

Acute Bouts of Assisted Cycling Therapy for People with Chronic Stroke-Related Deficits

by

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ABSTRACT

Background: Stroke is a leading cause of long-term disability in the United States (US). Assisted Cycling Therapy (ACT) incorporates the use of an electric motor to enhance the rotations per minute (rpm). ACT of about 80 rpm, has been associated with improvements in motor, cognitive, and clinical function. The acute effects of ACT on motor and cognitive function of persons with stroke induced deficits have not been investigated.

Purpose: To compare the acute effects of ACT, voluntary cycling (VC), and no cycling (NC) on upper and lower extremity motor function and executive function in adults with chronic stroke (age: 60 ± 16 years; months since stroke: 96 ± 85).

Methods: Twenty-two participants (gender: female = 6, male = 16; types: ischemic = 12, hemorrhagic = 10; sides: left lesion = 15, right lesion = 7) completed one session of ACT, one session of VC and one session of NC on separate days using a 3 x 3 crossover design.

Results: ACT lead to greater improvements in lower and upper extremity function on the paretic and non-paretic side than VC or NC (all $p < 0.05$), except in the non-paretic lower extremity where ACT and VC produced similar improvement (both $p < 0.05$). ACT and VC, but not NC, were associated with improvements in inhibition ($p < 0.05$). A positive relationship between cadence and motor function ($P < 0.05$) was found. Ratings of perceived exertion shared an inverted-U shaped relationship with measures of processing speed ($p < 0.05$) and a negative linear relationship with measures of executive function ($p < 0.05$).

Conclusion: ACT appears to benefit paretic and non-paretic motor function globally whereas the benefits of VC are more task specific. Faster cycling cadence was associated with greater improvements in global motor function. ACT and VC seem to carry similar acute benefits in inhibition.

DEDICATION

I dedicate my dissertation to my wife, Jenny Holzapfel, who has made sacrifices and compromises in countless ways that allowed me to pursue my Ph.D. She has provided me with unwavering support, given me courage and motivation, and listened to my complaints and worries. I could not dream of a better partner in life and count myself the luckiest person to have her by my side. Thank you, Jenny!

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Chapter 1

INTRODUCTION

Stroke or central nervous system infarction refers to ischemia-induced cell death in the brain, spinal cord, or retina (Sacco et al., 2013). In 2006, stroke accounted for one in every 18 deaths in the US (Lloyd-Jones et al., 2009). The proportion of people who have had a stroke has stayed constant at 2.6% from 2006 to 2010 and the stroke survival rates have increased since 2000, which indicates an increase in the total number of people who have survived a stroke (Centers for Disease Control and Prevention, 2012; Donnan, Fisher, Macleod, & Davis, 2008; National Center for Health Statistics, 2016). Moreover, stroke-related care was the fastest growing Medicare expense (Dobkin, 2005). The prevalence of persons with post-stroke residual neurological deficits is approximately 5.8 million and stroke is the leading cause of disability in adults in the United States (Dobkin, 2005; Go et al., 2014).

The post-stroke period is usually subdivided into the acute (time since last stroke ≤ 3 months), the subacute (time since the last stroke >3 to <6 months), and the chronic (time since last stroke ≥ 6 months) period. Forty percent of people in the chronic post-stroke period suffer from residual hemiparesis in combination with other neurological deficits, such as impaired cognitive function (Gresham, Duncan, & Stason, 1995; Haring, 2002). Of those who suffer from acute paralysis in the leg, 35% do not regain useful function, and approximately 25% require full assistance to walk, whereas 17% remain completely unable to walk (Dobkin, 2005; Keenan, Perry, & Jordan, 1984). Fifty percent of people who survive a stroke do not recover to community ambulation speeds (Keenan et al., 1984). Furthermore, the average walking speed of people post-stroke is reduced by 41% compared to age-matched controls (Severinsen, Jakobsen, Overgaard, & Andersen, 2011).

