The Acute Effects of Resistance Training and Assisted Cycling Therapy (Act) on Cognitive Function and Enjoyment of Adults With Down Syndrome: A Pilot Study

by

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ABSTRACT

Background: Down syndrome is the leading genetic cause of intellectual disabilities. Executive function is an area that people with Down syndrome have a diminished capacity compared to those in the general population. In recent years it has been determined that acute and chronic exercise has a small but positive effect on measures of executive function in typically developed individuals. The effect has been recorded separately in both aerobic, high-rate passive and resistance exercises in adolescents with DS but has not been compared between exercise types in adults with DS. Methods: A randomized crossover study was utilized to determine the effect of resistance exercise, assisted cycling therapy, and no exercise on executive function and enjoyment in adults with Down syndrome. Resistance Training (RT)- participants completed a total of 16- repetitions of approximately 75% of a 1-RM in the leg press, chest press, seated row, and latissimus pulldown. ACT- participants completed 30-minutes of cycling at 35% above voluntary (e.g., self-selected pace) rate. No-Training (NT)- participants spent 35-minutes playing board games. Cognitive assessments were recorded pre- and post- intervention. The Physical Activity Enjoyment Survey was collected post-intervention. Statistics: The cognitive measures and Physical Activity Self-efficacy scale were analyzed using the delta scores (pre-post) in a Linear mixed models analyais. The main effect of sequence (A, B, C) and intervention (RT, ACT, NT), and visit were assessed. Significance level was set with α=0.05. If any differences were detected, the Bonferroni post-hoc test was used to determine differences. Physical Activity Enjoyment Scale post scores were compared using a General Linear Model.

Alpha was set at 0.05 with a Bonferroni post-hoc test to determine differences. A secondary analysis was conducted investigating the effect of participants that completed testing individually compared to those that completed the testing in a group setting.
Results: There were no significant difference in the delta score of any of the measures. The secondary analysis also found no significant difference but showed a trend that those tested individually had opposite results than those tested in a group.

DEDICATION

I want to dedicate my dissertation to my wife and son, Lorraine and Jayden. They have been beside me throughout my college career and pushed me toward my dream of a Ph.D.. The sacrifices that my family has made for me to pursue my doctorate is awe inspiring. Thank you.

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CHAPTER 1

INTRODUCTION

Background

Down syndrome (DS) is the most common congenital birth with a prevalence of 1 in 790 zero to four-year olds (De Graaf, Buckley, and Skotko,2017). DS is the leading genetic cause of intellectual disabilities (Parker *et al.*, 2010). In 2011, it was estimated that the average yearly cost of health care, therapy, and other expenses for people with DS was $4,287 (Geelhoed, Bebbington, Bower, Deshpande and Leonard, 2011) with 40% of families having a parent dropping out of the workforce (Schieve, Boulet, Kogan, Van Naarden-Braun and Boyle, 2011). As people with DS age, the financial cost shifts from medical and therapy expenses to respite care (Geelhoed *et al*. 2011).

People with DS have reduced function within their Executive Functions (EF): inhibition, working memory, shifting, planning, attention, and processing speed (Barkley, 2012; Greco *et al*. 2015). Problems with EF have been linked to issues of caloric intake, quality of life, school and job success in typically developed adults (Diamond, 2013). Higher levels of EF have been found in people with DS who are employed compared to those unemployed (Su, Lin, Wu, and Chen, 2008). We theorize that improving EF in people with DS will generalize to increasing their independence and employability and lower the economic burden on their families.

Studies have shown improvement in ***cognitive function*** following both acute and chronic aerobic exercise in the typical population from youth to older adults (Sibley and Etnier, 2003; Colcombe and Kramer, 2003; Verburgh, Königs, Scherder, and Oosterlaan, 2014) The largest effect sizes have been recorded in areas of ***executive function*** (Smith *et* *al*. 2010; Verburgh *et al.* 2014). Similar results have been recorded in the typical population following acute and chronic ***resistance training*** (Wilke *et al*., 2019; Landrigan, Bell, Crowe, Clay, and Mirman, 2019). The improvements in cognitive function after both aerobic and resistance training in the typical population has been linked to increases in neurotrophic factors: brain-derived neurotrophic factor (BDNF), insulin like growth factor (IGF-1), among others (Szuhany, Bugatti, and Otto, 2015; Yarrow, White, McCoy, and Borst, 2010; Church *et al*., 2016).

The effects of exercise on ***cognitive function in people with DS*** has very limited research (Pastula, Stopka, Delisle, and Hass, 2012; Lee, Seo, and Lim, 2014; Chen, Ringenbach, Crews, Kulinna, and Amazeen, 2015; Holzapfel, *et al.*, 2015; Ringenbach, *et al*., 2016; Chen and Ringenbach, 2016). Results from aerobic and assisted exercise, exercise on a bike with a motor to increase the pedal rotations above voluntary rate, in the DS population have mirrored many of the results of the typical population. Research in acute bouts of aerobic exercise has found an inverse-U relationship with intensity and cognitive function outcomes (Chang *et* al., 2012; Chen *et al.*, 2015). Acute and chronic aerobic exercise and assisted exercise has been shown to improve measures of executive function in adolescents and adults with DS (Chen, *et al.*, 2015; Holzapfel, *et al.*, 2015; Ringenbach, *et al*., 2016; Chen and Ringenbach, 2016). One study found increases in BDNF, IGF-1, and vascular endothelial growth factor following aerobic exercise (Lee, Seo, and Lim, 2014). However, to our knowledge, there is no research on the effects of ***resistance training on cognitive function in people with DS***; the closest published study used a moderate-intensity circuit training protocol (Pastula, *et al.*, 2012). While this study found improvements in three subtests of the Woodcock-Johnson III Test (**long-**

term Retrieval, Short-Term Memory, Processing Speed, Auditory Processing, Visual-Spatial Thinking, Comprehension-Knowledge, and Fluid Reasoning), the study's intensity was determined via heart rate, not resistance and included people with ID, not just DS.

While research into the effect of resistance training on cognitive function in people with DS is lacking, there are few studies that investigated the viability of resistance training for people with DS. Resistance training for people with DS has been shown to improve muscular strength (Shields, Taylor, and Dodd, 2008; Cowley *et al.*, 2011; Shields, *et al.*, 2013), muscular endurance (Shields, Taylor, and Dodd, 2008), muscular function (Shields, Taylor, and Dodd, 2008) and physical activity engagement (Shields *et al.*, 2013). Since these studies show that people with DS show similar physiological responses to typically developed individuals, it would be expected that the cognitive response to resistance training would be similar to those seen in typically developed individuals.

Finally, when trying to design any therapy or intervention, continued participation in lifestyle after the research has concluded has to be paramount. Exercise interventions for people with DS have been met with some challenges due to some physiological and psychological issues associated with DS. People with DS have a lowered cardiorespiratory response (Fernhall, 1996), lowered motor skills (Kim, Kim, Kim, Jeon, and Jung, 2017), and lower muscular strength (Croce, Pitetti, Horvat, and Miller, 1996; Pitetti, Climstein, Mays, and Barrett, 1992). They also have a lack of motivation to participate in physical activity (Stanish, Temple, and Frey, 2006), lack self-efficacy in their ability to perform physical activity, consider physical activity "boring", and are self-described as “lazy” (Heller, Hsieh, and Rimmer, 2004). Finding exercise and therapy interventions that people with DS find enjoyable should increase involvement following the research intervention. Resistance training has been associated with higher levels of enjoyment and continued participation in exercise programs for men with type II diabetes at three, six, and nine months as compared to only aerobic programs. (Tulloch *et al.* 2013).

Statement of the Problem

Previous studies have shown that acute aerobic and resistance training are effective in eliciting an improvement in EF in typically developing individuals. Research into the cognitive effects of aerobic and passive exercise (ACT) in individuals with DS have shown promise in the use of ACT in promoting larger increases in EF compared to typical aerobic exercise. However, there are no published studies on the cognitive effects of resistance exercise in individuals with DS. Research into physical activity habits of individuals with DS have shown a higher than normal aversion to physical activity. Therefore, the purpose of this study is to determine the effect of an acute bout of resistance exercise compared to ACT and no exercise in adults with DS. This study has two specific aims and hypotheses.

Specific Aims and Hypotheses

Aim 1: To investigate the effect of an acute bout of resistance training and an acute bout of ACT on the executive function of adults with Down syndrome. Primary outcomes will assess changes in processing speed, controlled processing speed, short-term memory, cognitive planning, and inhibition between the pre and post-test.

Hypothesis 1: The RT will significantly improve cognitive measures compared to the ACT and NT. Hypothesis 2: The ACT will significantly improve cognitive measures compared to the NT.

Aim 2: To determine the effect of an acute bout of resistance exercise and ACT on self-efficacy and enjoyability of exercises in adults with Down syndrome. Primary outcomes will assess the post intervention enjoyability of each intervention and the post-pre difference of self-efficacy. Hypothesis 1: RT will have a higher level of self-efficacy and enjoyability measured by the Physical Activity Enjoyment Scale compared to ACT. Hypothesis 2: Self-efficacy will increase more following RT as compared to ACT and NT, and ACT will improve more than NT.

Positive results from this study will be used for directing future chronic intervention studies within people with DS and aid in the development of future therapy and exercise programs for adults with DS.

CHAPTER 2
REVIEW OF LITERATURE

Background on Down syndrome

Down syndrome (DS) is the most common congenital birth defect in the United States of America, with a prevalence of 1 in 790 people from zero to four-years of age (De Graaf, Buckley, and Skotko, 2017). DS is diagnosed as trisomy 21, **or the presence of an extra 21st chromosome** and has the prominent feature of Intellectual Disability (ID) (Greco, Pulsifer, Seligsohn, Skotko, and Schwartz, 2015). Along with the intellectual difficulties, people with DS also have issues with communication and adaptive behavior skills (Molloy *et al,* 2009), decreased motor skills (Kim *et al.,* 2017), lower levels of cardiorespiratory function (Fernhall, 1996), and lower muscular strength (Croce, *et al.*, 1996; Pitetti, Climstein, Mays, and Barrett, 1992).

Neurophysiology in DS

When compared to typically developed individuals, people with DS have lower brain volume (Coyle, Oster-Granite, and Gearhart, 1986; Kesslak, Nagata, Lott, and Nalcioglu, 1994; Pinter, Eliez, Schmitt, Capone, and Reiss, 2001), marked by a smaller brain stem, cerebellum, hippocampus, temporal lobe, and frontal lobe in both white and grey matter (Pinter *et al*. 2001). These smaller brain structures may help explain some of the neuropsychology exhibited by individuals with DS. First, the Intellectual Quotient (IQ) range of those with DS can range from 30-70; however, the mean IQ is 50 (Parker *et al*., 2010). Unlike typically developing individuals, the IQ of people with DS declines throughout the lifespan and many individuals with DS will never pass a mental age of eight (Gibson, 1978). The lowered IQ has been postulated to be related to the lowered level of language skills exhibited in people with DS (Pennington, Moon, Edgin, Stedron, and Nadel, 2003). Because IQ tests are predominately based on language skills, Pennington *et al.* (2003) connected the issues with verbal short-term memory, which have been well documented in people with DS, to the lowered IQ scores through the correlation between verbal short-term memory and language skills. Both short-term memory and language skills have been associated with the temporal lobe functions (Ojemann, 1978; Smith, Stapleton, and Halgren, 1986), which is one of the diminished areas of the brain in people with DS.

While the lowered IQ is the most common disability associated with DS, people with DS also have deficiencies in the learning process. A 1992 study found that infants with DS performed below age matched typical infants in place-learning, or the process of being able to remember the “what” and “where” of an event (Mangan, 1992). Explicit and implicit learning have been studied within the population with DS, and deficits in explicit learning have been demonstrated (Vicari, Bellucci, and Carlesimo, 2000; Vicari, 2006). Both of these learning deficits (place-learning and explicit learning) have been linked to deficits in hippocampal processes (Mangan, 1992; Vicari, 2006; Komorowski, Manns, and Eichenbaum, 2009).

IQ and learning are problems that can affect people with DS over the course of their lifetime. Executive functions (EF) are processes that are typically thought to occur in the frontal and prefrontal cortex and can affect everyday occurrences. EF includes: inhibition, working memory, shifting, planning, attention, and processing speed (Barkley, 2012; Greco *et al*. 2015). EF levels have been associated with social functioning, emotional control, school performance, job performance, quality of life, and caloric intake in typical populations (Best, Miller and Jones, 2009; Diamond, 2013). Deficits in inhibition, working memory, shifting, and planning emerge to be the foundation, and most studied aspects of EF (Barkley, 2012). People with inhibition issues have trouble with emotional control because they cannot inhibit the emotion, and often react on emotional impulses. Similarly, social functioning can be impacted when the impulse to say or do things that are socially accepted are not "controlled" as well as in a person with proper inhibition. Along with the lack of inhibition, a deficit in planning hinders the ability to foresee the consequences of these social actions. When it comes to job performance, all these come into play. First, there is the social and emotional functioning that is needed to be productive at a job. Second, working memory and attention influence the tasks that can be assigned to a person with EF deficits. Deficits in planning and task shifting can lead to problems with time management and problem solving. When added together, the problems associated with EF lead to a lack of independence for people with DS.

Many of the therapy strategies for people with DS are for early in life to encourage development. As previously mentioned, as people with DS age much of the financial burden changes from therapies to care. However, exercise interventions can help improve the cognitive problems and the physical problems that accompany DS. While the benefits of exercise on physical health have been well documented (Wescot, 2012), the benefits of exercise on cognitive outcomes, especially EF, have recently become a focus of exercise research.

Executive Function and Aerobic Exercise

The effect of exercise on cognitive function has been researched across many different paradigms: acute and chronic aerobic exercise, acute and chronic resistance exercise, and more recently acute and chronic assisted exercise. Multiple meta-analytical analyses have concluded that aerobic exercise has a positive effect on cognitive function in typical populations (Etnier *et al*., 1997; Colcombe and Kramer, 2003; Sibley and Etnier, 2003; Smith *et al.* 2010; Lambourne and Tomporowski, 2010; Chang, Labban, Gapin, and Etnier, 2012); however, the effect varies dependent on multiple variables.

Etnier *et al*. (1997) was one of the first reviews that included a meta-analytical component. The analysis concluded that exercise had a total effect size of 0.29 ($p< 0.05$) on cognitive performance across all exercise paradigms and study designs. When Etnier *et al*. separated the studies by training design (*e.g.* cross-sectional, chronic, acute), they found cross-sectional studies had the largest effect size (0.53), followed by chronic (0.33) and acute (0.16). They warned that the cross-sectional studies need to be taken lightly as the studies fundamentally lack cause-effect. To help determine a cause-effect relationship Etnier *et al*. followed up the chronic analysis by investigating the effect of chronic exercise on individuals that were previously sedentary and concluded an effect size of 0.18, again small but significantly different from zero.

Colcombe and Kramer (2003) followed up Etnier *et al*.'s (1997) meta-analytical review with their meta-analysis on the effects of chronic exercise on cognitive performance of older adults. Colcombe and Kramer introduced their four theories/hypotheses that seemed to be directing cognitive testing at the time: the speed hypothesis, the visuospatial hypothesis, the controlled-processing hypothesis, and the executive-control hypothesis. They posed that researchers supporting the speed hypothesis tested the effects of exercise on reaction time or finger tapping, processes that occur at a lower level of the nervous system and do not require higher level thought. Researchers that support the visuospatial hypothesis investigated the effects of exercise on the ability to read and recognize shapes among other skills. The controlled-processing hypothesis included testing controlled, effortful processes such as learning a new skill. Finally, the executive-control hypothesis tests EF. Controlled-processing and executive-control were considered separate because the skills tested or learned in controlled-process could become automatic- such as throwing a ball. Colcombe and Kramer concluded that across all cognitive tasks, typical control groups and exercise groups improved during the chronic intervention studies. Control groups had a small effect (ES=0.164), while the exercise groups improved significantly more (ES=0.478). When Colcombe and Kramer looked at the cognitive process, executive function had the largest effect size (ES=0.68) as compared to the other processes. While they concluded executive function processes saw the largest effect of exercise, the other processes still recorded significant effects: speed (0.274), spatial (0.426), and controlled-processing (0.461). Finally, Colcombe and Kramer found that training interventions that included a combined training (included both resistance training and aerobic training) improved significantly more than aerobic training alone. Colcombe and Kramer's meta-analysis shifted the focus of exercise and cognitive function to the exercise and executive function that is more common in research today.

Sibley and Etnier (2003) examined the effect of different physical education activities on the cognitive performance of typical children through meta-analytic methods. They included studies that investigated resistance/circuit training, aerobic training, or general physical education classes in acute, chronic, or cross-sectional methods. They concluded that there was an effect size of 0.32 across all methods and intervention types. The larger effect size recorded in this meta-analysis compared to Etnier *et al*.'s (1997) effect size of 0.26, could indicate that children, and those with developing brains, could experience more benefit from physical activity, regardless of the type of exercise.

Smith *et al*. (2010) investigated the effect of aerobic exercise on different cognitive domains (*e.g.* attention and processing speed, executive function, working memory, and memory) specifically in randomized control trials lasting longer than one month and had a non-exercise control group. Furthermore, Smith *et al*. investigated the effects between individuals with mild-cognitive impairment and individuals without impairment. Exercise had a small effect size (0.158) on attention and processing speed with combined aerobic (having resistance training included) was significantly better (0.250) than aerobic only (0.098). Exercise had a small effect size (0.123) on EF with no differences in any moderators. Overall, exercise had no significant effect on working memory; however, combined training had a positive effect size (0.288) as compared to aerobic exercise alone within working memory. Finally, exercise had a small effect (0.128) on memory; individuals with mild-cognitive impairment had a larger effect (0.237) on memory, but not significantly different than the effect (0.096) on non-impaired individuals. The results of Smith *et al*.'s meta-analysis add to the growing evidence that exercise does cause changes in cognitive function that is being recorded through these interventions.

Lambourne and Tomporowski (2010) revisited the effects of acute bouts of aerobic exercise on cognition in typical adults. In their meta-regression analysis, they concluded that exercise had a total negative effect (-0.14) when the cognitive tests were administered during exercise; however, they concluded that when the test were given within the first 20 minutes of exercise the effect was negative but positive after 20 minutes. When tests were administered during exercise treadmill walking/running they had a negative effect and cycling had a small positive effect. Post exercise tests saw a positive effect (0.20) of exercise cognitive function. When broken down further, cycling again had a larger effect than treadmill and tests of processing had a smaller effect than tests of memory.

Following Lambourne and Tomporowski's meta-analysis findings, Chang *et al.* (2012) dug deeper into the moderators of exercise on cognitive function. Chang *et al.* specifically looked at the intensity of exercise, cognitive test timing, type of cognitive task, and initial fitness levels of participants. Across all studies, a very small but significant effect size (0.097) was found. Chang *et al.* determined that cognitive test administered during exercise altered the effect: tests in the first 10 minutes of exercise had no effect, after 11-20 minutes had negative effect, and test after 20 minutes had positive effect. Test of EF were the only cognitive tests that saw a significant effect and it was positive when administered during exercise. Fitness level also affected cognitive function effects during exercise: high-fit increased, moderate-fit had no effect, and low-fit had negative effect. When analyzing immediately after exercise, intensities below vigorous improved the effect and intensities above vigorous were not significant. Tests of attention, crystalized intelligence, and executive function all had positive effects following exercise but were not different from one another; information processing had smaller effects and were still significantly different from zero. High- and low-fit individuals had positive effects while moderate-fit did not see any effect when testing occurred following exercise. When cognitive effects were administered after a delay very light intensities had a negative effect and all other intensities had positive effects. Tests of crystalized intelligence and EF were positively affected, and tests of information processing, reaction time, and memory recorded no effect following the rest period. Finally, exercise duration had to be longer than 10 minutes to elicit effects after exercise. The results of this and Lambourne and Tomporowski's meta-analysis had led to different hypotheses on the mechanisms that underly the relationship between aerobic exercise and cognitive performance that will be discussed later.

