inflammation biomarkers and neural biomarkers indicative of BBI status or contrast enhanced neuroimaging techniques to more directly measure BBI integrity. The potential neuroprotective effects relative to exercise mode, intensity, and duration could ultimately optimize exercise prescriptions for different groups, such as those with neurological problems, and exercise preferences. Understanding the neuroscientific basis of mood and inhibitory control responses to chronic resistance exercise should contribute to informing personalized exercise interventions aimed at enhancing cognitive health and emotional well-being. By integrating neuroscience into exercise science, clinicians and researchers can advance strategies for managing neuroinflammatory conditions, optimizing cognitive outcomes, and promoting overall brain health through regular physical activity.

Future research should also examine psychophysiological responses to different resistance exercise intensities as well as sex-specific differences. Comparison of sex-specific responses to acute resistance training are needed to elucidate changes in S100β as it has been reported that females have higher S100β in CSF following TBI compared to men (Goyal, 2013). If female responses to neurological trauma are more severe than men then S100β potentially could serve as a diagnostic tool to sex-specific responses to deviations in BBI permeability and resistance exercise and resistance exercise training could assist in achieving BBI homeostasis. S100β has also been reported as either being a damage associated molecular pattern protein (DAMP) or responding to DAMP proteins (Sorci, 2010), not simply a diagnostic tool of BBI permeability, but potentially indicative of a healthy response at certain extracellular concentrations.

Research on biomarker responses to exercise encounters several challenges that researchers must navigate. One significant hurdle is the variability in biomarker responses among individuals. This variability stems from factors like age, sex, genetics, and overall health. Another complexity lies in the temporal dynamics of biomarker responses (Amar, 2024). When we exercise, biomarkers can change rapidly and potentially unpredictably based on the type, intensity, and duration of the activity, not to mention the multitude of psychobiological and historical individual differences. For researchers, this means carefully timing sample collection and the exercise stimulus to both capture time-based fluctuations accurately and minimize time-based error variance. Moreover, understanding the extent to which exercise affects biomarkers over time—both immediately after a session and in the long term— is complicated because changes are based on release, transport in tissues, and circulation and metabolism which adds another layer of complexity to interpreting results, especially regarding novel biomarkers.

Exercise and body mass composition, particularly fat mass or lean mass, alters metabolism. In addition to adaptations to metabolism that occur with resistance exercise training, metabolism changes across the lifespan with a marked decline in older adults, particularly for females (Pontzer, 2021). The metabolism of biomarkers due to resistance exercise, therefore, might not be readily observable in an acute study and would be better analyzed in a training study with a more rigorous control over prior resistance exercise training. Metabolism of CRP in response to different exercise training intensities and durations has been shown to have no significant differences though a medium effect (d=-0.56) in favor of moderate intensity continuous exercise was shown in healthy adults under 30 years old (Mattioni-Maturana, 2021). However, resistance exercise training, let alone high intensity resistance exercise, with different durations or number of workouts per week might elicit meaningful distinctions.

Metabolic flux of CRP and S100β in relation to age and body composition should be considered in future research. In the present investigation, in an unreported exploratory analysis that excluded baseline levels, there was significant, large effects between the TR and UT groups for both S100β and CRP during the 30-minute window following exercise (T2 to T3) compared to the rest condition (df=1, 34, F=4.45 p=0.042, $\eta^2 = 0.12$; df=1, 34, F=6.71, p=0.014, $\eta^2 = 0.17$, respectively). While both measures remained significant when BMI was added as a covariate, the effect for CRP became more pronounced (df=1, 34, F=7.64, p=0.009, $\eta^2 = 0.18$) while S100β remained significant but decreased (df=1, 34, F=4.13, p=0.05, $\eta^2 = 0.11$). With the current study, to what extent body composition contributed to this interaction cannot be determined. While the effect remained significant for both biomarkers when BMI was added as a covariate, it is possible that body composition contributed to post-exercise metabolism because BMI is not an accurate measure of body composition. It is reasonable to assume the UT group had higher amounts of adipose tissue relative to the TR group. Adipose tissue contribution to S100β metabolism might be pertinent as S100β has been shown to act as an adipokine in a cell-culture model to mediate the effects of inflammation (Fujiya, 2014). Conversely, the TR group likely having a higher percentage of muscle mass, and therefore a greater metabolic response to muscle damage after a high intensity bout of resistance exercise, will have upregulated overall metabolic effects. Future studies should monitor post-exercise delayed onset muscle damage markers.