Sixty-five percent of people with chronic stroke are also unable to use the affected hand in activities of daily living (ADL; Kwakkel, Kollen, Grond, & Prevo, 2003). Only 25% reach full physical functioning and levels of participation equal to stroke-free community members (Lai, Studenski, Duncan, & Perera, 2002). Consequently, hemiparesis is associated with partial or total dependence in regards to ADL in 25% to 50% of persons who have had a stroke (Gresham et al.,

1995). Not surprisingly, limitations in ADL also have a negative impact on many aspects of life satisfaction (Viitanen, Fugl-Meyer, Bernspång, & Fugl-Meyer, 1987).

Cognitive impairments exacerbate neuromotor deficits. Approximately 35% of people with post-acute stroke suffer from cognitive impairments (< 24 on the Mini Mental State Examination; MMSE; Patel, Coshall, Rudd, & Wolfe, 2003) and about 25% of people with chronic stroke are diagnosable with dementia. The relative risk of dementia after a stroke is 2 to 10 times higher than in the general population for at least three to five years post-stroke (Kokmen, Whisnant, O'Fallon, Chu, & Beard, 1996). Approximately, 50% of patients with acute stroke also have significant deficits in executive function, whereas certain tests, which include measures of processing speed, attention, working memory, cognitive flexibility, cognitive persistence, incidental learning, orientation, and language, yield a prevalence of impairment of up to 75% (Tatemichi et al., 1994; Zinn, Bosworth, Hoenig, & Swartzwelder, 2007). The largest and most frequent non-memory related cognitive deficits occur in the speed of information processing and attention (Almkvist, Bäckman, Basun, & Wahlund, 1993; Lafosse et al., 1997; Mendez & Ashlamendez, 1991; Padovani et al., 1995; Villardita, Grioli, Lomeo, Cattane, & Parini, 1992).

Executive function refers to higher order thinking skills which manage lower-level cognitive processes and goal-oriented behaviors. Executive function domains include those mentioned previously in addition to planning ability, inhibitory control, problem-solving, and set-shifting (Alvarez & Emory, 2006). Executive function deficits may be present after stroke without signs of dementia. In fact, patients who had a stroke but do not have dementia have similar degrees of impairment in executive function as persons with Alzheimer's disease. However, the memory of patients who had a stroke seems preserved compared to patients with Alzheimer's disease (Ballard, Rowan, Stephens, Kalaria, & Kenny, 2003). Reduced executive functioning, specifically information processing speed, limits neuromotor rehabilitation by reducing the rate of sensorimotor learning and the performance of fast or sequentially ordered movements such as dressing, toileting, and transferring (Dancause, Ptito, & Levin, 2002; Walker, Sunderland, Sharma, & Walker, 2004; Zinn et al., 2007). It has been shown that executive functions such as attention and decision-making are involved in balance (Stelmach, Zelaznik, & Lowe, 1990),

ambulation (Hausdorff, Yogev, Springer, Simon, & Giladi, 2005), driving (Hoffman, McDowd, Atchley, & Dubinsky, 2005), reaching, and rasping (Flanagan, 1996) and that post-stroke cognitive impairment reduces independence (Haring, 2002; Saxena, Ng, Koh, Yong, & Fong, 2007). Impairments in memory, orientation, language, and attention have been associated with increased risks of functional impairment and dependent living, independent of age and physical functional status (Tatemichi et al., 1994). Set-shifting ability is positively related to the capacity to complete instrumental ADL in older individuals (Cahn-Weiner, Boyle, & Malloy, 2002). To date, limited evidence exists for the beneficial effects of aerobic exercise on post-stroke executive function (Cumming, Tyedin, Churilov, Morris, & Bernhardt, 2012).

