PROMOTING BRAIN HEALTH AND RESILIENCE: THE EFFECT OF THREE TYPES OF EXERCISE ON BLOOD-BASED NEUROTROPHINS

By

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Abstract:

Exercise is positively related to aspects of brain health through mechanisms involving blood-based neurotrophins released in the brain and from skeletal muscle. Neurotrophins are neuroprotective, promoting the growth and plasticity of neurons in the brain. However, the differences and/or similarities of exercise type on neurotrophic release in the cardiovascular system have yet to be established. We evaluated the acute effects of moderate-intensity continuous exercise, high-intensity interval exercise, and resistance exercise on Brain Derived Neurotrophic Factor, a protein involved in promoting neuroplasticity along with secondary measures of brain health: heart rate variability (HRV), self-reported positive and negative affect, and grip strength. In a repeated measures cross-over design, 12 participants over 5 weeks underwent all three exercise types while phlebotomy, cardiac, affect and grip strength measures were taken pre-, immediately post-, 30-minutes, and 60-minutes post-exercise. Results showed a significant change in plasma BDNF concentrations across all exercise types from immediately post-exercise to the 60-minute post-exercise time interval. Cardiac measures showed a decrease in heart rate variability immediately post-exercise, followed by a gradual increase to above pre-exercise levels at 60-minutes post exercise. A decrease in negative affect following exercise was also observed from immediately post- to 60-minutes post-exercise. No significant changes in grip strength were observed. Taken together, the results suggest that although exercise type did not differentially affect BDNF, HRV, or negative affect, all three measures suggested a consistent trend of physiological and psychological improvement or recovery trend at 60-minutes post exercise, highlighting the potential widespread benefits of various forms of exercise on aspects of brain health.

Keywords: brain-derived neurotrophic factor, brain health, exercise, biomarkers,

Table of Contents

Introduction

Throughout our journey in life, challenges are presented to us along the way. The human brain is experiential, processing and interfacing with the external environment, as well as writing and overwriting experiences, and its outcomes are utilized for future encounters. We learn from these experiences and develop ways to make life more predictable. We use our memories of previous experiences, develop new tactics, and overcome stressful challenges to help us regulate and maintain optimal internal functioning, both mentally and physically. The human brain is equipped with the tools needed to achieve such challenges but necessitates proper nourishment to function at its best. Therefore, to target resilience as an outcome, we must maintain a healthy brain by incorporating health-promoting behaviours into our lives to prevent disease onset, both physically and mentally.

Physical exercise is an intentional behaviour that, when performed each time, we deliberately and repeatedly impose stressful and unfamiliar conditions on ourselves. These behaviours can improve our threshold for stress and increase our resilience capacity while promoting a healthier brain. Physical exercise induces multifaceted cellular responses that enhance brain health and, thus our capacity to form adaptive responses to physical and mental stress. This manuscript will focus on the crucial role of physical exercise from the perspective of blood-based neurotrophins. These molecules differentiate and reinforce the structure and function of neurons in the brain. As a result, brain areas affected by these molecules are preserved, strengthened, and even change their function based on the demands of the external environment, facilitating a more adaptive response to adversity. Such underlying mechanisms of physical exercise on the body and brain truly represent a fascinating and crucial field of scientific research.

Here, we will review the current knowledge connecting brain health and resilience. We will discuss the function of Brain-Derived Neurotrophic Factor, a neurotrophin implicated in reinforcing brain health, and its synthesis following different types of physical exercise. Lastly, we will describe a gap in the research and why it represents a crucial evaluation of brain health and resilience.

Brain Health and Resilience

Brain health is a dynamic state of cognitive, emotional, and motor systems within the brain sustained by multiple interacting neurobiological mechanisms (Chen et al., 2021). Adequate brain health facilitates a balance between cognition, emotions, and motor function, allowing individuals to fully utilize their capabilities across the lifespan (World Health Organization, 2023). Poor brain health is associated with mental and neurological illness, collectively representing 16.5% of global Disability-Adjusted Life Years (DALYs) that are associated with death and disability (Feigin et al., 2019; Patel et al., 2018; Santomauro et al., 2021). DALYs lead to poor quality of life, burdening healthcare systems and shortening the lifespan. Fortunately, brain health is modifiable through preventative behaviours such as nutritional choice, sleep quality, sociability, and, most relevant to this manuscript, physical exercise (Mintzer et al., 2019). Physical exercise is associated with the enhancement of neuroplasticity, synaptogenesis, cerebral blood flow, and energy metabolism (Cotman et al., 2007; Di Liegro et al., 2019), all factors that improve brain function and neuron survivability, and potentially reduce DALYs.

The positive association between brain health and physical exercise is an operationalization of the broader concept of human resilience, which is the capacity to change one’s behavior and physiology to respond diversely, quickly, and effectively despite physical and mental hardship (Eaton et al., 2022). This is because physical exercise is associated with improved neuron

function and survivability within areas of the brain, all of which play an essential role in regulating cognition and emotions, thus strengthening resiliency to neurological and mental illness. For example, the literature highlights across the life span that cardiorespiratory fitness induced by physical is associated with increases in frontal and temporal grey matter volume, including the hippocampus and amygdala, suggesting physical exercise as a mediator of brain health facilitating the neural resources required to handle stress (Arida & Teixeira-Machado, 2021; Erickson et al., 2011; Feder & Nestler, 2009; Macintyre et al., 2018). Furthermore, the literature suggests many other neurobiological underpinnings encompassing resilience (See reviews: Feder et al., 2019; Feder & Nestler, 2009). Included is the hypothalamus-pituitary-adrenal axis involved in cortisol release to regulate physiological stress, or the noradrenergic system regulating nor-epinephrine in areas of the brain involved in emotion (amygdala), reward (nucleus accumbens), memory (hippocampus), and cognitive control (prefrontal cortex). Furthermore, neurotransmitters such as serotonin and dopamine regulate our mood and anticipation of reward, influencing our psychosocial approaches to managing stress and emotions. These factors combined are underpinned by the genetics we acquire from birth and expressed throughout development, shaping how we respond to stress in our environment.

Collectively, these factors shape the brain's fear and reward circuitry, influencing the psychosocial behaviours we utilize to cope and manage adversity. Highly resilient individuals demonstrate an advanced capacity to regulate stress by facing their fears with psychosocial approaches such as proactive coping, better emotional regulation through positive memory reappraisal, and higher trait optimism, allowing more affordances to negate the effects of adversity on their well-being (Feder & Nestler, 2009). However, given the prevalence of neurological and mental illness, resilience varies widely across humans, and the neurobiological

mechanisms that arise from physical exercise may provide critical insights into unlocking human potential by improving the facets of brain health and subsequent psychosocial behaviours that follow.

Physical Exercise & Brain Health

Physical exercise is implicated in the reduction of age-related decline in cognition, preventing disease onset, and improving learning outcomes as well as emotions (Basso & Suzuki, 2016; Cotman et al., 2007; Di Liegro et al., 2019; McIntyre et al., 1990). Physical exercise is regarded as a non-pharmaceutical remedy for reducing symptoms of systemic inflammation and is also involved in comorbid symptoms of depression (Basso & Suzuki, 2016; Di Liegro et al., 2019; Mintzer et al., 2019; Venezia et al., 2023) while Accordingly, physical exercise is associated with the enhancement of prefrontal-cortex activity, influencing attention and consolidation of memory into the hippocampus with emotional context of the memory shaped by the amygdala (Basso & Suzuki, 2016; Di Liegro et al., 2019; Mintzer et al., 2019; Venezia et al., 2023) while simultaneously increasing brain plasticity, and regulating autonomic, cardiovascular and cerebrovascular functioning (Cotman et al., 2007; Di Liegro et al., 2019). Research suggests that acute bouts of exercise are associated with increased post-exercise cognitive task performance in humans (Griffin et al., 2011; Powers et al., 2015; Schmolesky et al., 2013; Winter et al., 2007). For example, acute graded aerobic exercise on an ergometer increases mood immediately post-exercise (Ligeza et al., 2023) and hippocampal-dependent performance on memory tasks 90 minutes post-exercise (Griffin et al., 2011). Graded treadmill exercise has also been combined with exposure therapy to enhance fear extinction in those being treated for PTSD (Powers et al., 2015). Similarly, acute high-intensity running for intervals of 3 minutes improves learning

during language learning tasks, testing learning speed, associative learning, memory retention, and recall ability (Winter et al., 2007).

Although varying in type, generally, acute physical exercise affects brain health, as reflected in the cognitive improvements described above. However, the modalities of physical exercise can vary significantly. We therefore focus on three operationally defined types of physical exercise. High-Intensity Interval Exercise (HIIE), Moderate Intensity Continuous Exercise, and Resistance Exercise (RES). HIIE is characterized by shorter bouts of high-intensity exercise with >80% peak heart rate and aerobic capacity, interspersed with a recovery period of low intensity or rest (Steele et al., 2021). Conversely, MICE is characterized by more extended periods of repetitive rhythmic muscle movements that exert <80% of maximum heart rate and aerobic capacity (Steele et al., 2021). Lastly, RES is a type of exercise in which repeated movement of external or body weight taxes the skeletal muscle to increase strength, hypertrophy, power and muscular endurance (Phillips & Winett, 2010). Concerning cognition, HIIE and MICE are associated with performance increases in tests of attention, working memory, executive function, and reasoning (de Lima et al., 2022). Furthermore, the literature corroborates these findings, which found increased hippocampal volume memory performance after aerobic exercise (Erickson et al., 2011). Conversely, resistance training in middle to late-age adults before completing a Stroop task is associated with higher performance than controls (Chang et al., 2014). These results are consistent with a recent review finding that acute resistance exercise performed at a moderate intensity improves executive functioning more than vigorous or light intensity (T.-Y. Huang et al., 2022). However, the mechanisms of how physical exercise affects brain health are still debated; one potential mechanism of how EX affects brain plasticity is the upregulation of neurotrophins such as Brain-Derived Neurotrophic Factor.

Brain-Derived Neurotrophic Factor

One potential explanation for the improvement in memory, attention, and emotions associated with physical exercise is Brain-Derived Neurotrophic Factor (BDNF), a neurotrophin synthesized from skeletal muscle satellite cells during exercise (Mousavi & Jasmin, 2006). BDNF is also synthesized in the brain, promoting neuron differentiation and potentiation in areas of the brain involved in memory consolidation, learning, cognitive control, and emotional well-being (Basso & Suzuki, 2016; Cotman et al., 2007; Di Liegro et al., 2019; Macintyre et al., 2018; Mandolesi et al., 2018; Miranda et al., 2019). In animal models, BDNF is found in the amygdala, cerebellum, and cerebral cortex, with the highest levels in the hippocampus (Hofer et al., 1990), especially after physical exercise (Rasmussen et al., 2009; Sleiman et al., 2016). Both animal and human BDNF concentrations can also be detected peripherally through blood-based measures of serum and plasma (Di Liegro et al., 2019; Gejl et al., 2019). Furthermore, experiments with animal models show that plasma BDNF crosses in both directions across the blood-brain barrier (Pan et al., 1998; Poduslo & Curran, 1996), whereas serum-based platelet-derived BDNF cannot (Radka et al., 1996). Furthermore, associations of peripheral plasma BDNF are found in central nervous system BDNF across different mammalian species (Klein et al., 2011). However, despite these findings, there is still disagreement on the mechanisms of peripheral BDNF at the blood-brain barrier, with recent literature emphasizing BDNF models that describe a cell-signaling process that induces BDNF expression in the brain rather than direct diffusion or active transport of BDNF at the blood-brain barrier itself (Fujisawa et al., 2022). Despite this controversy, the potential benefits of BDNF on brain health on brain health and resilience are still evident.

At the molecular level, mature BDNF is neuroprotective, initiating several cell-signaling cascades, enabling long and short-term potentiation of neurons (Figurov et al., 1996; Ying et al.,

2002), and facilitating neurotransmitter signaling, neuronal cytoskeleton remodeling, axon and dendritic growth, thus sustaining neuron survival and proliferation (Deinhardt & Chao, 2014; E. J. Huang & Reichardt, 2003; Kowiański et al., 2018). However, reduced levels of BDNF are implicated in depression (Hsieh et al., 2019; Schröter et al., 2020), age-related decline of hippocampal volume of older adults (Erickson et al., 2010), and neurodegenerative diseases (Azman & Zakaria, 2022) when compared to healthy controls (Ng et al., 2019; Rahmani et al., 2019). Thus, BDNF serves as an essential mediator of brain health and resilience.