While there is a plethora of evidence that aerobic exercise has a small but significant positive effect on cognitive function in typically developed individuals, the question remains, "Does aerobic exercise improve cognitive function in people with DS?" After single bout of moderate walking increases were seen choice reaction time and in inhibition (Chen *et al*. 2015, Chen and Ringenbach, 2016). The improvements in choice reaction time showed a negative effect of high intensity, improvements in inhibition were still improved, counter to the findings in typically developed (Chen and Ringenbach, 2016). Ringenbach *et al*. (2016) found increases in task switching and language fluency semantic scores following an eight-week cycling intervention in adolescents with DS.

Executive Function and Resistance Exercise

While the effect of aerobic exercise on cognitive function has been thoroughly studied, the effects of resistance exercise (i.e. weight lifting) have just recently started to be investigated. Even with the research being limited, two meta-analyses have been published in the last year that investigated the relationship between resistance exercise and cognitive function (Wilke *et al*., 2019; Landrigan, Bell, Crowe, Clay, and Mirman, 2019). Wilke *et al*. meta-analytically investigated acute bouts of resistance exercise on cognition and Landrigan *et al*. investigated chronic bouts of resistance exercise.

Wilke *et al*. used 12 randomized control trials (parallel group or cross-over design) that included healthy adults who participated in resistance training and tested cognitive function acutely. They found an effect size of 0.56 when compared to no-exercise groups. The effect was largest in cognitive tests of inhibition (ES=0.73) and cognitive flexibility (ES=0.36). They also found that high and low intensity provided the significant effects of resistance exercise, but not moderate. When comparing resistance exercise to aerobic exercise, no significant effect was found.

Landrigan *et al*. used 24 studies that used resistance exercise in adults (>18 years of age) and directly measured cognitive function after a minimum of four weeks and had a passive or active control group. The goal for Landrigan *et al*. was to determine the effects of solely resistance training on cognitive function, therefore mixed intervention studies were excluded from analysis. Resistance exercise had a strong effect (1.28) on tests of cognitive impairment (*e.g.* MMSE), a positive effect (0.39) on tests of executive function, and no effect on measures of working memory. When determining moderators of these effects, Landrigan *et al*. determined that individuals with unspecified cognitive impairment saw the most improvement. Exercise interventions less than 16 weeks and included an active control group produced higher effects on cognitive performance.

So, while the evidence is not as conclusive for resistance exercise as it is for aerobic exercise, there is viable evidence that resistance exercise, whether acute or chronic can improve cognitive function. The positive improvements follow resistance training has not been adequately investigated in people with DS. A single study attempted to investigate the effect of resistance training in people with DS, however, the study used a circuit training system that relied on percent of heart rate max to determine exercise intensity (Pastula, *et al.*, 2012). Therefore, more research is needed in this area.

Executive Function and Assisted Exercise

Forced/assisted exercise has been repeatedly shown to have positive improvements in spatial learning, memory (Ang, Dawe, Wong, Moochhala, and Ng, 2006; O'Callaghan, Ohle, and Kelly, 2007; Alomari, Khabour, Alzoubi, and Alzubi, 2013), and motor control in rats (Tillerson, Caudle, Reveron, and Miller, 2003; Poulton and Muir, 2005). Based on this research, Ridgel and colleagues (Ridgel, Vitek, and Alberts, 2009; Ridgel, Kim, Fickes, Muller, and Alberts, 2011) conducted two separate studies investigating a form of forced exercise in adults with Parkinson's disease. In 2009, Ridgel *et al*. concluded that forced exercise on a bicycle improved motor control in patients with Parkinson's disease but not after voluntary exercise. Forced exercise was achieved through a tandem bike with a trainer pedaling the bike 30% faster than participant's voluntary pace. In this particular study, participants keep their heart rate within a targeted heart rate zone. In the 2011 study, Ridgel *et al*. tested the effects of passive exercise performed on a motorized bike on the executive function of participant's with Parkinson's disease. They had participants complete exercise at cadences of 60, 70, and 80 rotations per minute (RPM). While no difference was recorded between the cadences, improvements of executive function was reported after cycling.

Since Ridgel and colleagues first studies, Ringenbach and colleagues have used passive cycling, which they have coined "assisted cycling therapy", with people with Down syndrome and other special populations. In an acute study investigating the difference between assisted cycling (AC) and voluntary cycling (VC), Ringenbach, Albert, Chen, and Alberts (2014) found that reaction time and cognitive planning improved after AC but not VC for people with DS. Following this, Ringenbach, Holzapfel, Mulvey, Jimenez, Benson, and Richter (2016) conducted an 8-week chronic intervention with adolescents with DS and concluded improvements in inhibition control but not set-shifting (two main measures of executive function). Ringenbach, Arnold, Lopez, Holzapfel, and Rodgriguez (2018) conducted a similar study with older adults with DS and found improvements in cognitive planning after 8-weeks of ACT. The building evidence leads us to believe that ACT is a viable option for cognitive improvements for people with DS and other cognitive issues.

Mechanisms of Executive Function Change during Exercise

It has been determined that brain derived neurotrophic factor (BDNF) is a main driving factor in improvements in cognitive function following exercise. The mediating effects of BDNF have been seen in rat studies that utilized BDNF blocking proteins, either stopping BDNF from being formed or from binding to neurons (Vaynman, Ying, and Gomez-Pinilla, 2004; Mu, Li, Yao, and Zhou, 1999), or by injecting extra BDNF (Cirulli, Berry, Chiarotti, and Alleva, 2004). BDNF is a key aspect of many different brain neuron life, including neuronal cell survival, differentiation, migration, dendritic arborization, synaptogenesis, and plasticity (Wrann *et al*. 2013). BDNF, like many other neurotrophins is signaled through neuron activation (Loprinzi and Frith, 2019). Neural activation has been recorded during exercise in areas of autonomic function, the motor cortex, sensory cortex, and in cerebellum (Vissing, Andersen, and Diemer, 1996; Christensen *et al*., 2000).

Interestingly, BDNF is directly related to exercise intensity- higher intensity creates more BDNF (Ferris, Williams, and Shen, 2007). Even with the higher amounts of BDNF, EF has been shown to have an inverse-U relationship with exercise intensity (Chang *et al*. 2012, Chang and Etnier, 2009). Two theories have been developed to help explain this relationship: the transient hypofrontality (Dietrich, 2006) and the reticular-activating hypofrontality (Dietrich and Audiffren, 2011). The transient hypofrontality theory is built on the fact that exercise elicits neural activation and that our brains have limited metabolic resources through a fixed percentage of cardiac output being sent to the brain. Therefore, as exercise intensifies, those metabolic resources are redistributed to the necessary regions of the brain responsible for movement (i.e., pulls resources from the prefrontal cortex to the cerebellum and motor cortex). The reticular-activating hypofrontality theory (RAH) builds on this with the idea of arousal built into their model. The RAH has the basics of the transient hypofrontality, but adds a few other components. First, while exercise is a mode of stressful arousal, the arousal is mediated by catecholamines. Second, the RAH proposed that the brain runs on two distinct levels, the explicit and implicit, and that there is a flexibility/efficiency tradeoff during different task, and this tradeoff is again dependent on the amount of muscle mass required, intensity, and duration of the exercise.

Both the transient hypofrontality and RAH were developed to explain the decrease in high thought processes and increase in lower/automatic processes during exercise. However, these same ideas can be extrapolated out to post-exercise conditions. During post-exercise testing, test of reaction time consistently shows increases with intensity, while EF has the inverse-U relationship (Chang *et al.* 2012). After exercise, the brain redistributes the resources back to the explicit systems as the need in the implicit systems diminishes. As the blood flow returns to normal in the pre-frontal and frontal cortices, it is now enriched with BDNF, insulin-like growth factor, norepinephrine, epinephrine, dopamine, among other neurotrophins and catecholamines leading to the improved EF exhibited during tests after exercise. The more intense the exercise the more of the neurotrophins and catecholamines are absorbed by the cerebellum, motor cortex, brain stem, and other structures involved in the implicit processes.

Recently, a study in typical adults found improvements in the Stroop tests following an acute bout of moderate aerobic exercise correlated to increased dorsolateral prefrontal activation (Yanagisawa *et al.* 2010). In this study, participants were attached to a functional near-infrared spectroscopy (fNIRS) and completed either an exercise session or a rest session. Prior to both sessions, participants completed a Stroop Task while the fNIRS recorded brain activation. The exercise group then exercised at 50% of VO_{2max} for 30 minutes, rested for 15 minutes and then completed the Stroop Task again. The rest group rested on the recumbent bike for 45 minutes and then completed the

Stroop Task again. This finding again adds to the idea that resources are reallocated to the prefrontal cortex following exercise and rest.

Aerobic exercise has the most compelling evidence for the relationship between exercise and BDNF (Ferris *et al,* 2007; Piepmeier and Etnier, 2015); furthermore, resistance exercise and forced exercise has evidence showing increases in BDNF (Cassilhas *et al*. 2012; Alomari *et al.* 2013; Ji *et al*. 2014). While increases in BDNF has not yet been associated with passive exercise, or ACT, there has been an fMRI study that found increased brain activity during passive range of motion manipulation (Morita and Takizawa, 2013) and during passive cycling (Christensen *et al*. 2000). Passive cycling has also been recorded to increase cerebral blood flow and blood pressure (Nobrega, Williamson, Friedman, Araujo, and Mitchell, 1994; Christensen *et al*. 2002). With the increased cerebral activation, blood flow and blood pressure it can be deduced that ACT would still fall within the RAH theory for cognitive changes.

Rationale for Resistance Exercise

Therefore, if aerobic, resistance, and assisted exercise all increase EF, why should we investigate resistance exercise over the other forms? While resistance exercise has been shown to increase BDNF by 98% acutely (Yarrow, White, McCoy, and Borst, 2010), Cassilhas *et al*. (2012) found that chronic resistance exercise significantly increases insulin-like growth factor (IGF-1) over that of aerobic exercise. Chronic resistance exercise did not significantly increase BDNF over no exercise but showed the same results as an aerobic exercise group on the Morris Water Maze in typical rats. This different pathway could help explain why meta-analyses have found that chronic exercise interventions that utilize both aerobic and resistance training have a larger effect than aerobic alone (Smith *et al*. 2010). The increase in both BDNF and IGF-1 that has been recorded following a light and maximal acute resistance training program (Vega, Knicker, Hollmann, Bloch, and Strüder, 2010) lead us to believe that an acute resistance training provides a chance for improved EF increases as compared to an acute bout of aerobic training.

Along with the role of BDNF, IGF-1, and other neuro-chemicals, recent research has started to emerge that stress the importance of mental engagement during exercise to promote improvements in EF and memory (Tomporowski, McCullick, Pendleton and Pesce, 2015). Activities in these studies employed multi-limb coordination movements (Budde, Voelcker-Rehage, Pietraßyk-Kendziorra, Ribeiro, and Tidow, 2008), games and circuit training (Pesce, Crova, Cereatti, Casella, and Bellucci, 2009), or exergames (Best, 2012). It is possible that the metabolic resources within the prefrontal cortex are maintained because of the decision making and task shifting required during coordinative movements of these activities. With resistance exercise requiring multi-limb coordination, we believe resistance exercise will also help preserve these resources and improve EF above typical aerobic exercise. This benefit may be limited with the use of weight stack machines as less coordination is required to complete the movements.

Along with the psychological issues accompanying a diagnosis of DS, there are the physiological issues. As previously mentioned, people with DS have lower cardiorespiratory function and lower muscular strength. People with DS also commonly are diagnosed with osteoporosis, obesity, diabetes, and early onset Alzheimer's Disease (Glasson, Dye, and Bittles, 2014). Resistance training in the typical population has been shown to improve several of these issues (Westcott, 2012), while resistance training specifically in people with DS has been shown to increase muscular strength (Shields, Taylor, and Dodd, 2008; Cowley *et al.*, 2011; Shields *et al*. 2013), muscular endurance (Cowley *et al*. 2011), the ability to perform activities of daily living (Shields, Taylor, and Dodd, 2008) and physical activity adherence following intervention (Shields *et al*. 2013).

Rationale for ACT

As previously mentioned, passive exercise has been linked to increased brain activity (Christensen *et al*. 2000; Morita and Takizawa, 2013) and increased cerebral blood flow and pressure (Nobrega, Williamson, Friedman, Araujo, and Mitchell, 1994; Christensen *et al*. 2002), two mechanisms related to the RAH theory of cognitive changes. Furthermore, ACT has been recorded to have significantly greater outcomes on EF tests than voluntary cycling in people with DS (Ringenbach, Chen, and Albert, 2012; Holzapfel *et al*. 2015; Ringenbach *et al*. 2016) and people with Autism (Ringenbach, Lichtsinn, and Holzapfel, 2015). ACT has also been shown to improve working memory (Holzapfel *et al*. 2016) in adolescents with DS, an area that has had mixed results in the typical population.

Self-Efficacy, Exercise Perception, and Enjoyment

It has been shown that many people with DS show a lack of motivation to participate in physical activity (Stanish, Temple, and Frey, 2006), lack self-efficacy in their ability to perform physical activity, consider physical activity “boring”, and are self-described as “lazy” (Heller, Hsieh, and Rimmer, 2004). These are issues that need to be addressed when building interventions or exercise therapies for people with DS to improve enjoyment and involvement.

Exercise self-efficacy has been linked to improved exercise adaptation, or inclusion of exercise in a person's lifestyle, and exercise maintenance (McAuley and Blissmer, 2000). Both acute and chronic exercise has been shown to increase a person's self-efficacy (McAuley and Blissmer, 2000). Resistance training has been found to increase self-efficacy in women surviving breast cancer (Cheema, Gaul, Lane, and Singh, 2008), postpartum women (LeCheminant *et al.*, 2014), and typical children of both sexes (Lubans, Aguiar, and Callister, 2010). ACT has not been recorded to have improvements in self-efficacy. Determining how these exercises affect self-efficacy could help determine the long term adherence to the interventions.

Exercise perception, or a person's belief/attitude about exercise, is another area that should be explored in creating a lasting intervention. Exercise perception questionnaires explore how a person believes exercise will affect them: improve their health, help them lose weight, make them look better, etc. These beliefs about exercise both encouraged and discouraged obese women from engaging in different types of exercise (Guess, 2012). Positive beliefs that aerobic exercise would help with weight loss encouraged engagement, but a belief that resistance exercise was "manly" discouraged engagement in resistance training. Another study investigating physical activity engagement among people with type-I diabetes found similar positive beliefs in exercise lead to more engagement of exercise interventions (Lascar, *et al*., 2014). Community and group exercise interventions have been shown to increase positive attitudes towards exercise in people with intellectual disabilities (Heller, McCubbin, Drum, and Peterson, 2011). The Theory of Planned Control is used to explain why people undertake a voluntary action, in this theory is the attitude towards the voluntary action (i.e. exercise); therefore, ensuring that an exercise intervention increases the positive beliefs of the intervention is paramount.

Resistance training has been seen to improve enjoyment and social inclusion in other disabled populations (Allen, Dodd, Taylor, McBurney, and Larkin, 2004). In a study of men with Type-II diabetes, feelings of greater enjoyment with interventions including resistance training were associated with continuation of intervention after three and six months as compared to aerobic training alone. Resistance training alone had reported feelings of enjoyment after nine months (Tulloch *et al.* 2013). To our knowledge, there are no studies investigating the enjoyment of resistance exercise or ACT for people with DS. Therefore, investigating the effect of resistance training and ACT on the measures of self-efficacy, exercise perception, and enjoyment is important to start understanding how to encourage prolonged exercise involvement for people with DS.

Summary

People with DS have distinct issues with cognitive functioning and most therapies for these issues are targeted towards children with DS. In the past 20 years the concept of exercise improving cognitive function has become a large area of study within exercise psychology. Multiple meta-analyses have concluded that exercise, both acute and chronic, have a small but significant positive effect on cognitive function, especially within EF. While most of the research has focused on aerobic interventions, a few studies have found that acute and chronic resistance exercise can also elicit improvements in cognitive function. A majority of the research has focused on the effects of exercise on cognitively normal individuals, but an emerging area of research focuses on the effects on special populations. Within people with DS, aerobic exercise and ACT have been shown to positively improve cognitive function. Resistance exercise provides a new area of focus within cognitive function in people with DS. Furthermore, resistance exercise and ACT has the potential to be more enjoyable and encourage continued involvement in exercise compared to aerobic exercise for people with DS.

CHAPTER 3

RESEARCH DESIGN AND METHODS

Overview

This was a randomized 3x3 cross-over experimental design. Participants reported to the Lincoln Family Downtown YMCA for a total of 4 visits with researchers. All protocols for this study were approved by the Human Subjects Institutional Review Board of Arizona State University

Recruitment

Participants were recruited from the greater Phoenix metropolitan area. Potential participants from previous studies, who gave permission to be contacted for future research, and community outreach programs were contacted via email and/or phone calls. A flyer (Appendix A) was used to aid in the recruitment process. The flyer was sent to participants of the Exercise for Adults with Down Syndrome, to Sharing Down Syndrome Arizona, the Down Syndrome Network of Arizona, Civitan Foundation, and the Arizona Recreation Center for the Handicap. The flyer was also posted on the Sensorimotor Development Research Laboratory's Facebook, Instagram, and website.

Inclusion and Exclusion Criteria

Qualifying participants for this study needed to have a diagnosis of Down syndrome (*e.g.* trisomy 21 or the presence of an extra 21st chromosome), be between 18 and 65 years of age, and accompanied by a parent/guardian. Participants who could not fit on ACT bike or resistance training equipment or with upper or lower body limitations and any medical or musculoskeletal contraindications to exercise (determined by the PARQ+) would have been excluded from the study.

Protocols

The first visit was for consenting and baseline assessments, 1-repetition max (1RM), and voluntary (e.g., self-selected pace) cadence measurements. Each participant and/or their guardian (if appropriate) provided informed consent or assent to participate in the research. Following the first session, the participants were randomized, through block randomization, into either Sequence A, Sequence B, or Sequence C. Sequence A completed Resistance Training (RT), Assisted Cycling Therapy (ACT), and then No-Training (NT). Sequence B completed ACT, NT, and finished with RT. Sequence C completed NT, RT, and finished with ACT.

The next three sessions, participants reported to the YMCA and completed the intervention protocols that they were assigned for that visit. Dependent measures were recorded before and after the intervention. Dependent measures were conducted in an order that was dependent on the time of completion and availability of other tests. The specific order of each dependent measure for each participant was not documented. The dependent measures were tested by research assistants. Every attempt was made to have the same research assistant conduct the same dependent measure test, however, there was some variability depending on which research assistants were present. Furthermore, all research assistants were trained for six weeks on the testing protocol for each test and were under the direct supervision of the principal investigator. The total time of the experimental session lasted from 2 to 4 hours. This was influenced by whether the participant tested individually or as part of a larger group (e.g., 6). There was a total of five cognitive dependent measures which is consistent with the number of measures in this population and this type of acute intervention study in previous studies. (Ringenbach, Albert, Chen & Alberts, 2014; Ringenbach, Lichtsinn & Holzapfel, 2015).