The need for an exercise therapy beyond acute rehabilitation which can decrease the degree of chronic motor and cognitive deficits is substantial. Unfortunately, rehabilitation services are usually limited from a few weeks to three months, until a plateau in the performance of ADL is reached or no noticeable improvements have been documented (Dobkin, 2005). There are no therapeutic exercise modalities which people with severe stroke-related impairments can perform independently at home, even though long-term exercise therapies have shown to be beneficial (Dam et al., 1993; Dobkin, 2005). People in the acute and chronic post-stroke period typically do not engage in exercise training at intensities associated with salient effects (MacKay-Lyons & Makrides, 2002a) and, in fact, most people after a stroke are sedentary. The daily physical activity energy expenditure of 58% of people post-stroke with only mild impairments falls below the 142 kcal/day recommendation for older adults (Mazzeo & Tanaka, 2012; Rand, Eng, Tang, Jeng, & Hung, 2009). Average accelerometer activity counts over the course of three days indicated a mean activity count of 62.8 per minute, which is an activity count associated with sedentary activities. Others reported that 68% of people after a stroke do not engage in regular exercise based on the National Health and Nutrition Examination Survey (NHANES III; Towfighi, Markovic, & Ovbiagele, 2012). Michael and Macko (2007) reported an average daily step count of 1389 steps, which is well below recommended amounts. Interestingly, an average of only 78 steps/day at a high intensity (≥ 30 steps/min) were taken by their participants. This evidence

supports the claim that post-stroke exercise intensities are usually not sufficient for salient cardiovascular or neurological benefits.

Commonly cited reasons for insufficient physical activity include physiological limitations such as pre-morbidly low fitness levels, low muscle strength, and hemiparesis or motor impairments (Gordon et al., 2004). The low physical activity levels lead to further declines in fitness and function which further reduce activity levels, leading to a vicious cycle. Social and emotional barriers, the inexperience of healthcare professionals in exercise prescription and programming, and the general lack of physical activity counseling also contribute to inactive lifestyles (Gordon et al., 2004). According to the American College of Sports Medicine (ACSM), “exercise interventions that go beyond the early subacute period are needed to optimize functional capacity for the long term [...] It is important that outpatients eventually transition from a medically supervised program to an independent (i.e., self-monitored and unsupervised) home exercise program” (American College of Sports Medicine, 2013). During any phase of the rehabilitation process (acute, subacute, or chronic), independent home-based therapy can accelerate improvement because the participant can complete additional training outside of therapy sessions, it eliminates transportation to rehabilitation clinics and affords a familiar environment, which allows the patient to train without scrutiny, perceived social pressures, and/or embarrassment. Due to the absence of physical therapy personnel, people who have stroke-related deficits will also be forced to overcome environmental challenges and engage in problem-solving which can carry additional benefits in regards to activities of daily living (Dobkin & Duncan, 2012).

Assisted Cycling Therapy (ACT) with the lower extremities at 80 rpm, but not unassisted cycling (i.e., voluntary cycling: VC), has been demonstrated to improve upper extremity function and clinical functions in persons with Parkinson’s disease (PD; Alberts, Linder, Penko, Lowe, & Phillips, 2011; Ridgel, Vitek, & Alberts, 2009) and in persons with Down syndrome (DS; Holzapfel et al., 2015; Ringenbach et al., 2014). During ACT, an electrical motor in a stationary, recumbent bicycle augments the cadence to a rate which is at least 35% faster than the participant’s voluntary cadence. The ACT interventions which were tested in patients with PD patients and

persons with DS were performed at a mean cadence of approximately 80 rpm (Holzapfel et al., 2015; Ridgel et al., 2009; Ringenbach et al., 2016; Ringenbach et al., 2014). The motor can be programmed to turn the pedals at a set cadence, which ensures that the participant will be pedaling at that rate regardless of their power contribution.