Exercise Type and Brain-Derived Neurotrophic Factor

Typically, BDNF increases immediately after moderate or intense exercise and returns to baseline within 30-60 minutes after exercise (Nofuji et al., 2012). However, comparing standardized exercise protocols such as MICE, HIIE, and RES concerning peripheral BDNF release is crucial to understanding how physical exercise improves brain health and resilience. The literature has shown individually how these exercise protocols are associated with post-exercise BDNF, but none have compared BDNF levels between all exercise types. Standardized aerobic exercise protocols such as MICE and HIIE gain important significance. MICE is associated with an increase in BDNF from baseline with higher intensity and duration accompanying more extensive blood serum and plasma BDNF levels (Fernández-Rodríguez et al., 2022; Marquez et al., 2015; Schmolesky et al., 2013). HIIE stimulates an immediate BDNF increase from baseline (Cabral-Santos et al., 2016) but is associated with a larger BDNF response in comparison to both MICE (de Lima et al., 2022) and continuous exercise at a high intensity (Saucedo Marquez et al., 2015). This higher BDNF response in HIIE could be attributed to increased stress and metabolic demands on the body and higher energy expenditure. However, the mechanisms underlying these processes only exist as current speculation.

Compared to endurance exercises like MICE and HIIE, RES also promotes peripheral BDNF release through both acute exercise and long-term training (Babiarz et al., 2022; Yarrow et al., 2010). Concerning higher exercise intensity RES, high-volume repetitions are associated with a larger BDNF response, indicating that greater physical and metabolic stress on the body could be related to higher BDNF levels in the blood (Church et al., 2016). Interestingly, lower-leg resistance exercise is associated with almost twice as much peripheral BDNF response as upper-body and whole-body exercises, suggesting that larger muscle groups play an essential role in BDNF synthesis (Lira et al., 2020). However, no comparisons have been made between MICE, HIIE, and RES in reference to peripheral BDNF levels, representing a significant gap in the current literature.

Other Measures of Resilience

Heart Rate Variability, a measure of autonomic integrity between the peripheral autonomic and central nervous system (R. Smith et al., 2017), is another important index of resilience (An et al., 2020) and can be improved with exercise (Routledge et al., 2010). Higher HRV is associated with improved cognitive aspects of affective regulation, attention, working memory, and executive function, along with physiological improvements surrounding stress management and cardiovascular health implicated with parasympathetic tone, speaking to its dual role in the homeostatic regulation of visceral and cortical functions (R. Smith et al., 2017; Thayer & Lane, 2000, 2009). Importantly, acute aerobic and strength exercise show differential post-HRV changes, with aerobic exercise being associated with greater decreases in HRV (De Paula et al., 2019), lending to the idea that regular physical exercise improves vagal recovery of HRV (Routledge et al., 2010).

Grip strength, another index of resilience, is a measure of neuromuscular functioning and neurological integrity in areas associated with motor function and mental health. (Cui et al., 2021; Jiang et al., 2022; Mather et al., 2020; Shaughnessy et al., 2020). Higher grip strength is associated with increased grey matter volume in subcortical regions such as the basal ganglia and limbic system, areas responsible for motor learning, executive function, and emotions (Jiang et al., 2022; Lanciego et al., 2012). Grip strength is also used as a predictor of resilience to life stress (Neumann et al., 2022), inversely related to depressive symptoms (L. Smith et al., 2019), and lower values being associated with neurodegenerative disorders that cause cognitive decline and dementia (Cui et al., 2021).

As stated throughout the manuscript, there are a myriad of neurobiological markers of resilience that are important for evaluating human brain health and resilience. However, exercise-induced BDNF may play a crucial role in promoting neuron plasticity and synaptogenesis in the human nervous system and is associated with better cognition in areas concerned with emotion, executive function, and memory (Cotman et al., 2007; Di Liegro et al., 2019; Figurov et al., 1996; Macintyre et al., 2018; Mandolesi et al., 2018; Ying et al., 2002). Other peripheral markers include autonomic nervous system activity responsible for maintaining homeostatic regulation of heart rate and rhythm variability and measures associated with activity in cortical regions involved in cognition and emotion (R. Smith et al., 2017; Thayer & Lane, 2000, 2009). Figure 1 displays a theoretical activation pattern after the onset of physical exercise, increased BDNF, and autonomic activity, two measures of brain health. Following that, a chain reaction ensues where the combination of sympathetic activation and neurotrophic synthesis upregulates cognitive and neurological processes that constitute brain health, which in turn increases resilience thus inhibiting the onset of mental and neurological illness. More

specifically, this indirect effect of physical exercise on brain health helps the individual mentally evaluate a stressor, promoting proactive coping strategies and ultimately, resolving the reaction to the stressor using a more dynamic approach (Pascual-Leone & Bartres-Faz, 2021). Thus, physical exercise concerning brain health and resilience represents a significant cornerstone of neurological and mental illness, creating more affordances for navigating adversity within the external and internal environment.

Present study

Given that the acute effects of MICE, HIIE, and RES on BDNF concentrations have not been previously compared, this area of brain health and exercise warrants investigation. The proposed study aims to determine if an acute bout of MICE, HIIE, and RES exercise causes a differential BDNF response. We used a 5-visit repeated-measures cross-over design. In the first two visits, participants underwent a standardized peak ventilatory threshold (VO2 peak) test (a measure of maximal oxygen intake during exercise) and maximum strength testing. The final three visits (i.e., visits 3-5) entailed the primary experimental phases of the study. Participants completed one of three acute exercise interventions in each visit: High-Intensity Interval Exercise, Moderate Intensity Continuous Exercise, and Resistance Exercise. Our primary dependent variables were plasma BDNF levels, which were collected pre-exercise, post-exercise, 30-minute, and 60-minute post-exercise. We tested the primary prediction that in each exercise type, there would be an acute increase in blood plasma BDNF immediately following exercise (post versus pre). We also predicted a sustained elevation in BDNF for 30-minutes post-exercise, which will return to baseline by 60-minutes post-exercise (Nofuji et al., 2012). Additionally, we hypothesized that high-intensity interval exercise would show a significantly higher increase in plasma concentrations of BDNF in comparison to MICE and RES (de Lima et al., 2022; Marquez et al.,

2015). We also evaluated secondary predictions relating to autonomic reactivity (HRV), neuromuscular functioning (grip test), and cognitive well-being (PANAS).

Methods

Participants

The study sample consisted of 12 physically active participants (defined by any self-structured exercises ≥ 2x per week) between the ages of 18 and 45. To determine our sample size, we used GPower analysis (Faul et al., 2007) for repeated measure within-subjects ANOVA; the calculated estimated sample size was 12 to detect a significant effect between exercise conditions at $\alpha = 0.05$ and $\beta = 0.1$ with an effect size (ηp2) estimation to be 0.42. The sample size was also determined by a similar study that compared three exercise protocols on BDNF across time; however, no effect size was reported (Paul, 2016). Participants were recruited through word of mouth and recruitment posters in the University of Manitoba Recreation Centre and local gyms around Winnipeg. Participants were screened for any recent use of anti-inflammatory medication or supplements, diagnosis of inflammatory disease, cognitive or physical disability, clinical diagnoses of psychological (e.g., depression, anxiety, schizophrenia) or neurological (e.g., stroke, dementia) conditions, recent (≤ 6 months) clinical history of head trauma (e.g., concussion), surgically implanted electronic devices (e.g., pacemaker), history of drug or alcohol dependence, current pregnancy, current musculoskeletal injury. The inclusion/exclusion parameters were developed to remove any potential confounds that could disrupt measures of the neurotrophic biomarkers and to reduce potential risk to participants from exercising. All participants consented individually for each stage of the study (5 consent forms for each experiment) and were compensated $15.00 for each time they consented for a total of $75.00. Participants were free to withdraw at any time during any stage of the study.

Participants also completed the Canadian Society for Exercise Physiology: Get Active Questionnaire, a document used to guide individuals through questions about their health to determine whether they should seek advisement from a health care practitioner or exercise professional before undergoing structured physical activity. Users are asked to answer YES or NO to questions that address various medical conditions and physical limitations that may impede the ability to engage in structured physical exercise safely. Individuals are then asked to determine how many minutes per week they undergo moderate to vigorous-intensity aerobic exercise and are then informed of the recommended weekly minutes of exercise for adults and children. Lastly, individuals are then notified with general advice about becoming more active and guided through a declaration process. If individuals answered NO to all questions, they can sign the form, and if they answered YES to any question, they must declare that they have either consulted a health care provider or exercise professional who has recommended they become more physically active, or that they are comfortable themselves with become more physically active on their own (Akben-Marchand, 2023).

Procedure

The study duration was 5 visits (once per week to allow for physical recovery) for ~90 minutes per visit. See Figure 1 for a visual depiction of the overall procedure. On day 1, we recorded participant's demographic information, including biometric measures including total lean tissue mass (kg), total fat mass (kg), body fat percentage, body mass (kg), height (m), and body mass index (kg/m^2) using a bioimpedance scale (InBody270, InBody Canada, Ottawa, ON, Canada). Visits 1 and 2 entailed a VO2 peak protocol followed by a 1-repetition maximum protocol as a baseline for peak aerobic capacity and maximum strength to achieve a standard measure of physical fitness. Peak aerobic capacity was measured using a VO2 peak protocol on a

cycle ergometer, and a 1-repetition maximum (1RM) protocol measured maximum strength and recorded as the maximum volume of weight they can lift for a single complete repetition of each resistance exercise.

On days 3-5, three experimental recording sessions occurred: High-intensity interval exercise (HIIE), moderate-intensity continuous exercise (MICE), and resistance exercise (RES). Participants underwent phlebotomy, cardiac and hand grip strength measurements, and a positive and negative affect questionnaire known as the Positive and Negative Affect Schedule (PANAS) immediately before, after, 30-minutes, and 60-minutes after each experimental exercise protocol. See Figure 2 for a depiction of the experiment procedure. Please note the details of these measures are provided in the measures section. Furthermore, participants had to sit for 30-minutes prior to their first blood draw to control for variability in baseline levels of BDNF. They were also asked to maintain a consistent diet, record what they eat in a food diary, and refrain from exercising three days before each experiment.

Standardized Fitness Tests:

One-repetition maximum test (1RM)

The 1RM test is a reliable measure of muscle strength irrespective of gender or muscle size and is used to measure the maximum amount of weight each participant can lift for one complete repetition for a given exercise (Seo et al., 2012). A complete repetition in the context of this study was defined to the participants as a movement that engages a full range of motion ending back at the starting point (Niewiadomski et al., 2008). The current study uses 6 resistance exercises to target several muscles in the body maximally: chest press, leg press, seated row, knee extension, shoulder press, and knee flexion. A similar protocol was used to test 1RM for each muscle group, referring to the National Strength and Condition Association (Baechle &

Earle, 2008). Each participant underwent a warmup phase where they lifted weights at 40-60% of their perceived 1RM for 5-10 repetitions followed by 1 minute of rest. Gradually increasing the weight, participants decrease their repetitions to 3-5 at 60-80% of their perceived 1RM with 3-5 minutes of rest. Finally, participants were given ≤ 4 attempts with 3-5 minutes of rest to a achieve a 100% 1RM.

Peak Ventilatory Threshold test (VO2 peak)

Participants had their aerobic capacity measured using a VO2 peak test, which measures an individual's maximal oxygen intake while undergoing vigorous exercise (Kour Buttar et al., 2019). The test entailed a graded exercise exposure on a cycle ergometer. Experimenters incrementally increased the participant's workloads by 0.5 kg every 3 minutes while maintaining 60 revolutions per minute (RPM) using The Monark Ergomedic 894E Peak Bike (Monark Sports & Medical, n.d.). The parameters for reaching and measuring VO2 peak included three of the following: reaching an estimated maximum heart rate (220-age) during exercise; a rating of 17 on the perceived exertion Borg 6-20 scale, a tool used to assess subjective rating of perceived exertion from the participant with 6 indicating lowest effort and 20 indicating maximal effort (Williams, 2017); and a respiratory exchange ratio of 1.10 (Niekamp et al., 2012). All measures were assessed every 3 minutes by the same experimenter at each increase in effort as adjusted on the ergometer. We collected metrics of aerobic capacity, the peak consumption volume of oxygen per minute per kilogram of weight (V'O2/kg [(mL/min)/kg]), and the max resistance (maximum weight achieved pedaling on the ergometer at the final 3-minute interval) were used to determine the resistance on the ergometer for the experimental trials.

Exercise Intervention

Visits 3-5 of the procedure involved participants undergoing three different types of exercise interventions: MICE, HIIE, and RES. Conditions were counterweighted for each participant to control for order effects. Details for each intervention are provided below.