Baseline Measures

During the initial visit, participants' sex, mental age, chronological age, ethnicity, physical activity levels, and body mass index (BMI) were collected. Sex, ethnicity, BMI, and physical activity levels have all shown to be correlated to cognitive function (Kimura, 1996; Schwartz *et al*., 2004; Cournot *et al*., 2006). Participants' sex, chronological age, ethnicity, was collected from parent/guardian forms (Appendix D). In addition, the participant or guardian completed the PARQ+ (Warburton, Jamnik, Bredin, & Gledhill, 2011) to confirm participant did not have any contraindications for activity within this study.

Mental age was collected through the Peabody Picture Vocabulary Test (PPVT) (Stockman, 2000). The PPVT has been used as a determinant of mental age in other studies involving DS (Chen *et al*., 2015; Holzapfel *et al*. 2015; Ringenbach *et al*. 2016). Participants' level of physical activity was assessed through the Godin-Shepard Leisure Time Physical Activity questionnaire (Shephard, 1997) (Appendix E). Participants' BMI was assessed through the equation: weight (kg)*(height (m)$^{-2}$). This data was used as possible confounders during the statistical analysis.

1-RM was assessed using weight-stack machines for the leg press, chest press, seated row, latissimus dorsi pulldown, shoulder press, and hamstring curl. 1-RM testing procedures followed the American College of Sports Medicine guidelines (American College of Sports Medicine, 2016). The 1-RM for each of the exercises was then used to develop the resistance training plan for each participant.

Voluntary Cycling Pace assessments occurred on the Theracycle™ recumbent bicycle. Participants pedaled at a voluntary (e.g., self-selected pace) pace for 15 minutes. The voluntary rotations per minute were recorded every minute. The average of these recordings was used to determine the participants' voluntary pace.

Resistance Training Protocols

Participants reported to the YMCA and were fitted with a Polar FT-7™ heart rate monitor. They then had their cognitive performance assessed and asked the Physical Activity Self-Efficacy questionnaire. Next, participants were led through a 5-minute dynamic warm-up consisting of: high knees, hip circles, butt kickers, arm swings, and arm circles. Following the warm-up, participants completed a 30-minute resistance session. Participants completed 2 sets of 8-12 repetitions of approximately 75% of participant's 1RM on stack-weight machines for: leg press, chest press, latissimus dorsi pulldown, seated row, shoulder press, and prone hamstring curl. If participants were unable to complete eight repetitions at 75% of 1-RM, weight was lowered by approximately 5% for the next set. This process continued until a minimum of 16 repetitions were completed for each exercise. Participant's actual lifted weight and number of repetitions and sets were recorded. A 60 to 120-second rest period was given between each set and exercise. Heart Rate and Rating of Perceived Exertion (RPE) was recorded at the end of the warm-up period and after the conclusion of the final repetition of each exercise. After the completion of the resistance training intervention, participants were given a 10-minute rest before dependent measures were re-assessed.

ACT Protocols

Participants reported to the YMCA at their designated time and were fitted with a Polar FT-7™ heart rate monitor. They had the cognitive measures assessed prior to starting a 5-minute warm-up consisting of voluntary (e.g., self-selected pace) cycling on the Theracycle™ recumbent bike. Following the warm-up, the assisted cycling began, the motor was set at a 35% greater cadence than the voluntary rate recorded at baseline up to 95 revolutions per minute (rpm) as that is the max of Theracycle**™**. ACT lasted 30-minutes. Heart rate and RPE were recorded at the end of the warm-up period and every five minutes thereafter. After the completion of the ACT intervention, participants were given a 10-minute rest period before cognitive measures were re-assessed.

Theracycle™

The Theracycle™ is a recumbent bicycle with a motor at the front. The motor can turn the pedals automatically at rates between 5-95 rotations per minute (rpm). The motor can also be left off for voluntary (e.g., self-selected pace) cycling. The bicycle has handles in front of and next to the seat in a similar fashion to other recumbent bicycles. The bike is equipped with an emergency stop magnet on the main block of the bicycle. The main block also has a computerized read out that shows the current rpms of the bike and the controls to adjust the rpms. Pedals on the bike allow the secure attachment of participant's feet to restrict the feet from slipping out of the pedal and causing injury.

Figure 1Picture of a Theracycle

No Training Protocols

Participants reported to the YMCA and were fitted with a Polar FT-7™ heart rate monitor. Dependent measures were then assessed. After the pre-assessments, participants spent 35-minutes playing either Candy Land® or Shoots and Ladders® with a research assistant. These games were chosen because they were believed to have a low cognitive engagement for participants but still provide the researcher-to-participant engagement, similar to RT and ACT. Heart rate and RPE were recorded every 5-minutes after the beginning of the NT intervention. After the 35 minutes, participants had a 10-minute break before having dependent measures re-assessed.

Timeline

Participants were required to wait a minimum of 48 hours between all visits to the YMCA. This allowed any rise in BNDF, IGF-1, arousal, etc. to return to baseline (Rasmussen, Brassard, Adser, Pedersen, Leick *et al.* 2009) and limited any learning effect of repeated exposure to the tests. Participants were asked to refrain from physical activity outside of the protocols for the duration of the study. All sessions were required to be completed within two months of the baseline session.

Dependent Measures

	INSTRUMENT	RELIABILITY	*DOMAIN*
Aim1: Cognitive	Corsi Block-Tapping Test	(INTERNAL) .75	Assesses short-term working memory
	Tower of London (TOL)	.80	Assesses cognitive planning
	Simple Reaction Time		Assesses processing speed
	Choice Reaction Time		Assesses controlled processing
	Flanker Task	.87	Assesses inhibition
Aim 2: Psychological	Physical Activity Enjoyability Scale	.87 (for children)	Assesses enjoyment of an activity
	Physical Activity and Self-Efficacy	.92	Assesses exercise self-efficacy and perception

Cognitive tests

Corsi Block-Tapping Test: The Corsi Block-Tapping test is a measure of short-term *working memory*. It was administered on a laptop computer. The program has eight blue blocks arranged on the screen. Participants were given three trials to ensure they understand the rules of the test prior to the test beginning. For a trial, a series of boxes turn yellow. The participant is required to remember the sequence in which the boxes turned yellow. The computer program then calculated the block span, trials correct, memory span, and a total score based on the testing responses. This is an easily understood and administered test of working memory.

Tower of London (TOL): The TOL is a measure of *cognitive planning* as it requires participants to think about multiple steps to problem solve. In this test, participants were presented with a block with three pegs with three colored balls. The first peg is large enough for one ball, the second peg fits two balls, and the third peg fits all three balls. The pegs and balls were set in their default pattern and then the participants were shown a new pattern. The participants were required to match the pattern within a set number of moves, with the number of moves increasing as trials were successful. Participants were only allowed to move one ball at a time, and all balls were required be on a peg when not being moved (i.e., ball cannot be placed on the table or held in opposite hand). The test was concluded five minutes after the participants first move, or when the participant could not complete three consecutive trails. Participants were given up to one minute to complete each trail. If a participant did not complete the trial in one-minute, the number of moves made were added to the minimum moves for the total moves for that trial. ToL was scored with the total number of moves, minimum number of moves possible, ToL score, number of trails attempted, number of trails correct, and a percent correct. TOL score was calculated by minimum number of moves possible divided by total moves.

Simple Reaction Time: The Simple Reaction Time tests the participants' *processing speed*. This task utilized a timed circuit. Participants were presented with a light and switch button. When the researcher turns on the light, participants pushed the button as fast as they could. The reaction time was then displayed on a separate screen for researcher to record. The researcher oversaw initiating the stimuli after the completion of a successful trial. A total of 20 stimuli were presented to the participants. Median response time was used in the analysis. Median response time was used because of the variability in participant attention during the testing.

Choice Reaction Time: The Choice Reaction Time tested the participants' *controlled processing speed*. This task was assessed using the Go/No-Go task on the website cognitivefun.net. In this task, participants were presented with either a green ball or a patterned ball. If they were presented with the green ball, participants pushed the space bar on the keyboard as fast as they could. If they were presented with the patterned ball, participants did nothing. The stimuli within the program were presented on a ratio of 1:1 of Go to No-Go stimuli. The participant signaled for the next stimuli by pressing the space bar when they were ready for the next stimulus. Stimulus onset delay varied from 600-8,000ms. Participants were presented with 12 stimuli. The choice reaction time program recorded average response time, fastest response time, and slowest response time. Average response time was used in the analysis

Flanker task: The Flanker task tests the participants' ***inhibition*** control. This task was assessed using Flanker task on the website cognitivefun.net. In the Erikson Flanker task, participants were presented with a series of arrows. The series could have been a row of three arrows up to a matrix of arrows. The stimuli were presented as: 2/3 of the stimuli were a row of three (1 target and 2 flanking) arrows; of those, 1:1 were presented as either far apart or close together. The other 1/3 of the stimuli were presented 1:1 of the stimuli were 5 arrows (1 target and 4 flanking) or 25 arrows (1 target and 24 flanking). The center arrow was the target arrow and was either congruent or incongruent with the other arrows. Stimulus onset delay varied from 600-8,000ms. Participants were presented with a series of 20 stimuli. Participants were to answer using the left and right arrow button on the keyboard with the direction of the center arrow. The Eriksen Flanker Task program recorded percent correct, average congruent response time, average incongruent response time. An inhibition time was calculated by finding the difference between the incongruent and congruent response times and was used in the analysis.

Psychological Measures

Physical Activity Enjoyment Scale (Enjoyment Scale): The Enjoyment Scale consisted of 18 7-point Likert scale questions (Appendix B) developed by Kendzierski, D., & DeCarlo, K. J. in 1991 that assesses the enjoyment of different physical activities by asking questions related to feelings of enjoyment. The scale has been validated for use within children (Moore *et al*., 2009). This test was scored with 50% of the questions being counterbalanced. A score of "1" indicated least agreement with the question and a score of "7" indicated the most agreement with the statement. Counterbalanced questions were transformed (e.g., 1=7, 2=6, …, 6=2, 7=1) for final scoring. To increase understanding, questions were asked by researchers. This allowed those participants that could not read to participate and allow researchers to best describe words that were hard for participants to understand.

Physical Activity and Self-Efficacy (PASE)**:** The PASE is a two-part questionnaire (Appendix C) (Heller, 2001). Part 1 is six questions concerning a person's belief in their ability to complete physical activity. Participants answered with a "yes", "no", or "maybe" scored as 3, 1, 2, respectively with a max score of 18. Part 2 is nine questions concerning a person's beliefs about exercise. Again, participants answered with a "yes", "no", or "maybe" and was scored as 3, 1, 2, respectively, with a max score of 27.

Statistical Analyses

Linear mixed models (LMM) were used to test the effects of sequence (ABC, BCA, vs. CAB), subjects within the sequence, intervention (RT, ACT, NT), and visit (Day 1, Day 2, Day 3).

General linear models (GLM) were used to test change in mean differences for cognitive measures and PASE between pre and post measures. A two-tailed α of 0.05 was used to determine statistical significance across intervention groups.

All delta scores (differences between pre and post scores) for measures were tested for normality prior to the primary analysis. Those measures that were not normally distributed were transformed into normally distributed data.

A secondary analysis was conducted to examine the differences between participants that completed the study individually and in a group. This was analyzed using the delta scores of each intervention. A Mann-Whitney U test used to determine if there was a difference between the two testing groups (Individually tested, Grouped tested). Significance was set at $\alpha=0.05$. All statistical procedures were performed by the IBM Statistical Package for Social Sciences (SPSS) version 27.0 (IBM Corp, Armonk, NY).

CHAPTER 4

MANUSCRIPT #1 THE ACUTE EFFECTS OF RESISTANCE TRAINING AND ASSISTED CYCLING THERAPY ON EXECUTIVE FUN

ABSTRACT

Background: Down syndrome is the leading genetic cause of intellectual disabilities. Thus, executive function is important to examine. In recent years it has been determined that acute and chronic exercise has a small but positive effect on measures of executive function in typically developed individuals. The effect has been recorded in both aerobic and resistance exercises. In addition, the use of passive exercise has been used to elicit improvements in executive function in adolescents with Down syndrome.

Methods: A randomized crossover study was utilized to determine the effect of Resistance Training (RT), Assisted Cycling Therapy (ACT), and No Training (NT) on measures of executive function in adults with Down syndrome. Resistance Training (RT)- participants completed a minimum of 16 repetitions of approximately 75% of a 1-RM in the leg press, chest press, seated row, and latissimus dorsi pulldown. ACT-participants completed 30-minutes of cycling at 35% above voluntary rate. No-Training (NT)- participants spent 35-minutes playing board games. Cognitive measures were recorded pre- and post- intervention.

Statistics: The cognitive measures were analyzed using delta score in a linear mix models analysis. The main effect of sequence (1, 2, 3), intervention (RT, ACT, NT), and visit (1, 2, 3) were assessed. Significance level was set with α=0.05. If any interactions were detected, the Bonferroni post-hoc test was used to examine differences. A secondary

analysis was conducted investigating the effect of testing type (individual or grouped). A Man-Whitney U analysis was used to determine difference at each intervention.

Results: No differences were found the sequence, intervention, or visit for any of the measures. No significant differences were found between the individual or grouped testing.

Discussion: The results were interpreted with respect to the Reticular-Activation Hypofrontility Theory and self-regulation hypotheses

Introduction

Down syndrome (DS) is the most common congenital birth defect occurring in 1 of every 737 live births (Parker *et al*., 2010). DS is the leading genetic cause of intellectual disabilities (Parker *et al.*, 2010). In 2011, it was estimated that the average yearly cost of health care, therapy, and other expenses for people with DS was $4,287 (Geelhoed, Bebbington, Bower, Deshpande and Leonard, 2011) with 40% of families having a parent dropping out of the workforce (Schieve, Boulet, Kogan, Van Naarden-Braun and Boyle, 2011). As people with DS age, the financial cost shifts from medical and therapy expenses to respite care (Geelhoed *et al*. 2011).

The intellectual deficits people with DS have problems with are primaily executive functions (EF): inhibition, working memory, shifting, planning, attention, and processing speed (Barkley, 2012; Greco *et al*. 2015). Problems with EF have been linked to issues of caloric intake, quality of life, school and job success in typically developed adults (Diamond, 2013). Higher levels of EF have been found in people with DS who are employed compared to those who are unemployed (Su, Lin, Wu, and Chen, 2008). We theorize that improving EF in people with DS will increase their independence and employability and lower the economic burden on their families.

Studies have shown improvement in ***cognitive function*** following both acute and chronic aerobic exercise in the typical population from youth to older adults (Colcombe and Kramer, 2003; Sibley and Etnier, 2003; Verburgh, Königs, Scherder, and Oosterlaan, 2014) The largest effect sizes have been recorded in areas of ***executive function*** (Smith *et al*. 2010; Verburgh *et al.* 2014). Similar results have been recorded in the typical population following acute and chronic ***resistance training*** (Wilke *et al*., 2019;

Landrigan, Bell, Crowe, Clay, and Mirman, 2019). The improvements in cognitive function after both aerobic and resistance training in the typical population have been linked to increases in neurotrophic factors: brain-derived neurotrophic factor (BDNF), and insulin like growth factor (IGF-1), among others (Szuhany, Bugatti, and Otto, 2015; Yarrow, White, McCoy, and Borst, 2010; Church *et al*., 2016).

The effects of exercise on ***cognitive function in people with DS*** has very limited research (Pastula, Stopka, Delisle, and Hass, 2012; Lee, Seo, and Lim, 2014; Chen, Ringenbach, Crews, Kulinna, and Amazeen, 2015; Holzapfel, *et al.*, 2015; Ringenbach, *et al*., 2016; Chen and Ringenbach, 2016). Results from aerobic and Assisted Cycling Therapy (ACT), exercise on a bike with a motor to increase the pedal rotations above voluntary rate, in the DS population have mirrored many of the results of the typical population. Research in acute bouts of aerobic exercise has found an inverse-U relationship with intensity and cognitive function outcomes (Chang *et* al., 2012; Chen *et al.*, 2015). Acute and chronic aerobic exercise and ACT have been shown to improve measures of executive function in adolescents and adults with DS (Chen, *et al.*, 2015; Holzapfel, *et al.*, 2015; Chen and Ringenbach, 2016; Ringenbach, *et al*., 2016). One study found increases in BDNF, IGF-1, and vascular endothelial growth factor following aerobic exercise in the typical population(Lee, Seo, and Lim, 2014). However, to our knowledge, there are no published research studies examining the effects of ***resistance training on cognitive function in people with DS***; the closest published study used a moderate-intensity circuit training protocol (Pastula, *et al.*, 2012). While they found improvements in three areas of the Woodcock-Johnson III test, the study's intensity was determined via heart rate, not resistance and included people with ID, not just DS.

While research into the effect of resistance training on cognitive function in people with DS is lacking, there are a few studies that investigated the viability of resistance training for people with DS. Resistance training for people with DS has been shown to improve muscular strength (Shields, Taylor, and Dodd, 2008; Cowley *et al*., 2011; Shields, *et al*., 2013), muscular endurance (Shields, Taylor, and Dodd, 2008), muscular function (Shields, Taylor, and Dodd, 2008) and physical activity engagement (Shields *et al*., 2013). Since these studies show that people with DS show similar physiological responses to typically developed individuals, it would be expected that the cognitive response to resistance training would be similar to those seen in typically developed individuals.

Methods

This was a randomized 3x3 cross-over experimental design. Participants reported to the Lincoln Family Downtown YMCA for a total of 4 visits with researchers. All protocols for this study were approved by the Human Subjects Institutional Review Board of Arizona State University.

Inclusion and Exclusion Criteria

Qualifying participants for this study needed diagnosis of Down syndrome (*e.g.* trisomy 21 or the presence of an extra 21st chromosome), be between 18 and 65 years of age, and be accompanied by a parent/guardian. Participants who could not fit on ACT bike or RT equipment were not eligible for the study. Participants with upper or lower body limitations and any medical or musculoskeletal contraindications to exercise (determined by the PARQ+) were excluded from the study.

Protocols

The first visit was for consenting and baseline assessments, 1-repetition max (1RM) measurements, and voluntary (e.g., self-selected pace) cadence measurements. Each participant and/or their guardian (as necessary) provided informed consent and/or assent to participate in the research. Following the first visit, the participants were randomized, through block randomization, into either Sequence A, Sequence B, or Sequence C. Sequence A completed Resistance Training (RT), Assisted Cycling Therapy (ACT), and then No-Training (NT). Sequence B completed ACT, NT, and finished with RT. Sequence C completed NT, RT, and finished with ACT.

For the next three visits, participants reported to the YMCA and completed the intervention protocols they were assigned for that visit. Dependent measures were recorded before and after the intervention. Dependent measures tests were conducted randomly depending on the time of completion and availability of other tests. Because of the random pattern of the dependent measure testing, the timing of the testing was not recorded. The dependent measures were tested by research assistants. The same research assistant conducted the same dependent measure test when they were available. Although research assistants ran one test, all research assistants were trained for several weeks on the testing protocol for each dependent measure and were under the direct supervision of the principal investigator. The total time of the experimental session lasted from 2 to 4 hours. This was influenced by whether the participant tested individually or as part of a larger group (e.g., 6). There were a total of five cognitive dependent measures, which is consistent with the number of measures used in this type of acute intervention in previous studies with this population (Ringenbach, Albert, Chen & Alberts, 2014; Ringenbach, Lichtsinn & Holzapfel, 2015).