The preliminary studies of ACT in persons with PD or DS provide evidence for beneficial effects of ACT on central motor processing and global motor function. Improvements in motor function are thought to be global because upper extremity function was improved after assisted lower extremity exercise. Phenotypically, persons with PD and persons with hemiparesis due to a stroke share similar impairments, such as partial loss of motor control, bradykinesia, akinesia, muscle weakness, and gait abnormality (Nutt & Wooten, 2005; Olney & Richards, 1996). Based on these commonalities and improvements found after ACT in patients with PD, ACT may lead to lower and upper extremity motor improvements in people with stroke-induced motor deficits. The only evidence regarding ACT at a relatively fast cadence in people post-stroke comes from a case report (Linder, Rosenfeldt, Rasanow, & Alberts, 2015). A 46-year old male who had experienced a stroke 10.5 months prior to the study, completed 8 weeks of three 45-minute ACT sessions per week at approximately 80 rpm. Following each ACT session, he also completed 45 minutes of repetitive task practice with the paretic upper extremity. The pre- to post-test changes met or exceeded the threshold of minimal clinically important differences for the functional ability scale of the Wolf Motor Function Tests and the Fugl-Meyer Assessment. Improvements on the 9-Hole Peg Test and the 6-Minute Walk Test were also recorded. Due to the upper extremity repetitive task practice, we cannot conclude that ACT benefited upper extremity motor control, but the improvements in lower extremity function are most likely attributable to ACT. It has been hypothesized that the augmented rate of movement above voluntary rates delivered through ACT is necessary to induce neuroplasticity in the motor cortex and improve global motor function (Ridgel et al., 2009). ACT may be especially beneficial for people post-stroke because they do not engage in high intensity activity, defined by Michael and Macko (2007) as a step rate of ≥ 30 steps/min, for more than 3 minutes per day. This research seeks to expand the applicability of ACT and its therapeutic effects to people with stroke-related hemiparesis.

The benefits of ACT also extend to executive function domains and processing speed. For instance, ACT has been associated with acute improvements in inhibitory control in adolescents with autism spectrum disorder (Ringebach, Lichtsinn, & Holzapfel, 2015) and with acute improvements in cognitive planning ability and processing speed in adolescents with DS (Ringebach et al., 2014). Chronic benefits of eight weeks of ACT on various domains of executive function of adolescents with DS have also been reported (Holzapfel et al., 2015, 2016; Ringebach et al., 2016). Ridgel and colleagues (2011) have reported acute improvements in set-shifting ability of participants with PD following a single bout of ACT. The effects of ACT on post-stroke cognitive and motor function have not been tested before, with the exception of the above mentioned case report (Linder et al., 2015). While the results of the case study are promising, clearly more research is needed regarding the effects of ACT on post-stroke cognitive function.

Animal studies have provided most of the preliminary evidence about the effects of forced exercise on brain health. For instance, in rats with induced stroke, forced exercise which required them to run on a treadmill at greater than preferred speeds produced greater neuroprotection than voluntary exercise (Hayes et al., 2008). In humans, functional electrical stimulation cycling has been researched more thoroughly. Functional electrical stimulation cycling has been demonstrated to improve motor function and health in humans with neurological deficits (Ambrosini, Ferrante, Pedrocchi, Ferrigno, & Molteni, 2011). In people who had a stroke, functional electrical stimulation cycling has improved aerobic capacity and maximal power output (Janssen et al., 2008). However, there seems to be no evidence of the effects of functional electrical stimulation cycling on cognitive function. Additionally, functional electrical stimulation cycling is not suitable for independent home use as it requires the correct placement of three electrodes directly on the skin, and due to the high cost of the required equipment, insurance companies typically do not pay for it. Thus, exercise recommendations beyond the acute rehabilitative phase usually only consist of walking, bending, stretching, range of motion exercises, and resistance training (National Stroke Association, 2014), if feasible.