Moderate intensity continuous exercise (MICT)

MICT is a level of unceasing exercise maintained at <80% of peak heart rate or aerobic capacity for a duration of 20 to 30 minutes (Steele et al., 2021). Participants cycled on an ergometer at 35% of the weighted load (in kg) they pedaled at during their peak oxygen consumption (VO2peak) for 30 minutes at 60 revolutions per minute (RPM). This weighted load approach should result in participants working at <80% of their peak heart rate and aerobic capacity. The intensity level for the MICE protocol was chosen to provide a balanced effort level between physically fit individuals and those who are not physically fit as we anticipated some differences in overall physical fitness between participants.

High-intensity interval exercise (HIIE)

HIIE is an interval exercise that is performed at an intensity ≥80% of the maximum heart rate and VO2 peak with short periods of recovery exercise with less effort (Steele et al., 2021). Participants cycled on an ergometer at 15% of the percent of weighted load achieve at VO2peak for 1 minute and then at 90% of the percent of weighted load achieve at VO2peak for 1 minute, which was repeated for 10 sets in a row at 60 RPM for a total exercise time of 20 minutes. HIIE protocols are designed to tax both the anaerobic and aerobic systems and have been shown to produce improvements in cardiovascular health (Ito, 2019).

Resistance Exercise Session (RES)

Following the same exercise performed during the 1RM session, participants completed a whole-body resistance exercise routine (80% of 1-repetition maximum for 3 sets by 8 reps per set) (Baechle & Earle, 2008) using plate-loaded weight machines, including chest press, leg press, seated row, knee extension, shoulder press, and knee flexion to target whole-body muscle groups. These exercises were the same as those tested during the 1RM session.

Dependent Measures

The dependent measures utilized in the experiment are plasma-Brain Derived Neurotrophic Factor; extracted using phlebotomy and measured using The Human Neurotrophic Factors 4-Plex ProcartaPlex Panel, Heart rate variability; extracted using an H10 polar heart sensor and calculated using the Polar Flow application, Positive and Negative Affect Scale; a 20-item questionnaire, and grip strength; measured using a JAMAR Hydraulic Hand Dynamometer. All measures were taken pre-, immediately post, 30-minutes, and 60-minutes post-exercise. Each measure is described in detail below.

Phlebotomy

Each participant had a baseline blood draw after 30 minutes of rest immediately preceding each exercise. Using a 21-gauge butterfly or safety needle fitted with a vacutainer vessel, a phlebotomist conducted the blood draws, and ~ 6 mL of blood was collected from the medial or cephalic vein and placed in a cooled Ethylenediamine Tetra acetic Acid (EDTA) coated vacutainer blood draw tube to prevent clotting (Banfi et al., 2007). Afterward, each participant underwent the exercise bout for that session and returned immediately for a post-exercise blood draw. Blood draws were repeated at 30-minutes and 60-minutes post-exercise in the same manner described above for a total of 4 blood draws per session.

Once the four blood draws were completed, we separated plasma and clotting factors by centrifuge at 2,500x RPM for 10 minutes using a refrigerated centrifuge at 4°C. After, the EDTA vacutainer blood draw tube was taken to a prepared and activated biological safety cabinet. Blood plasma was then extracted into a micropipette set to 500µL fitted with a tip cone for safe extraction. The 500µL of plasma was aliquoted into four 1.5-2.0 ml aliquots labeled with the participant's assigned ID number and stored at -80°C in Room 232 until the assays were performed. After freezing, samples were visually inspected for hemolysis, which could alter the analysis results.

Blood analysis was conducted using Millipore Milliplex, a Luminex/xMAP technology (Luminex, Austin Texas), and a commercial Neurotrophic Factors 4-plex Human ProcartaPlex™ Panel kit (Thermo Fisher Scientific, 2021). The kit is used to measure blood plasma concentrations of four neurotrophic factors in human plasma: Brain-Derived Neurotrophic Factor (BDNF), Glial Cell-Derived Neurotrophic Factor (GDNF), Nerve Growth Factor (NGF) and Neurotrophin-3 (NT-3). All sample preparation steps were followed using the instructions in the neurotrophin panel kit. For this manuscript, only BDNF will be used for analysis in this study, given our timing of blood collection follows previously supported research that focuses on BDNF (Nofuji et al., 2012). The average coefficient of variation for BDNF was 26.5% ± 20.1, indicating a moderate to high variability of the sampled values around the mean.

Heart Monitor

Cardiac measurements were taken for 5-minutes at time points pre-, immediately post, 30-minutes, and 60-minutes post-exercise using a Polar H10 heart rate monitor while participants were seated in a comfortable chair. Cardiac measures were conducted for ~5-minutes using the Polar H10 heart rate sensor in combination with the Polar Unite Fitness watch to extract and

record the data from the H10. The heart rate sensor is secured to a chest strap and placed just at the base of the sternum (xiphoid process) as depicted in the Polar H10 instruction manual (Polar H10 Heart Rate Sensory, n.d.). Cardiac electrical activity was captured by moistened embedded electrodes in the chest strap connected to the heart monitor. Data was uploaded to the Polar Flow app, which automatically calculates Heart Rate Variability (HRV) and exports it to a CSV file. HRV represents the R-R interval between each consecutive heartbeat. The R in an R-R interval represents the ventricle's peak depolarization, leading to a cardiac contraction's onset (Ashley & Niebauer, 2004). The HRV values were sampled at 1000Hz for a period of 5-minutes and the root mean square of successive differences (RMSSD) was then calculated from that range of values (Koenig et al., 2014). We used HRVtool, an opensource MATLAB software specialized for organizing and filtering cardiac data (Vollmer, 2019).

Positive and Negative Affect Scale (PANAS)

The PANAS is a reliable self-report mood scale that measures the current state of positive and negative emotions (Watson et al., 1988). This questionnaire contains 20 items, 10 of which measure positive affect and 10 measure negative affect. The participant completed this questionnaire using Qualtrics, a digital survey application. Participants are asked to rate the extent to which they experienced each emotion on a 5-point Likert scale: 1 (very slightly or not at all), 2 (a little), 3 (moderately), 4 (quite a bit), and 5 (extremely). This scale consists of several words that describe different feelings and emotions that are positively or negatively valenced. Positive affect is measured by the mean response to the items: Interested, Excited, Strong, Enthusiastic, Proud, Alert, Inspired, Determined, Attentive, and Active. Negative affect is measured by the mean response to the items: Distressed, Upset, Guilty, Scared, Hostile, Irritable, Ashamed, Nervous, Jittery, and Afraid. The participant was instructed to read each item and then

mark the appropriate multiple-choice answer, indicating the extent to which they feel in that present moment. The PANAS was administered to each participant at time points pre-, immediately post, 30-minutes, and 60-minutes post-exercise. PANAS responses were measured between exercises and between time points for each exercise.

Hand Grip Dynamometer

The Grip strength is a measure of neuromuscular integrity and is correlated with aspects of brain and mental health (Cui et al., 2021; Jiang et al., 2022; Shaughnessy et al., 2020; L. Smith et al., 2019). Grip strength was compared with participant BDNF and 1RM measures in participants. Hand grip strength was measured using the gold standard measurement device: JAMAR Hydraulic Hand Dynamometer. Following the instruction manual, participants were asked to sit with their shoulder and arm placed at the midline of the body and neutrally rotated with the elbow bent at 90 degrees, forearm in a neutral position, and wrist between 0 degrees and 30 degrees dorsoflexion and between 0 degrees and 15 degrees ulnar deviation (Performance Health, n.d.). Setting the JAMAR Hand dynamometer to the second handle position from the inside, we instructed the participants to squeeze as hard as they could for three seconds in each hand. Hand grip measures were taken at time points pre-, immediately post, 30-minutes, and 60-minutes post-exercise.

Data Analysis

All statistical analyses were conducted using R, a statistical programming software used to perform statistical operations for research and data analysis. To evaluate the three predictions regarding the primary variable: BDNF, we used a 3 (exercise-type; within-subjects) x 4 (time; within-subjects) repeated measures Analysis of Variance (ANOVA) to analyze for main effects of exercise-type and time, as well as their interaction. All other secondary variables (BDNF,

heart rate variability, Handgrip strength, and PANAS responses) were analyzed using the same design. Statistical assumption checks were conducted for normality, sphericity, and linearity. If normality was violated, the data was square root transformed to correct for it. A nonparametric approach using aligned rank-transformed factorial ANOVA was conducted if normality was still violated after normality corrections were applied. This procedure creates a model ranking the data from smallest to largest based on the main effects and interaction effects (including the random variability between subjects). This procedure allows for ANOVA procedures on nonparametric multifactor designs, especially with repeated measures designs without inflating type-1 error (Wobbrock et al., 2011). If sphericity was violated, a Greenhouse Geisser correction was performed. If linearity was violated, square root transformations were conducted to correct the data. Post hoc tests (pairwise t-test for parametric and multifactor contrast tests for nonparametric) were performed to determine where the differences lie between exercise type and the time points. The multifactor contrast test is a valid procedure for non-parametric rank-aligned data that does not inflate type 1 errors (Elkin et al., 2021). To reduce the risk of type 1 error, the Holm-Bonferroni correction was utilized.

Using the boxplot method, graphing the blood samples with the RStatix package in R revealed potential statistical outliers. Specifically, an individual sample was considered an extreme outlier if it exceeded a value above quartile 3 + 3x(interquartile range) or below quartile 1 – 3x(inter quartile range). Extreme outliers were removed if they were both previously identified as potentially hemolyzed and considered to be an extreme outlier as described above.

BDNF samples were analyzed in duplicate, and the average concentrations were calculated. In total, 4 observations were excluded or missing in four independent participants. Specifically, two observations were excluded as they were deemed hemolyzed BDNF outliers (n = 2; 30-minutes

post-exercise; MICE), one observation was missed due to no blood collection (n = 1 condition; 30-minutes post-exercise; RES), and one observation was missed due to a physiological invalid multiplex reading (n =1; pre-exercise; RES). Regarding HRV data collection, four separate invalid HRV recordings for individual participants (n = 4). As repeated measure ANOVA requires an equal number of samples per participant to meet the assumptions and perform all comparisons, a K-nearest neighbors algorithm with a k = 3 using a Euclidian distance function was utilized for imputation of the missing measures (Chase et al., 2020), with one exception. One of the missing observations was one of three baseline measurements for a specific participant. In this case, the imputed value (n =1; pre-exercise; RES) was calculated by taking the average of the two baseline measures of the other two exercise conditions. Any trending findings will be described for transparency in the results section but will not be discussed further.

Results

Participants

Participant demographic and anthropometric characteristics are summarized in Table 1. In addition, descriptive statistics for performance metrics in experiments 1 (VO2 Peak) and 2 (1 Rep Max) are summarized in Table 2.

Brain-Derived Neurotrophic Factor (BDNF)

The average concentrations and variability of BDNF are displayed in Table 3. A Levene's test, $F(11, 132) = 0.79$, $p = .65$) revealed no significant differences across the variance of the data, indicating the variability within the data was not significantly different across all conditions. A Shapiro-Wilk Test on each group pairing revealed that the data was non-normally distributed in the following conditions: HIIE-pre ($W = 0.84$, $p = .03$), MICE-immediately post

(W = 0.74, p= .002), HIIE-30 minutes-post (W = 0.77, p = .005), MICE-30 minutes-post (W = 0.73, p = .002), RES-30 minutes-post (W = 0.81, p = .01), and MICE-60 minutes-post (W = 0.83, p = .02) indicating that a data-transformation or non-parametric analysis was needed for inferential statistics. These results can be visualized in a quantile-to-quantile (Q-Q) plot in supplemental Figure 1 in the appendix. A square-root transformation was conducted on the data, and the Shapiro-Wilk Test was reapplied. The results indicated that the data followed a non-normal distribution. A residual versus fitted test was conducted to assess the linearity of the data. As seen in supplemental Figure 2., the residuals appear evenly distributed above and below the horizontal axis (y = 0). However, toward the end of the horizontal axis, the distribution shifts downward along with the line of best fit, indicating a nonlinear trend at later timepoints.

BDNF Inferential Statistics

As the BDNF results did not meet the assumptions of normality, a nonparametric factorial ANOVA was conducted to examine the effects of Time (pre-, immediately post, 30-minute, and 60-minute post-exercise) by Exercise Type (HIIE, MICE, RES) on aligned rank transformed BDNF values. The results showed a significant effect of Time on BDNF values, F(3, 121) = 3.651, p = 0.015, indicating that BDNF levels changed significantly across the four time points irrespective of Exercise Type (see figure 4). There were no significant main effects of Exercise Type, F(2, 121) = .060, p >.05, nor interactions between Time by Exercise Type F(6, 121) = .801, p >.05. See figure 3 for depiction.

Given the significant main effect of Time on BDNF values, we conducted non-parametric pairwise comparisons using an aligned rank transformation procedure for multifactor contrast tests individually for Time and Exercise type, as there was no interaction effect. The analysis revealed that immediate post-exercise BDNF concentrations were significantly higher than 60-

minutes post-exercise BDNF, t(121) = 2.93, p_{adj} = .024. Two other comparisons were trending towards significance with pre-exercise being higher than 60-minutes post-exercise, t(121) = 2.584, p_{adj} = .0547, and 30-minutes post-exercise being higher than 60-minutes post-exercise, t(121) = 2.519, p_{adj} = .0547.

Heart Rate Variability (HRV) Root Mean Squared of Successive Differences (RMSSD)

The descriptive features of RMSSD HRV are listed in Table 4. We conducted a repeated measures ANOVA to examine the main effects of Time (pre-, post, 30-minute, and 60-minute post) by Exercise Type (HIIE, MICE, RES) on square root-transformed HRV RMSSD values. We square root transformed the data to correct for nonlinearity. Greenhouse Geisser corrections were utilized to correct for sphericity violations.

HRV RMSSD Inferential statistics

The results showed a significant main effect of Time, F(1.85, 20.34) = 17.580, $p < .001$, η^2 = .119 (See figure 6). There was also a significant main effect of Exercise Type, F(2, 22) = 6.794, p = .005, η^2 = .054. However, there were no significant interaction effects between Exercise Type and Time F(2.90, 31.92) = 2.130, $p > .05$, η^2 = .015 on RMSSD values (see figure 5).

Given that the repeated measures ANOVA revealed a significant main effect of Time on RMSSD values, we conducted pairwise comparisons using paired samples T-tests to inspect where the significant differences occurred between the four-time points. The results indicate a significant decrease from pre-exercise to immediately post-exercise, t (35) = 4.820, p_{adj} = <.001, with a large effect size (d = 0.803), a significant increase from pre-exercise to 60-minutes post-exercise, t (35) = - 3.324, p_{adj} = .032, with a moderate effect size (d = - 0.554), a significant increase from immediately post-exercise to 30-minutes post-exercise, t (35) = -6.23, $p_{adj} < .001$,

with a large effect size (d = -1.043), a significant increase from immediately post-exercise to 60-minutes post-exercise, t (35) = - 7.128, p_{adj} <.001, with a large effect size (d = -1.188) and lastly a significant increase from 30-minutes post-exercise to 60-minutes post-exercise, t (35) = -3.281, p_{adj} = .0140, with a moderate effect size (d = -0.547).

As the repeated measures ANOVA also found a significant main effect of Exercise Type, pairwise comparisons were carried out separately across Time and Exercise Type to reveal significant relationships between each condition. This indicated that HIIE was significantly lower than MICE, t(47) = -4.737, p = <.001, with a moderate effect size (d = -0.684), and that MICE was significantly higher than RES, t (47) = 4.306, p <.001, with a moderate effect size as well (d = 0.621). These results illustrate the pattern of significance across Time and Exercise Type and display that HRV varies widely across these domains. See Figures 5 and 6.

Positive and Negative Affect Scale (PANAS)

The descriptive features of the PANAS are listed in table 5. A Levene's test, F(11, 132) = 0.81, p = .62) revealed no significant differences across the variance of negative affect responses, indicating that the variability within the data was not significantly different across all conditions. A Shapiro-Wilk Test on each group pairing revealed that the data was non-normally distributed. The results indicated that the data were not normally distributed for the following conditions: HIIE-pre (W = 0.76, p = .003), MICE-pre (W = 0.78, p = .006), RES-pre (W = 0.81, p = .01), HIIE-immediately post (W = 0.70, p < .001), MICE-immediately post (W = 0.80, p = .008), HIIE-30 minutes-post (W = 0.73, p = .001), MICE-30 minutes-post (W= 0.77, p = .004), RES-30 minutes Post (W = 0.70, p < .001), HIIE-60 minutes post (W= 0.80, p = .008), MICE-60 minutes Post (W = 0.77, p = .004), and RES-60 minutes Post (W = 0.59, p < .001) indicating a rejection of the null hypothesis of normality at the 5% level of significance. These results can be

visualized on a Q-Q plot in supplemental Figure 3 in the appendix. A square-root transformation was conducted on the data, and the Shapiro-Wilk Test was reapplied. The results indicated that the data followed a non-normal distribution. A residual versus fitted test (see Supplemental Fig. 4) was conducted to assess the linearity of the data. As seen in supplemental Figure 3., the distribution of the residuals shift downward with the line of best fit below the horizontal axis (y = 0), indicating a nonlinear trend at later timepoints.

PANAS Inferential Statistics

As the negative affect results did not meet the assumptions of normality, a nonparametric factorial aligned transformed factorial ANOVA was conducted to examine the effects of Time (pre-, immediately post, 30-minutes, and 60-minutes post-exercise) by Exercise Type (HIIE, MICE, RES) on aligned rank transformed values of negative affect. The results showed a significant main effect of Time $F(3, 121) = 2.883$, $p = .039$. Furthermore, Figure 7 depicts a downward trend in negative affect from pre- to 60-minutes post-exercise. There was no significant main effect of Exercise Type $F(2, 121) = 0.496$, $p = .610$, or the interaction between Time and Exercise Type $F(6, 121) = 1.295$, $p = .265$.

Given the significant main effect of ranked Time on negative affect values, we conducted non-parametric pairwise comparisons using an aligned rank transformation procedure for multifactor contrast tests for Time. The analysis revealed that pre-exercise negative affect was trending towards greater than 60-minute post-exercise negative affect, $t(121) = 2.58$, $p = .053$.

For positive affect, there were no significant main effects of Time, $F(3,33) = 0.141$, $p = .935$, $\eta^2 = 0.0005$, Exercise Type $F(2, 22) = .091$, $p = .913$, $\eta^2 = 0.001$, nor an interaction between Time and Exercise Type $F(6, 66) = .502$, $p = .805$, $\eta^2 = 0.002$.

Grip Strength

The descriptive characteristics of grip strength are listed in Table 6. Grip strength was evaluated using a 2-way repeated measure ANOVA to examine the effects of Time (pre, post, 30-minutes, and 60-minutes post) and Exercise Type (HIIE, MICE, RES). For the left hand, there were no significant main effects of Time $F(3,30) = 0.453$, $p = .717$, $\eta^2 = .0009$, nor of Exercise Type $F(2, 20) = 2.290$, $p = .127$, $\eta^2 = 0.004$. There was no interaction between Time and Exercise Type $F(3.91, 39.12) = .253$, $p = .903$, $\eta^2 = .0007$ on grip strength. For the right hand, there were also no significant main effects of Time $F(1.50,14.96) = 1.404$, $p = .269$, $\eta^2 = .006$, nor of Exercise Type $F(2, 20) = 1.526$, $p = .242$, $\eta^2 = .007$. There was also no interaction between Time and Exercise Type $F(1.44, 14.42) = 0.537$, $p = .539$, $\eta 2 = .005$ on grip strength.

Discussion

Interpretation of Primary Results:

The current study aimed to measure the differences and/or similarities across Exercise Type and Time on the primary variable: Brain-Derived Neurotrophic Factor (BDNF), and secondary variables: Heart Rate Variability (HRV), affect, and grip strength. The first hypothesis that plasma BDNF concentrations would significantly increase from pre-exercise to immediately post-exercise was not supported. However, we did observe a significant decrease in plasma BDNF concentrations from immediately post- to 60-minutes post-exercise in all exercise conditions. The second hypothesis that BDNF concentrations would stay elevated until 30-minutes post-exercise with a gradual decrease towards baseline at 60-minutes post-exercise was partially supported with a gradual drop towards pre-exercise levels at 60-minutes post-exercise but no sustained elevation until 30-minutes post-exercise. The third hypothesis that HIIE would show a significantly higher increase in plasma concentrations of BDNF compared to MICE and

RES (de Lima et al., 2022; Marquez et al., 2015) was also not supported, with no significant differences across exercise types. We also explored the secondary measures of brain health: RMSSD-HRV, positive and negative affect, and grip strength. Although no predictions were made regarding these variables, we observed significant decreases in RMSSD-HRV values from pre- to immediately post-exercise with gradual increases to levels above pre-exercise at the 60-minute post-exercise time point (see Table 4 and Fig. 6). This pattern was significantly greater in HIIE and RES compared to MICE (Fig. 5). We also found that negative affect significantly decreased from pre- to 60-minutes post-exercise (Table 5 and Fig. 7).

The results suggest a differential response in the mechanisms of exercise on different aspects of brain health. While we did not observe a significant increase in plasma BDNF levels across time and exercise type, we did observe significant decreases in plasma BDNF after exercising. The observed significant decrease in plasma BDNF (45.1% decrease) from immediately post- to 60-minutes post-exercise was interesting. It revealed decreased BDNF levels to that below pre-exercise levels at 60-minutes post-exercise across all exercise types. However, BDNF concentrations at 60-minutes post-exercise were not significantly lower than pre-exercise concentrations. Although the present study cannot evaluate whether the acute reduction in plasma BDNF 60 minutes post-exercise is associated with positive brain health, the findings in the secondary measures suggest the reduction might be associated with positive brain health and resilience. The post-exercise effects on HRV and affect were similar to BDNF in that 60-min post-exercise was associated with significant changes relative to immediately post-exercise for HRV, while affect was trending towards reductions in negative affect at 60-minutes post-exercise compared to immediately post-exercise. Additionally, the increase in HRV coincided with decreases in negative affect. However, the effect on HRV was more pronounced in HIIE

and RES compared to MICE, suggesting that parasympathetic tone is more sensitive to higher-intensity protocols. Taken together, these measures of brain health show that all exercise types produce measurable improvements at 60-minutes post-exercise. At the same time, cardiac measures of HRV are more sensitive to different exercise types and display larger improvements. These measures signify the potential widespread benefits of different forms of exercise on aspects of brain health. The findings will be discussed in each section below.

Although not hypothesized, the study's main finding of BDNF significantly dropping from immediately post-exercise to 60-minutes post-exercise is similar to that seen in previous literature (Rasmussen et al., 2009; Roeh et al., 2021; Yarrow et al., 2010). Acute drops in BDNF below baseline and post-exercise levels after 60-minutes of recovery have been identified in previous research (Yarrow et al., 2010). They found that serum BDNF levels significantly decreased to 41% below baseline concentrations and 55% below immediately post-exercise concentrations. Other research testing plasma BDNF concentrations extracted from the jugular vein in response to upper body rowing exercises recorded significant decreases in levels below baseline during the exercise recovery phase one hour post-exercise (Rasmussen et al., 2009). Looking at long-term recovery, Roeh et al. (2021) found decreased serum BDNF levels compared to baseline in participants 72 hours after completing a marathon. These results reflect a potentially important attenuating mechanism reducing BNDF concentrations below baseline. The body's inflammatory response towards exercise could contribute to attenuating the response of BDNF during recovery. Research on rats shows that injections of pro-inflammatory cytokine-inducing endotoxins (interleukin-1β) demonstrate a decrease in BDNF gene expression in the rat hippocampus (Lapchak, 1993) and at the protein level as well (Guan & Fang, 2006). Given that physical exercise increases several immune system cytokines (Cornish et al., 2020), the

persistent immune system response after exercise may drive the reduction in BDNF via several immunological pathways. However, few studies have assessed this relationship further in humans.

In the current study, the descriptive features of BDNF such as those listed in Table 1 showed variable responses across the Time and Exercise Type dimensions of the data with high standard deviation values reflecting large fluctuations in plasma BDNF concentrations across time and exercise type. A Levene test revealed no significant differences across the data variance, suggesting that the variability was systemic throughout the experiment and across participants. When visualizing the results (Figures 3 and 4), the data pattern reflects its variability, depicting no reliable trajectory of BDNF across the Exercise Type. In addition, Shapiro's Test revealed that the data was non-normally distributed in nearly half the data, and Q-Q plots confirmed the data was non-normally distributed across all groups (See. Supplemental Fig. 2.). These features potentially reflect the response variability of plasma BDNF between individuals. For example, plasma BDNF concentrations are quite variable compared to serum and tend to decrease with age (Lommatzsch et al., 2005). In the current study, the coefficient of variation for age and BDNF was 25.7% and 26.5% respectively, indicating a moderate to high level of variability between the age of the participants and across the conditions in the BDNF. However, a study comparing the differences in BDNF concentrations across different kit types shows that the coefficient of variation for the current study was consistent with intra-assay variations seen using the Millipore Milliplex multiplexing assay (Polacchini et al., 2015).

Comparison with Prior Research:

Given that Hypotheses 1 and 3 were not supported and Hypothesis 2 was only partially supported, it is important to discuss the various considerations when measuring plasma-based

BDNF response. Comparing BDNF levels across studies can be challenging because of many methodological considerations and research degrees of freedom. These include the kit types or brands used to analyze the sample, the preparation protocols, the storage procedures (Gejl et al., 2019), and anthropometric and demographic differences between participants (Lommatzsch et al., 2005). For instance, those who regularly undergo physical exercise exhibit lower baseline BDNF compared to untrained individuals (Babaei et al., 2014), which could reflect smaller acute pre-post changes after physical exercise. Additionally, the differential elements of blood (i.e., the use of serum versus plasma) affecting BDNF are extremely important to consider (Pareja-Galeano et al., 2015). For example, systematically lower concentrations have been found in plasma BDNF (which the current study measured) compared to serum BDNF (Lommatzsch et al., 2005; Radka et al., 1996). A large proportion of peripheral BDNF is stored in platelets, resulting in relatively low plasma BDNF concentrations (Fujimura et al., 2002), reflecting nearly a 100-fold difference between blood-based plasma BDNF concentrations (Radka et al., 1996). Furthermore, serum-derived platelet BDNF cannot cross the blood-brain barrier (Radka et al., 1996), whereas plasma BDNF freely crosses in both directions (Pan et al., 1998; Poduslo & Curran, 1996). In addition, plasma levels of BDNF decrease as age and weight increase and are lower in females than males (Lommatzsch et al., 2005). These findings discussed above collectively suggest that peripheral plasma BDNF more accurately reflects concentrations in the brain among other components affecting the degree of response. Lastly, equipment used for analysing peripheral blood-based responses in BDNF varies in accuracy, intra/inter-assay variability, range, and sensitivity when measuring BDNF (Polacchini et al., 2015). We used a Millipore Milliplex, a Luminex/xMAP technology which has been shown to have a higher detection range than other enzyme-linked immunosorbent assays (ELISA) but does display

higher intra/inter-assay variability compared to other kits, suggesting that although it may be more accurate, it may be less reliable compared to other kits. However, it should be mentioned that Polacchini et al. (2015) conducted their experiment using serum BDNF as opposed to plasma BDNF, although the analysis instructions between serum and plasma are identical. Overall, plasma levels of BDNF offer a better advantage to measuring aspects of brain health relative to serum but suffer some disadvantages.

Considering the many factors listed above, a cautioned approach to comparing their relative concentrations of BDNF across studies is recommended. The results of the current study did not fully align with the predictions based on previous research. The first prediction regarding significant pre-post changes in BDNF failed to reach significance across all exercise types, a surprising finding with many studies reflecting a significant pre-post increase (Cabral-Santos et al., 2016; Church et al., 2016; de Lima et al., 2022; Marquez et al., 2015; Nofuji et al., 2012; Yarrow et al., 2010). However, the results were in line with our second prediction, reflecting a gradual decrease of BDNF to baseline levels within 60-minutes post-exercise, a result seen in previous research (Nofuji et al., 2012). Furthermore, the third prediction regarding HIIE demonstrating a higher response in BDNF failed to reach significance with no significant difference in BDNF concentrations across exercise types despite previous research indicating that HIIE had a greater effect on BDNF concentrations (de Lima et al., 2022; Saucedo Marquez et al., 2015). However, all the above studies adopted different methodological approaches, kit types, blood compounds (plasma, serum BDNF), and target populations. Furthermore, concentrations of plasma BDNF across each participant in the current study (see Table 3) were considerably lower than those reported in other studies (Cabral-Santos et al., 2016; Church et al., 2016; de Lima et al., 2022; Marquez et al., 2015; Nofuji et al., 2012; Yarrow et al., 2010), but

still within ranges similarly reported by other researchers (Dinoff et al., 2016; Sreter et al., 2020). However, given the above considerations about the variability of the BDNF response, much of the variability and low concentrations in the current study could be attributed to the choice of plasma BDNF relative to serum BDNF, the choice of kit, and the analysis approach. Furthermore, participants in the current study were only eligible if they participated in structured exercise ≥ 2 times per week, which could reflect the lower baseline concentrations found in previous studies of trained versus untrained individuals (Babaei et al., 2014).

Despite the lack of significant pre-post changes and differential response across exercise types, other studies have found no pre-post difference in BDNF after an acute bout of exercise. Goekint et al. (2010) tested the acute effect of resistance exercise on BDNF concentrations in resistance-trained and untrained participants. They found that despite training participants for 10 weeks at three training sessions per week, there were no significant differences in both groups' pre-post concentrations of BDNF after a single bout of resistance exercise. Similarly, Schiffer et al. (2009) found no significant pre-post difference in BDNF response after a 12-week strength training program. Furthermore, when comparing the BDNF responses across exercise types, our findings were consistent with those of other research. For example, a recent meta-analysis by Fernández-Rodríguez et al. (2022) found no significant differences in BDNF output between high-intensity and moderate-intensity exercise. However, no studies have compared aerobic exercise to resistance exercise secretion of plasma BDNF.

The current study also offers a novel look into the comparative relationship between aerobic and resistance exercise on BDNF, attempting to fill an important gap in the research. While the effect of aerobic exercise on BDNF concentrations is a widely researched topic, the influence of resistance exercise is less understood with inconsistent findings across studies; over half report

no effect of resistance training on BDNF (See systematic review: Babiarz et al., 2022). The review highlights the importance of utilizing a 1-rep max protocol to accurately estimate a participant's repetitions and intensity to achieve the desired effect, whether it be hypertrophy or strength. These aspects of resistance exercise are important to consider when evaluating the peripheral BDNF response and other exercise-related blood factors. The current study's resistance protocol included the following exercises performed at 80% of 1-rep max for 3 sets at 8-repetitions per set: Chest press, leg press, seated rows, leg extension, shoulder press, and leg flexion. Resting sessions were 1 minute between sets and 2 minutes between exercises. The selected exercises were chosen to comprehensively capture each major muscle group and maximize the overall impact on muscle contractions. Each participant had a full exercise session that lasted approximately 60 minutes. Despite our protocol, the findings suggest that RES offers potentially similar benefits to MICE and HIIE concerning brain health, given that BDNF concentrations were not significantly different across exercise types.

These blood-based mechanisms of brain health represent the dynamic and multifaceted nature of the body's response to physical exercise. Indeed, the current study showed that physical exercise induces significant yet small changes in BDNF in physically active participants. However, the methodological considerations discussed above, and the equipment used for analysis could explain the low concentrations and lack of significant pre-post changes. These results reflect the difficulty in measuring acute changes in brain health via blood-based mechanisms and contribute to the current scientific debate on whether peripheral BDNF impacts brain health. Importantly, no research exists examining the implications of higher versus lower peripheral BDNF concentrations on brain health and the resulting improvements in cognitive processes.

Interpretation of Secondary Results

Heart Rate Variability

The current study also took an exploratory look at secondary measures of brain health: RMSSD-HRV, positive and negative affect, and grip strength. We found that parasympathetic-mediated HRV (RMSSD-HRV) across all exercise types decreased from pre- to immediately post-exercise with a gradual increase back to levels above baseline. We also found that both HIIE and RES displayed a significantly greater effect on RMSSD with lower average values than MICE (see Fig. 5 and 6 for depictions of the results and Table 4 for a summary of the descriptive statistics). These results suggest that acute physical exercise exerts beneficial effects across exercise types on brain health through autonomic-mediated cardiac activity with distinctly greater effects in HIIE and RES than MICE. Such acute changes in parasympathetic-mediated HRV after physical exercise are similar in other literature (Michael et al., 2017; Mongin et al., 2022). However, a very interesting finding in the current study was that 60-minutes post-exercise HRV values increased to above pre-exercise levels. Michael et al. (2017) and Stanley et al. (2013) both observed similar patterns seen in cardiac parasympathetic reactivation after an acute bout of exercise and suggest that arterial-baroreflex stimulation induced by physical exercise compensates by increasing parasympathetic reactivation through a negative feedback loop lasting 24-48 hours post-exercise. For example, this baroreflex response is caused when exercise increases sympathetic-mediated heart rate and blood pressure, stimulating baroreflex receptors in the aorta and carotid arteries, which signal activation of the parasympathetic nervous system, slowing heart rate followed by decreased blood pressure (Shaffer et al., 2014; Shaffer & Ginsberg, 2017). This response scales with the level of hypervolemia (increased blood pressure) and is dependent on the intensity of the physical exercise conducted, which may explain why

HRV returns to levels higher than baseline (Michael et al., 2017) and is seen in greater magnitudes within those who are highly trained compared to those who are not (Stanley et al., 2013). The effects of exercise intensity on RMSSD values were reflected in the current study with greater drops in RMSSD values in RES and HIIE compared to MICE. However, the higher RMSSD value viewed at 60-minutes post-exercise compared to baseline was seen in all exercise types, suggesting that the recovery pattern remains the same across exercise types, despite different intensity levels. These results indicate that parasympathetic tone plays a significant role in autonomic recovery across HIIE, MICE, and RES. Still, the response across all time points is more pronounced in HIIE and RES and could be reflected by their intensity. As a reminder, intensity in the current study was reflected by the percentage of weighted load achieve at VO2peak pedaled during VO2 peak in MICE (35% of VO2 peak for 30 minutes) and HIIE (15% and 90% of VO2 peak alternating every minute for 20 minutes) and in by percentage of 1-rep max and number of reps in RES (80% 1-rep max for 8 reps). These parameters reflect the differences in intensity across exercise types in the current study and could explain the difference in the magnitude of response across each exercise type. Alternatively, some research suggests that sympathetic withdrawal may also represent acute changes in autonomic recovery with parasympathetic recovery being slower and more drawn out (Casonatto et al., 2011). This means a decrease in sympathetic activity (rather than an increase in parasympathetic activity) could contribute to autonomic restabilization after physical exercise. However, the interactions between the parasympathetic and sympathetic branches of the autonomic nervous system do not exist on a single dimension and often interact reciprocally and coactively, suggesting a complex joint contribution by both autonomic branches (Berntson et al., 1994). Therefore, quantifying the involvement of a single autonomic branch is difficult through HRV metrics alone. Although our

findings did not measure sympathetic activity, they are consistent with an increase in parasympathetic tone 60-minutes post-exercise, consistent with previous research outlining the parasympathetic nervous system's major role in autonomic regulation post-exercise.

The increased parasympathetic tone observed in the initial study could reflect overall resilience and brain health improvements. There is a large portion of research reflecting the positive relationship between higher HRV and aspects of psychological resilience like better behavioural flexibility to stress, improvements in attention shifting and sustainability, and better ability to regulate emotions, all of which stem from a greater top-down inhibition from the prefrontal cortex (Thayer & Lane, 2000, 2009). These implications and the results from the present research lead to the idea that the effects of acute exercise on parasympathetic tone are immediate with higher than baseline HRV-mediated parasympathetic tone just 60-minutes after exercising. This suggests cognitive flexibility to manage stress through the above improvements (i.e., brain health and resilience) can be improved through physical exercise.

Positive and Negative Affect Scale

When measuring positive and negative affect using the PANAS scale, we found a significant decrease in negative affect levels across time (see Figure 7 for depiction and Table 5 for descriptive statistics). Specifically, we observed a decrease in negative affect from pre- and 60-minutes post-exercise. This discrepancy suggests that while the overall trend is significant, the individual comparisons should be interpreted cautiously. In visualizing the data (see Fig. 7.), we observed a downward trend of negative affect from pre- to 60-minutes post-exercise. This pattern has been viewed in the literature, reporting acute decreases in negative affect immediately after exercising using the PANAS questionnaire, with the effects lasting up to 24 hours post-exercise (see review; Basso & Suzuki, 2016). Furthermore, the current study’s findings coincide with the

observed improvements in HRV after exercising. Higher HRV has been associated with improved emotion regulation and enhanced functional connectivity between brain regions responsible for regulating one's emotions (Mather & Thayer, 2018). Specifically, improved functional connectivity has been observed between brain regions such as the ventromedial prefrontal cortex and amygdala potentially providing a link between the beneficial effects of exercise on HRV and its effect on affect states and emotion regulation. The authors suggest that these improvements in functional connectivity and emotion regulation could be directly attributed to oscillations in HRV amplitude as a causal factor. These predictions have been tested using resonance breathing, a slow breathing exercise known to increase HRV oscillations and amplitude over time. This breathing technique has shown to reduce stress, anxiety and improve emotion regulation, suggesting that functional connectivity between brain areas involved in emotion regulation are affected too. Exercise-induced increases in HRV could therefore have the same effect as resonance breathing on affect, emotion regulation and potentially increased functional connectivity between these brain areas.

The current study also found no significant changes in positive affect after exercising, indicating that despite the decrease in negative affect, positive aspects of emotional affect remained unaffected by physical exercise. These results are consistent with research suggesting that positive and negative affect exist on separate, distinct dimensions of affect and independently respond to different situations (Schmukle et al., 2002). This contrasts with models of affect that suppose positive and negative affect are different ends of a single dimension (i.e., a valence dimension). A potential explanation for no significant change in positive affect could be that participants' baseline levels of positive affect were already high, leaving no room for improvement from exercise. Another could be the uncomfortable nature of the blood draws.

Blood draws occurred directly before participants completed the PANAS questionnaire, which could have had counterintuitive effects on the positive effects of exercise on positive affect.

Grip Test

The current study observed no differences in grip strength across Exercise Type or Time (see Table 6 for descriptive statistics). Some research shows acute changes to grip following exercise in sports that involve targeted grip strength. For instance, Medernach et al. (2015) found increases in grip strength over 4 weeks for those who participated in climbing sports (rock climbing/bouldering). Participants in their study were assigned to two groups that trained grip strength with a fingerboard or by bouldering. Their results showed that those who trained on fingerboard relative to bouldering had significant increases in grip strength as measured through handgrip dynamometry. These results suggest that while some exercises are sufficient to target grip strength, others are not. Additionally, acute changes in brain health may not be sensitive enough to reflect through changes in grip strength, but perhaps through other mechanisms. For instance, Mather et al. (2020) found that hand grip exercises with an exercise ball modulated locus-coeruleus activity in young women, a brain area involved in modulating attention and nor-epinephrine release. Participants who conducted handgrip exercises within an MRI scanner had decreased tonic activity in the locus-coeruleus and increased attentional performance. This study demonstrated that acute grip strength and endurance interventions significantly influenced brain activity in areas involved with attentional control. The literature reflects these findings with grip strength being positively associated with higher grey matter volume in the brain's basal ganglia and limbic areas when controlling for demographic, anthropometric, and socioeconomic confounds. Furthermore, these volumetric brain structure improvements coincide with reaction time improvements, a behavioural representation of cognitive processing speed and executive

function (Jiang et al., 2022). Declines in age-related cognition and the onset of dementia are strongly associated with lower grip strength, making grip strength a very important aspect of brain health and resilience disease onset (Cui et al., 2021). Additionally, grip strength is inversely correlated with depression symptoms (Ganipineni et al., 2023). Specifically, higher grip strength is associated with lower depression severity, with higher rates occurring in females. The literature discussed above suggests that hand grip strength continues to be used as a non-invasive diagnostic tool for early detection of a myriad of cognitive aspects of brain health. Potential mechanisms regarding grip strength and its relationship with brain health decline are multifaceted, suggesting an age-related decline in neural and muscular system integrity, including brain areas (Shaughnessy et al., 2020) and biological imbalances of hormones and neurotransmitters (Ganipineni et al., 2023). Given that the current study found no acute differences in grip strength after exercising. These results suggest that acute exercise and the specific exercise interventions used in the study are not sensitive enough to capture changes in grip strength. Furthermore, changes in grip strength could occur more slowly such as across the lifespan and into older age, suggesting that a longitudinal or cross-sectional study between younger and older age groups may see improvements in grip strength.

Limitations and Future Considerations

There were several limitations to the current study that are worthy of discussion. Participants were not categorized based on their athleticism, and their training was only assessed based on aspects of the quantity and duration of their exercises, as inquired about in the Get Active Questionnaire and inclusion criteria (exercise ≥ 2x per week). BDNF levels appear to vary across different fitness levels (Muñoz Ospina & Cadavid-Ruiz, 2024), and thus, generalizing the current findings to more sedentary populations or populations of elite athletes should be made

cautiously. Time of day (Begliuomini et al., 2008) and nutrition (Fakhoury et al., 2022; C. Phillips, 2017) are other factors that generally affect both BDNF and exercise performance. In the current study, participant availability varied from early morning to late afternoon hours across the 5 weeks, potentially contributing to the variability of BDNF concentrations within the data. Despite this limitation, actions were taken to mitigate potential nutritional confounds. Participants were given a nutritional diary to keep track of what they ate and were instructed to keep a consistent diet one day prior to their exercise session, therefore providing some control for dietary differences influencing BDNF levels across time. Research shows that BDNF levels are lowest during the follicular phase of menstruation (Begliuomini et al., 2007). The current study did not control for menstrual cycle due to participant availability, which could contribute to the variability within the data. These factors represent significant limitations that should be addressed in future research on physical exercise and BDNF.

Future research is required to address the potential mediators of peripheral BDNF release in response to physical exercise and within our environment. For instance, baseline BDNF is sensitive to a multitude of factors related to nutrition, time of day, and menstrual cycle, all of which play an important role in regulating its release. Furthermore, exercise protocols evaluating BDNF release should account for the parallel effects on other biological factors such as inflammatory cytokines and myokines, that influence peripheral BDNF. Lastly, further research is needed to address the efficacy of such methodological considerations that could affect how BDNF concentrations are measured. As listed above, it is evident that serum and plasma BDNF are sensitive to various considerations related to kit choice, storage procedures and analysis technology, age, gender, and environmental factors. These various approaches should be considered when measuring BDNF in any experimental paradigm, and they signify the need for a

standardized approach to measuring such sensitive biomarkers. Considering these mediators of BDNF, controlling for each could help address the current research debate. Given that BDNF levels are associated with age-related factors, a follow-up study is needed to elucidate potential differences in response across the lifespan. The cognitive benefits of exercise and BDNF outweigh the risks for older adults (Erickson et al., 2010, 2011; Leckie et al., 2014, 2014; Xu et al., 2023), helping to improve brain health and resilience to neurodegenerative diseases.

Conclusion

Ultimately, physical exercise collectively is critical for promoting brain health and resilience across the life span, largely due to its function in preserving brain function, altering metabolism, and regulating autonomic activity, and decreasing negative affect. Beyond the present study, incorporating regular physical activity into our daily routine can maintain brain health, ensure resilience to cognitive decline across the lifespan, and improve our baseline health across several domains. The current research emphasizes the role of exercise on brain health and promotes further inquiry into other mechanisms affecting brain health to take preventative action and increase quality of life. Future research should continue to explore the multifaceted benefits of physical exercise and promote public inquiry into improving health initiatives to foster healthier communities.

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Appendix

Tables

Table 1.

Demographic and anthropometric characteristics of participants.

Variables	*Mean*	*SE*	*SD*	*Range*	*Min*	*Max*
Age (years)	30	2.2	7.7	23	20	43
Height (cm)	172.3	3.1	10.9	33.7	154.8	188.5
Total Lean Muscle Tissue Mass (kg)	52.6	*4.7*	16.3	53.3	17.9	71.2
Total Fat Mass (kg)	19.4	3.0	10.4	33.5	8.6	42.1
Body Fat %	25.2	3.0	10.4	28.5	11.4	39.9
Body Mass (kg)	75.5	6.0	20.8	84.1	29	113.1
BMI (kg/m^2)	25.6	1.2	4.1	13.2	21.4	34.6
Systolic (mmHg)	120.1	2.7	9.4	31	109	140
Diastolic (mmHg)	80.4	1.8	6.3	19	69	88
Resting Heart rate (bpm)	77.8	4.0	13.8	49	60	109

Note: Includes demographic variables and anthropometric variables obtained from bioimpedance measures, automated blood pressure readings and a manual height scale. Cm = centimeters, Kg/m^2 = kilograms per metre squared, MmHg = Milometers of Mercury, Bpm = Beats per minute, SE = Standard Error, SD = Standard Deviation, Min = Minimum, Max = Maximum

Table 2.

Performance metrics for VO2 peak and 1 repetition Max of participants.

Variables	*Mean*	*SE*	*SD*	*Range*	*Min*	*Max*
VO2 (mL/kg^{-}1.min^{-1})						
At Rest	13.3	0.6	2.2	6.6	9.9	16.5
Peak	36.1	2.4	8.2	25.7	24.7	50.4
Rate of Perceived Exertion (RPE)	18.9	0.3	1.0	3.0	17.0	20.0
Heart Rate at Peak Load	182.9	3.8	12.5	41.0	166.0	207.0
Peak Resistance in Kg	3.8	0.3	1.2	3.5	2.0	5.5
1 Rep Max metrics (lbs)						
Chest Press	148.8	25.2	87.4	234.9	45.1	280
Leg Press	302.9	24	83	230	220	450
Seated Row	190	22.5	78	230	80	310
Leg Extension	167.1	14.8	51.3	180	90	270
Shoulder Press	121.7	20.1	69.7	190	40	230
Leg Flexion	118.2	9.7	33.5	110	75	185

Note: Includes all relevant performance metrics summarized for VO2 peak and 1 Rep Max testing. **mL/kg^{-}1.min^{-1} = Milliliters per kilogram per minute,** SE = Standard Error, SD = Standard Deviation, Min = Minimum, Max = Maximum, Kg = Kilograms.

Table 3.

BDNF summary characteristics across exercise type and over time.

BDNF (pg/mL)	*Exercise Type Mean* ± SD		
Time	*HIIE*	*MICE*	*RES*

Pre	3.0 ± 2.0	3.8 ± 2.5	3.2 ± 1.8
Immediately-Post	3.5 ± 2.1	3.5 ± 3.0	3.8 ± 1.9
30-minutes Post	4.2 ± 3.7	4.1 ± 4.2	3.5 ± 2.3
60-minutes Post	2.9 ± 1.3	2.4 ± 1.6	2.2 ± 1.7

Note: Includes all average BDNF concentrations and their variability across Time and Exercise Type. BDNF: Brain Derived Neurotrophic Factor, pg/mL = picograms per millilitre, HIIE = High Intensity Interval Exercise, MICE = Moderate Intensity Continuous Exercise, RES = Resistance Exercise.

Table 4

RMSSD summary characteristics across exercise type and over time.

RMSSD	*Exercise Type Mean* ± SD		
Time	*HIIE*	*MICE*	*RES*
Pre	45.0 ± 26.0	54.3 ± 38.3	49.1 ± 3
Immediately-Post	27.8 ± 18.9	45.4 ± 30.3	20.8 ± 17.1
30-minutes Post	48.5 ± 26.9	63.8 ± 41.9	42.1 ± 30.3
60-minutes Post	59.5 ± 41.7	69.5 ± 42.6	52.9 ± 34.7

Note: Includes all average RMSSD values and their variability across Time and Exercise Type. RMSSD: Root Mean Squared of Successive Differences, HIIE: High Intensity Interval Exercise, MICE: Moderate Intensity Continuous Exercise, RES: Resistance Exercise.

Table 5

PANAS summary characteristics across exercise type and over time.

PANAS Positive	*Exercise Type Mean* ± SD

Time	*HIIE*	*MICE*	*RES*
Pre	31.2 ± 10.8	30.6 ± 11.5	30.5 ± 9.8
Immediately-Post	31.7 ± 10.0	31.5 ± 11.9	31.0 ± 10.4
30-minutes Post	32.2 ± 12.6	29.8 ± 12.4	30.6 ± 10.6
60-minutes Post	30.8 ± 12.1	30.3 ± 11.8	31.6 ± 9.6
PANAS Negative	*Exercise Type Mean* ± SD		
Time	*HIIE*	*MICE*	*RES*
Pre	13.8 ± 4.8	11.8 ± 1.7	13.3 ± 4.1
Immediately-Post	11.8 ± 2.6	11.9 ± 2.5	11.8 ± 1.6
30-minutes Post	11.6 ± 2.3	11.6 ± 2.2	12.1 ± 3.1
60-minutes Post	11.8 ± 2.1	11.8 ± 2.3	11.1 ± 2.0

Note: Includes all averaged positive and negative PANAS values and their variability across Time and Exercise Type. PANAS: Positive and Negative Affect Scale, HIIE: High Intensity Interval Exercise, MICE: Moderate Intensity Continuous Exercise, RES: Resistance Exercise.

Table 6

Grip Strength summary characteristics across exercise type and over time.

Right Hand Grip Strength	*Exercise Type Mean* ± SD		
Time	*HIIE*	*MICE*	*RES*
Pre	98.7 ± 29.7	94.9 ± 24.4	102.9 ± 23.7
Immediately-Post	97.5 ± 31.5	97.1 ± 29.4	96.4 ± 30.6
30-minutes Post	97.6 ± 26.1	95.9 ± 30.0	100.3 ± 28.0
60-minutes Post	96.4 ± 27.1	88.4 ± 33.2	97.6 ± 25.5

Left Hand Grip Strength	*Exercise Type Mean* ± SD		
Time	*HIIE*	*MICE*	*RES*
Pre	89.3 ± 26.3	89.2 ± 24.9	92.6 ± 22.0
Immediately-Post	85.6 ± 29.6	88.6 ± 30.6	90.2 ± 29.2
30-minutes Post	88.0 ± 26.6	87.9 ± 26.9	91.1 ± 26.1
60-minutes Post	90.3 ± 26.1	90.5 ± 24.9	94.3 ± 22.5

Note: Includes all averaged right- and left-hand Grip Strength values in pounds and their variability across Time and Exercise Type. HIIE: High Intensity Interval Exercise, MICE: Moderate Intensity Continuous Exercise, RES: Resistance Exercise.

Figures

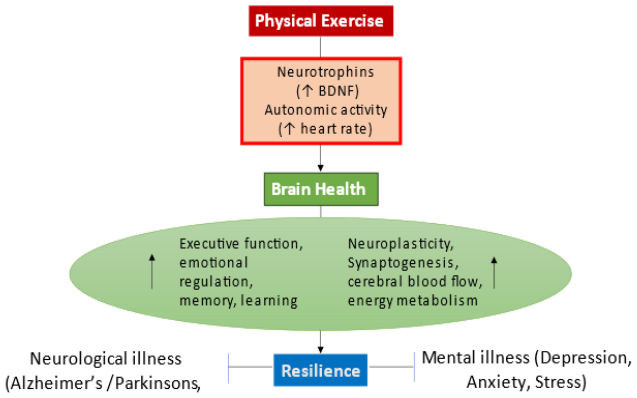


Figure 1. Depicting physical exercise as a root mechanism of resilience and brain health. Physical exercise stimulates the release of neurotrophins, proteins that promote neuroplasticity and synaptogenesis from muscle tissue. Autonomic upregulation increases activity, increasing heart rate and improving cerebral blood flow. These two processes enhance both cognitive and neurological processes that make up brain health, and thus promote resilience and thus inhibiting the onset of mental and neurological illness.

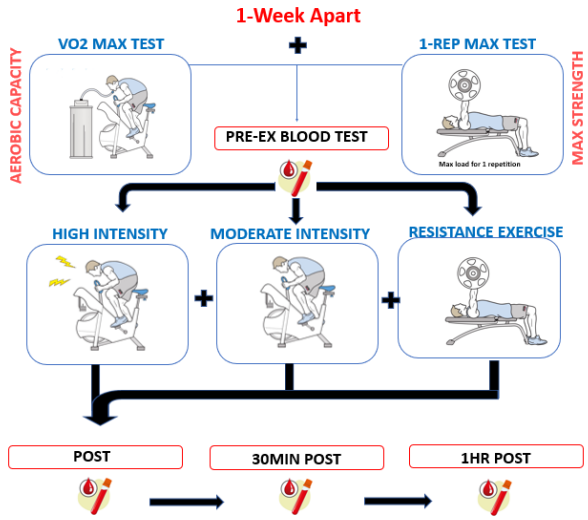


Figure 2: Experiment procedure depicting 1RM, VO2 Peak, and experimental measurements of exercise. Blood draws followed by cardiac, PANAS, and grip testing occur before, after, 30-minutes after and 60-minutes after exercise sessions. Cardiac measurements were taken for 5-minutes using a heart rate monitor. PANAS questionnaires and Hand grip dynamometer measurements were taken after cardiac measures.

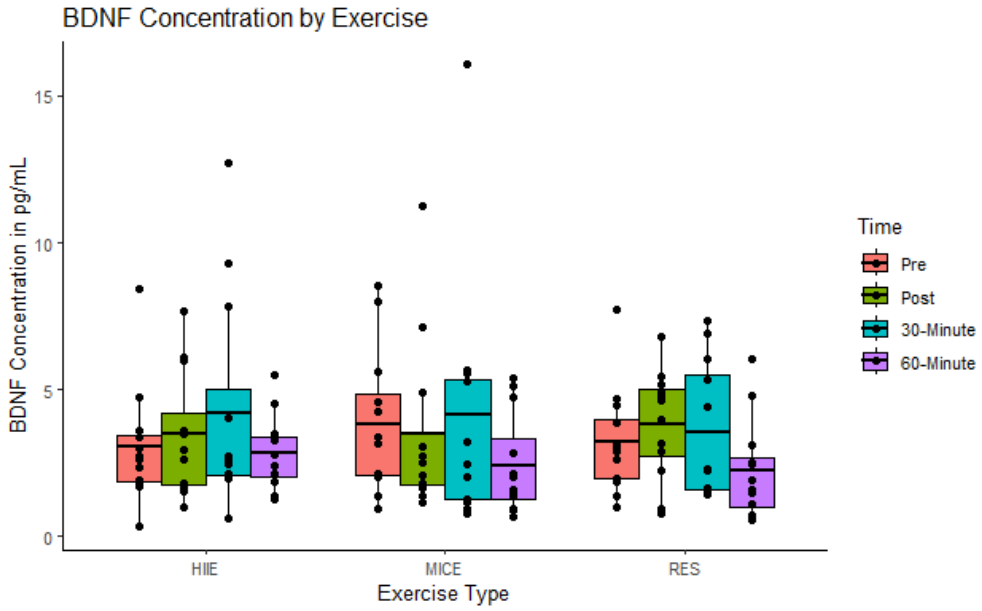


Figure 3. The results presented include the interpolated values for 4 observations as noted in the main text. Box and whisker plot displaying the average change in BDNF concentrations in picograms per ml (pg/ml) over Exercise Type and Time. Exercise is indicated by HIIE, MICE and RES and time is indicated by pre, immediately post-, 30-minutes post-, 60-minutes post-exercise. Each dot represents each individual data point of BDNF concentration across time and exercise. The ends of the vertical lines reflect the minimum and maximum values that are not considered outliers. The horizontal line within each box represents the mean while the top and bottom ends of the boxes represent the upper quartile 3 and bottom quartile 1. Any data point outside the whiskers are considered outliers.

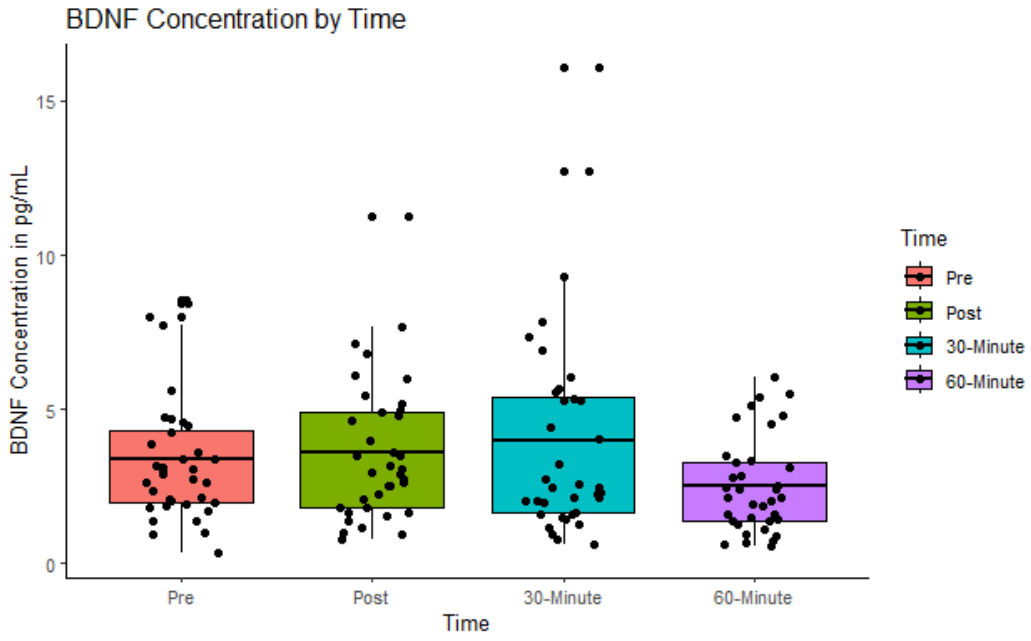


Figure 4. The results presented include the interpolated values for 4 observations as noted in the main text. Box and whisker plot displaying the average change in BDNF concentrations in picograms per ml (pg/ml) over Time. BDNF concentrations are represented by the values located on the Y-axis. Time is indicated by pre, immediately post-, 30-minutes post-, 60-minutes post-exercise. Each dot represents each individual data point of BDNF concentration across time. The

ends of the vertical lines reflect the minimum and maximum values that are not considered outliers. The horizontal line within each box represents the mean while the top and bottom ends of the boxes represent the upper quartile 3 and bottom quartile 1. Any data point outside the whiskers are considered outliers.

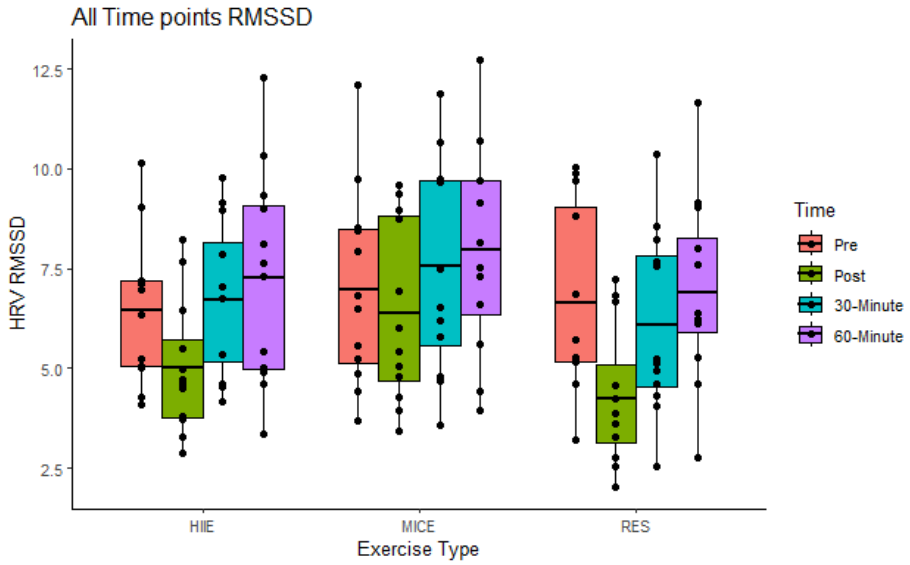


Figure 5. The results presented include the interpolated values for 4 observations as noted in the main text. Box and whisker plot displaying boxplots depicting average change in Root Mean Squared of Successive Differences-transformed HRV values across Exercise Type and Time. Exercise is indicated by HIIE, MICE and RES and Time is indicated by pre, immediately post-, 30-minutes post-, 60-minutes post-exercise. Each dot represents an individual RMSSD value for every participant across exercise type and time. The ends of the vertical lines reflect the minimum and maximum values that are not considered outliers. The horizontal line within each box represents the mean while the top and bottom ends of the boxes represent the upper quartile 3 and bottom quartile 1.

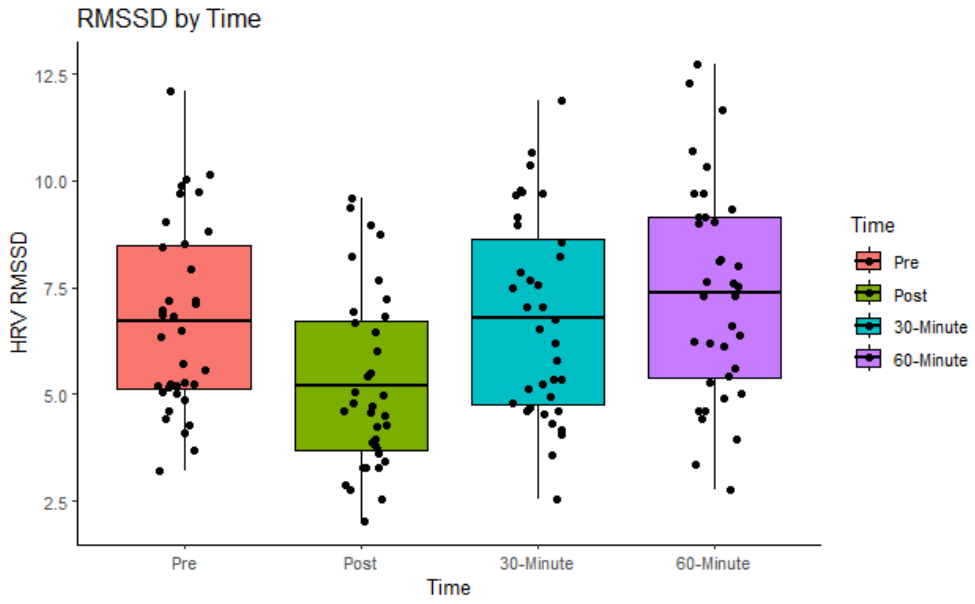


Figure 6. The results presented include the interpolated values for 4 observations as noted in the main text. Box and whisker plot displaying boxplots depicting average change in Root Mean Squared of Successive Differences-transformed HRV values across and time. RMSSD is indicated by the values on the Y-axis. Time is indicated by pre, immediately post-, 30-minutes post-, 60-minutes post-exercise on the X-axis. Each dot represents an individual RMSSD value for every participant across exercise type and time. The ends of the vertical lines reflect the minimum and maximum values that are not considered outliers. The horizontal line within each box represents the mean while the top and bottom ends of the boxes represent the upper quartile 3 and bottom quartile 1.

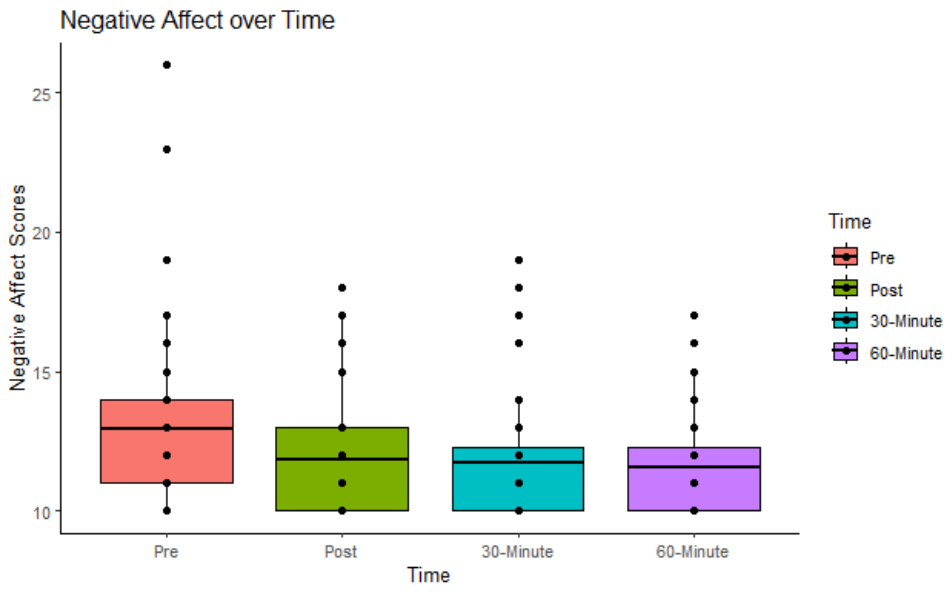
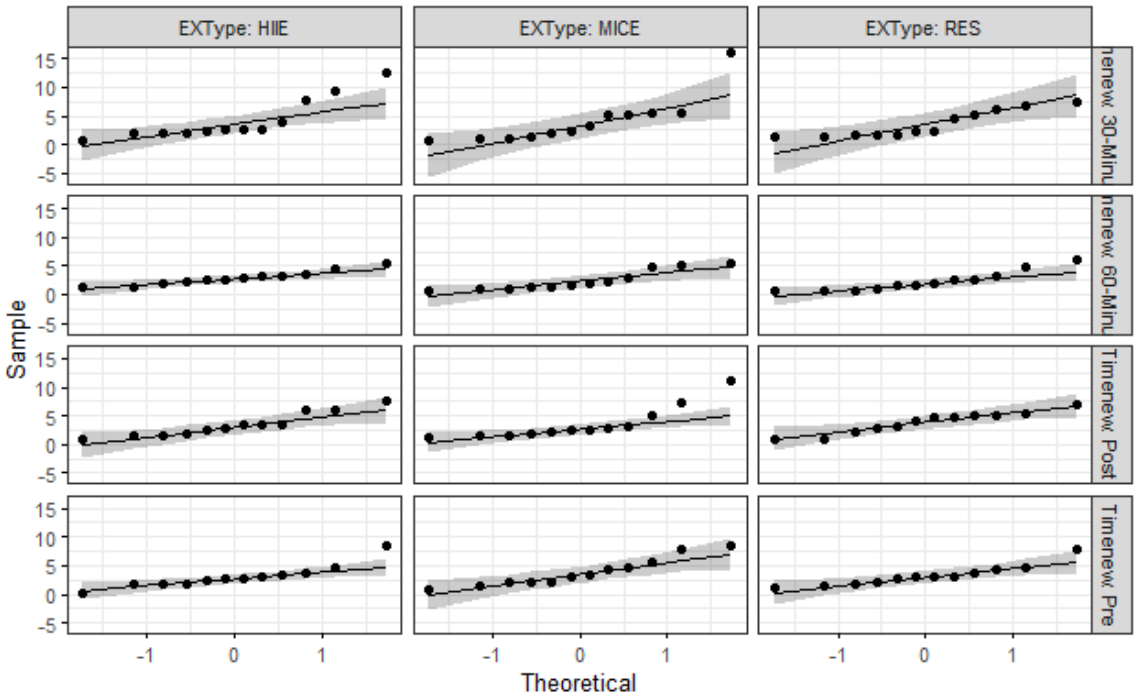
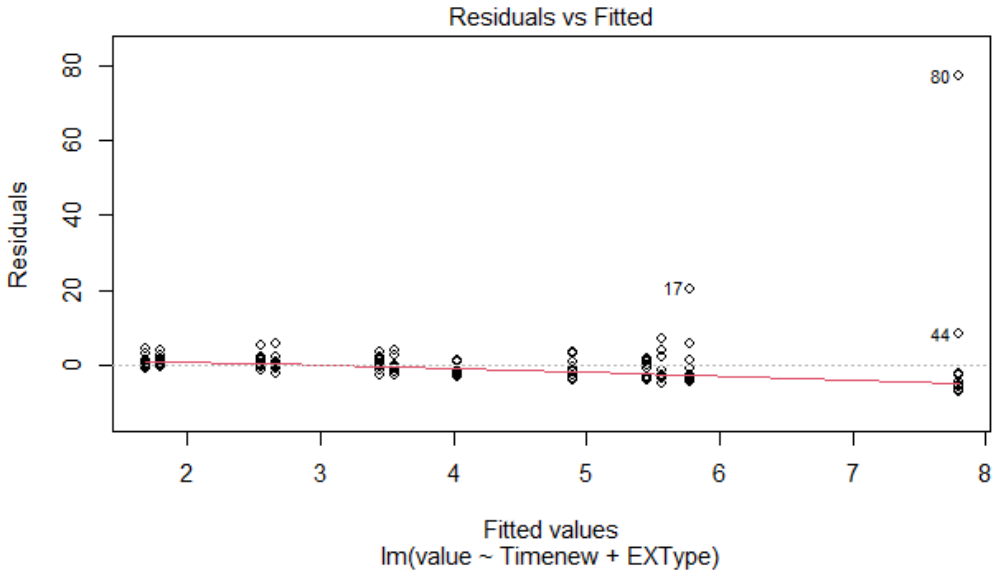


Figure 7. Box and whisker plot displaying the average change in Negative affect over the condition of Time. Note that the Y-axis contains scores of negative affect while Time is indicated by pre, immediately post-, 30-minutes post-, 60-minutes post-exercise. Each dot represents the averaged negative affect score for each participant. The ends of the vertical lines reflect the minimum and maximum values that are not considered outliers. The horizontal line within each box represents the mean while the top and bottom ends of the boxes represent the upper quartile 3 and bottom quartile 1. Any data point outside the whiskers are considered outliers.

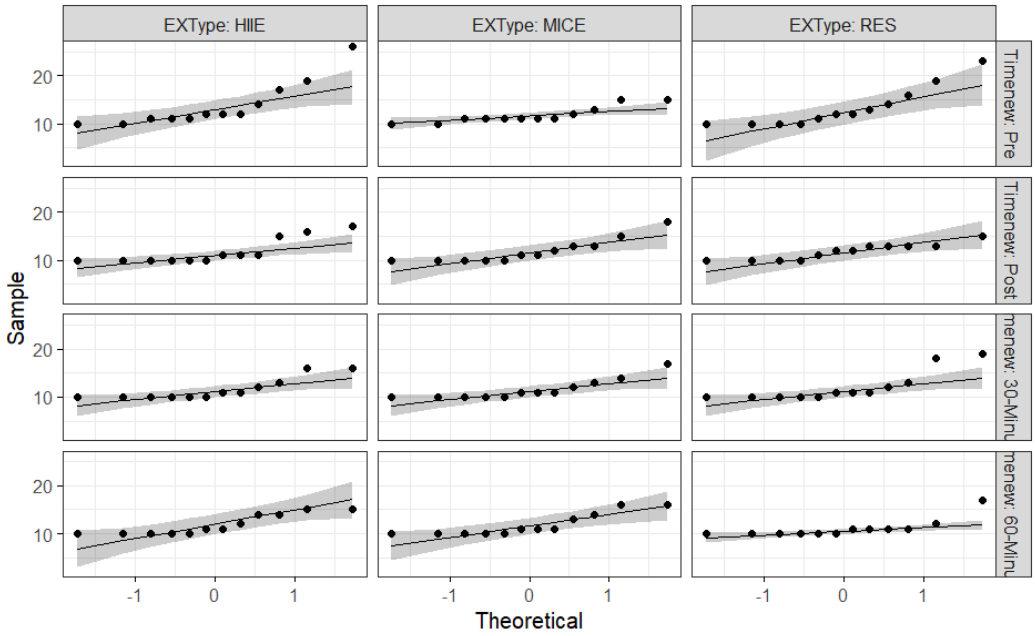
Supplemental Figures



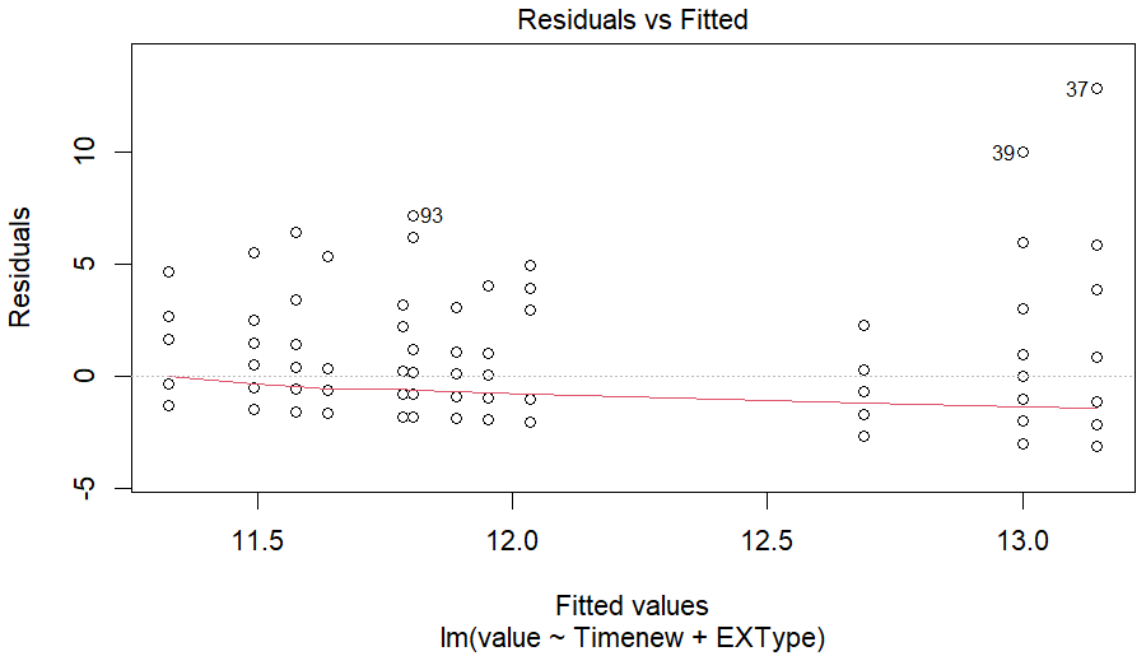
Supplemental Figure 1. A quantile-quantile (Q-Q) probability plot of BDNF concentrations comparing the distribution of the data for each condition pairing (exercise vs Time) to a theoretical distribution (solid black line) to determine if distribution of quantiles for each condition are normally distributed.



Supplemental Figure 2. A Residuals versus fitted plot for BDNF concentrations, depicting the linearity of a residuals in BDNF concentration data points as represented by their position on the line of best fit.



Supplemental Figure 3. A quantile-quantile (Q-Q) probability plot for the PANAS negative affect responses comparing the distribution of the data for each condition pairing (exercise vs Time) to a theoretical distribution (solid black line) to determine if distribution of quantiles for each condition are normally distributed.



Supplemental Figure 4. A Residuals versus fitted plot for the PANAS negative affect responses, depicting the linearity of a residuals in BDNF concentration data points as represented by their position on the line of best fit.