Baseline Measures

During the initial visit, participants' sex, mental age, chronological age, ethnicity, physical activity levels, and body mass index (BMI) was collected. Sex, ethnicity, BMI, and physical activity levels have all shown to be correlated to cognitive function (Kimura, 1996; Schwartz *et al*., 2004; Cournot *et al*., 2006). Participants' sex, chronological age, ethnicity, were collected from parent/guardian forms (Appendix D). Along with the parent/guardian forms, the participant or guardian completed the PARQ+ (Warburton, Jamnik, Bredin, & Gledhill, 2011) to confirm participant did not have any contraindications for activity within this study.

Mental age was collected through the Peabody Picture Vocabulary Test (PPVT) (Stockman, 2000). The PPVT has been used as a determinant of mental age in other studies involving DS (Chen *et al*., 2015; Holzapfel *et al*. 2015; Ringenbach *et al*. 2016). Participants' level of physical activity was assessed through the Godin-Shepard Leisure Time Physical Activity questionnaire (Shephard, 1997) (Appendix E). Participants' BMI was assessed through the equation: weight (kg)*(height (m)$^{-2}$). This data was used as possible confounders during the statistical analysis.

1-RM was assessed using weight-stack machines for the leg press, chest press, seated row, latissimus dorsi pulldown, shoulder press, and hamstring curl. 1-RM testing procedures followed the American College of Sports Medicine guidelines (American

College of Sports Medicine, 2016). The 1-RM for each of the exercises was then used to develop the resistance training plan for each participant.

Voluntary Cycling Pace occurred on the Theracycle™ recumbent bicycle. Participants pedaled at a voluntary (e.g., self-selected pace) pace for 15 minutes. The voluntary rotations per minute were recorded every minute. The average of these recordings was used to determine the participants' voluntary pace.

Resistance Training Protocols

Participants reported to the YMCA and were fitted with a Polar FT-7™ heart rate monitor. They then had their cognitive performance assessed. Participants were then led through a 5-minute dynamic warm-up consisting of: high knees, hip circles, butt kickers, arm swings, and arm circles. Following the warm-up, participants completed a 30-minute resistance session. Participants completed 2 sets of 8-12 repetitions of approximately 75% of participant's 1RM on stack-weight machines for: leg press, chest press, latissimus dorsi pulldown, seated row, shoulder press, and prone hamstring curl. If participants were unable to complete 8 repetitions at 75% of 1-RM, weight was lowered by approximately 5% for the next set. Process continued until a minimum of 16 repetitions were completed for each exercise. Participant's actual lifted weight and number of repetitions and sets were recorded. A 60 to 120-second rest period was given between each set and exercise. Heart Rate and Rating of Perceived Exertion (RPE) was recorded at the end of the warm-up period and after the conclusion of the final repetition of each exercise. After the completion of the resistance exercise session, participants were given a 10-minute rest before cognitive performance was re-assessed.

ACT Protocols

Participants reported to the YMCA at their designated time and were fitted with a Polar FT-7™ heart rate monitor. They had their cognitive performance assessed prior to starting a 5-minute warm-up consisting of voluntary (e.g., self-selected pace) cycling on the Theracycle™ recumbent bike. Following the warm-up, the motor assisted cycling began, the motor was set at a 35% greater cadence than the voluntary rate recorded at baseline up to 95 revolutions per minute (rpm) as that is the max of Theracycle**™**. ACT lasted 30-minutes. Heart rate and RPE were recorded at the end of the warm-up period and every five minutes thereafter. After the completion of the ACT session, participants were given a 10-minute rest period before cognitive performance was re-assessed.

Theracycle™

The Theracycle™ is a recumbent bicycle with a motor at the front. The motor can turn the pedals automatically at rates between 5-95 rotations per minute (rpm). The motor can also be left off for voluntary (e.g., self-selected pace) cycling. The bicycle has handles in front of and next to the seat in a similar fashion to other recumbent bicycles. The bike is equipped with an emergency stop magnet on the main block of the bicycle. The main block also has a computerized read out that shows the current rpms of the bike and the controls to adjust the rpms. Pedals on the bike allow the secure attachment of participant's feet to restrict the feet from slipping out of the pedal and causing injury.

No Training protocols

Participants reported to the YMCA and were fitted with a Polar FT-7™ heart rate monitor. They then had their cognitive performance assessed. Participants then spent 35-minutes playing either Candy Land or Shots and Ladders with a research assistant. Heart rate and RPE were recorded every 5-minutes after the beginning of the NT session. After the 35 minutes, participants had a 10-minute break before having their cognitive performance re-assessed.

Timeline

Participants were required to wait a minimum of 48-hours between all visits to the YMCA. The participants averaged 150-hours [48 to 336-hours] between sessions. This allowed any rise in BNDF, IGF-1, arousal, etc. to return to baseline (Rasmussen, Brassard, Adser, Pedersen, Leick *et al.* 2009) and limited any learning effect of repeated exposure to the tests. Participants were asked to refrain from physical activity outside of the protocols for the duration of the study. All sessions were required to be completed within two months of the baseline session.

Cognitive tests

<u>Simple Reaction Time</u>: The Simple Reaction Time tested the participants' *<u>processing speed</u>*. This task utilized a timed circuit. Participants were presented with a light and switch button. When the researcher turned on the light, participants pushed the button as fast as they could turn off the light. The reaction time was then displayed on a separate screen for researcher to record. Stimuli was presented at the discretion of the researcher.

Participants completed 20 trials total. The median reaction time was used for analysis to combat the any attention span issues of participants.

Choice Reaction Time: The Choice Reaction Time tested the participants' *controlled processing speed*. This task was assessed using the Go/No-Go task on the website cognitivefun.net. In this task, participants were presented with either a green ball or a patterned ball. If they were presented with the green ball, participants pushed the space bar on the keyboard as fast as they could. If they were presented with the patterned ball, participants did nothing. The stimuli were presented in a 1:1 ratio of Go vs No-Go with a stimuli onset delay of 600-8,000 ms. Participants initiated each stimulus by pressing the space bar. The choice reaction time program recorded average response time, fastest response time, and slowest response time. The average response time was used in the analysis.

Flanker task: The Flanker task tested the participants' ***inhibition control***. This task was assessed using the Flanker Task on the website cognitivefun.net. In the Erikson Flanker task, participants were presented with a series of arrows. The center arrow is the target arrow and is either congruent or incongruent with the flanker arrows. Participants were to answer using the left and right arrow buttons on the keyboard with the direction of the center arrow. The Flanker program presented the stimuli in one of four presentations: a series of three arrows (1 target, 2 flankers) close to each other, a series of three arrows (1 target, 2 flanker) far apart, a series of 5 arrows (1 target, 4 flankers), or a matrix of 25 arrows (1 target, 24 flankers). The presentation of stimuli was 2/3 of the stimuli were the series of 3 arrows, 1/6 were the series of 5 arrows, and 1/6 were the matrix of 25 arrows. The stimuli onset delay for the flanker task was 600-8,000ms. The onset of the next stimuli was initiated by the response of the previous stimuli. The Flanker Task program recorded percent correct, average congruent response time, average incongruent response time. An inhibition time was calculated by finding the difference between the congruent and incongruent times and this score was used in the analysis.

Corsi Block-Tapping Test: The Corsi Block-Tapping test is a measure of short-term *working memory*. It was administered on a laptop computer. The program had eight blue blocks arranged on the screen. For a trial, a series of boxes turn yellow. The participant was required to remember the sequence in which the boxes turned yellow. Participants were given three practice trials to ensure they understand the rules of the test prior to test beginning. The stimulus was presented when the participant initiated the trial. The computer program then calculates the block span, trials correct, memory span, and a total score based final test. This is an easily understood and administered test of working memory.

Tower of London (TOL): The TOL was a measure of *cognitive planning* as it required participants to think about multiple steps to problem solve. In this test, participants were presented with a block with three pegs and three colored balls. The first peg is large enough for one ball, the second peg fits two balls, and the third peg fits all three balls. The pegs and balls were set in their default pattern and then the participants were shown a pattern. The participants must match the pattern within a set number of moves.

Participants were only allowed to move one ball at a time, and all balls were required to be on a peg when not being moved (i.e. the ball cannot be placed on the table or held in the participant's hands). The test concluded at five minutes or when the participant could not complete three consecutive trails. Participants were given up to one minute to complete each trail. The five-minute time frame started when researcher presented the participant with the first pattern. Similarly, the one-minute time for each trial started when researcher presented the new pattern. If a participant did not complete the trial in one-minute, the number of moves made were added to the minimum moves for the total moves for that trial. The total number of moves, minimum number of moves possible, number of trails attempted, number of trails correct, and a percent correct, ToL score were recorded. TOL score was calculated by minimum number of moves possible divided by total moves and was used for the primary analysis for Cognitive Planning.

Statistical Plan

Linear mixed models (LMM) were used to test the effects of sequence (ABC, BCA, vs. CAB), subjects within the sequence, intervention (RT, ACT, NT), and visit (Day 1, Day 2, Day 3).

General linear models (GLM) were used to test change in mean differences for cognitive measures and PASE between pre and post measures. A two-tailed α of 0.05 was used to determine statistical significance across intervention groups.

All delta scores (differences between pre and post scores) for measures were tested for normality prior to the primary analysis. Those measures that were not normally distributed were transformed into normally distributed data. This was accomplished through the percentile rank transformation.

A secondary analysis was conducted to examine the differences between participants that completed the study individually and in a group. This was analyzed using the delta scores of each intervention. A Mann-Whitney U test was used to determine if there was a difference between the two testing groups (Individually tested, Grouped tested). Significance was set at $\alpha=0.05$. All statistical procedures were performed by the IBM Statistical Package for Social Sciences (SPSS) version 27.0 (IBM Corp, Armonk, NY).

Results

Participants

There were 16 participants that were recruited and started this study. One participant completed the study and was removed from analysis because he failed to complete many of the cognitive tests. Another participant was removed because participation in the study was cut short by the Novel Coronavirus-19. Another five participants were recruited; however, these participants were unable to start because of closure of the YMCA due to the Novel Coronavirus-19 quarantine, this would have brought the sample size to 21 which is closer to the intended sample size of 30. The consort diagram for this study can be seen in Figure 2. The breakdown of participant baseline characteristics is found in Table 1.

Participants completed a minimum of 16 repetitions on each of the resistance exercises with a minimum of 65% of their 1-RM. ACT was completed with an average cadence 128% of voluntary cycling cadence. The average cadence being below the desired 135% of voluntary is because some of the participants' 135% was above the 95-rpm capacity of the Theracycle. More concise information on the exercises can be found in Table 2.

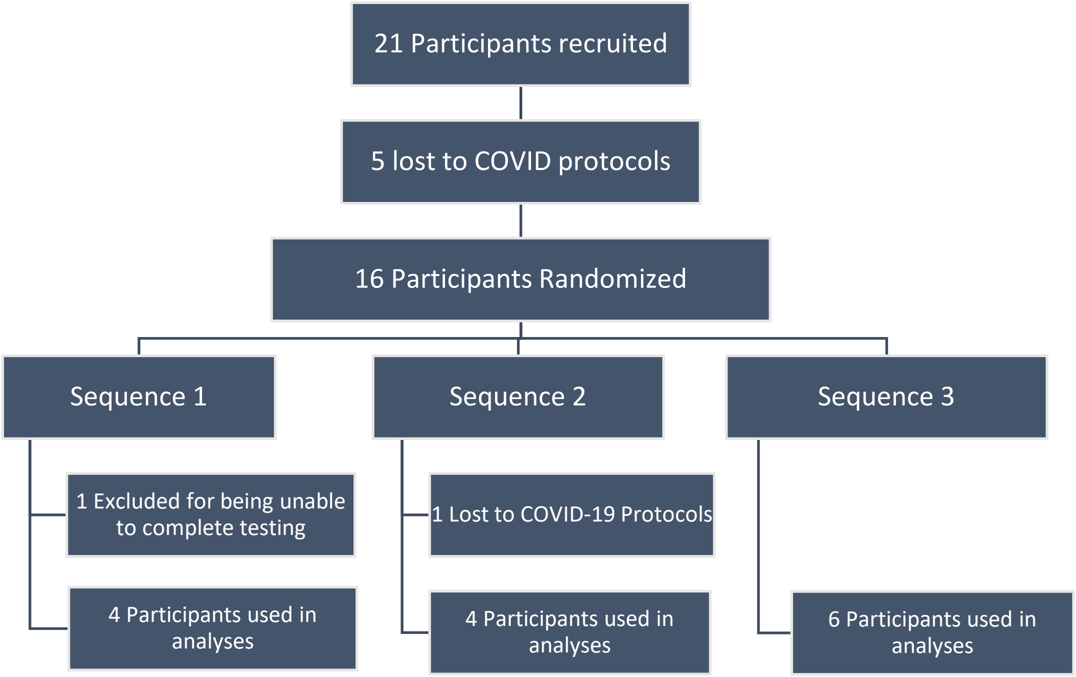

Figure 2. CONSORT diagram

Table 1. Participant Demographics and Characteristics

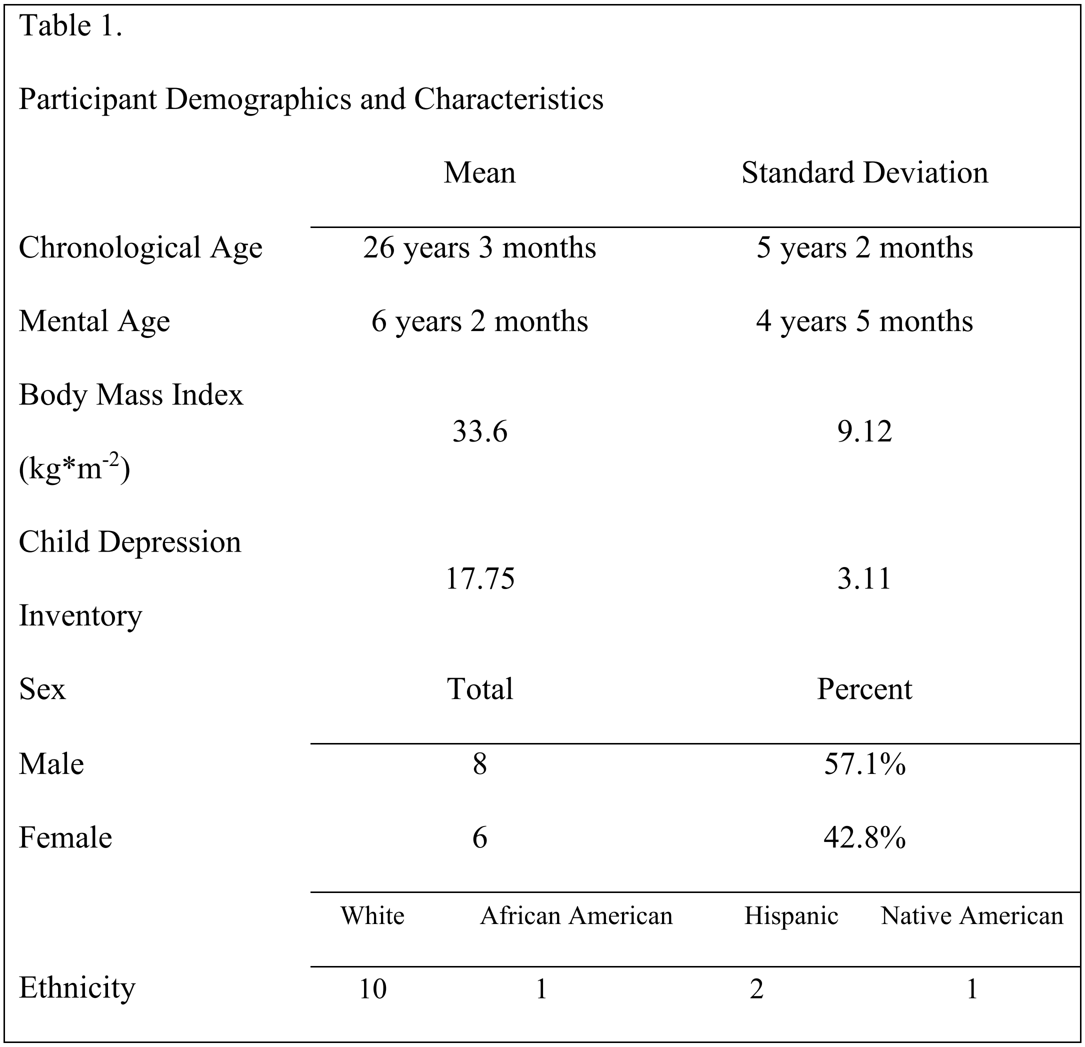

Table 1.

Participant Demographics and Characteristics

	Mean		Standard Deviation	
Chronological Age	26 years 3 months		5 years 2 months	
Mental Age	6 years 2 months		4 years 5 months	
Body Mass Index (kg*m^{-2})	33.6		9.12	
Child Depression Inventory	17.75		3.11	
Sex	Total		Percent	
Male	8		57.1%	
Female	6		42.8%	
	White	African American	Hispanic	Native American
Ethnicity	10	1	2	1

Table 2. Exercise Completion data

Table 2.

Exercise completion data

	Resistance Training							
	Total Repetitions		Percent of Max (%)		Heart Rate (BPM)		RPE	
	M	SD	M	SD	M	SD	M	SD
Leg Press	16.57	1.59	70.18	5.17	100.21	15.14	1.79	0.77
Chest Press	16.79	1.78	68.92	6.23	104.64	17.14	2.14	1.06
Lat Pulldown	17.14	2.47	73.04	10.78	102.93	14.63	2.43	1.12
Seated Row	17.14	1.96	67.76	7.72	104.71	17.65	2.29	0.88
Leg Curl	16.71	1.79	71.12	10.42	104.93	19.19	2.43	1.12
Shoulder Press	16.79	1.61	67.67	10.31	108.36	19.10	2.64	1.17
	Assisted Cycling Therapy							
	Average Cadence (RPM)		% of Voluntary Cadence		Heart Rate (BPM)		RPE	
ACT	64.36	22.53	128	16	91.31	17.08	1.5	0.66
	No Training							
					Heart Rate (BPM)		RPE	
NT					75.88*	9.82	1.64	0.71

*= $p<0.05$ for NT Heart rate compared to all RT

Covariate analyses

Covariates that were collected at baseline were used in analyses. These covariates made no difference to final p-values; therefore, all results are reported without the covariates included.

Processing Speed

The delta score (pre-post) of the median reaction time was used for the analysis of Simple Processing Speed. Pre-post was used to calculate delta so improvements were displayed as positive numbers.

There were no significant differences in the delta scores for the processing speed for the for sequence, intervention, or visit (Table 3).

Table 3. Median Reaction Time AOVA Table

Tests of Between-Subject Effects

Dependent Variable: Median Reaction time

Source	**Type III Sum of Squares**	**Df**	**Mean Square**	**F**	**Sig.**
Corrected Model	.152[a]	15	.010	.830	.639
Intercept	.003	1	.003	.254	.620
Sequence	.006	2	.003	.200	.822
Intervention	.005	2	.003	.224	.801
Visit	.002	2	.001	.068	.935
Error	.232	19	.012		
Total	.387	35			
Corrected Total	.383	34			

a. **R Squared=.393 (Adjusted R Squared = -.081)**

Controlled Processing Speed

The delta score (pre-post) of the average choice reaction time was used for the analysis of choice processing speed. Pre minus Post was used so improvements in controlled processing speed would be positive. The data was found to be non-normally distributed and was transformed for analysis.

There was no significant difference found for controlled processing speed in either the sequence, intervention, or visit (Table 4).

Table 4. The Average Choice Processing Speed ANOVA table

Tests of Between-Subject Effects

Dependent Variable: Choice Reaction time

Source	Type III Sum of Squares	Df	Mean Square	F	Sig.
Corrected Model	37160517.4[a]	17	2185910.789	.653	.813
Intercept	4649595.665	1	4649595.655	1.390	.251
Sequence	4931807.042	2	2465903.521	1.585	.248
Intervention	548452.758	2	274226.379	.082	.922
Visit	14366479.63	2	7183239.813	2.147	.141
Error	73598976.00	22	3345408.000		
Total	114419506.7	40			
Corrected Total	110759493.4	39			

a. R Squared = .336 (Adjusted R Squared = -.178)

Inhibition

The delta score (pre-post) inhibition time (incongruent – congruent response times) was the primary outcome measure for inhibition control. Pre-post was used to calculate delta score so that improvements in time were positive numbers. The delta scores were found to be non-normally distributed and were transformed.

No significant differences were found for sequence, intervention, or visit for inhibition control (Table 5).

Table 5. Inhibition Time ANOVA table

Tests of Between-Subject Effects

Dependent Variable: Flanker Inhibition Score

Source	Type III Sum of Squares	Df	Mean Square	F	Sig.
Corrected Model	99825301.7[a]	16	6239081.355	.883	.595
Intercept	1783258.642	1	1783258.642	.252	.621
Sequence	1602300.917	2	801150.458	.0858	.918
Intervention	2620267.151	2	1310133.575	.185	.832
Visit	1851861.348	2	925930.674	.131	.878
Error	148392956.2	21	7066331.246		
Total	250305740.3	38			
Corrected Total	248218257.8	37			

a. R Squared = .402 (Adjusted R Squared = -.053)

Working Memory

The delta score (post-pre) on the Corsi memory score was used for the analysis of working memory. Delta scores for the working memory were found to be non-normally distributed and were transformed prior to analysis.

No significant differences were found for sequence, intervention, or visit for working memory (Table 6).

Table 6. Memory Score ANOVA Table.

Tests of Between-Subject Effects

Dependent Variable: Memory Score

Source	Type III Sum of Squares	Df	Mean Square	F	Sig.
Corrected Model	12.633[a]	17	.743	1.964	.066
Intercept	.028	1	.028	.073	.790
Sequence	3.681	2	1.840	3.031	.089
Intervention	.142	2	.071	.188	.830
Visit	1.676	2	.838	2.214	.132
Error	8.703	23	.378		
Total	21.421	41			
Corrected Total	21.336	40			

a. R Squared = .592 (Adjusted R Squared = .291)

Cognitive Planning

The delta score (post-pre) for TOL score (minimum number of moves/total number of moves) was used to assess cognitive planning. Two participants were removed from analysis because they used a different form of the TOL leaving N=12 for this measure.

No significant differences were found in the sequence, intervention, or visit for cognitive planning (Table 7).

Table 7. Cognitive Planning ANOVA Table

Tests of Between-Subject Effects

Dependent Variable: TOL Score

Source	Type III Sum of Squares	Df	Mean Square	F	Sig.
Corrected Model	.195[a]	14	.014	.345	.976
Intercept	.005	1	.005	.126	.726
Sequence	.009	2	.004	.250	.785
Intervention	.030	2	.015	.370	.696
Visit	.016	2	.008	.203	.818
Error	.724	18	.040		
Total	.926	33			
Corrected Total	.919	32			

a. R Squared = .212 (Adjusted R Squared = -.401)

Individual vs Grouped

There were three participants that completed the study individually and 11 participants that completed the study in a group setting. This small sample size contributed to the non-significance between the individual vs grouped participants.

However, a trend showing differing delta scores for those completed the study individually as compared to those completed the study in a group setting.

Processing Speed

While not significant p >.05, within the processing speed (median reaction time), participants that were completed the study trended in the opposite direction of those grouped (Figure 3). Pre-post was used to calculate delta so improvements were displayed as positive numbers. Individually tested participants in RT and NT and grouped participants in ACT had improvements in processing speed.

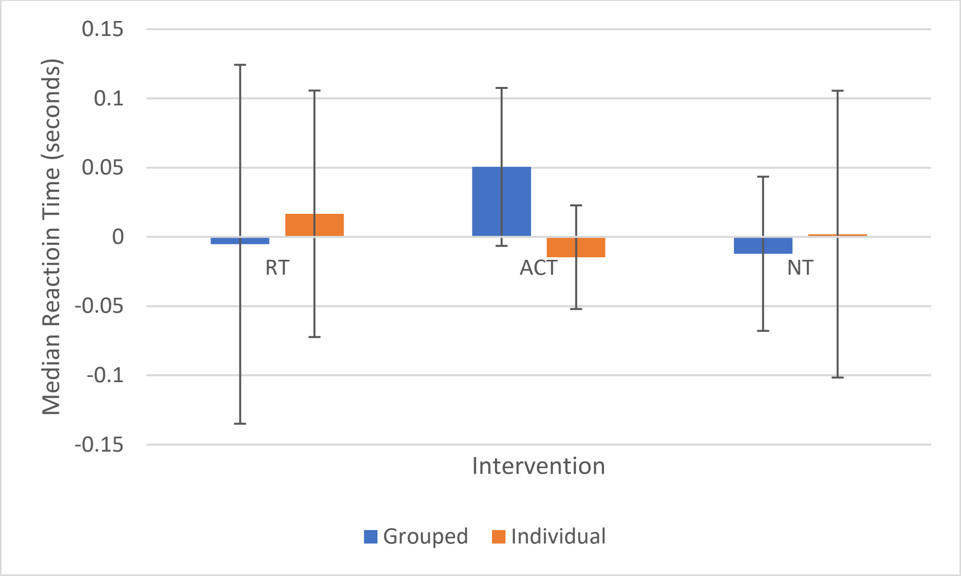

Figure 3. Delta Median Reaction Times (seconds) for participants that were tested Grouped vs Individually.

Choice Processing Speed

While not significant p >.05, the choice processing speed (average choice reaction time) saw the RT and ACT trending in the opposite direction for the individuals vs the grouped (Figure 4). Pre-post was used to calculate delta so improvements were displayed as positive numbers.

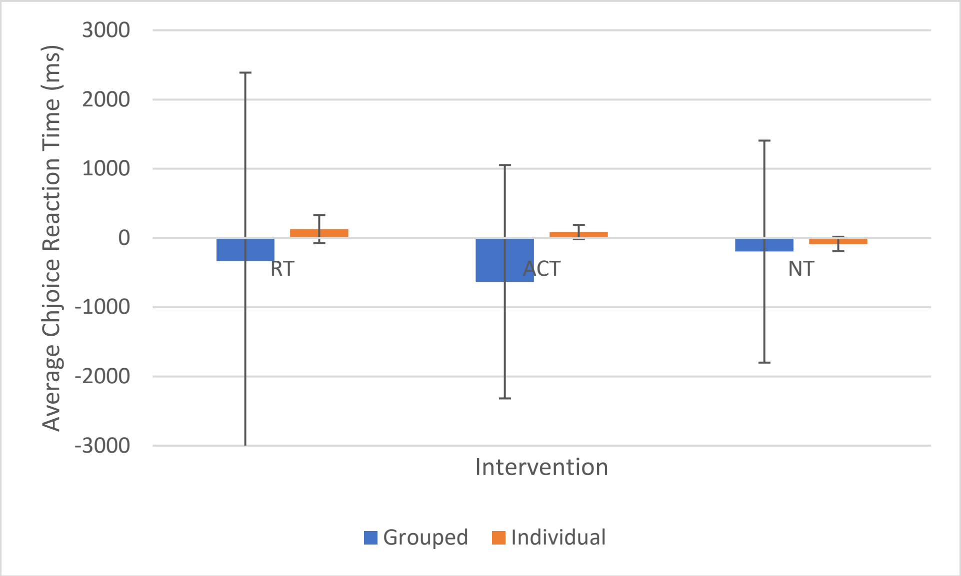

Figure 4.Delta Average Choice Reaction time (ms) for Individually vs Grouped Participants

<u>Inhibition</u>

While not significant p >.05, for inhibition, the trends were varying for both the indiviual and grouped participants (Figure 5). The RT intervention had Individually

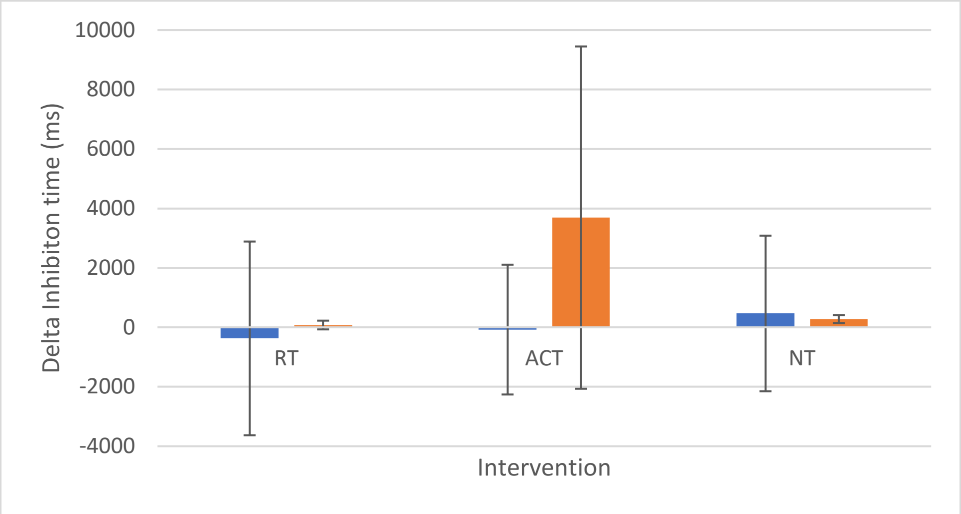

Figure 5. Delta Inhibition times (ms) for Individual vs Grouped Participants.

tested participants increasing while the Grouped participants decreasing. The ACT intervention had both the individual and grouped participants increasing, with individual participants increasing more. The NT intervention had both increasing with grouped participants improving more than individual.

Memory

While not significant (p>.05), the memory (Corsi Memory Score) analysis found that individual participants had increases following RT, ACT, and NT; while only the NT had increases for the grouped participants (Figure 6).

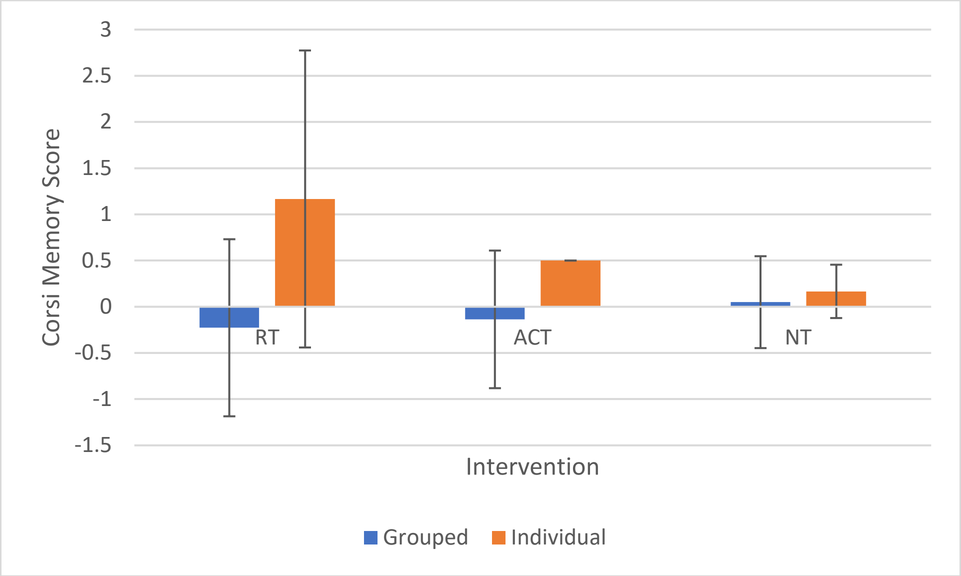

Figure 6. Delta Corsi Memory score for participants tested Individually vs Grouped

Cognitive Planning

Two of the three participants that tested individually used a different form of the Tower of London and therefore could not be used in this analysis; leaving only one participant in the individually tested participants. This analysis could not be completed with only one participant in the Individually tested group.

Discussion

The result of this study did not support our hypotheses. We also expected to see an increase in executive function following RT. We also expected to see an increase in executive function following ACT; however, these results were opposite the information that has previously been within our own research (Ringenbach, Albert, Chen & Alberts, 2014; Ringenbach, Lichtsinn & Holzapfel, 2015).

This result does, however, follow the some of the concepts behind the RAH theory (Dietrich and Audiffren, 2011). With the participants resting for 10-minutes at the end of their intervention, the cognitive resources should have had time to divert from the implicit system to the explicit system. With the shift from implicit to explicit, we would expect to see small or no improvements in the simple reaction times as we observed in this study. However, there should have been improvements in inhibition control and cognitive planning that was not achieved in this study as those are explicit level functions.

The lack of significant improvements in the RT intervention over NT intervention and the negative delta scores seen in many of the group testing (Figures 2-5) has two possible explanations. First, it is possible that resistance training was still a novel exercise for many of the participants. While we tried to limit the novelty of the exercises by using stack weight machines and using participants that have been involved with exercise programs (12 participants), some instruction was still needed to keep participants safe from injury while completing the movements. Because the movements were still novel, more resources were allocated to learning and controlling the unfamiliar movements within the frontal and pre-frontal cortices. The depletion of resources in the executive function from the learning and concentration of these novel movements is explained by the local resource depletion model (Brzezicka, Kaminski, and Wróbel, 2013) that was derived from the theory of opportunity cost (Kurzban, Duckworth, Kable, and Myers, 2013). It was believed that having some activation of the explicit system for the coordination of the movements during exercise would help the post-exercise scores (Tomporowski, McCullick, Pendleton and Pesce, 2015); however, if the movements were still too novel and not just coordinative, then there would be more activation and fatigue within the prefrontal cortex and cerebellum (Taylor and Ivry, 2014). By having more activation within the frontal and pre-frontal cortices, the RAH model is violated as well. If blood flow is never diverted from the explicit system (e.g. learning and concentration), the loading of the blood with BDNF and IGF-1 in the implicit system does not occur.

Second, it is possible that the RT was not intense enough to elicit the maximum amount neurotrophic factors. Wilke *et al*. (2019) indicated that high intensity or low intensity RT was needed to elicit the greatest changes in executive function. With the use of the weight stack machines, we were not able to perfectly set 75% of 1-RM for each participant. The trade-off of not having exactly 75% was that the machines would require less learning for the participants to complete safely. Compounding not being able to use exactly 75% of 1-RM, some participants were reduced even further when they were unable to complete the first set of the workout. The average percent of 1-RM across all the exercises was 69.63% (Table 2), falling into a moderate range.

The lack of ACT intervention results is also counter the previous studies within our lab (Ringenbach, Chen, and Albert, 2012; Ringenbach, Albert., Chen, and Alberts, 2014; Ringenbach, *et al.* 2016; Ringenbach *et al.* 2018) and Ridgel's (2009 & 2011) initial work with the ACT bike and model for people with Parkinson's disease. Ridgel's model for ACT mechanisms (Figure 7) indicates that increased intrinsic feedback from the motor driven pedals causes increased levels of BDNF, Dopamine, GDNF and IGF. One limitation may have been that we were not able to achieve a 35% increase in pedal speed above voluntary, however there was still assistance occurring.

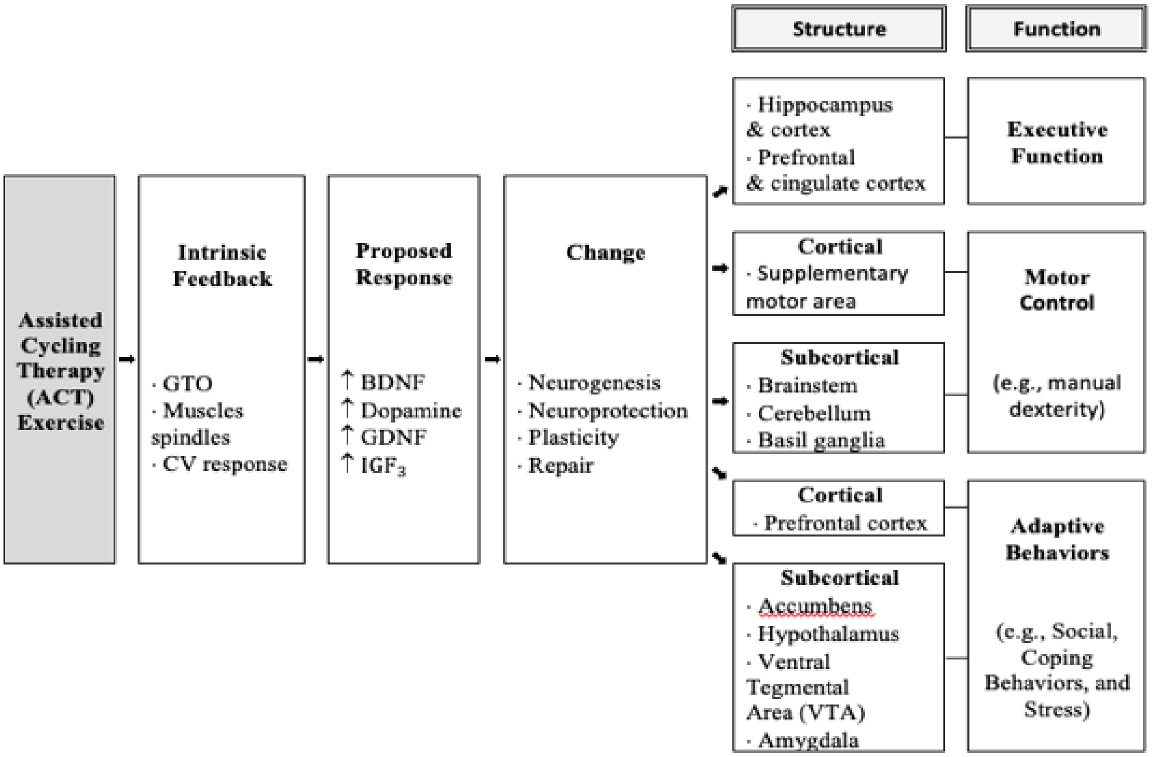

Figure 7 Ridgel's Model of mechanisms of ACT

The NT intervention served as our control and had no significant difference compared to RT or ACT interventions, which is in line with other studies from our lab (Ringenbach, Albert, Chen, and Alberts, 2014; Ringenbach, Arnold, Lopez, Holzapfel, and Rodgriguez, 2018). However, we did present a different NT group as compared to our other studies, we had participants complete a session of what we thought were non-cognitive stimulating board games with researchers. Since the design and implementation of this study, another study was released that found board games in children (ages 10-12 years old) improved EF after six weeks (Benzing, 2019). Based on this finding, and the fact that the mean mental age of our participants was around 6 years old, playing board games which was our NT control group may have also improved EF in our population. Looking at the individual delta scores of the individual vs grouped analyses, there is some improvement within the NT intervention delta scores (Figure 4 & 5). While these improvements were not significant, these improvements may have contributed to the lack of significant results between NT and RT and ACT.

The trends that were seen within the individual vs grouped analyses confirm observations made by the research team, that attention and focus seemed to affect participants within the grouped testing. Because of the small population of adults with DS in Phoenix, many of the participants knew each other. Therefore, many of the participants within the grouped testing sessions had to be reminded to focus and keep their attention on the testing as rather than talking with friends. The contrasting trends between those tested individually and those tested in groups can be explained again by the theory of opportunity cost (Kurzban, Duckworth, Kable, and Myers, 2013). The participants were having their attention split between the task that the researcher was asking and talking with a friend. The theory of opportunity cost suggest that it is neurologically fatiguing to choose a less enjoyable activity over a more desirable activity. The participants in group testing had to inhibit the desire to talk to their friends and concentrate on the task that the researcher wanted. The more the participants engage in these activities while passing on the more desirable “talking to friends” the more their EF’s are going to fatigue.

Conclusions

While the results of this study did not follow the typical results of exercise and executive function changes, it did shed some light on issues that should be addressed in future studies with exercise in people with DS. First, it is important to limit the amount of stimulation (i.e., number of people in the testing area) that people with DS are encountering during testing. Second, future studies should have some form of NT that still has researcher-to-participant interaction, but one that does not tax the EF.

CHAPTER 5

MANUSCRIPT #2 THE ACUTE EFFECTS OF RESISTANCE TRAINING AND ASSISTED CYCLING THERAPY ON SELF-EFFICACY AND ENJOYMENT

ABSTRACT

Background: It has been shown that people with DS have a lack of motivation to participate in physical activity, lack self-efficacy in their ability to perform physical activity, consider physical activity “boring”, and are self-described as “lazy”. Exercise self-efficacy, exercise perception, and enjoyment have been linked to improved exercise adaptation, or inclusion of exercise in a person’s lifestyle, and exercise maintenance. Therefore, it is important to understand how different exercises improve these psychological constructs for people with DS to create meaningful life changes.

Methods: A randomized crossover study was utilized to determine the effect of Resistance Training, Assisted Cycling Therapy, and No training on self-efficacy, exercise perception and enjoyment in adults with Down syndrome. Resistance Training (RT)- participants completed a minimum of 16 repetitions of approximately 75% of a 1-RM in the leg press, chest press, seated row, and latissimus dorsi pulldown, shoulder press, and hamstring curl. ACT- participants completed 30-minutes of cycling at 35% above voluntary rate. No-Training (NT)- participants spent 35-minutes playing board games. Cognitive assessments were recorded pre- and post- intervention.

Statistics: Post Physical Activity Enjoyment Scale scores were compared using Linear mix models (LMM) analysis with main effects of sequence (A,B,C), intervention (RT, ACT, NT), and visit (1,2,3). Self-efficacy and exercise perception were analyzed using

delta scores (post-pre) within a LMM with the main effect of sequence, intervention, and visit. Significance level was set with α=0.05. If effects were significant, the Bonferroni post-hoc test was used to determine differences. A secondary analysis was conducted using a Man-Whitney U analysis to determine difference between those that completed study in a group or individual setting

Results: No differences were recorded within the measures.

Discussion: It is believed that a ceiling effect occurred for the PASE as participants gave the best answers each time they were asked the questions. While the Enjoyability Scale was validated for children within the mental range for the overall population of people with DS, our population averaged 2 years lower. Because of this our Enjoyability Scale was results were limited.

Introduction

It has been shown that people with DS have a lack of motivation to participate in physical activity (Stanish, Temple, and Frey, 2006), lack self-efficacy in their ability to perform physical activity, consider physical activity “boring”, and are self-described as “lazy” (Heller, Hsieh, and Rimmer, 2004). These are issues that need to be addressed when building interventions or exercise therapies for people with DS to improve enjoyment and involvement.

Both acute and chronic exercise has been shown to increase a person’s self-efficacy (McAuley and Blissmer, 2000). Resistance training has been found to increase self-efficacy in women surviving breast cancer (Cheema, Gaul, Lane, and Singh, 2008), postpartum women (LeCheminant *et al.*, 2014), and typical children of both sexes (Lubans, Aguiar, and Callister, 2010). Self-efficacy improved following 8 weeks of ACT and VC in older adults with DS (Ringenbach, Arnold, Tucker & Holzapfel, 2018) and improved following 8 weeks of ACT in adolescents with DS (Ringenbach, Holzapfel, & Wallace, 2016). Determining how different exercises affect self-efficacy could help determine the long-term adherence to the interventions in adults with DS.

Exercise perception, or a person’s belief/attitude about exercise, is another area that should be explored in creating a lasting intervention. Exercise perception questionnaires explore how a person believes exercise will affect them: improve their health, help them lose weight, make them look better, etc. These beliefs about exercise both encouraged and discouraged obese women from engaging in different types of exercise (Guess, 2012). Positive beliefs that aerobic exercise would help with weight loss encouraged engagement, but a belief that resistance exercise was “manly” discouraged engagement in resistance training. Another study investigating physical activity engagement among people with type-I diabetes found similar positive beliefs in exercise lead to more engagement of exercise interventions (Lascar, *et al*., 2014). Community and group exercise interventions have been shown to increase positive attitudes towards exercise in people with intellectual disabilities (Heller, McCubbin, Drum, and Peterson, 2011). The Theory of Planned Control (Ajzen, 1991) is used to explain why people undertake a voluntary action, in this theory it is the attitude towards the voluntary action (i.e., exercise); therefore, ensuring that an exercise intervention increases the positive beliefs of the intervention is paramount.

Resistance training has been seen to improve enjoyment and social inclusion in other populations with disabilities (Allen, Dodd, Taylor, McBurney, and Larkin, 2004). In a study of men with Type-II diabetes, feelings of greater enjoyment with interventions including resistance training were associated with continuation of intervention after three and six months as compared to aerobic training alone. Participants in resistance training alone had reported feelings of enjoyment after nine months (Tulloch *et al.* 2013). To our knowledge, there are no studies investigating the enjoyment of resistance exercise or ACT for people with DS. Therefore, investigating the effect of resistance training and ACT on the measures of self-efficacy, exercise perception, and enjoyment is important to start understanding how to encourage prolonged exercise involvement and lifestyle changes for people with DS.

Methods

This was a randomized 3x3 cross-over experimental design. Participants reported to the Lincoln Family Downtown YMCA for a total of 4 visits with researchers. All protocols for this study were approved by the Human subject Institutional Review Board of Arizona State University.

Inclusion and Exclusion Criteria

Qualifying participants for this study needed to be diagnosed with Down syndrome (*e.g.* trisomy 21), be between 18 and 65 years of age, and be accompanied by a parent/guardian. if participants could not fit on ACT bike or RT equipment and participants with upper or lower body limitations and any medical or musculoskeletal contraindications to exercise (determined by the PARQ+) would have been excluded from the study. No recruited participants were excluded from study.

Protocols

The first visit to the YMCA was for consenting and baseline assessments, 1-repetition max (1-RM) measurements on the leg press, chest press, latissimus dorsi pulldown, seated row, shoulder press, and hamstring curl, and voluntary (e.g. self-selected) cadence measurements. Each participant and/or their guardian (if appropriate) provided informed consent or assent to participate in the research. Following the first visit, the participant was randomized into a sequence through block randomization. Sequence A completed Resistance Training (RT), Assisted Cycling Therapy (ACT), and finished with No Training (NT). Sequence B completed ACT, NT, and finished with RT. Sequence C participated in NT, RT, and finished with ACT.

For the final three visits, participants reported to the YMCA and completed the intervention protocols that were assigned to them through the randomization process for that day. The Physical Activity Self-Efficacy (PASE) questionnaire was administered prior to the visits assigned intervention. The participant then completed the assigned intervention and then sat for 10-minutes. After the 10-minute rest period the post-intervention PASE and the Physical Activity Enjoyability Scale (Enjoyability Scale) questionnaire were given. PASE and the Enjoyability Scale were administered by research assistants. The same research assistant was responsible for administering each of the questionnaires to limit inter-rater variability. However, if research assistant schedules did not permit attendance to a research visit, another research assistant administered the test. All research assistants were trained for several weeks on how to administer both questionnaires.

Baseline Protocols

During the initial visit, participants' sex, mental age, chronological age, ethnicity, physical activity levels, and body mass index (BMI) was collected. Sex, ethnicity, BMI, and physical activity levels have all shown to be correlated to cognitive function (Kimura, 1996; Schwartz *et al*., 2004; Cournot *et al*., 2006). Participants' sex, chronological age, ethnicity, were collected from parent/guardian forms (Appendix D). Along with the parent/guardian forms, the participant or guardian completed the PARQ+ (Warburton, Jamnik, Bredin, & Gledhill, 2011) to confirm participant did not have any contraindications for activity within this study.

Mental age was collected through the Peabody Picture Vocabulary Test (PPVT) (Stockman, 2000). The PPVT has been used as a determinant of mental age in other studies involving DS (Chen *et al*., 2015; Holzapfel *et al*. 2015; Ringenbach *et al*. 2016). Participants' level of physical activity was assessed through the Godin-Shepard Leisure Time Physical Activity questionnaire (Shephard, 1997) (Appendix E). Participants' BMI was assessed through the equation: weight (kg)*(height (m)$^{-2}$). This data was used as possible confounders during the statistical analysis.

1-RM was assessed using weight-stack machines for the leg press, chest press, seated row, latissimus pulldown, shoulder press, and hamstring curl. 1-RM testing procedures followed the American College of Sports Medicine guidelines (American College of Sports Medicine, 2016). The 1-RM for each of the exercises was then used to develop the RT intervention plan for each participant.

Voluntary Cycling Pace occurred on the Theracycle™ recumbent bicycle. Participants pedaled at a voluntary (e.g., self-selected) pace for 15 minutes. The voluntary rotations per minute were recorded every minute. The average of these recordings was used to determine the participants' voluntary pace and the ACT intervention pace.

Resistance Training Protocols

Participants reported to the YMCA and were fitted with a Polar FT-7™ heart rate monitor. They were asked the PASE questionnare. Participants were then led through a 5-minute dynamic warm-up consisting of: high knees, hip circles, butt kickers, arm swings, and arm circles. Following the warm-up, participants completed a 30-minute resistance session. Participants completed 2 sets of 8-12 repetitions of approximately 75% of participant's 1RM on stack-weight machines for: leg press, chest press, latissimus dorsi pulldown, seated row, shoulder press, and prone hamstring curl. If participants were unable to complete 8 repetitions at 75% of 1-RM, weight was lowered by approximately 5% for the next set. Process continued until a minimum of 16 repetitions were completed for each exercise. Participant's actual lifted weight and number of repetitions and sets were recorded. A 60 to 120-second rest period was given between each set and exercise. Heart Rate and Rating of Perceived Exertion (RPE) was recorded at the end of the warm-up period and after the conclusion of the final repetition of each exercise. After the completion of the resistance exercise session, participants were given a 10-minute rest before the PASE was re-assessed and the Enjoyability scale questionnaire was administered.

ACT Protocols

Participants reported to the YMCA at their designated time and were fitted with a Polar FT-7™ heart rate monitor. They were asked the PASE questionnaire prior to starting a 5-minute warm-up consisting of voluntary cycling on the Theracycle™ recumbent bike. Following the warm-up, the assisted cycling began, the motor was set at a 35% greater cadence than the voluntary rate recorded at baseline or to 95 revolutions per minute (rpm) as that is the max of Theracycle™. ACT lasted 30-minutes. Heart rate and RPE was recorded at the end of the warm-up period and every five minutes thereafter. After the completion of the ACT session, participants were given a 10-minute rest period before PASE was re-administered and the Enjoyability Scale questionnaire was asked.

Theracycle™

The Theracycle™ is a recumbent bicycle with a motor at the front. The motor can turn the pedals automatically at rates between 5-95 rotations per minute (rpm). The motor can also be left off for voluntary cycling. The bicycle has handles in front of and next to the seat in a similar fashion to other recumbent bicycles. The bike is equipped with an emergency stop magnet on the main block of the bicycle. The main block also has a computerized read out that shows the current rpms of the bike and the controls to adjust the rpms. Pedals on the bike allow the secure attachment of participant's feet to restrict the feet from slipping out of the pedal and causing injury.

No Training Protocols

Participants reported to the YMCA and were fitted with a Polar FT-7™ heart rate monitor. They then were asked the PASE questionnaire. Participants then spent 35-minutes playing either Candy Land or Shots and Ladders with a research assistant. Heart rate and RPE was recorded every 5-minutes after the beginning of the NT session. After the 35 minutes, participants had a 10-minute break before having PASE re-administered and the Enjoyability Scale questionnaire asked.

Timeline

Participants were required to wait a minimum of 48 hours between all visits to the YMCA. The participants averaged 150-hours [48 to 336-hours] between sessions. This was in an attempt to limit any learning effect of repeated exposure to the questionnaires. Participants were asked to refrain from physical activity outside of the protocols for the duration of the study. All sessions were required to be completed within two months of the baseline session.

Measures

Physical Activity Enjoyment Scale (Enjoyment Scale): The Enjoyment Scale consisted of 18 7-point Likert scale questions (Appendix B) developed by Kendzierski, D., & DeCarlo, K. J. in 1991 that assesses the enjoyment of different physical activities by asking questions related to feelings of enjoyment. The scale has been validated for use within children (Moore *et al*., 2009). This test was scored with 50% of the questions being counterbalanced. A score of “1” indicated least agreement with the question and a score of “7” indicated the most agreement with the statement. Counterbalanced questions were transformed (e.g., 1=7, 2=6, …, 6=2, 7=1) for final scoring. To increase understanding, questions were asked by researchers. This allowed those participants that could not read to participate and allow researchers to best describe words that were hard for participants to understand.

Physical Activity and Self-Efficacy (PASE)**:** The PASE is a two-part questionnaire (Appendix C) (Heller, 2001). Part 1 is six questions concerning a person’s belief in their ability to complete physical activity. Participants answered with a “yes”, “no”, or “maybe” scored as 3, 1, 2, respectively with a max score of 18. Part 2 is nine questions concerning a person's beliefs about exercise. Again, participants answered with a "yes", "no", or "maybe" and was scored as 3, 1, 2, respectively, with a max score of 27.

Statistical Analysis

Linear mixed models (LMM) were used to test the effects of sequence (ABC, BCA, vs. CAB), subjects within the sequence, intervention (RT, ACT, NT), and visit (Day 1, Day 2, Day 3).

General linear models (GLM) were used to test change in mean differences for PASE between pre and post measures and post measures of the Enjoyability Scale. A two-tailed α of 0.05 was used to determine statistical significance across intervention groups.

All delta scores (differences between pre and post scores) for measures were tested for normality prior to the primary analysis. Those measures that were not normally distributed were transformed into normally distributed data. This was accomplished through the percentile rank transformation.

A secondary analysis was conducted to examine the differences between participants that completed the study individually and in a group. This was analyzed using the delta scores of each intervention. A Mann-Whitney U test used to determine if there was a difference between the two testing groups (Individually tested, Grouped tested). Significance was set at $\alpha=0.05$. All statistical procedures were performed by the IBM Statistical Package for Social Sciences (SPSS) version 27.0 (IBM Corp, Armonk, NY).

Results

Participants

There were 16 participants that were recruited and began this study. One participant completed the study and was removed from analysis because he failed to complete any psychological tests. Another participant was removed because participation in the study ended by the Novel Coronavirus-19 after two sessions. Another five participants were recruited; however, these participants were unable to start because of the Novel Coronavirus-19 procedures. The consort diagram can be seen in Figure 2. The breakdown of participant baseline characteristics is found in Table 1.

Participants completed a minimum of 16 repetitions on each of the resistance exercises with a minimum of 65% of their 1-RM. ACT was completed with an average cadence 129% of voluntary cycling cadence. The Theracycle was not able to achieve 130% of voluntary cycling cadence for all participants. More concise information on the exercise can be found in Table 2.

Physical Activity Enjoyment Scale:

The post exercise enjoyment scale scores were found to be non-normally distributed and were transformed prior to analysis. There were no significant differences in the sequence, intervention, or visit for the Enjoyability scale (Table 8).

Table 8 Enjoyability Score ANOVA Table

Tests of Between-Subject Effects

Dependent Variable: Enjoyability Scale

Source	Type III Sum of Squares	Df	Mean Square	F	Sig.
Corrected Model	7932.900[a]	15	528.860	2.485	.029
Intercept	368736.897	1	368736.897	1732.866	<.001
Sequence	534.474	2	267.237	.360	.708
Intervention	351.023	2	175.511	.825	.453
Visit	457.332	2	228.666	1.075	.360
Error	4255.803	20	212.790		
Total	395649.766	36			
Corrected Total	12188.703	35			

a. R Squared=.651(Adjusted R Squared = .389)

Physical Activity Self-Efficacy:

The PASE was split into delta scores (post-pre) for exercise self-efficacy and exercise perception. Both self-efficacy and exercise perception delta scores were found to be non-normal and were adjusted prior to analysis. There were no significant differences in sequence, intervention, or visit for either the self-efficacy (Table 9) or exercise perception (Table 10) questionnaires.

Table 9. Exercise Self-Efficacy Score ANOVA Table

Tests of Between-Subject Effects

Dependent Variable: Self-Efficacy Score

Source	Type III Sum of Squares	Df	Mean Square	F	Sig.
Corrected Model	93.949[a]	17	5.526	1.645	.132
Intercept	17.598	1	17.598	5.239	.032
Sequence	2.274	2	1.137	.186	.833
Intervention	8.484	2	4.242	1.263	.302
Visit	15.709	2	7.855	2.338	.119
Error	77.256	23	3.359		
Total	187.167	41			
Corrected Total	171.205	40			

a. R Squared=.549 (Adjusted R Squared = .215)

Table 10 Exercise Perception ANOVA Table

Tests of Between-Subject Effects

Dependent Variable: Exercise Perception Scores

Source	Type III Sum of Squares	Df	Mean Square	F	Sig.
Corrected Model	143.592[a]	17	8.447	2.979	.008
Intercept	1.827	1	1.827	.644	.430
Sequence	2.072	2	1.036	.088	.916
Intervention	5.017	2	2.508	.885	.426
Visit	5.230	2	2.615	.922	.412
Error	65.215	23	2.835		
Total	209.326	41	2.835		
Corrected Total	208.806	40			

a. R Squared=.688 (Adjusted R Squared = .457)

<u>Individual vs Grouped testing</u>

There were only three participants that were tested individually for this study. The low number of participants in the individually tested group likely played a factor in the non-significant. However, there were some trends that should be acknowledged.

<u>Enjoyability Scale</u>

While not significant (p>.05), participants that were completed the study individually reported slightly higher levels of enjoyment following all interventions as compared to those who completed the testing in a group (Figure 8).

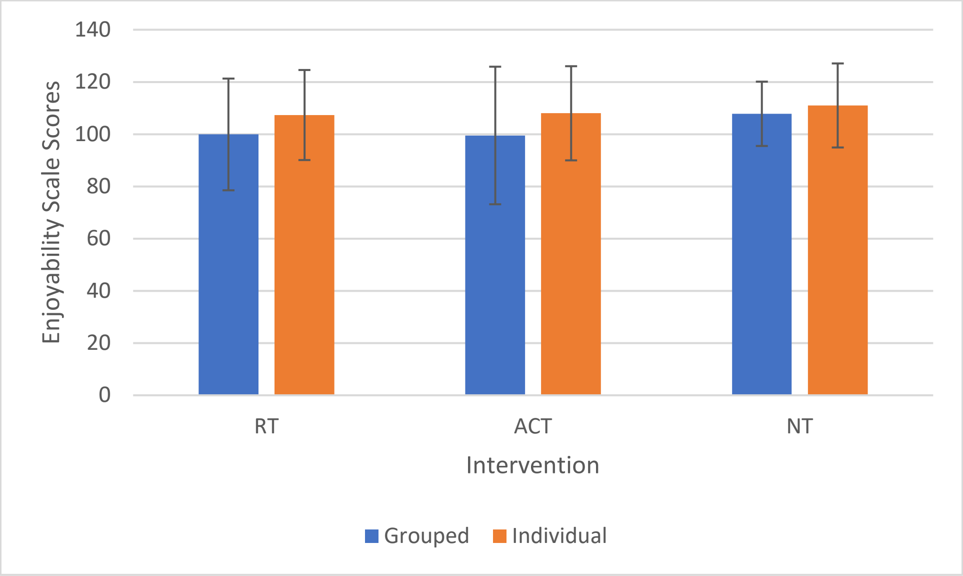

Figure 8 Enjoyability Scale Scores for those tested Individually vs Grouped

<u>Self-Efficacy</u>

For the RT intervention, individual participants had an opposite effect compared to grouped participants. For the ACT, individual participants had larger improvements in self-efficacy. For the NT, grouped participants had a larger improvement in self-efficacy (Figure 9).

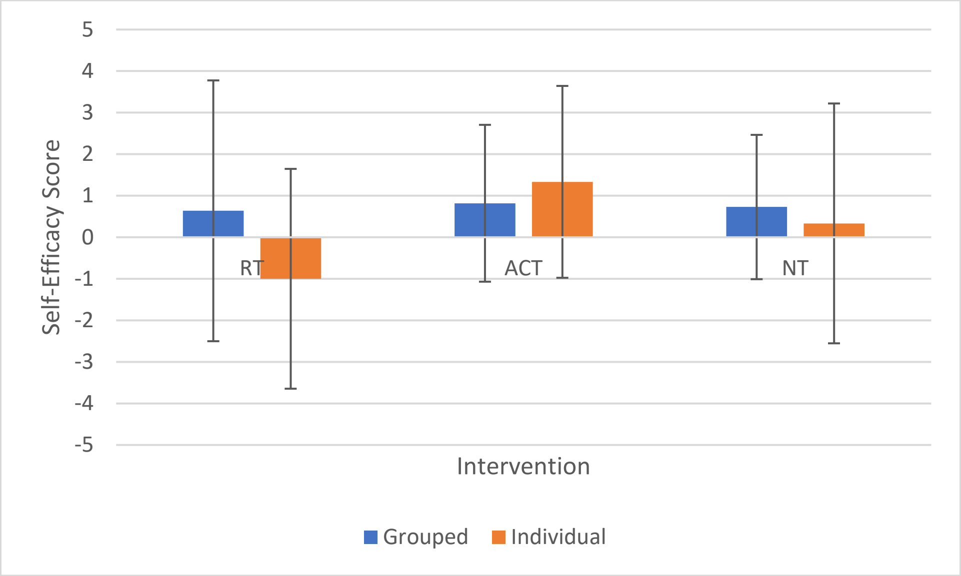

Figure 9 Delta Self-Efficacy Scores for those tested Individually vs Grouped

Exercise Perception

The Individual participants had negative effects after each intervention compared to each intervention improving in the grouped participants (Figure 10)

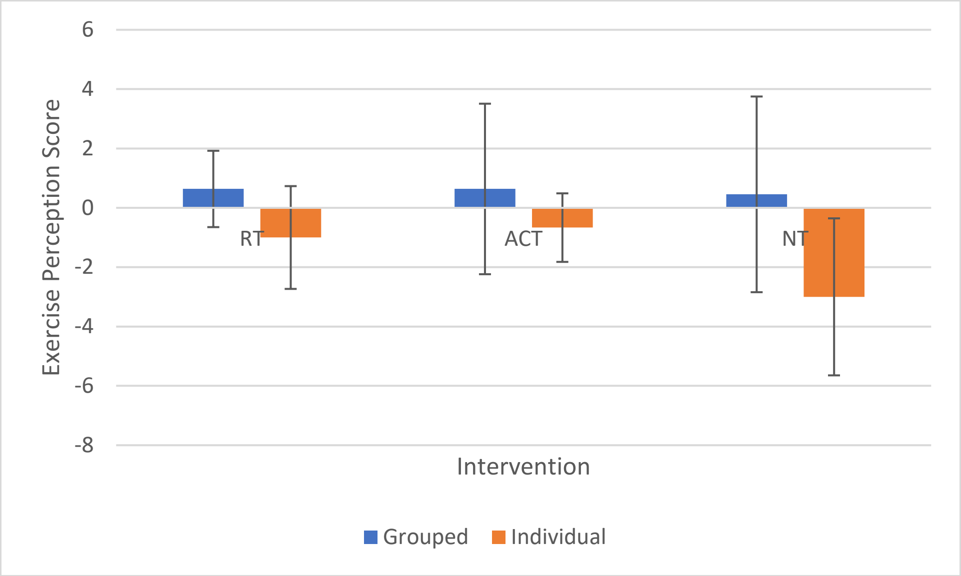

Figure 10 Delta Exercise Perception Scores for those tested Individually vs Grouped

Discussion

This was the first study, to our knowledge, that investigated the impact of resistance training on the enjoyment, self-efficacy, and exercise perception of adults with DS. We believe that determining the impact of resistance, and Assisted Cycling Therapy will help develop a program that can encourage a lifestyle change in adults with DS from a sedentary lifestyle to a lifestyle that includes more physical activity.

The Enjoyment Scale results showed that all three interventions were considered enjoyable, but not one more so than another. However, this result is skewed as we believe that the questionnaire was not understood by all the participants. Even though the Enjoyment Scale has been validated for children as young as eight (Moore *et al*., 2009), we found that the 7-point likert scale was hard for participants to understand and respond to. While the average mental age of the population with Down syndrome 8-years of age (Gibson, 1978), our sample had a mental age 6 ±4 years of age (Table 1), and only one participant had a mental age above 8-years. Because of the participants not understanding a Likert scale that big, many of the participants used a more of a three-point scale of the most agreeable answer (1 or 7), the least agreeable answer (1 or 7), or in the middle (4). Only a few participants answered outside of 1, 7, or 4 to the questions.

The results of the PASE were not consistent with our hypothesis or previous studies with ACT in people with DS and self-efficacy (Ringenbach et al., 2016; Ringenbach et al., 2018). In the current study, the no significant differences in exercise perception scores are possibly due to a ceiling effect. Because the PASE was based on a three- point scale (Yes, No, Maybe/I do not know), participants were typically giving what they thought was the best answer for the question. The highest possible score for self-efficacy was an 18 and the highest possible score for the exercise perception was 27. The participants had a pre-intervention average of 13 ± 4 for self-efficacy and an average of 24 ± 3 for exercise perception; this left little room for improvement following exercise.

Another factor leading to these high pre-intervention scores was that many of the participants within this study have been part of other studies within our lab. As part of our other research projects, these participants have been exposed to the PASE. These participant's possibly have already improved their exercise self-efficacy and perception to their highest levels or the multiple exposures to the questionnaire have allowed these participants to guess or know which answers are more desirable.

Conclusions

While the results of this study did not support the hypotheses, we did learn from this study. First, participants that have been part of previous exercise studies through our laboratory have a high level of self-efficacy and exercise perception. Secondly, participants found ACT and RT enjoyable. Future studies investigating the acute effect of exercise on self-efficacy and exercise perception in adults with DS should attempt to find participants that have not previously been evaluated with the PASE questionnaire. Future studies investigating enjoyment of exercise for adults with DS should find another questionnaire that has been validated for participants lower than the 8 years of age of the Enjoyment Scale.

CHAPTER 6

SUMMARY

This study found no significant results for the cognitive measure or the psychological measures. Therefore, we must reject all of our hypotheses. The results of this study did not follow the typical results of exercise and executive function changes, it did shed some light on issues that should be addressed in future studies with exercise in people with DS. It is also important to understand that participants that participated in this study found RT, ACT, and NT enjoyable and that participants that have been part of previous exercise studies through our laboratory have a high level of self-efficacy and exercise perception.

LIMITATIONS

This study had a few limitations that can be addressed in future research. First, the participants had attention issues with completing many of the cognitive tasks. The tasks recorded on the computers required participants to wait for varying amounts of time between responses. During these periods, researchers were consistently redirecting participants back to the screens. Even during the simple reaction time, which was done by manually turning on a light and then recording each response time, participants were needing to be redirected back to the task.

Second, adding to the attention issue, the cognitive and psychological testing took up to an hour to an hour and half for each pre and post session. This alone taxed the attention span of the participants. The participants were in the research area for two to three hours. Boredom within these participants was obvious. Some participants began to just give up or were not following directions to the tests. One participant even began to pretend to fall asleep during the tests to show his disdain for the time he had been in the testing area.

Again, adding to the issue of completing the tasks, we completed many of the testing sessions in the afternoon, starting at 4:00 pm. Energy to complete testing and intervention was another issue that we noticed with some of the participants. Some of the participants had jobs they completed during the day and then finished the interventions. Some participants were more concerned with dinner and nightly plans than with the completion of the testing.

We attempted to have multiple participants complete the interventions at the same time to make it convenient for the participants who were used to coming at this time for a group class. Having multiple participants in the research area at the same time added to the attention span issues. Because the participants knew each other from different programs around the Phoenix area, they were just as interested in talking and being with their friends as they were in completing the tests.

The Enjoyability Scale was too complicated for participants with DS. Many of the participants only understood half of the questions, leaving researchers to re-ask questions with different explanations of what the question was asking. Then when the participants did answer they typically answered a one or seven depending on what they thought was better.

CHAPTER 7

FUTURE RESEARCH

There are a few suggestions for future researchers to consider when investigating the impact of resistance training and ACT on executive function in adults with Down syndrome. First, when investigating acute effects on people with DS, the amount of testing should be considered. Limiting the number of tests to keep the pre- and post- tests to under 30-minutes should be optimal. When testing ventured towards the one-hour mark, participants began to get overloaded and looked to move on from the testing. Maximizing the basal attention span of the participants could help tease out a better understanding of the effects of exercise on the executive function.

Second, when investigating acute resistance training, or other complex exercises, have a month of familiarization with the exercises followed by a washout period. This month of training can help move the exercises from a novel movement needing explicit processes to implicit processes. As Tomporowski, McCullick, Pendleton and Pesce (2015) pointed to having some of the prefrontal cortex used in the coordination of movements can have beneficial effects on executive function. However, in this study, there seemed to be more of a novel learning activation as compared to just coordination of the movements. If possible, having participants that are already training with the machines/exercises would be the most beneficial as no learning is needed.

Finally, when testing participants with short basal attention span, whether it be people with DS, attention deficit/hyperactivity disorder, or otherwise, keeping the number of distractions to a minimum is encouraged. Limiting the people within the research area to the researcher administering the tests and the participant. Even when we were able to limit to a single participant, parent/guardians within the testing area proved to be a distraction for the participant as much as having multiple participants within the research area.

Our future research we will look to make these adjustments and continue to investigate if resistance training can be an effective tool for improving the cognitive function of adults with DS. First, would be going back to advance this study from a pilot study to a full study with more participants and the adjustments suggested above. Also looking at the chronic affect of resistance training on adults with DS.

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APPENDIX A

RECRUITMENT FLYER

Adults with Down syndrome needed for new therapy research

We are in need of adults diagnosed with Down syndrome to participate in a research study testing the effects of resistance training and Assisted Cycling Therapy.

Improving Cognitive Function

Participants will complete four sessions. First session will be to get baseline information. The next three session will be a 30-minute resistance session, 30-minute Assisted Cycling Therapy session, and a 30-minute board game session. Cognitive function will be assessed before and after each therapy session to determine if improvements occured

Qualification

- Be between 18-65
- Be accompanied by parent/guardian
- Not have upper limb mobility issues
- Not have lower limb mobility issues
- Not be diagnosed with ADHD, depression, or Alzheimer's Disease
- Be able to visit the Lincoln Family Downtown YMCA for four visits

More information

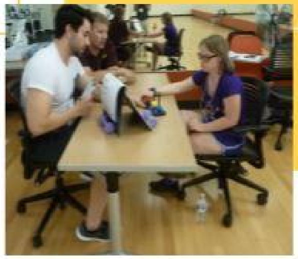
Contact: Nate Arnold MEd.

Phone: (513)907-4898

Email: asu.sensorimotor.lab@gmail.com

Facebook: @asusensorimotorlab

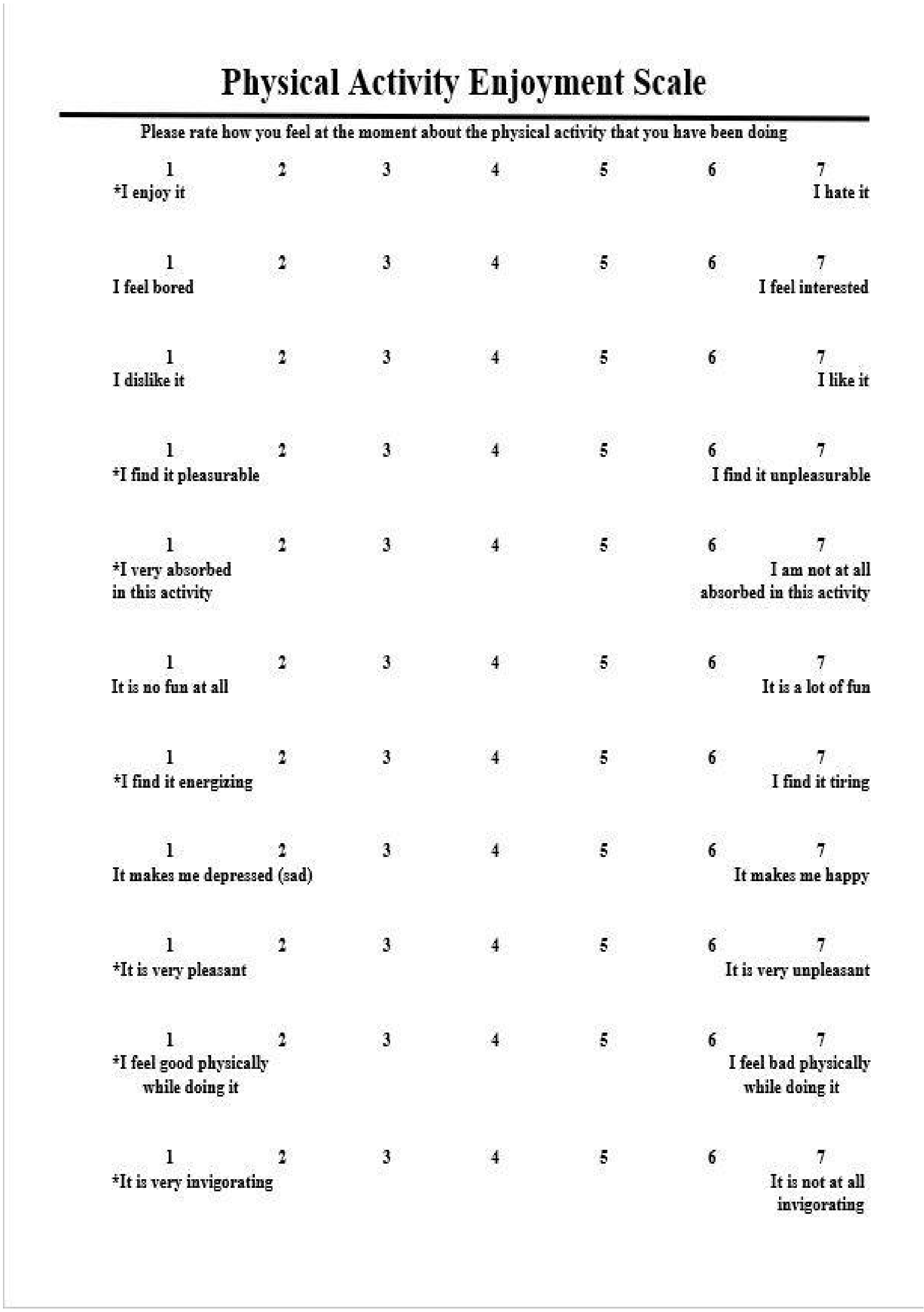
Website: https://asu-sdrl.weebly.com



SENSORIMOTOR DEVELOPMENT RESEARCH LAB

APPENDIX B

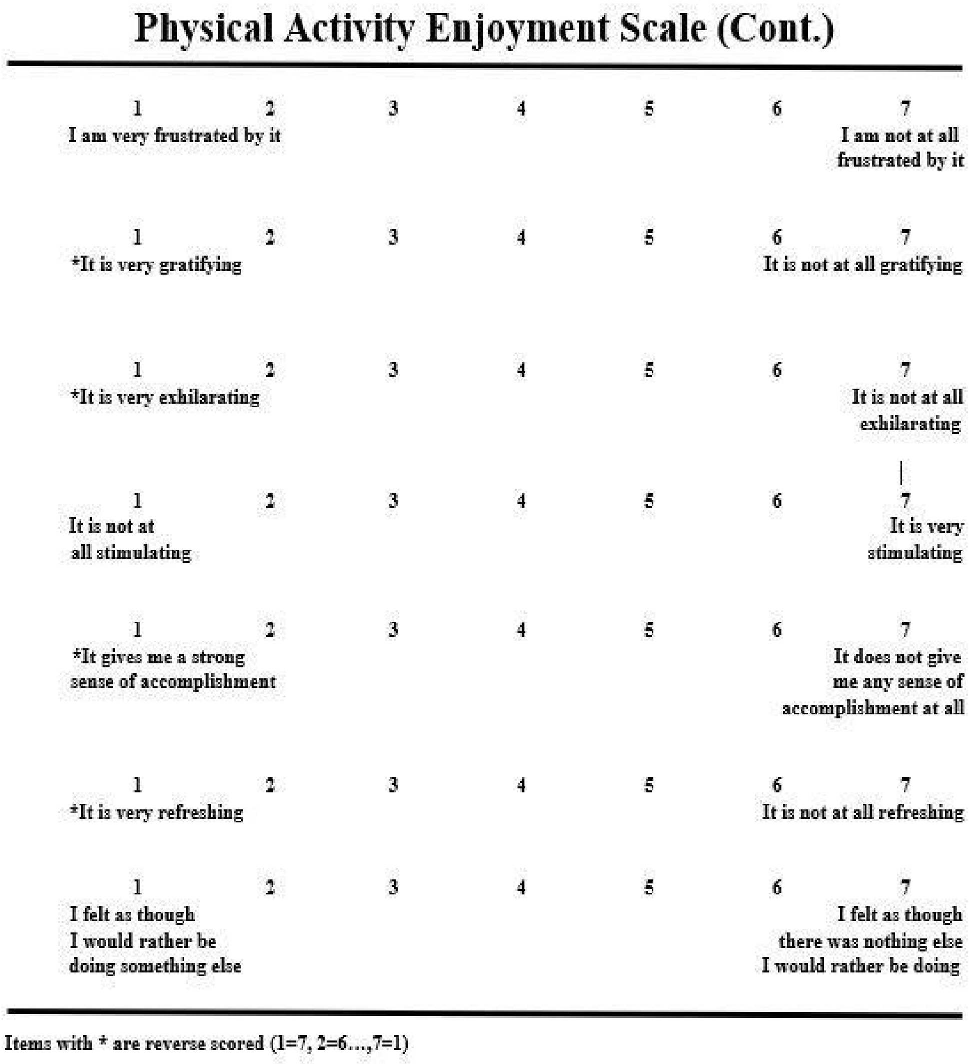
PHYSICAL ACTIVITY ENJOYMENT SCALE



Physical Activity Enjoyment Scale

Please rate how you feel at the moment about the physical activity that you have been doing

1	2	3	4	5	6	7
*I enjoy it						I hate it
I feel bored						I feel interested
I dislike it						I like it
*I find it pleasurable						I find it unpleasurable
*I very absorbed in this activity						I am not at all absorbed in this activity
It is no fun at all						It is a lot of fun
*I find it energizing						I find it tiring
It makes me depressed (sad)						It makes me happy
*It is very pleasant						It is very unpleasant
*I feel good physically while doing it						I feel bad physically while doing it
*It is very invigorating						It is not at all invigorating



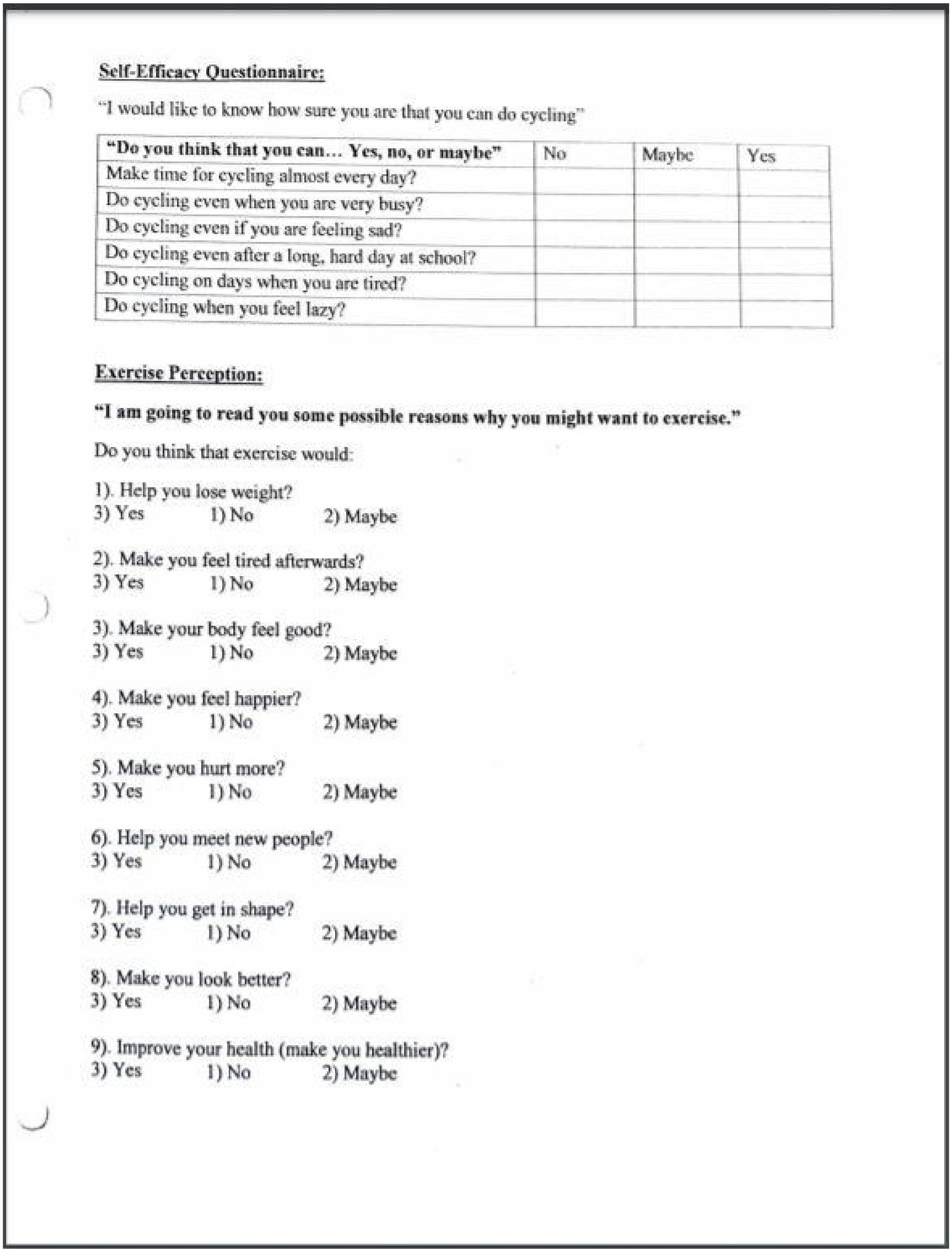
Physical Activity Enjoyment Scale (Cont.)

1	2	3	4	5	6	7
I am very frustrated by it						I am not at all frustrated by it
*It is very gratifying						It is not at all gratifying
*It is very exhilarating						It is not at all exhilarating
It is not at all stimulating						It is very stimulating
*It gives me a strong sense of accomplishment						It does not give me any sense of accomplishment at all
*It is very refreshing						It is not at all refreshing
I felt as though I would rather be doing something else						I felt as though there was nothing else I would rather be doing

Items with * are reverse scored (1=7, 2=6…,7=1)

APPENDIX C

PHYSICAL ACTIVITY SELF-EFFICACY QUESTIONNAIRE



Self-Efficacy Questionnaire:

"I would like to know how sure you are that you can do cycling"

"Do you think that you can… Yes, no, or maybe"	No	Maybe	Yes
Make time for cycling almost every day?			
Do cycling even when you are very busy?			
Do cycling even if you are feeling sad?			
Do cycling even after a long, hard day at school?			
Do cycling on days when you are tired?			
Do cycling when you feel lazy?			

Exercise Perception:

"I am going to read you some possible reasons why you might want to exercise."

Do you think that exercise would:

1). Help you lose weight?
3) Yes 1) No 2) Maybe

2). Make you feel tired afterwards?
3) Yes 1) No 2) Maybe

3). Make your body feel good?
3) Yes 1) No 2) Maybe

4). Make you feel happier?
3) Yes 1) No 2) Maybe

5). Make you hurt more?
3) Yes 1) No 2) Maybe

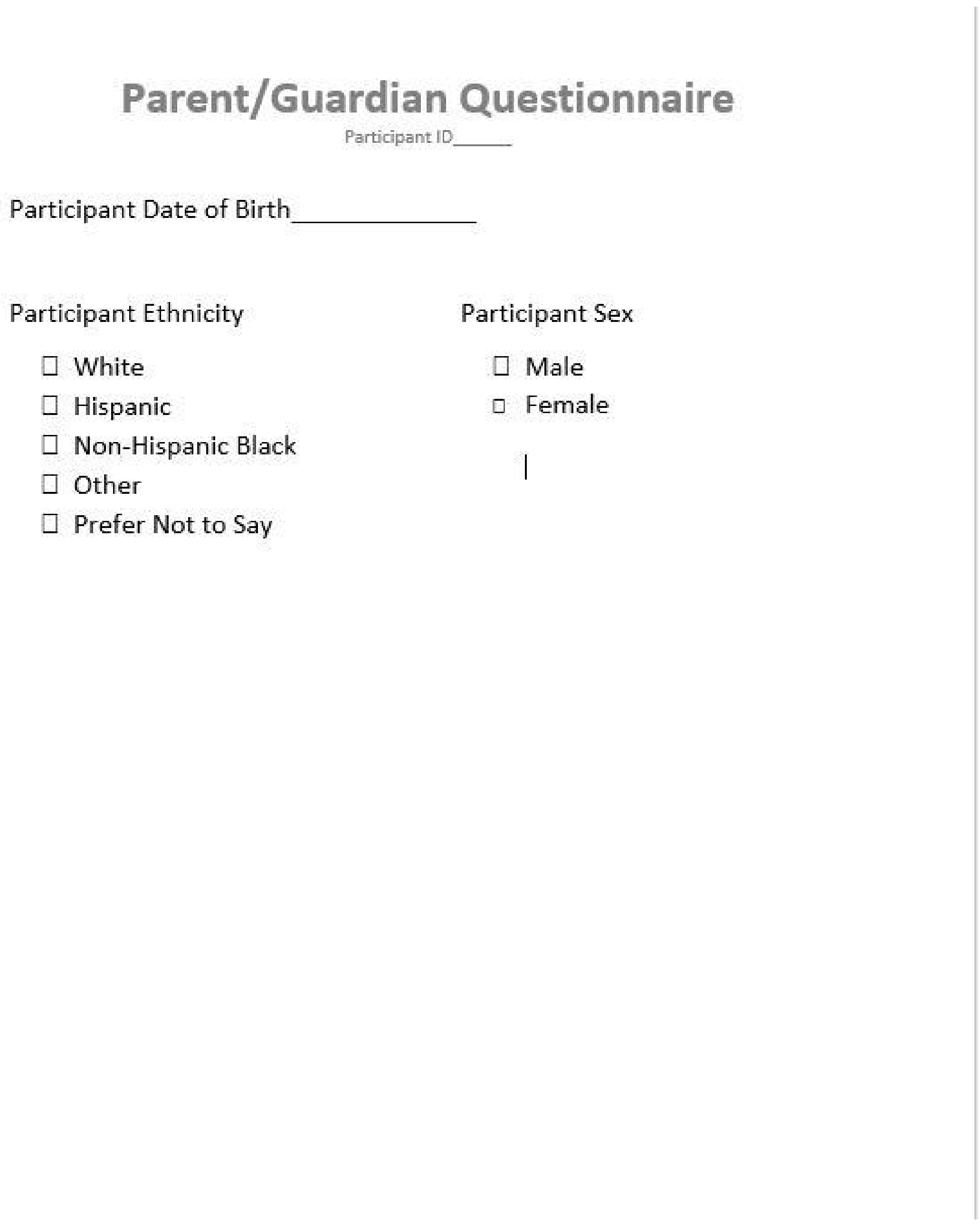
6). Help you meet new people?
3) Yes 1) No 2) Maybe

7). Help you get in shape?
3) Yes 1) No 2) Maybe

8). Make you look better?
3) Yes 1) No 2) Maybe

9). Improve your health (make you healthier)?
3) Yes 1) No 2) Maybe

APPENDIX D
PARENT/GUARDIAN QUESTIONNAIRE



Parent/Guardian Questionnaire

Participant ID______

Participant Date of Birth______________

Participant Ethnicity

- ☐ White
- ☐ Hispanic
- ☐ Non-Hispanic Black
- ☐ Other
- ☐ Prefer Not to Say

Participant Sex

- ☐ Male
- ☐ Female

APPENDIX E111

GODIN LIESURE-TIME EXERCISE QUESTIONNAIRE

Godin Leisure-Time Exercise Questionnaire

INSTRUCTIONS

In this excerpt from the Godin Leisure-Time Exercise Questionnaire, the individual is asked to complete a self-explanatory, brief four-item query of usual leisure-time exercise habits.

CALCULATIONS

For the first question, weekly frequencies of strenuous, moderate, and light activities are multiplied by nine, five, and three, respectively. Total weekly leisure activity is calculated in arbitrary units by summing the products of the separate components, as shown in the following formula:

Weekly leisure activity score = (9 × Strenuous) + (5 × Moderate) + (3 × Light)

The second question is used to calculate the frequency of weekly leisure-time activities pursued "long enough to work up a sweat" (see questionnaire).

EXAMPLE

Strenuous = 3 times/wk

Moderate = 6 times/wk

Light = 14 times/wk

Total leisure activity score = (9 × 3) + (5 × 6) + (3 × 14) = 27 + 30 + 42 = 99

Godin Leisure-Time Exercise Questionnaire

1. During a typical **7-Day period** (a week), how many times on the average do you do the following kinds of exercise for **more than 15 minutes** during your free time (write on each line the appropriate number).

Times Per Week

a) STRENUOUS EXERCISE
(HEART BEATS RAPIDLY) __________
(e.g., running, jogging, hockey, football, soccer,
squash, basketball, cross country skiing, judo,
roller skating, vigorous swimming,
vigorous long distance bicycling)

b) MODERATE EXERCISE
(NOT EXHAUSTING) __________
(e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)

c) MILD EXERCISE
(MINIMAL EFFORT) __________
(e.g., yoga, archery, fishing from river bank, bowling, horseshoes, golf, snow-mobiling, easy walking)

2. During a typical **7-Day period** (a week), in your leisure time, how often do you engage in any regular activity **long enough to work up a sweat** (heart beats rapidly)?

OFTEN	SOMETIMES	NEVER/RARELY
1. ☐	2. ☐	3. ☐

APPENDIX F

INSTITUTIONAL REVIEW BOARD APPROVAL

ASU Knowledge Enterprise Development

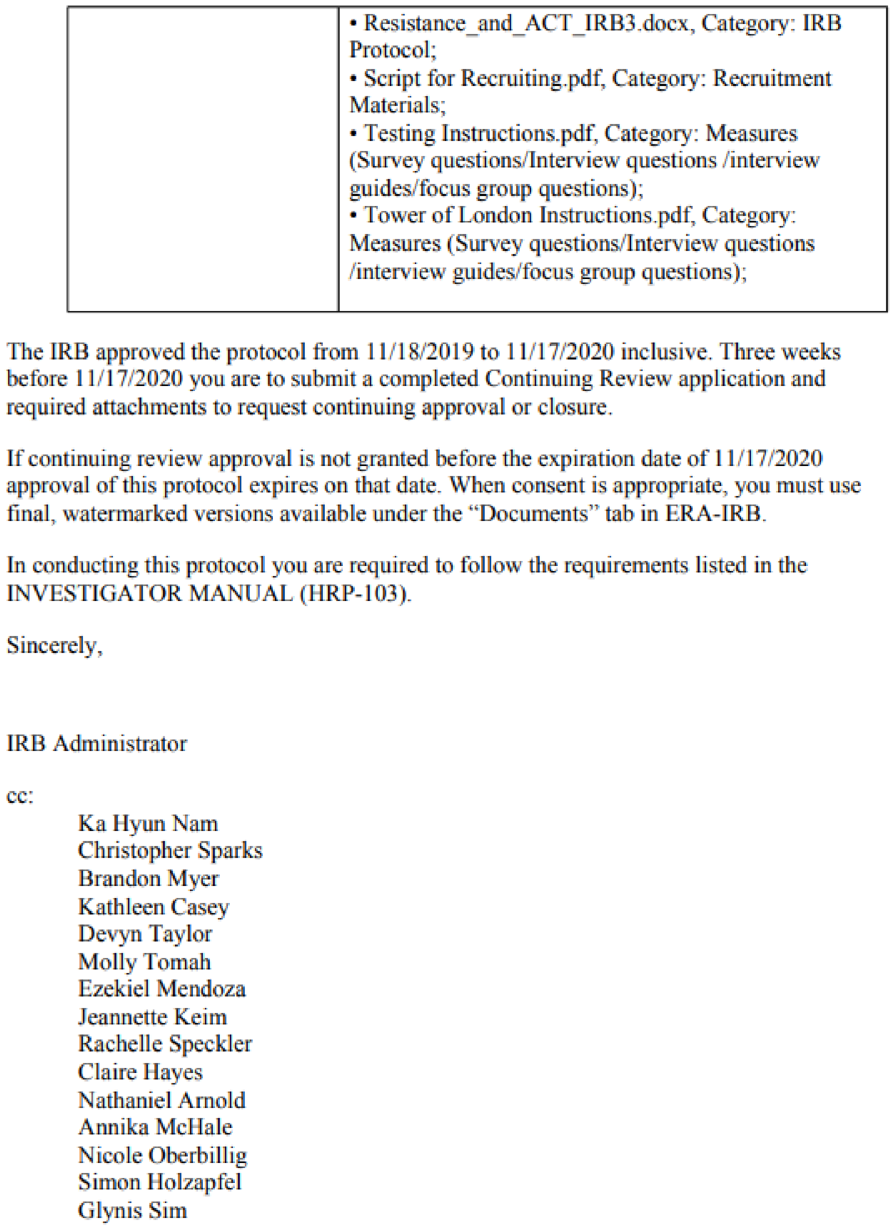
APPROVAL: EXPEDITED REVIEW

Shannon Ringenbach
Exercise Science and Health Promotion
480/861-9927
Shannon.Ringenbach@asu.edu

Dear Shannon Ringenbach:

On 11/18/2019 the ASU IRB reviewed the following protocol:

Type of Review:	Initial Study
Title:	The Acute Effects of Resistance Training and Assisted Cycling Therapy (ACT) on executive function and enjoyment of people with Down syndrome
Investigator:	Shannon Ringenbach
IRB ID:	STUDY00010752
Category of review:	
Funding:	None
Grant Title:	None
Grant ID:	None
Documents Reviewed:	• Physical Activity Enjoyment Scale.pdf, Category: Measures (Survey questions/Interview questions /interview guides/focus group questions); • Physical Activity Self-Efficacy Scale.pdf, Category: Measures (Survey questions/Interview questions /interview guides/focus group questions); • Goodin_Leisure-time.pdf, Category: Screening forms; • RT_ACT Flyer.JPG, Category: Recruitment Materials; • PAR-Q.pdf, Category: Screening forms; • Assent form ACT DD 2013.pdf, Category: Consent Form; • consent form RT & ACT.pdf, Category: Consent Form; • Recruitment Email.pdf, Category: Recruitment Materials;



	• Resistance_and_ACT_IRB3.docx, Category: IRB Protocol; • Script for Recruiting.pdf, Category: Recruitment Materials; • Testing Instructions.pdf, Category: Measures (Survey questions/Interview questions /interview guides/focus group questions); • Tower of London Instructions.pdf, Category: Measures (Survey questions/Interview questions /interview guides/focus group questions);

The IRB approved the protocol from 11/18/2019 to 11/17/2020 inclusive. Three weeks before 11/17/2020 you are to submit a completed Continuing Review application and required attachments to request continuing approval or closure.

If continuing review approval is not granted before the expiration date of 11/17/2020 approval of this protocol expires on that date. When consent is appropriate, you must use final, watermarked versions available under the “Documents” tab in ERA-IRB.

In conducting this protocol you are required to follow the requirements listed in the INVESTIGATOR MANUAL (HRP-103).

Sincerely,

IRB Administrator

cc:

Ka Hyun Nam
Christopher Sparks
Brandon Myer
Kathleen Casey
Devyn Taylor
Molly Tomah
Ezekiel Mendoza
Jeannette Keim
Rachelle Speckler
Claire Hayes
Nathaniel Arnold
Annika McHale
Nicole Oberbillig
Simon Holzapfel
Glynis Sim