ACT represents an exercise modality suitable for home use which differs from the traditional recommendations in regards to the fast and repetitive movement rate involving large

muscle masses and which has potential benefits beyond the traditional exercises recommended for independent application. ACT makes possible the involvement of large muscle groups in rapid and repetitive movements which otherwise may not be voluntarily producible (i.e., jogging or cycling) by persons with stroke-induced hemiparesis. Additionally, ACT is a modality of assisted exercise which does not require assistance from trained physical therapists or complicated procedures, and which can be performed despite central nervous system fatigue, which is common post-stroke (Chaudhuri & Behan, 2004). Central nervous system fatigue can also be exacerbated by medications such as antihypertensives and β -adrenergic blockers, and it is a predictor of long-term morbidity and cardiovascular disease (Chaudhuri & Behan, 2004; Staub & Bogousslavsky, 2001). Central nervous system fatigue can lead to increased perception of effort, reduced aerobic endurance, and reduced mental capacities which can all result in reduced physical activity levels (Chaudhuri & Behan, 2004). Currently, there is no treatment strategy for central nervous system fatigue (Chaudhuri & Behan, 2004), but ACT could overcome these barriers and potentially reduce chronic central nervous system fatigue by normalizing dopamine regulation in the brain (Alberts et al., 2011).

Improvements in cognitive, motor, and clinical functions in people with DS and PD have indicated the positive effects of ACT on neuroplasticity in the central nervous system, especially the motor cortex (Ridgel et al., 2009). Positive results in persons with stroke-induced deficits will underline the translatability of this exercise modality. ACT holds promise to improve motor function along with health outcomes in populations with other neurological deficits such as stroke without localized paralysis, cerebral palsy, and spinal cord injury. ACT has the potential to reduce the \$36.5 billion in annual health care cost associated with all types of stroke (Go et al., 2014), by reducing the health care cost for those with stroke-related deficits. Additionally, ACT can be performed at home and does not require assistance or the ability to balance. This is a decisive advantage over walk training modalities as fear of falling inhibits practice (Dobkin & Duncan, 2012). Furthermore, those with greater motor deficits may not be ambulatory which means they cannot engage in traditional exercise modalities such as treadmill or overground walking. ACT has the potential to overcome this barrier to exercise and improve lower extremity motor control

and function. ACT also requires only minimal effort by the patient as the movement output is facilitated by the motor in the bicycle.

The very safe nature of ACT will allow for the inclusion of participants with low motor function, poor balance, and mild to moderate cognitive impairment. Typically, persons with reduced visuospatial abilities and visual fields, spatial inattention and impaired recall and planning ability have been eliminated in clinical trials which limits the generalizability of the results to higher functioning individuals (Dobkin & Duncan, 2012). Our results will apply to a broader spectrum of baseline abilities in terms of motor, sensory, and cognitive function. The contribution of the proposed research is to provide evidence for a safe exercise intervention which improves motor and cognitive functions in people with post-stroke deficits and which can be performed independently.

The objective of this investigation was to conduct a within-subjects counterbalanced cross-over trial to test the efficacy of a single bout of ACT during the chronic period (≥ 6 months) after stroke. The central hypothesis was that ACT would produce significantly greater improvements in upper and lower extremity motor function and executive function compared with voluntary cycling (VC) and no cycling (NC). This hypothesis was formulated based on successfully completed trials using forms of assisted or forced exercise or functional electrical stimulation cycling and other populations with neurological disorders (Alberts et al., 2011a; Chen, Ringenbach, & Albert, 2014; Hayes et al., 2008; Holzapfel et al., 2016; Janssen et al., 2008; Ridgel et al., 2009; Ringenbach et al., 2014; Yuede et al., 2009). The rationale for the proposed research included: 1) the need for a safe exercise therapy which can be performed independently at home, 2) the need for a safe exercise therapy which can help people with chronic stroke impairments improve motor and cognitive function to regain independence in ADL, and 3) the current lack of research on the effects of ACT during the post-stroke period.

The central hypothesis was tested with the following three specific aims:

1. Test the effects of a single bout of ACT on upper extremity motor function (Box and Blocks

Test [BBT; primary outcome measure]) in adults with chronic stroke. HYPOTHESIS: ACT

will result in significantly greater improvements in upper extremity motor function than VC or NC.

2. Test the effects of a single bout of ACT on lower extremity motor function (Lower Extremity Motor Coordination Test [LEMOCOT; primary outcome measure]) in adults with chronic stroke. HYPOTHESIS: ACT will result in significantly greater improvements in lower extremity motor function than VC or NC.
3. Test the effects of a single bout of ACT on executive function (Flanker Task, Trail Making Test [TMT], Stroop Test, and Digit Span Test [secondary outcome measures]) in adults with chronic stroke. HYPOTHESIS: ACT will result in significantly greater improvements in executive function than VC or NC.

Chapter 2

LITERATURE REVIEW

Aerobic Exercise and Lower Extremity Function

Exercise therapies such as body weight-supported treadmill training and robot-assisted step training have not been any more successful than traditional therapies, such as over-ground gait training, in the recovery of walking ability and lower body strength after stroke (Dobkin & Duncan, 2012). Overall, there is very little research regarding the effects of aerobic exercise on lower and/or upper extremity motor function in people with chronic stroke-related impairments. A few studies investigating aerobic exercise effects on lower extremity function, such as gait and mobility, have produced consistent results.

For instance, Hesse and colleagues (1995) compared the effects of three weeks of body-weight supported treadmill walking on walking ability and gross motor function to three weeks of standard physical therapy (Hesse et al., 1995). Training consisted of five 30 minute sessions per week and the percentage of body weight which was supported was progressively reduced from 70% to 0%. The treadmill training speed increased from approximately 0.15 mph to 0.50 mph through the 3 weeks of intervention. Gait, as measured by the Functional Ambulation Category instrument, improved significantly more in response to body weight-supported treadmill walking than standard physical therapy. Leg and trunk motor function improved non-significantly more during treadmill training compared to physical therapy.

In a three-month single group pre/post-test study, treadmill walking without body weight support at 60-70% of heart rate reserve for 40 minutes, three times per week, produced improvements in mobility in people with chronic stroke (Silver, Macko, Forrester, Goldberg, & Smith, 2000). Specifically, the average time for the timed-up-and-go test decreased from 8.2 to 6.5 seconds. However, this was not a clinically significant improvement.

Macko and colleagues (2005) found clinically meaningful improvements in the six-minute walk test and a 30 ft walk test at preferred speeds and fast speeds in participants with stroke induced chronic hemiparesis (Macko et al., 2005). However, clinically significant improvements in the 30 ft walk tests were also found in the active control group. The exercise intervention

consisted of six months of three 40-minute treadmill walking sessions per week at 60-70% of heart rate reserve. The control intervention consisted of equal frequencies and durations, but instead included 13 stretching exercises and five minutes of treadmill walking at 30-40% of heart rate reserve. Similar to the six-minute walk test, only the treadmill intervention group showed improvements on the Walking Impairment Questionnaire.

A study with almost identical interventions also used the six-minute walk test and a 10m walk test as outcome measures (Luft et al., 2008). Peak treadmill walking velocity was also assessed before and after the intervention. The intervention group experienced clinically meaningful improvements in peak effort treadmill velocity after the first three months and continued to improve for the remaining three months. Over the six months, their velocity increased from 0.77 m/s to 1.11 m/s. The control group also had significant improvements after six months (from 0.79 m/s to 0.88 m/s). The six-minute walking speed increased from 0.55 m/s to 0.63 m/s in the intervention group and did not change in the control group. The intervention group experienced a clinically significant improvement from 0.72 m/s to 0.82 m/s in the 10m walk test while the control group did not improve by a clinically significant amount. It is worth mentioning that the activation during paretic-limb movement increased by 72% in the cerebellum and by 18% in the midbrain in the intervention group only. This preliminary evidence points to the beneficial effects of aerobic exercise on neural activation in the brain and it provides insight into the causal mechanisms underlying improved lower extremity motor function following aerobic exercise.

A meta-analysis of aerobic walking training studies in persons with chronic stroke summarized 10 studies (Saunders, Greig, Young, & Mead, 2004). A clinically important improvement of 0.42 m/s was found. Overall, there is sufficient evidence to show that aerobic walking training without body weight support or robot-assisted stepping improves walking function and mobility during the chronic post-stroke period. However, people with more severe hemiparesis may not be able to walk without body weight support. Such limitations may make independent exercise on a conventional treadmill or simple over-ground walking impossible. A different rehabilitation strategy is necessary to help those with severe impairments to first regain walking ability before being able to engage in and reap the benefits of aerobic walking training.

Cycling exercise may help those with severe post-stroke mobility impairments improve their lower extremity function through mechanisms of neuroplasticity in the motor cortex and other brain regions.

Body weight-supported treadmill walking, robot-assisted walking, and non-supported treadmill walking are grounded in the theory of central pattern generation. The theory of central pattern generation in regards to locomotion postulates that circuits in the lumbar spine can produce patterns of over-ground locomotion in the lower extremities in response to sensory or proprioceptive afferent input. Thus, central pattern generation is a monosynaptic reflex activity which contributes to the automatic execution of gait without input from the motor cortex (Dobkin & Duncan, 2012). This has been demonstrated in animal studies (Barbeau & Rossignol, 1987; Grillner, 1985; Ichiyama et al., 2008; Lovely, Gregor, Roy, & Edgerton, 1990).

Evidence of central pattern generation in humans was also documented (Nadeau, Jacquemin, Fournier, Lamarre, & Rossignol, 2010). Patterns of alternating flexion and extension in the lower extremities in response to an external stimulus were reported in select patients with complete or incomplete spinal cord injury. Body weight-supported treadmill training has been shown to increase the EMG (electromyogram) amplitude and coordination of flexion and extension at the hip, knee, and ankle joints in some cases (Dobkin, Harkema, Requejo, & Edgerton, 1994; Harkema et al., 1997). However, electrical stimulation or an external stimulus such as pain or a moving treadmill belt seem to be necessary to elicit the central pattern generation. The extent to which central pattern generation applies to the recovery of paretic leg function of people who have suffered a stroke is not fully known (MacKay-Lyons, 2002).

Similar to body-weight supported treadmill walking, ACT has the potential to stimulate central pattern generation and corticomotor excitability through afferent input to the brain of people post-stroke with intact spinal columns (Christova, Rafolt, Golaszewski, & Gallasch, 2011) and it could, therefore, improve motor functions. For instance, improvements in gait speed and symmetry were found in two out of three people with chronic stroke after six sessions of stationary biofeedback cycling (Ferrante et al., 2011). Cycling sessions consisted of two sets of one minute of passive cycling (30 rpm) and two minutes of voluntary cycling with eight minutes of

biofeedback cycling in between the sets. Biofeedback cycling included visual feedback of the power contribution of each leg and participants were instructed to produce equal power with both legs. Interestingly, this intervention included short bouts of passive cycling at a relatively low cadence without biofeedback. Based on the description by the authors, it can be assumed that their passive cycling paradigm is identical to the ACT paradigm except for faster cadences during ACT. The result of cycling interventions such as voluntary cycling with the biofeedback may include greater subconscious control of gait by central pattern generation which could free up cognitive resources that would otherwise be engaged. The engagement of fewer attentional resources devoted to gait is associated with reduced fall risk (Woollacott & Shumway-Cook, 2002).

The only evidence of ACT at a relatively fast cadence (~80 rpm) comes from a case study (Linder et al., 2015). A 46-year old male who had experienced a stroke 10.5 months prior to the study completed 8 weeks of three 45-minute ACT sessions per week at approximately 80 rpm. Following the 8-week intervention the participant displayed clinically meaningful improvements in upper extremity motor function, the Fugl-Meyer Assessment, and the 6-Minute Walk Test. It was hypothesized that the increased afference to the motor and prefrontal cortex through ACT has the potential to stimulate neuroplasticity which may improve global motor function (i.e., in the upper extremities) as well as executive control function (Alberts et al., 2011).

Lower Extremity Function Assessment Tools

We planned to include people with varying degrees of stroke related hemiparesis including individuals who were non-ambulatory. We, therefore, chose to use the Lower Extremity Motor Coordination Test (LEMOCOT; Desrosiers, Rochette, & Corriveau, 2005) as the outcome measure for lower extremity motor control because the test is performed in a seated position (see Methods for more details). This test has demonstrated good test-retest reliability (ICC: 0.83-0.88). The test shows good convergent construct validity with the Lower Extremity Fugl-Meyer Assessment (LEFMA; $r = 0.79$), the Berg Balance Scale ($r = 0.67$), the Five-Minute Walk Test ($r = 0.67$), the Two Minute Walk Test ($r = 0.79$), and the mobility section of the Système de Mesure de l'Autonomie Fonctionnelle (functional assessment scale; $r = 0.66$). The test has discriminant

validity by distinguishing participants who live in long-term care from those who live in more independent arrangements. Additionally, the test has convergent validity with the modified MMSE ($r = 0.11$) and the Motor-Free Visual Perception Test ($r = 0.15$).

Aerobic Exercise and Upper Extremity Function

Only two studies appear to have investigated the effects of lower extremity exercise on global or upper extremity motor function after stroke. Quaney et al. (2009) found that eight weeks of aerobic cycle ergometer exercise can improve performance on a precision grip task and serial reaction time tasks. The learning of rapid sequential movements, which is necessary for complicated motor tasks (e.g., typing), is impaired after stroke. The improvements in the serial reaction timed task found by (Quaney et al., 2009) indicate that activity-dependent neuroplasticity occurred in the motor and parietal cortex, basal ganglia, and the cerebellum (Forkstam & Petersson, 2005; Grafton, Hazeltine, & Ivry, 1995). Neuroplasticity is also likely to have occurred in the frontal cortex, hippocampus, as well as basal ganglia as these regions are implicated in conditional motor learning dependent on visual or other context specific cues such as during the predictive grip force modulation task (Wise & Murray, 2000).

While these aforementioned measures do involve the less-affected upper extremity, they are measures of motor learning involving processing speed and neuromotor control systems, specifically feedforward mechanisms. Hence, these tests are measures of cognitive function (i.e., learning and information processing speed), motor control, and motor planning ability (Messinger, Squire, Zola, & Albright, 2005) rather than functional motor capacity of the upper extremities. The participants had sufficient upper extremity function at baseline to perform the tasks. If functional levels at baseline were too low to perform the required movements then improvements in motor control and reaction time (i.e., processing speed) during post-assessments would have been confounded by possible improvements in motor function. Also, the serial reaction time task is not a functional assessment of the upper extremities as it only required simple “key presses” and because the outcome variable “response time” is a measure of processing speed rather than motor function.

Acute improvements in the function of the hemiparetic arm, measured with the Action Research Arm Test, have been found after a single bout of 20% body weight-supported treadmill walking (Ploughman, McCarthy, Bossé, Sullivan, & Corbett, 2008). Hence, there is evidence to suggest that lower extremity aerobic exercise can improve upper extremity function of people with chronic stroke deficits. This suggests that organizational changes in cortical areas and improved corticospinal excitability elicited through exercise involving specific body parts are not localized to the corresponding motor cortex areas but rather that they are global. Specifically, exercise can improve motor cortex activation and reorganization in the hemisphere with the lesion. It has been shown that motor practice results in acutely improved motor cortex activation of the affected hemisphere in acute stroke patients (Liepert, Graef, Uhde, Leidner, & Weiller, 2000). During thumb abduction at baseline, the size of the cortical motor output area on the affected side was significantly smaller than on the unaffected side. