THE ACUTE EFFECTS OF SINGLE VERSUS MULTIPLE SET RESISTANCE EXERCISE ON COGNITION AND AFFECT IN UNTRAINED OLDER ADULT WOMEN

by

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The Acute Effects of Single Versus Multiple Set Resistance Exercise on Cognition and Affect in Untrained Older Adult Women

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Abstract

PURPOSE

Current evidence suggests chronic resistance exercise training (RET) improves older adults’ executive function; however, the effects of a single session of resistance exercise (RE) and dose (i.e., frequency, intensity, volume) on executive performance remains unclear. Thus, we investigated the effect of RE, at three different volumes, on executive function in healthy older women.

METHODS

This was a within-subjects, crossover study design of 21 untrained, older women (65-75 years). At baseline, participants were familiarized with four RE machines (leg press, chest press, knee-extension and lat pull down) and performed a 10RM. Following a minimum of 7 days, participants randomly completed 3 RE conditions: 1, 3, or 5 sets of 10 repetitions (70%1RM; 120 sec rest between sets) for each exercise, and a control (CON) condition. We measured two executive processes: 1) inhibitory control using the Flanker task, and 2) cognitive flexibility using the Dimensional Change Card Sort (DCCS) task. We also measured the affective response to RE using the Feelings Scale. Using a linear mixed model, we determined the effect of different RE volumes (i.e., condition) and time (i.e., visit number), adjusting for baseline performance, on change in inhibitory control (i.e., after RE – before RE) and cognitive flexibility. We also examined the effect of both RE volume and time on change in affect (i.e., after RE – before RE) using a linear mixed model.
RESULTS
At baseline, participants were physically healthy and did not have cognitive impairment (Montreal Cognitive Assessment (MoCA) scores > 26/30). There were no significant differences found for acute changes in flanker performance by condition performed (i.e., 1, 3, 5, or CON) ($p=0.12$) and by time (i.e., visit number) ($p=0.84$). Similarly, there was no effect of condition on acute changes in DCCS performance ($p=0.66$) or time ($p=0.57$). Change in affect was not significantly different by both condition ($p=0.56$) and time ($p=0.09$).

CONCLUSION
Contrary to evidence showing RE can promote executive performance, our results suggest a single bout of RE did not improve executive function in healthy older women, irrespective of volume.
Lay Summary

We examined the impact of a single bout of muscle strengthening exercise on higher-level cognitive functions and mood in older adult women. Each subject participated in three bouts of muscle strengthening exercise, each of a different amount of exercise (i.e., volume), and a resting control. We measured cognition and mood before and after each bout. We found a single bout of muscle strengthening exercise did not improve cognitive functions or mood and did not depend on the amount of exercise completed.
Preface

This thesis is original, unpublished, independent work by the author, L. Marcotte. The study reported in Chapters 2-5 was covered by University of British Columbia’s Clinical Research Ethics Board (H18-03556).
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1. BACKGROUND

1.1 Introduction

Aging is associated with both physical and cognitive changes (1). Following age 50, muscle mass declines, with more rapid losses observed in muscle strength and power (2). Cognitive performance is also significantly impacted in old age, specifically the cognitive domains of memory, attention and executive functions (3). Cognitive decline is an increasingly prevalent epidemic among older adults, which presents a large burden to the individual and Canadian healthcare system, as the estimated cost is expected to accumulate to 2 trillion dollars by 2030 (4). Given the number of older adults in Canada is expected to reach over 19 million in the next four decades, the need for effective interventions to reduce both physical and cognitive decline is a priority in scientific inquiry (5).

Exercise is a behavioural strategy that benefits both physical and cognitive function in older adults (6). Broadly, there are two main forms of exercise: 1) Aerobic, of both acute aerobic exercise (AE) and chronic aerobic exercise training (AET), comprised of dynamic movements that primarily stress the cardiovascular system and increase energy expenditure; 2) Resistance, of both acute resistance exercise (RE) and chronic resistance exercise training (RET), which acts upon skeletal muscles to improve muscular strength, mass, power and endurance (7). Evidence suggests that older adults who engage in regular exercise of both AET and RET have improved cognitive function (8). However, a majority of the literature within the field of exercise neuroscience is limited to AET (6,9–13).

There is a growing body of research investigating the potential of a single bout of exercise to improve cognition (14). Some evidence demonstrates cognitive improvements in younger and older adults following AE, although fewer studies have investigated the role of RE.
(15–17). To date, the evidence for the beneficial effects of RE on cognition remains equivocal, with some studies reporting benefits (18–25) and others showing no effect (21,26–28). Few of these studies are conducted in older adults and many trials utilize similar RE prescriptions (14). Thus, there is a paucity of evidence regarding the effect of RE ‘dose’ (ie. frequency, intensity, duration, volume) on cognitive function. Additionally, RE has the potential to significantly improve positive affect, which may foster exercise adoption and long-term adherence among older populations (29,30). Thus, the purpose of this study was to examine the effect of RE volume on executive function, specifically response inhibition and cognitive flexibility, and affect.

1.2 Aging and Cognitive Function

Aging is associated with reduced physical capacity and a decline in cognitive function (1). With advancing age, there is a gradual loss of both muscle mass and strength, both of which contribute to a reduction in mobility (31). In addition to physical changes, aging is associated with a decline in cognitive abilities (32). Changes in both of these domains often co-exist and may share common biological pathways (9,32). Cognitive function is critical for functional independence, the ability to carry out activities of daily life appropriately and independently. Specifically, cognition is a crucial for older adults to remember and retrieve information, take medications appropriately and communicate with others (33). Broadly, cognitive abilities can be divided into two categories: fluid and crystalized (33). Crystalized cognition refers to general knowledge such as language, skills and historical information. In contrast, fluid abilities require processing, problem solving and decision making at the time of a task (33). Crystalized cognition steadily increases until reaching a plateau around age 80, while fluid cognition declines steadily
beginning at age 20, until reaching a steeper decline at age 80 (33). Fluid cognition can be divided into several domains, including attention, memory, executive function, language, and visuospatial abilities. Each of the domains are vulnerable to age-related decline, especially, attention, memory and executive function (33).

Executive function encompasses cognitive processes including problem solving, decision making, planning, sequencing responses, and multitasking (33). Executive function involves the prefrontal cortex as well as integration from other brain regions, and encompasses three core processes: inhibition, working memory and cognitive flexibility (34). Inhibition refers to the ability to control attention, behaviour and responses, to ignore irrelevant stimuli and focus on task-relevant information, as well as change ones automatic response when presented with new information (34). Working memory requires remembering information while simultaneously using it to accomplish a task (34). Examples of working memory include updating a plan or doing math in your head. Cognitive flexibility involves changing how one thinks about something in the presence of new information or stimuli (34). Cognitive flexibility requires adjusting demands or priorities, especially in unexpected circumstances (34). Each of these domains of executive function decline with advancing age (33). Maintaining executive functions with age is crucial for older adults to continue to live independently as well as preventing the incidence of falls (35). Additionally, executive function appears to play a role in other cognitive domains, therefore improving executive processes may benefit other domains (34).

Brain structure is also largely impacted by aging, with atrophy occurring early on in the hippocampus, the brain region associated with learning and memory (36). The integrity of white matter, which encompasses myelinated axons connecting areas of gray matter for communication among brain regions, is also implicated resulting in lesions (37). Additionally, a reduced
production, concentration and receptor density of neurotrophic growth factors are among the mechanisms contributing to cognitive decline (36). Currently, there are no pharmacological treatments to prevent cognitive decline in aging adults (38). However, exercise is a potential behavioural strategy to promote brain health across the lifespan and preserve cognitive function in older age (3).