One of the possible metabolic effects has been studied in an acute injury mouse model in which it was shown that S100β was necessary for the muscle regeneration and repair process (Riuzzi, 2017). In both of these processes in which S100β functions as an adipokine or myokine, S100β acts in conjunction with the receptor for advanced glycation end-products (RAGE). RAGE triggers oxidative stress which has the downstream effect of nuclear factor kappa B (NF-κB) activation and translocation to the nucleus. This initiates a cascade of pro-inflammatory molecules from activation of RAGE and NF-κB (Bekircan-Kurt, 2015; Hofmann, 1999; Huttunen, 2000; Tóbon-Velasco, 2014). This is the hypothesized mechanism by which neuroinflammation is propagated. If so, elevated S100β might be sign that BBI repair is taking place and therefore, the effect of repeated bouts of vigorous resistance exercise might provide preventative benefit through minor, acute increases in inflammation essentially exercising the BBI response.

A review further supporting this dual-nature of S100β (Michetti, 2012) has shown a trophic 'Jekyll' effect at nanomolar biofluid levels whereas a toxic 'Hyde' effect presents when at micromolar levels. The trophic effects of S100β have been reported as promoting neurite extension, neuron survival, and regulation of muscle development and regeneration (Ahlemeyer, 2000; Barger, 1995; Bhattacharyya, 1992; Businaro, 2006; Haglid, 1997; Iwasaki, 1997; Kleindienst, 2006; Kligman, 1985; Sorci, 2003; (Winningham-Major, 1989). In contrast, toxic levels of S100β have been reported as inducing nitric oxide release in astrocytes and in microglia, up-regulating cyclooxygenase-2 expression in microglia and monocytes, inducing nitric oxide-dependent death of astrocytes and neurons, and increasing the production of reactive oxygen species in neurons (Adami, 2001; Bernardini, 2010; Bianchi, 2010; Esposito, 2008; Hu, 1996, 1997; Petrova, 2000; Shanmugam, 2008).

Given the evidence of NF-κB as a key regulator of inflammatory response, it should be included in future research involving serum analysis. NF-κB represents a family of proteins that are important regulators of genes involved in regulating the immune and inflammation response (Liu, 2017; Figure 4.1). NF-κB is a transcription factor located in all cells in an inactive state. The activation of NF-κB induces the production of pro-inflammatory molecules, including cytokines (e.g., IL-1β, TNF-alpha), chemokines (e.g., IL-8, MCP-1), and adhesion molecules (e.g., intercellular adhesion molecule-1, vascular cell adhesion molecule-1). NF-κB activation also allows for the two main DNA binding subunits of NF-κB (p50 & p65) to translocate to the nucleus where they can act on over 150 genes. NF-κB activation can also have protective effects on the BBI. NF-κB signaling is involved in the upregulation of various antioxidant enzymes and anti-apoptotic factors, which can counteract oxidative stress and prevent cell death. Moreover, NF-κB activation can induce the expression of anti-inflammatory cytokines and growth factors, which can help to resolve inflammation and promote tissue repair.

Regarding the effect of acute resistance exercise on NF-κB, a meta-analysis showed positive effects on NF-κB associated molecules (Salimans, 2022). One study in particular (Jiménez-Jiménez, 2008) demonstrated that 8 weeks of submaximal eccentric training attenuated the inflammatory response of an acute bout of eccentric training with accompanied positive changes of muscle soreness and strength loss (Figure 4.2) as well as analysis of blood samples for NF-κB (Figure 4.3), IκBs, lactate dehydrogenase (Figure 4.4), and DNA-binding subunits p50 and p65 (Figure 4.5).

In summary, future studies in this area would benefit by increasing sample size and variety of participants (e.g., young/old, with/without chronic disease), adding inflammatory and blood-brain interface biomarkers, timepoints of biomarker collection, and a body composition method to differentiate types of mass, particular muscle mass and fat mass.

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4.1 Figures

Figure 4.1 Illustration of the widespread effects on the immune system of NF-κB (Liu, 2017).

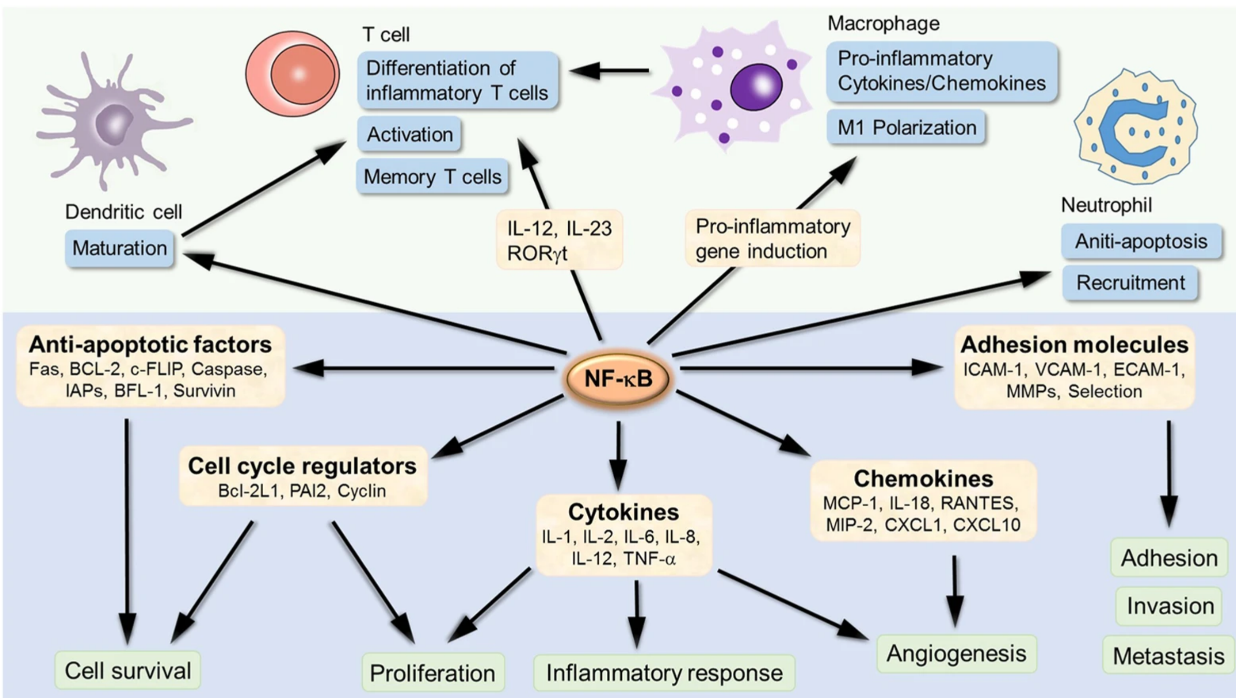
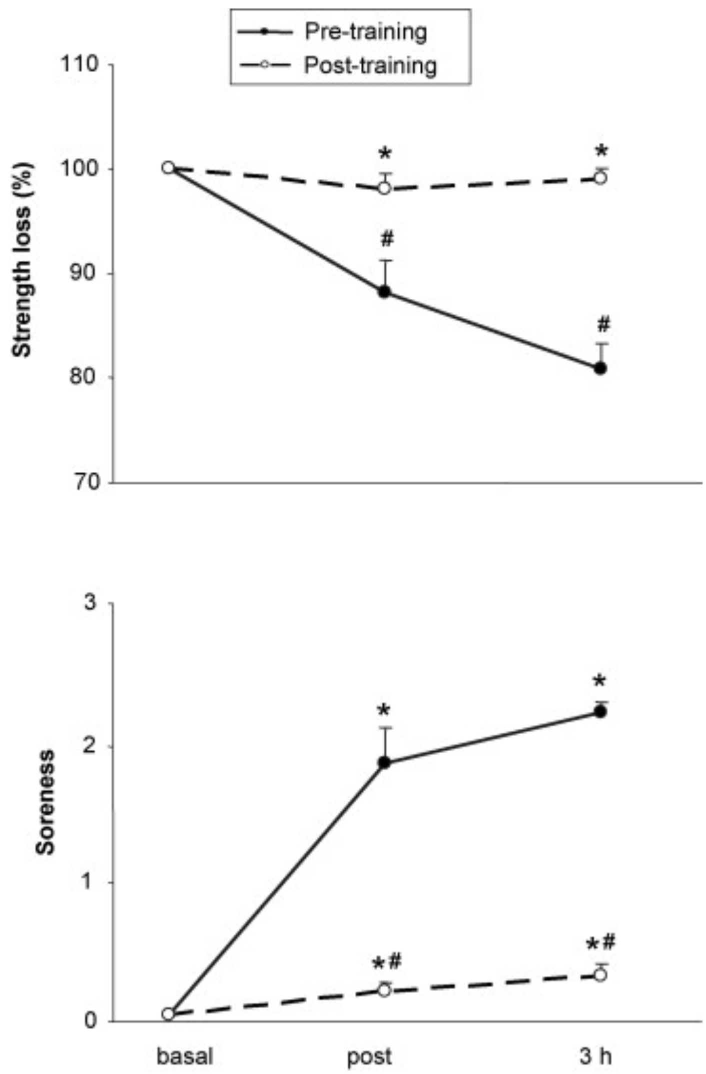


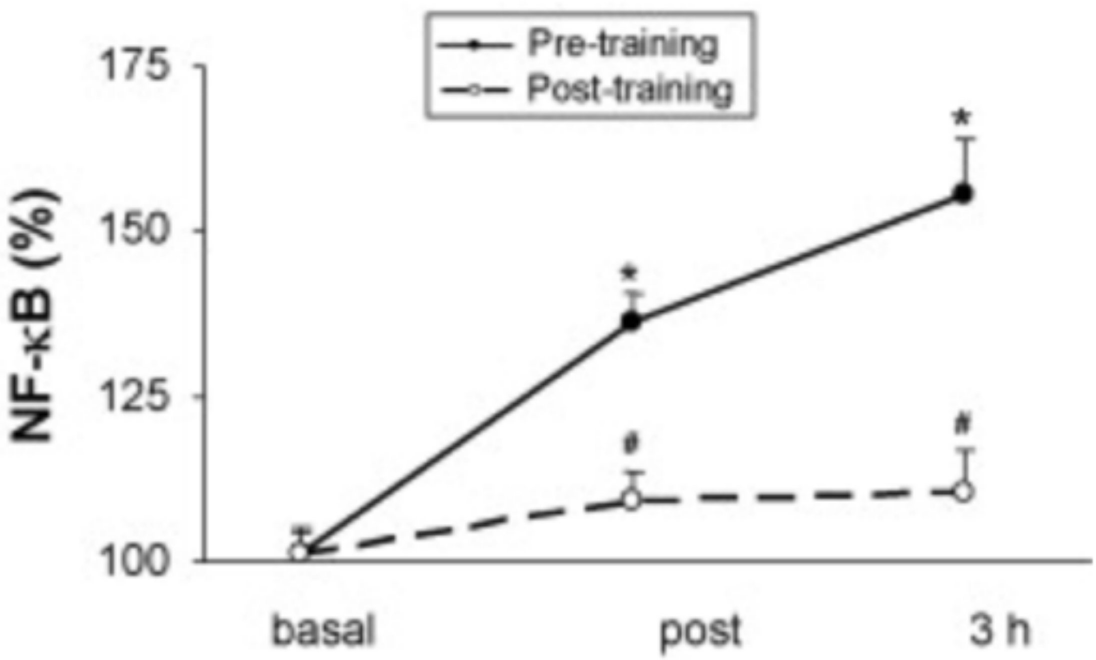
Figure 4.2 Percent change of muscle strength and muscle soreness to an eccentric resistance exercise bout before and after 8 weeks of resistance exercise (Jiménez-Jiménez, 2008).



[*]Significant changes compared to resting values ($p < 0.05$).

[#]Significant changes compared to pre-training values ($p < 0.05$).

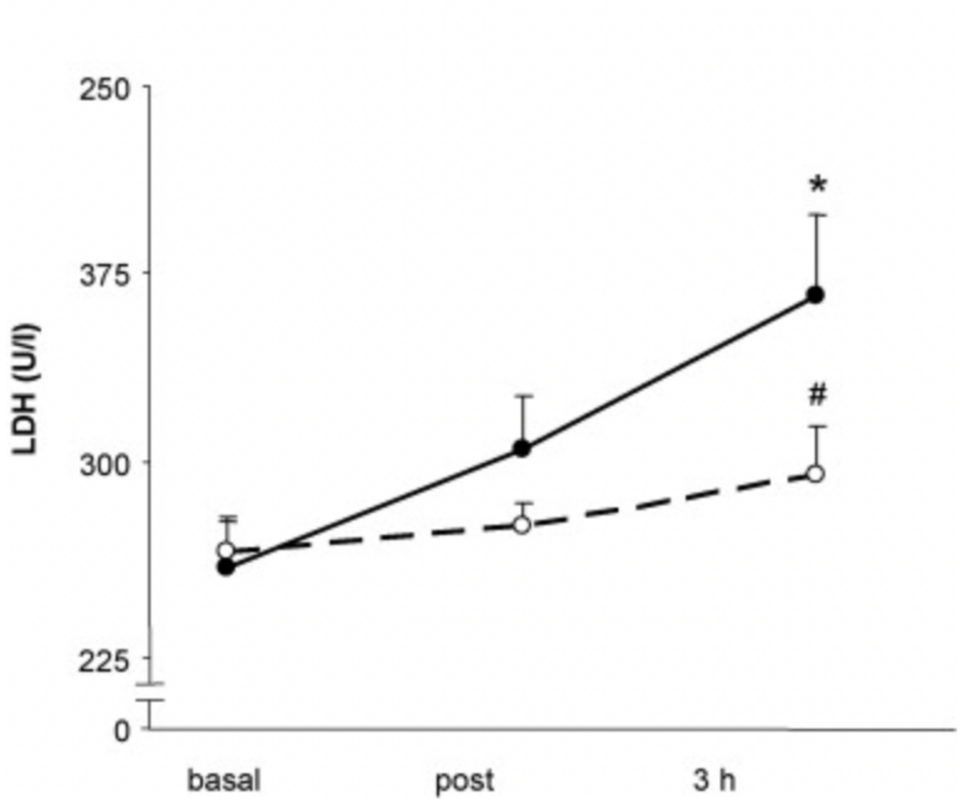
Figure 4.3 Percent change of NF-κB to an eccentric resistance exercise bout before and after 8 weeks of resistance exercise (Jiménez-Jiménez, 2008).



*Significant changes compared to resting values ($p < 0.05$).

#Significant changes compared to pre-training values ($p < 0.05$).

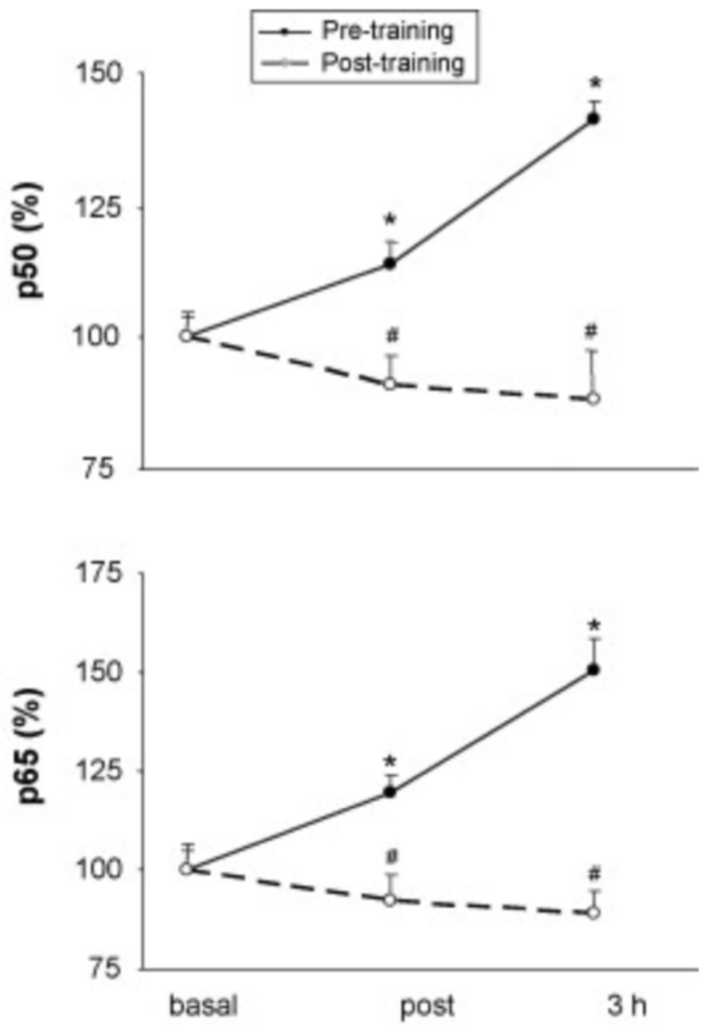
Figure 4.4 Change of in lactate dehydrogenase to an eccentric resistance exercise bout before and after 8 weeks of resistance exercise (Jiménez-Jiménez, 2008).



*Significant changes compared to resting values ($p < 0.05$).

#Significant changes compared to pre-training values ($p < 0.05$).

Figure 4.5 Percent change of DNA-binding subunits p50 & p65 activated by NF-κB nucleus translocation to an eccentric resistance exercise bout before and after 8 weeks of resistance exercise (Jiménez-Jiménez, 2008).



*Significant changes compared to resting values ($p < 0.05$).

#Significant changes compared to pre-training values ($p < 0.05$).