1.3 Physical Activity and Cognitive Function

There is accumulating epidemiological evidence demonstrating that physical activity (PA), defined as bodily movement that increases energy expenditure, reduces the incidence of cognitive decline and may positively impact brain structure (3). Meta-analytic data have further supported the relationship between PA and brain health; Hamer and Chida (2009) showed that higher levels of PA at baseline reduced the risk for developing dementia by 28% and Alzheimer’s disease by 42% (39). Another meta-analysis found that higher PA levels reduced the risk of cognitive decline in older age by up to 38% (40). In a prospective study from Podewils and colleagues (2005), 3,375 participants reported PA levels based on the time spent participating in various activity domains, which were then used to estimate leisure-time energy expenditure. An inverse association was found in PA and energy expenditure with dementia risk; however, this relationship was only observed in non-carriers of the APOE genotype (41). Using objectively measurements to capture PA levels in older adults, Buchman et al. (2012) demonstrated that lower PA levels (10th percentile) was associated with a 2-fold increase dementia risk compared to those with higher PA levels (90th percentile) (42).

Further contributing to this work, Erickson et al. (2010) examined the specific brain regions associated with PA and discovered greater volumes of grey matter in the frontal,
occipital, entorhinal, and hippocampal regions in older adults with greater levels of self-report PA, quantified as the number of blocks walked over 1 week (43). Additionally, the effect of PA maintenance over a 13-year period was examined among 141 community dwelling older adults. It was found that higher levels of self-reported time spent walking led to protective effects in both brain structure and cognitive performance (44). Over the course of 6-8 years, Yaffe et al. (2001) found an inverse relationship between energy expenditure and global cognition, assessed by the Mini-Mental State Examination (MMSE), a widely used test for cognitive functions of orientation, attention, memory, language and visuo-spatial abilities (45). Larson et al. (2006) demonstrated that older adults who exercised at least 3 times per week had a lower probability of dementia diagnosis (46). Lastly, Eggermont and colleagues (2009) showed higher levels of self-reported PA led to better performance on cognitive tasks, primarily those within the domain of executive function (47).

Prospective cohort studies have improved the understanding of the relationship between PA and cognitive decline. However, the possibility of reverse causality cannot be eliminated, as Sabia et al. (2017) reported no neuroprotective effects of physical activity (48). The authors attribute previous findings to a reduction in physical activity levels in individuals with early-stage cognitive decline and Dementia (48). Randomized controlled trials provide additional clarity to the relationship between specific forms of exercise and the impact on cognition.

1.4 Exercise and Cognitive Function

Exercise, a structured form of PA that aims to improve physical fitness, has been shown to have a neuroprotective effect on cognition in older adults (9). The two main forms of exercise discussed within the field of exercise neuroscience are AET and RET (7). A recent meta-analysis
from Falck et al. (2019) indicates that physical exercise is an effective intervention for improving both physical and cognitive health in aging (6). Northeyst et al. (2018), demonstrated that exercise, comprised of AET, RET, or a combination of both, significantly improved cognitive function in older adults, irrespective of their cognitive health status or the specific domain measured (8). To date, a majority of the evidence examining the relationship between exercise and cognition has focused on AET (6,9–13). Thus, this thesis will go into a more expansive review of both RET and RE, following a brief review of the AET literature.

1.4.1 AET

It is well documented that AET has neuroprotective effects, delaying age-associated cognitive decline (10). Dustman and colleagues (1984) demonstrated that AET, performed 3 times per week by sedentary older adults, produced significant improvements in aerobic fitness and performance on neuropsychological tests when compared to control and balance training (49). Further extending this work, Colcombe et al. (2004) demonstrated that compared to a non-aerobic control, a 6-month walking intervention led to improved cognitive performance and activity of the frontal and parietal regions of the brain in older adults (11). Erickson and colleagues (2011) found that AET, 3 times per week, increased hippocampal volume by 2%, a brain region responsible for learning and memory, compared to control (50). Additionally, these changes correlated with improvements in spatial memory and serum neurotrophic growth factor levels (50).

Aerobic exercise training may impact cognitive function by cellular mechanisms such as improving capillary density and cerebral blood flow, increased neurotrophic growth factor expression, neurogenesis, increased brain volume and a reduction in inflammatory markers (13,51). Moreover, it has been documented that participants who engaged in both aerobic and
resistance exercise training demonstrated greater improvements than those participating in AET alone, suggesting RET may provide additional cognitive benefits (6,8,13). However, compared with AET, less is known about the effects of RET on cognitive function in older adults (52).

1.4.2 RET

The age-related decline in both muscle mass and function, results in many consequences for the aging adult including increased risk for all-cause mortality (53,54). Between the ages of 30 and 50 years, there are small changes in muscle mass, strength and power; however, following age 50, muscle mass declines by 1-2% and strength by 1-3% per year (2). RET programs, composed of any type of weight bearing exercise performed with free weights, machines or resistance bands, are frequently prescribed to older adult populations to prevent these age-associated loses in lean body mass, strength and mobility (55,56). There is an emerging body of evidence indicating that both RE and RET may improve cognitive function in older adults (14,57–61). Epidemiological data suggests that older adults meeting the ACSM guidelines for RET (2 times per week), have improved executive functions compared to those who do not meet these guidelines (62). Notably, RET is especially beneficial for older adult women, who experience a greater prevalence of falls, osteoporosis and Alzheimer’s disease, as well as an accelerated progression of mild cognitive impairment, compared to males (38,57).

Unfortunately, both RE and RET are understudied within the field of exercise neuroscience (9–11,63). Given the considerable benefits of RET on muscular strength and physical function in older adults, an examination of the effects of RE and RET on cognitive abilities is warranted to inform evidence-based prescription.

Results from randomized-controlled trials examining the relationship between RET and cognition in healthy older adults indicate that RET induces both structural and functional brain
plasticity (58,64–66). Older women who engaged in RET twice per week experienced functional hemodynamic changes in the cortex, which was significantly associated with improved performance on the flanker task, a measure of response inhibition within the domain of executive function. Interestingly, these changes in functional plasticity of the cortex only occurred in those who participated in RET at a minimum frequency of twice per week (65). RET also impact brain structure and volume (58,66). Twice-weekly RET at a moderate intensity reduced the progression of white matter hyperintensities, which correlated with improved gait speed, but not executive function (66). Additionally, RET significantly reduced white matter atrophy at 2-years post intervention of twice weekly RET, but had no effect on cortical gray matter or hippocampal volume (58). Thus, the effects of RET on brain structure and function may be distinct from those of AET, which has been shown to induce hippocampal neurogenesis (50).

Participation in RET programs also has a positive impact on cognitive performance among older adults (67). Notably, Cassilhas and colleagues (2007), found that RET improved measures of memory, processing speed and executive function among community-dwelling, elderly men (59). Moreover, thrice weekly RET produced significant improvements in cognitive capacity, measured by the MoCA, in sedentary, older women (68). However, the domains that are most affected by RET remains unknown, with some studies finding effects of long-term RET on memory, and others only observing effects on executive functions (69,70). Meta-analytic data has shown RET facilitates improvements in executive functions, global cognition, and memory (67).

Although RET presents may cognitive benefits, there is a paucity of evidence regarding the ‘dose’ of RET (ie. frequency, intensity, duration, volume), to reap these benefits. Previous work from Liu-Ambrose et al. (2010), demonstrated that a low frequency of RET (1 time per week)
was sufficient to improve executive functions in older adult women (61). Additionally, in an examination of the dose-response relationship between RET intensity and cognitive function in the elderly, Cassilhas et al. (2007) found that equal benefits occurred following moderate and high intensity RET, defined as 50 and 80 percent of one repetition maximum respectively; however, low intensity RET was not examined (59). Results of a recent meta-analysis indicate that a minimum of 45-60 minutes of exercise, of both aerobic or resistance, is required to improve cognition in adults aged 50 and above (8). Fortes et al. (2018) demonstrated that both 3 and 5 sets of RET improved response inhibition in young adult men, while a single set did not result in any improvements (71). Thus, volume may be a critical moderator in the relationship between RET and cognition. Taken collectively, current literature indicates that there may be an important effect of RET ‘dose’ to promote cognitive gains. Whether this effect persists with a single bout of RE remains unknown.

1.4.3 RE

As little as a single session of RE has been shown to induce improvements in cognitive performance (14). However, studies examining the immediate effects of a single session of RE in older adults are scarce, with a majority of the investigations conducted in young adults and children (14). Alves et al. (2012) compared the effects of acute aerobic exercise (AE) and RE on two different measures of executive function using the Stroop Test (ST), a measure of selective attention and response inhibition, and Trail Making Test (TMT), which measures cognitive flexibility (19). Cognition was assessed both before and after RE, 2 sets of 15 repetitions of the major muscle groups, and 30 minutes of AE, walking at 50-60% HRR. Both AE and RE resulted in improved performance on the ST compared to control, with no difference between the groups, and neither exercise group had an effect on TMT performance. These findings indicate that
similar to AE, RE has immediate effects on cognitive performance in older adults; however, it is unknown which specific cognitive processes are impacted (19). Importantly, whether RE has the potential to improve accuracy on cognitive tests remains equivocal as a majority of studies examining the RE-cognition relationship report improvements in task speed only (18,19,24).

Chang et al. (2014) found selective improvement of specific processes of executive function, cognitive flexibility and response inhibition, immediately following 2 sets of total body RE at 10RM (72). Additionally, the same RE protocol was used to test the effects of RE on executive functions in a relatively younger cohort (35-65 years), and found significant effects in selective attention and response inhibition, but not cognitive flexibility (20). In another examination from Chang and colleagues (2012), whole body RE, composed of 2 sets at 10RM, positively impacted the planning process of executive function, as measured by the Tower of London Task (73). Dunsky et al. (2017) demonstrated RE of 3 sets at 10RM of the six major muscle groups improved executive functions but not attention (74). However, these studies all used the similar exercise protocols and were conducted in a relatively younger age group (35-75 years). Thus, the potential impact of critical RE parameters (intensity, duration, volume) could not be determined. A recent meta-analysis of RE trials aimed to improve cognition revealed that RE had the greatest impact on two processes of executive function, response inhibition and cognitive flexibility. However, additional studies are needed to elucidate the specific effects of RE on cognitive function in older adults, and the moderating effect of RE parameters.

Johnson et al. (2016), assessed the effect of duration of either acute AE or RE on cognitive performance (18). Community-dwelling older adults (average of 71.7 years), were randomized into either AE, at an RPE 13-14, or RE, 2 minutes of each exercise at 60% 1RM, for either 10 or 30 minutes in duration. Task speed significantly improved on the color and
inhibition ST, with effects persisting up to 60 minutes post-exercise in the shorter duration groups. These findings were independent of exercise mode, indicating as little as 10 minutes of either AE and RE is sufficient improve executive functions both immediately post-exercise to 60 minutes (18). However, the effects of RE volume on executive functions have yet to be assessed in this population.

1.5 Proposed Mechanisms

Although RET produces cognitive benefits, our current understanding of the mechanisms underlying these improvements largely stems from animal studies and is restricted to AET (51,57). Similar to AET, RET reduces cardio-metabolic risk factors associated with cognitive impairment, and stimulates production of neurotrophic growth factors (75). In an integrative model introduced by Cotman et al. (51), AET induces neurotrophic factor cascades, such as brain-derived neurotrophic factor (BDNF), a central mechanism mediating AET-dependent benefits in cognitive performance, synaptic plasticity, and neurogenesis. In humans, higher basal levels of circulating BDNF are associated with greater hippocampal volume, improved spatial memory, and mood (51,76). While it has been demonstrated that AET can stimulate BDNF production (10), the evidence for RET is equivocal, potentially due to a large variety in RET prescription and modality (machines vs. free weights) (77–83). Hence, it remains unknown whether the neurobiological mechanisms of RET are different than those of AET. Specifically, a rodent study demonstrated that AET preferentially increased BDNF while RET preferentially increased insulin-like growth factor-1 (IGF-1), another neurotrophic growth factor associated with neurogenesis and improved memory (63).
The mechanisms of RE-induced cognitive plasticity are hypothesized to be a result of improved arousal, increased cerebral blood flow, and mechanisms related to increased neurotrophic growth factor production (18,73). It has been suggested that increases in cardiac output during RE facilitate cognitive processing through increased metabolic resource availability and cerebral blood flow (26). It is plausible that RE volume may impact cognition through more total accumulated work, and thereby and increased cerebral blood flow. However, high-intensity RE is an acute hypertensive stimulus which may contribute to reductions in cerebral blood flow velocity and increase pulsality (84). Although transient increases in arterial stiffness and pulsality may not be detrimental, it is unknown how these changes relate to cognitive performance (27). Neurotrophic factors are known to play a neuromodulatory role in the promotion and maintenance of synaptic connectivity and are associated with increased cortical activation (26). However, whether neurotropic responses to exercise correlate with cognitive benefits is unknown because few studies assess both outcomes (85). Additionally, it is likely the effects of RE may differ from those of RET. The results of a recent investigation in apparently healthy males indicated that 12 months of RET significantly increased IGF-1, which correlated with improvements in reaction time but not accuracy rates on the oddball task, a measure for cognitive flexibility and attention (86). However, this finding was not consistent in RE, as IGF-1 levels returned to baseline within 20-minutes post-exercise, and did not correlate with cognitive outcomes of improved executive function (23). Thus, the production of neurotrophic growth factors may be a mechanism limited to chronic training.
1.6 Exercise and Affect

It has been well established that psychological responses to exercise are significantly correlated with future PA participation (87–89). According to the Hedonic theory of behavior change, human experience is followed by affective responses (ie. feeling good versus bad), which determine whether or not the behaviour will be repeated (90). Affect can be characterized by two main dimensions: arousal (high versus low) and valence (good versus bad) (91). Emotions represent a combination of both; for example, joy encompasses high arousal and good valence, while anxiety represents high arousal and bad valence (91). The hedonic theory primarily focuses on valence when describing the affect-exercise relationship (91). The affective response to exercise may be a stronger motivator and predictors of adherence than knowledge or beliefs in the benefits a particular health behaviour (92).

Despite the accumulating evidence that RET is beneficial for both cognitive and physical health in aging, only 13.5 % of older adults report meeting the ACSM recommendations which suggest a minimum of 2 sessions of RET per week (93,94). Additionally, retention rates are low among older adults that do participate in RET programs, with dropout rates reaching over 50% (95). Thus, exercise prescription is not only an issue of dose-efficacy, but also requires examining factors related to whether or not older adults will adhere to the prescription (95). RET has the potential to significantly improve psychological states and quality of life, which may translate to better exercise adoption and maintenance (29,30). Specifically, it has been documented in the literature that acute RE increases pleasure, reduces anxiety and promotes self-efficacy and motivation (96–98). However, the relationship between acute RE and affective responses have yet to be strongly established, as a majority of the literature has focused on AE (95,97). Thus, it is important to understand the affect-RE relationship to inform effective RE
prescription that generates positive affect and promotes further adoption and maintenance of RET.

Interestingly, psychological responses to acute RE may vary with RE parameters such as load, referring to the resistance or weight, and intensity, defined as the intensity of the load or effort. Arent et al. (2005) examined the dose-response relationship between RE and affect, and discovered a curvilinear relationship, with moderate intensity RE (3 sets of 10 at 70% 10RM) having the greatest improvement on affect (97). Greene and Petruzzello (2015) found that when compared to 100% 10RM, RE at 70% 10RM significantly improved enjoyment in college-age males and females (99). However, Focht and colleagues (2015) found similar improvements in affect across different self-selected intensities in trained women (100). Other factors related to RE prescription such as exercise selection, as well as levels of perceived discomfort and exertion, have also been shown to impact affective responses to RE (101,102). Interestingly, the positive affective responses to RE may also moderate the effects of RE on higher level executive functions (22). Thus, it is important to understand the effects of RE dose on affect.

While these results indicate acute RE impacts affect following exercise, the specific relationship between affect and RE dose remains unknown. In addition, a majority of these studies have been conducted in young adults, and the effect of RE volume on psychological states has yet to be examined (97,99,100). Higher volumes of RE demonstrate greater amounts of accumulated work and energy expenditure, which may be less tolerable and pleasurable. Additional investigations are needed to elucidate the relationship between RE and affect in clinical populations such as older adults, and provide insight to the factors affecting RE enjoyment and sustained RET adherence (103).
1.7 Objectives

The purpose of this study was to observe the acute effects of RE volume on:

1. The executive process of response inhibition as measured by the Flanker Task (104,105).

2. The execute process of cognitive flexibility as measured by the Dimensional Change Card Sort Task (104,105).

3. Affect as measured by the 11-point Feelings Scale (88).

1.8 Hypotheses

1. Both multi-set RE conditions will improve response inhibition, compared to control, with no difference between 1 set and control.

2. Both multi-set RE conditions will improve cognitive flexibility, compared to control, with no difference between 1 set and control.

3. Affect will improve following the completion of all RE conditions only. Affect will improve the most following low volume conditions (1 set).
2. METHODS

2.1 Ethical Approval

Ethical approval was obtained from the University of British Columbia’s Clinical Research Ethics Board (H18-03556). All participants provided written informed consent to participate.

2.2 Study Design

We conducted a within-subjects, crossover study in 21 older adult women living in Metro Vancouver, BC, Canada. We recruited only women to eliminate any confounding sex differences in the effects of exercise on cognitive function (106). Each participant underwent all 4 experimental conditions, including 3 conditions of RE of the major muscle groups, each at a different volume, and a resting control. All participants completed a baseline assessment and a familiarization to the RE machines and cognitive tests at least 1-2 weeks prior to study entry.

2.3 Recruitment

We recruited from the community, word of mouth, and the extensive pool of participants who were deemed ineligible for other studies within our laboratory (i.e., do not have cognitive impairment) and have agreed to be contacted for future research within the Dr. Liu-Ambrose Lab. Interested individuals were first screened by telephone to assess general eligibility according to the inclusion and exclusion criteria, and the Physical Activity Readiness Questionnaire-Plus (PAR-Q+) (107), a screening measure of physical readiness for exercise. Those who appeared eligible were scheduled for a screening assessment, where they were
provided with additional information about the study and eligibility was confirmed. Participants first provided informed consent. Each participant was informed of their confidentiality, potential risks of the study and their right to withdraw from the study at any time.

### 2.4 Participants & Sample Size

We recruited 21 community-dwelling, untrained older adult women (Figure 1). Assuming an effect size of 0.60 (Cohen’s $d$) according to previous studies in acute RE and cognition, and a similar study of RET volume and executive function (14,71), we needed 21 participants to have statistical power of 0.95, assuming an alpha of 0.05 (G*Power)(108).

#### 2.4.1 Inclusion Criteria

1) aged between 65 and 75 years; 2) preserved general cognition as indicated by a Mini-Mental State Examination (MMSE) score $\geq 24$ and Montreal Cognitive Assessment Score (MoCA) $\geq 26/30$; 3) able to walk independently; 4) are community-dwelling; and 5) must be in sufficient health to participate in the exercise programs. This was based on medical history assessed by the PAR-Q+.

#### 2.4.2 Exclusion Criteria

1) have engaged in regular (weekly) resistance exercise in the past 24 months ; 2) are diagnosed with depression as measured by a score $> 5/15$ on the 15-item Geriatric Depression Scale (GDS); 3) are clinically suspected to have neurodegenerative disease (e.g., multiple sclerosis, Parkinson’s disease, Huntington’s disease, frontotemporal dementia); 4) are at high risk for cardiac complications during exercise; 5) have clinically important peripheral neuropathy or severe musculoskeletal or joint disease that impairs mobility, as determined by his/her family physician; 6) are taking medications that may negatively affect cognitive function, 7) on any
hormone therapy (estrogen, progesterone, or testosterone) in the last 24 months; 8) are planning to participate, or already enrolled in, a concurrent clinical drug or exercise trial; 9) those with any planned time away during the exercise period; 10) are ongoing alcohol or drug abuse or dependence that in the opinion of the investigator may interfere with the subject’s ability to comply with the study procedures; 11) are on beta blockers; 12) have obstructive sleep apnea as determined by a physician, a score of >5 on the STOP-bang questionnaire, or are using a CPAP machine; 13) are currently smoking.

2.5 Study Procedures

This was a within-subjects, crossover study where each participant attended the laboratory for 5 total visits including a baseline assessment and 4 experimental conditions (i.e., control, 1 set, 3 sets and 5 sets of RE). The order of the conditions was randomized and counterbalanced across participants by a central internet randomization service (www.randomization.net). Randomization was performed by Dr. Teresa Liu-Ambrose, who was not involved in the day-to-day study procedures, including working with participants. Once randomized, participants attended the laboratory once per week for four consecutive weeks on same day and time each week (Figure 1). Prior to each condition, participants were asked to refrain from alcohol use and maintain their normal caffeine intake (determined at baseline). Participants did not engage in any additional resistance exercise for the duration of the study.
2.5.1 Screening (Visit 1)

The initial screening assessment took place at least 1-2 weeks prior to the experimental conditions. Initially, details of the study were provided, and informed consent was obtained.

Once informed consent was obtained, the participants proceeded with the in-person screening. Global cognitive function was assessed using the Mini Mental State Exam (MMSE) (109) and MoCA (110). The Geriatric Depression Scale was administered to test for depression (111,112). Lastly, the STOP-Bang tool was used to assess sleep apnea risk (113). Eligible participants then proceeded immediately with familiarization and baseline assessments.
2.5.2 Familiarization and Baseline (Visit 1 continued)

Demographic Information: During the baseline assessment, we measured age in years, education level, resting systolic and diastolic blood pressure, standing height in centimeters, and mass in kilograms. We also assessed baseline sleep quality using the Pittsburg Sleep Quality Index (PSQI) (114), baseline physical activity levels using the Physical Activity Scale for the Elderly (PASE) (115), and comorbidities by the Functional Comorbidity Index (FCI) (116).

Cognition: Participants were familiarized with the Flanker and Dimensional Change Card Sort (DCCS) task from the NIH Toolbox Cognition Battery (NIHTB-CB) (See 2.5.1 Cognitive Function) (104,105). The NIHTB-CB is delivered by iPad and includes automated written and verbal instructions. Each task includes a practice trial. After receiving automated instructions, instructions from a research assistant and a practice for each task, baseline scores were taken for the flanker and DCCS.

Pulse Wave Velocity (PWV): To determine arterial stiffness, we measured carotid-femoral PWV (CF-PWV) using the Complior device (ALAM Medical, France). Participants were instructed to lay quietly in a supine position for 5 minutes. We then measured automated blood pressure in the laying position. Participant information (age, height, weight, and resting blood pressure) was entered into the Compilor system. Carotid and femoral arteries were located and the distance between them (C-F distance) was recorded to the nearest millimeter. Sensors were placed directly over both the carotid and femoral arteries. Sensors were held in place until 10 valid pulses were detected from both the carotid and femoral sensors. Measurement was repeated if the tolerance was above 3 milliseconds. C-F PWV was recorded in meters per second. A valid C-F PWV measurement was not detected in 2 participants due to technical error.
**Maximal Strength:** To familiarize participants with the RE machines, all participants were shown a demonstration of each exercise followed by verbal instructions. Participants then performed 2 sets of 10-15 repetitions at a submaximal intensity for each exercise to ensure proper technique. After a brief rest period (~30 minutes), maximal strength was measured by the 10 repetition maximum assessment (10RM) (117,118). The 10RM was conducted according to the same exercises and order as the RE conditions. The result of the 10RM test was converted to 1-repetition maximum (1RM), using the Brzycki equation, and was be used to prescribe individual training loads for each participant (117). The 10RM test was conducted using the following protocol: each participant warmed up using a light resistance (~50% of estimate 1RM) and performed 10-15 repetitions. Following a 1-minute rest, another warm-up set was completed by increasing the weight by 5% (for upper body exercises) to 10% (for lower body exercises) for 10-12 repetitions. After a 2-3-minute rest, the weight was increased again to the estimated 10RM. If the participant performed within 3 repetitions of 10RM, the test was stopped, and an equation was used to calculate 1RM. If not, another attempt was given. A maximum of three attempts were provided for each exercise. The number of attempts was kept to a minimum to prevent muscular fatigue from confounding performance on the assessment. The 10RM test is a reliable and valid measure to predict 1RM strength (117), and is feasible and safe to conduct with older adults (118).

2.5.3 Experimental Conditions (Visits 2-5)

**RE Conditions:** The 3 RE conditions were prescribed by as follows: control, 1x10 at 70%, 3x10 at 70% and 5x10 at 70% of 1RM, with 120 seconds of rest between sets (Figure 2). The order and exercises were kept consistent for all RE conditions: leg press, chest press, lat pull down, knee extension (Keiser Sports Health Equipment, USA). Each RE condition included a
standard warm up and cooldown comprised of dynamic movements. Participants also performed a warmup set of 5-10 repetitions at approximately 50% of 1RM for each exercise.

![Figure 2. RE Condition Protocol](image)

(PRE= Immediately before condition, FS= Feelings Scale, Cog= Cognitive Assessment, RPE= Rating of Perceived Exertion, POST= Immediately after condition)

Figure 2. RE Condition Protocol

*Control:* The control condition was identical for all participants; participants sat at a desk and watched a nature television show for 45 minutes.

2.6 Outcomes

Before and immediately after each condition, we measured affect and executive function. The order of measurement was kept consistent across all participants and conditions.

2.6.1 Cognitive Function

Cognitive function was measured using the NIH toolbox Cognition battery (NIHTB-CB), with a focus on executive processes of cognitive flexibility and response inhibition, which have been shown to be most impacted by RE (14). We used 2 individual instruments to assess these processes: NIHTB-CB Flanker Test measuring response inhibition and NIHTB-CB Dimensional Change Card Sort Task (DCCS) measuring cognitive flexibility (119). Both assessments were
automated by iPad and include standard instructions and a brief practice. All cognitive assessments were completed under the same conditions (same room and order, Flanker then DCCS), and were proctored by a blinded assessor. Each task was 4 minutes in length. NIHTB-CB uses performance indices of reaction time and accuracy to produce a raw score for each task. NIHTB-CB raw scores were automatically converted to normally distributed scores and averaged to compute a composite and an age-adjusted score. The internal consistency (Cronbach’s alphas) for fluid scores is 0.83 and the test-retest reliability is 0.90. The NIHTB-CB composite score has a convergent validity of .89 (104,105).

2.6.2 Affect

Affect was measured before, during and immediately after each condition by the Feelings Scale (FS) (88), which has been shown to be a valid and reliable measure for examining the affect-exercise relationship (100,120). The FS is an 11-point rating scale that ranges from -5 (very bad), to +5 (very good), to capture feelings of pleasure and displeasure with an anchor at zero. Subjects were asked to report psychological feelings toward the RE condition, rather than physical feelings of exertion or discomfort during exercise. A script was used to standardize the explanation of the FS and a standard question, “How did you feel psychologically during the exercise?”, was used to collect FS ratings. FS measurements were always taken by the same assessor across all participants and conditions. FS ratings were recorded before and after each condition.

2.6.3 Rating of Perceived Exertion (RPE)

RPE was measured by the Borg 0-10 scale following each set of RE, and after each condition (sRPE) (121). Subjects were familiarized with the RPE scale and were asked to report subjective exertion (ie. How difficult the exercise feels physically). Participants were informed
that an RPE of 10 reflects volitional failure, meaning no further repetitions could be performed with proper form and range of motion at the prescribed load. Standardized scripts were used to explain and ask for RPE ratings. RPE ratings were taken by the same assessor across all participants and conditions.

2.6.4 Volume

Total repetitions per set were recorded and used to calculate total volume (TV; Sets x Reps). Load was also recorded for each set and exercise. If participants were not able to meet the prescribed repetitions and load, a short rest period (30s) was provided. If they were still unable to achieve 10 full repetitions, the load was reduced by 5%. The load was never reduced below 65% 1RM.

2.7 Data Analysis

Statistical analysis was conducted using R (R Core Team, 2013). Descriptive statistics were reported for variables of interest. Data is reported as means and standard deviations for continuous variables and frequencies or percentages for categorical variables. The overall alpha is set at 0.05.

Hypothesis 1: Both multi-set RE conditions will improve response inhibition, compared to control, with no difference between 1 set and control.

Hypothesis 2: Both multi-set RE conditions will improve cognitive flexibility, compared to control, with no difference between 1 set and control.
We used R (R Core Team, 2012) and lme4 (Bates, Maechler & Bolker, 2012) to conduct two mixed linear models. A mixed linear model was constructed to test the effects of condition and timepoint on cognitive performance using the change score (post-pre condition). Time was added to the model to test for improvements over time due to familiarity with RE. As fixed effects, baseline cognitive performance score was included as a covariate, time was a categorical variable representing visit number and condition was a categorical variable representing volume (CON, 1, 3, 5 Sets). Both models controlled for the within-subject effect by including random effects intercepts for each subject. Data was checked for assumptions of normality, using the Shapiro-Wilks test, and sphericity, using Mauchly’s test. Visual plots revealed modest departures from normality and sphericity. The Greenhouse-Geisser correction was automatically applied to factors violating the assumption of sphericity. Linear and quadratic polynomial contrasts were also conducted to determine the effect of training volume on change in response inhibition and cognitive flexibility. To account for any variance related to baseline cardiovascular health, both mixed linear models were repeated with PWV as a covariate.

*Hypothesis 3:* Affect will improve following the completion of all RE conditions only. Affect will improve the most following low volume conditions (1 set).

A mixed linear model was constructed to test the effects of condition and timepoint on affect using the feelings scale change score (post-pre condition). As fixed effects, we entered condition as a categorical variable (i.e., CON, 1, 3, 5 Sets) and timepoint as a categorical variable (i.e., visit number). As random effects, we had intercepts for each subject. Visual inspection of residual plots revealed modest deviations from homoscedasticity and normality.
3. RESULTS

The flow of participants is shown in Figure 3. All participants (n=21) completed each experimental condition and were included in the analyses (Table 1). At baseline, participants were physically healthy and did not have cognitive impairment (Montreal Cognitive Assessment (MoCA) scores > 26/30). Additionally, participants had a slightly lower PWV than normative values for women of the same age range, indicating slightly better than average cardiovascular health (122).

Figure 3. Flow of Participants
Table 1. Baseline Participant Characteristics (n=21)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69 (3.14)</td>
</tr>
<tr>
<td>Education, n (%)</td>
<td></td>
</tr>
<tr>
<td>High School</td>
<td>3 (14.3)</td>
</tr>
<tr>
<td>Some University</td>
<td>4 (19.0)</td>
</tr>
<tr>
<td>Undergraduate Degree</td>
<td>6 (28.6)</td>
</tr>
<tr>
<td>Graduate Degree</td>
<td>8 (38.1)</td>
</tr>
<tr>
<td>Mini-Mental State Examination (/30 pts)</td>
<td>28.6 (0.9)</td>
</tr>
<tr>
<td>Montreal Cognitive Assessment (/30 pts)</td>
<td>27.4 (1.1)</td>
</tr>
<tr>
<td>Physical Activity Scale for the Elderly</td>
<td>120.8 (48.6)</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>26.6 (4.9)</td>
</tr>
<tr>
<td>Resting Systolic Blood Pressure (mmHg)</td>
<td>127.1 (11.5)</td>
</tr>
<tr>
<td>Resting Diastolic Blood Pressure (mmHg)</td>
<td>77.5 (9.0)</td>
</tr>
<tr>
<td>Pulse Wave Velocity (m/s)</td>
<td>7.53 (2.20)</td>
</tr>
<tr>
<td>Leg Press 1RM (N)</td>
<td>1937 (467)</td>
</tr>
<tr>
<td>Knee Extension 1RM (N)</td>
<td>325 (86)</td>
</tr>
<tr>
<td>Chest Press 1RM (N)</td>
<td>364 (31)</td>
</tr>
<tr>
<td>Lat Pull 1RM (N)</td>
<td>331 (59)</td>
</tr>
<tr>
<td>Flanker Score*</td>
<td>92 (7.9)</td>
</tr>
<tr>
<td>Dimensional Change Card Sort Score*</td>
<td>105 (13.1)</td>
</tr>
</tbody>
</table>

*Age-corrected standard scores were used, for which the normative mean is a score of 100. Higher scores indicate better performance.

Table 2. Experimental Conditions Descriptive Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Load (%1RM)*</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0</td>
</tr>
<tr>
<td>1 Set</td>
<td>70.0 (1.4)</td>
</tr>
<tr>
<td>3 Set</td>
<td>69.9 (2.6)</td>
</tr>
<tr>
<td>5 Set</td>
<td>69.2 (1.6)</td>
</tr>
<tr>
<td>Average RPE</td>
<td></td>
</tr>
<tr>
<td>0.5 (0.8)</td>
<td>6.6 (1.6)</td>
</tr>
<tr>
<td>7.2 (1.3)</td>
<td></td>
</tr>
<tr>
<td>7.6 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Session RPE</td>
<td></td>
</tr>
<tr>
<td>0.5 (0.7)</td>
<td>4.4 (1.3)</td>
</tr>
<tr>
<td>5.31 (2.0)</td>
<td></td>
</tr>
<tr>
<td>6.3 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Total Volume (Sets x Reps)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>30</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>

*Load was decreased due to pain and/or fatigue in 8 out of 63 RE conditions. Load modifications were made in 5% increments. All conditions met a minimum load of 65% 1RM.
Flanker (Response Inhibition)

The change in flanker score was not statistically significantly different across the different conditions, F(3,53)=1.99, p=0.12 (Figure 4-5).

There was no significant effect of baseline performance (p=0.74) or time (p=0.84) on the flanker change score (p=0.44) (Figure 6). Additionally, when including PWV as a covariate in the model, the results suggest baseline cardiovascular health did not significant impact the change in flanker score (p=0.66). Both linear (p= 0.14) and quadratic (p=1.0) polynomial contrasts were not statistically significant.

Figure 4. Mean change in Flanker score (post-pre condition) across each condition. Higher change scores indicate greater improvements in cognitive performance. Boxes show the interquartile range, bold black lines represent the mean and vertical lines reflect the range. Individual scores are shown as dots.
Figure 5. Individual change scores are depicted by colored lines. Mean change score adjusted for baseline score is shown by the solid black line across condition. Higher change scores indicate greater improvements in cognitive performance.
Figure 6. Individual change scores are depicted by colored lines. Mean change score adjusted for baseline score is shown by the solid black line across time. Higher change scores indicate greater improvements in cognitive performance.

*DCCS (Cognitive Flexibility)*

The change in DCCS score was not statistically significantly different across the different conditions, \( F(3,67) = 0.54, p = .66 \) (Figure 7-8).

Additionally, there was a small, but non-significant effect of baseline performance (\( p = 0.056 \)). There was no effect of time on change in DCCS score (\( p = 0.57 \)) (Figure 9). These findings were independent from participants baseline cardiovascular health (\( p = 0.95 \)). Both linear (\( p = 0.14 \)) and quadratic (\( p = 0.95 \)) polynomial contrasts were not statistically significant.
Figure 7. Mean change in Dimensional Change Card Sort score (post-pre condition) across each condition. Higher change scores indicate greater improvements in cognitive performance. Boxes show the interquartile range, bold black lines represent the mean and vertical lines reflect the range. Individual scores are shown as dots.
Figure 8. Individual change scores are depicted by colored lines. Mean change score adjusted for baseline score is shown by the solid black line across condition. Higher change scores indicate greater improvements in cognitive performance.
Figure 9. Individual change scores are depicted by colored lines. Mean change score adjusted for baseline score is shown by the solid black line across time. Higher change scores indicate greater improvements in cognitive performance.

*Feelings Scale (Affect)*

The change in affect was not statistically different across conditions $F(3,49)= 0.70$, $p=0.56$ (Figure 10-11). There was no significant effect of time ($p=0.09$) (Figure 12).
Figure 10. Mean change in Feelings Scale rating (post-pre condition) across each condition.

Higher change scores indicate greater improvements in affect. Boxes show the interquartile range, bold black lines represent the mean and vertical lines reflect the range. Individual scores are shown as dots.
Figure 11. Individual change scores are depicted by colored lines. Mean change score is shown by the solid black line across condition. Higher change scores indicate greater improvements in affect.
Figure 12. Individual change scores are depicted by colored lines. Mean change score is shown by the solid black line across condition. Higher change scores indicate greater improvements in affect.
4. DISCUSSION

This is the first study to examine the effect of RE volume on executive function in an older adult population. The primary aim of this investigation was to evaluate the effect of RE volume on response inhibition. We also included measures of cognitive flexibility and affect. We employed a rigorous design, utilizing a within-subjects, crossover trial, with blind-assessors, and standardized cognitive testing. It was hypothesized that RE of higher volumes (3 and 5 sets) would promote greater improvements in both measures of executive function, response inhibition and cognitive flexibility. Our results show that there was no significant effect of RE at any volume on measures of executive function. Furthermore, volume did not impact the acute affective response to RE. While not statistically significant, we observed a trend towards greater improvement in response inhibition with increasing RE volume and the opposite for cognitive flexibility (i.e., worse performance with increasing volume). Our results suggest that while chronic RET may promote executive performance, a single bout of RE did not improve executive function in healthy older women, irrespective of volume.

4.1 RE, Executive Function

Contrary to the initial hypothesis, RE did not improve measures of executive function in older women compared to the resting control group. Specifically, RE volume did not impact performance of the primary outcome, response inhibition (p=0.12). Johnson et al. (2016) examined the effect of duration (10 vs 30 minutes of RE) on response inhibition in cognitively healthy older adults (MMSE= 29.2, mean age=71.7) (18). Improvements were found in response inhibition post-RE, independent of duration (10 vs 30 minutes). Although volume was not specifically quantified in this study, it can be inferred that 30 minutes of RE results in higher
volume compared to 10 minutes of RE. Similar to these findings, we did not find an effect of volume on response inhibition, although we did not find any significant improvements in performance following RE. The discrepancy in these results may be explained by four methodological differences. First, Johnson et al. (2016) did not have a control group, therefore the resulting improvements may be due to repeated exposure to cognitive assessments. Additionally, while Johnson et al. (2016) employed a between-subjects design, we utilized a more rigorous within-subjects paradigm which minimizes potential confounding due to individual differences. Third, the RE prescriptions induce different physiological stimuli. The intensity of RE was set at 60% of 1RM for an unspecified number of repetitions, with 30 seconds of rest, which is a more metabolic stimulus than our prescription of 10 repetitions at 70% 1RM, with 120 seconds of rest. A more metabolic RE prescription may better increase heart rate and cerebral blood flow, a proposed mechanism of RE induced cognitive plasticity. Lastly, major differences exist in the measurement of executive function. The NIHTB-CB uses a scoring algorithm that integrates accuracy and reaction time. In contrast, Johnson et al. (2016) defined executive performance by the average response time per Stroop condition (i.e., congruent and incongruent conditions). Scoring the Stroop Task in this manner is more reflective of processing speed, rather than the executive process, response inhibition (123). To measure the executive process of response inhibition, one should subtract congruent condition reaction time from incongruent condition reaction time (124).

We found no effect of RE, at any volume, on the executive process of cognitive flexibility (p=0.66). Few studies report limited influence of RE on cognitive flexibility (19–21,125). Brush et al. (2016) examined the effect of RE intensity (40, 70 and 100 % of 10RM) on executive function, including two distinct measures of cognitive flexibility, the Plus-Minus and
Dimension-Switching Tasks (21). At 15 and 180 minutes post-condition, they report no effect of RE, at any intensity, on response accuracy (21). However, significantly faster speed on the Plus-Minus task were found at 180 minutes (21). Chang and Etnier (2009) conducted an RCT where adults were randomized into either RE or control. They found no significant effect of group or time on cognitive flexibility as assessed by the TMT-B task (20). Also using the TMT-B, Alves et al. (2012) examined the effect of RE on executive function in trained adults and found significant improvements on measures on inhibition, but not cognitive flexibility (19). In an investigation that compared the effects of AE, RE and control on cognitive flexibility, it was found that while RE and AE significantly improved speed, only AE and control sessions had significant greater accuracy scores (125). The results from our study and previous investigations suggest RE may have a small effect on cognitive flexibility, limited to improvements in speed. Furthermore, AE may facilitate better performance of cognitive flexibility than RE (125).

There are a few key reasons why we believe our results do not support our initial hypothesis. First, our study design differed from previous studies that have reported significant effects of RE on executive function. Meta-analytic data shows that between-subjects study designs are significantly associated with a larger effect of RE, compared to control (14). Compared to between-subjects, within-subjects designs account for more confounding variables and have more power with a smaller sample size. In addition, few between-subjects studies have adequately controlled for potential confounding variables (i.e., sex, baseline performance, cardiovascular health) when using a between-subjects design (26).

We found that the changes in executive functions following RE were not significantly different than the changes following the control. Many studies within the RE and cognition literature have not employed a control group (14,18,22,126). This limits the conclusions of the
findings as it is unknown whether cognitive improvements are a result of RE or repeated exposure to cognitive testing. Thus, some effects reported may not be due to RE, but rather a learning effect.

Next, we may not have found an effect of RE because of a small sample size and inadequate power. Dunsky et al. (2017) examined the effect of RE on executive function and attention using performance indices of speed and accuracy (74). Their findings indicate small effects of RE on executive function (Cohen’s d=0.31), indicating RE may have the potential to improve executive function to a very small degree in which we were not powered to detect in our sample (74). A meta-analysis of RE trials in healthy adults found RE significantly impacted response inhibition (SMD= 0.73) and cognitive flexibility (SMD=0.36) compared to a non-exercise control (14). Taken collectively, it is plausible RE may have a small effect on executive functions that we were not powered to detect in the current investigation.

Age is another factor that may have contributed to differences in our results. Meta-analytic data showed younger age (<40 years) was significantly associated with a superiority of RE. Our investigation included older adults, who may need more alternate interventions to promote cognitive improvements due to rapid age-related declines in cognitive function. There is a limited understanding of the extent to which age influences the acute cognitive response as a majority of these studies are conducted with a relatively younger cohort (50-60 years) (19,20,72,74), with only two trials including adults over 65 (18,24). Taken collectively, RE may facilitate limited improvements of executive functions in older populations due to proposed underlying mechanisms (See section 4.4).

Studies examining the effect of RE on executive function utilize a variety of methods to measure executive functions (18–21,21–28). To date, a majority of the trials investigating the
relationship between RE and cognition have specifically focused on the executive process of response inhibition (19,21–23,26,28,74,126–128). Few studies have used more than one measurement tool to examine executive functions (21,26,126). Executive function is made up of multiple dimensions which may be differentially impacted by exercise (22,26,129). Thus, it is important to measure multiple processes when drawing conclusions regarding the impact of RE on executive functions.

Our results suggest that the acute cognitive response to RE was not moderated by baseline cardiovascular health, as measured by PWV. Previous research has suggested that cardiovascular health is a moderator in the relationship between acute exercise and cognition (12,130). Although, this relationship may be more related to cardiovascular fitness, as measured by VO2, rather than arterial stiffness (130). Cardiovascular fitness is positively associated with many aspects of cognition, indicating that individuals with higher fitness levels may reap greater cognitive benefits from exercise (26). It has also been suggested that fitness may act as a ‘primer’ for underlying biological mechanisms, although this relationship has only been examined in the context of AE (131). Our sample consisted of older women with better than average cardiovascular health and high levels of self-reported physical activity. Thus, cardiovascular health may be a more critical moderator in heterogenous samples of participants with high variability in cardiovascular health status (130). Similar to our findings, Weng et al. (2015) found acute changes in response inhibition and working memory were independent of self-reported physical activity levels (129). Our study is limited as we did not measure baseline cardiovascular fitness to further examine this relationship.
4.2 Affect

We found the affective response to RE improved across all conditions, demonstrated by positive change scores, however there was no significant effect of condition (p=0.56). These findings partially corroborate with previous research examining the acute affective response to RE. Engeroff et al. (2019) demonstrated there was no effect of RE at different intensity (60, 75, 90% of 1RM) or workload on affect (22). Similarly, when examining the dose-response relationship between RE intensity (40, 70 and 100% 10RM) and affect, there was no difference in the affective response (126). Arent et al. (2005) examined the dose-response relationship between RE and affect and discovered a curvilinear relationship between RE intensity and affect. However, Arent et al. (2005) measured affect using the PANAS, which includes descriptors of different feelings and emotions other than simply valence (i.e., good or bad) and thus may be more sensitive to affective changes (97). Focht et al (2015) demonstrated self-selected and imposed loads of RE resulted in similar changes in affect, however intention and self-efficacy were significantly different (132). Other factors, such as previous exercise history, personal preference, and other motivational correlates may influence the affective response more than RE prescription.

4.3 RE Dose

Although not statistically significant, we found trends in higher volume promoting greater improvements in response inhibition and the opposite for cognitive flexibility, whereas the greatest performance resulted following lower volume (1 set). These findings partially corroborate with existing research demonstrating that processes of executive function may be differentially impacted by dose (22). Chang and Etnier investigated the dose-response
relationship between RE intensity (40, 70 and 100% of 10RM) on cognitive function (126). They found a significant linear improvements in processing speed with increasing intensity, and an inverted-U relationship between RE intensity and both response inhibition and working memory (126). Similarly, a study exploring the interaction of workload and intensity found greater changes in processing speed following high workload, high-intensity RE (90% 1RM), and response inhibition following lower intensity RE (60% 1 RM) (22). Conversely, Brush et al. (2016) showed a significant linear relationship of faster speeds with increasing intensity for response inhibition, 15 minutes after exercise, and the opposite relationship for cognitive flexibility at 180 minutes (21). Vonk et al. (2019) showed no relationship between executive function and RE intensity as there were no differences in performance following moderate intensity RE and load-less movement (28). Additionally, the actual intensity of RE may be less important than the physiological stimulus itself (ie. high intensity, long rest vs. low intensity, short rest). The general lack of evidence regarding a mechanistic link between RE and cognition make manipulation of critical RE parameters difficult. Together, the effect of RE dose on executive function is not well understood and may depend on the specific process measured and the underlying mechanisms.

4.4 Underlying Mechanisms

There have been numerous physiological mechanisms discussed in the context of RE (e.g., arousal, increased cerebral blood flow, neurotrophic factors, etc.); however, there is little known about these mechanisms and their relation to cognitive processes, such as executive functions (1,7,19). Understanding these mechanisms is critical in the interpretation of our results and, ultimately, in understanding the link between acute and chronic changes in cognition.
The most prominent mechanism for acute cognitive changes following RE is arousal (26). It has been suggested that an inverted-U relationship exists between cognition and arousal, whereas the greatest benefits occur after moderate levels of arousal (70% of 10RM) (126). It is plausible that our RE prescription was too high for optimal arousal levels, as our prescription was near maximal intensity (~95% of 10RM). However, some have argued the arousal-cognition link may be too general and simplistic to explain the complexities of cognitive function (26,133). The relationship with arousal may differ depending on the specific cognitive process measured, such that arousal may contribute to changes in cognitive domains such as processing speed, but may not be complex enough to explain changes in higher-level executive functions (133).

Another widely discussed mechanism is that of cerebral blood flow. It has been suggested that increases in cardiac output during RE facilitate cognitive processing through increased metabolic resource availability in the brain (26). However, high-intensity RE is an acute hypertensive stimulus which may contribute to reductions in cerebral blood flow velocity and increase pulsality (84). Although these transient increases in arterial stiffness and pulsality may not be detrimental, it is unknown how these changes relate to cognitive performance (27). Chang et al. (2017) compared moderate-intensity combined AE and RE with high-intensity RE on executive function and cerebral oxygenation (134). They found attenuated cognitive performance and reduced tissue oxygenation index in the prefrontal cortex following high intensity RE (134). Therefore, improving cerebral blood flow and tissue oxygenation may require a metabolically stressful RE stimulus, or the incorporation of AE (134). Palmiere et al. (2018) found that while aortic stiffness and pulse pressure increased following RE compared to control, there were no significant changes in executive function in young adults (27). Interestingly, when compared to young adults, older adults elicit less increases in cerebral blood flow velocity and greater pulsile
velocity to the brain following RE (84). Thus, it remains unknown to what extent cerebral blood flow is augmented following RE, and how this may vary as a function of age and RE prescription.

To gain understanding of the underlying mechanisms of RE and cognition, electroencephalography (EEG) has been used to provide insights into cortical changes (23,28,125). Event-related potentials (ERPs) have been used to characterize cortical activity linked to cognitive changes, with P3 being the most widely studied ERP (28). One study examined P3 amplitudes after RE and load-less movement and found peaks at 30-40 minutes after RE, while executive function was minimally affected (28). Similarly, while P3 amplitudes were significantly augmented following AE and RE, the accompanying changes in cognitive flexibility were limited to task speed (125). Previous research has suggested that changes in neuroelectric brain function may be more sensitive to acute exercise than behavioural measures (129). Tsai et al. (2014) demonstrated improvements in executive function and P3 amplitude following RE at both a moderate and high intensity when compared to control (23). Interestingly, post-RE cortisol levels correlated with improvements in P3 amplitude (23). However, Wang et al. (2019) reported significantly higher levels of cortisol post-RE that were not correlated to changes in executive performance (135).

Lastly, neurotropic factors such as BDNF, IGF-1 and VEGF, are commonly discussed in the context of RET and cognition for their role in cortical processing and neuronal growth, survival and differentiation (79). Neurotropic factor levels have been shown to increase in concentration following RE (76). However, evidence linking acute increases in neurotrophic factors and cognitive function has been limited to chronic exercise (86). Tsai et al. (2017) demonstrated acute increases in IGF-1 following RE, but it was not correlated with changes in
executive function (23). However, changes in IGF-1 were correlated with executive performance after 12 months (86). Church et al. (2017) showed that BDNF concentration improved following RE and these levels further increased after 7 weeks of RET (136). Transient increases in neurotrophic factors may not be sufficient to improve cognitive function and sustained bouts of RE over time may be needed to induce cognitive changes. Changes in complex cognitive functions may be a result of long-term adaptations such as an upregulation of neurotrophic factors, improved physical fitness and structural brain adaptations.

4.5 RET, Executive Function

Although there are mixed results in the acute literature, more consistent improvements in executive functions have been observed with chronic RET (58,61,71,137). Fortes et al. (2018) examined the effect of volume on response inhibition in younger adults using a similar paradigm to our study (1, 3 and 5 sets of 10 repetitions at 10RM, 180s of rest), albeit a longer program duration (8-weeks) (71). They found an effect on both accuracy and speed of response inhibition, where better performance was demonstrated following 3 and 5 sets when compared to 1 set (71). When compared to a multi-component training program, significant improvements in executive functions following 12 weeks of RET were mediated by gains in knee flexor strength (137). In an investigation of the underlying mechanisms guided by program duration, short term (1 day to 16 weeks) promoted functional changes in connectivity, neural activation, cerebral blood flow and neurotrophin production while long term exercise led to structural changes in brain volume, white, and gray matter and improved cardiovascular and muscular health (138). Taken collectively, improving executive function may require a program of a longer duration (>8 weeks) and result from chronic mechanistic changes.
4.6 Qualitative Findings

Although we did not find specific improvements of RE on executive functions, we did note some important qualitative findings. We recruited older adult women who have not previously participated in RE. After participating in the current study, a majority of women reported intentions to continue with RET by joining gyms, hiring personal trainers, and exercising with experienced friends and family. The participants reported feelings of accomplishment, strength and empowerment after only 3 bouts of RE. Although we did not collect data, nor target the study specifically for behaviour change, we believe this is an incredibly important finding for both individual well-being and exercise adoption.
5. CONCLUSION, LIMITATIONS AND FUTURE DIRECTIONS

As the aging population grows, the number of older adults with cognitive impairments is expected to rise. Lifestyle strategies, such as RET, have been suggested to combat these declines and improve cognitive function. Whether cognitive changes may occur after a singular bout of RE is a growing area of research, although studies present equivocal results. Additionally, the relationship between dose of RE (frequency, intensity, duration, volume) is not well understood. Thus, the aim of this study was to examine the effect of RE at different volumes on executive process of response inhibition and cognitive flexibility in older adult women. We also measured the affective response to RE, as it has been previously suggested as an important determinant to exercise adoption and adherence.

Using a within-subjects, crossover trial, our study found that RE did not improve executive processes of response inhibition or cognitive flexibility at any volume. We did find trends toward greater improvements in response inhibition and a reduction in cognitive flexibility with higher volumes. We also found that RE volume did not impact the affective response to RE. However, this study is not without limitations. First, our study is limited by the small sample size. With our sample of 21, we were powered to detect and effect size of 0.60 (Cohen’s $d$). The effect size of the primary outcome, the Flanker Task, has been reported to range from 0.2 to 0.95 following exercise (26). Thus, we were unable to detect a small, existing effect of RE on executive measures.

Another methodological limitation to note is the use of the 10RM test to inform RE prescription. The 10 RM test is not without limitations, as it has been previously reported that 2-9 strength testing sessions are required to determine a consistent strength assessment in older women (118,139). To minimize these limitations we employed one familiarization session, a
10RM test, and utilized the Bryzcki equation which was has been shown to be an valid 1RM prediction equation (117). The same assessor performed all strength assessments to improve consistency. However, the strength assessments and subsequent load prescriptions may have varied accuracy. Participants reported low average RPE (6.6-7.6), when 10 repetitions at 70% 1RM represents near momentary muscular failure (RPE 8-10), indicating potential under-loading. Additionally, the load was reduced in 8 of 63 conditions, indicating the load may have been too strenuous for some participants and presents a limitation of inconsistent loading.

Other methodological limitations exist in the measurement of executive functions. We measured executive processes immediately following RE; thus, we were unable to elucidate the sustainability or long-term adaptations from the acute response. However, it has been reported that the greatest improvements in cognition occur 15 minutes post-exercise (26). We used the NIHTB-CB to measures executive processes, which uses performance indices of speed and accuracy. Thus, changes in speed or accuracy alone could not be determined. In addition, there is potential for a learning effect in the measures used and a training effect in the RE protocol. To account for this, we examined the effect of time in each model, and found no significant effects. Additionally, the RE conditions were randomized and counterbalanced to minimize the training effect. This study also has limited generalizability. We recruited only healthy, untrained women who were without cognitive impairment and these findings may not extend to other populations. Lastly, we did not measure critical mechanisms such as arousal, neurotrophic factors and cerebral blood flow. Thus, we could not examine any underlying mechanisms to explain our findings.

Although our findings did not indicate an effect of RE on executive function, we observed large variability in individual responses. Studies examining the effect of AE on
executive function have found that individual cognitive responses predicted changes in functional connectivity with chronic training (140). Future research is needed to examine if this effect persists in RE. Additionally, future studies should examine potential changes in connectivity following RE, as this outcome has not been examined within the context of RE. Secondly, we did not find that changes in executive function varied as a function of RE volume. However, Fortes et al. (2018) found that after 8 weeks of training, RET programs of higher volumes led to improvements in inhibitory control (71). These findings suggest there may be a minimum threshold in program duration, by which changes in executive function are observed. Future research should examine RET program duration to inform the time-course by which cognitive changes occur. Lastly, until we understand the underlying mechanisms linking RE and cognition, it will be difficult to determine the proper stimulus needed to maximize cognitive gains with RE and RET. Few trials combine examine both mechanisms and cognitive function, making it difficult to determine which physiological underpinnings attribute to cognitive changes. Thus, more research is needed examining both cognition and potential mechanisms, such as cerebral blood flow, arousal, catecholamines, neurotrophic growth factors and neuroelectric changes.
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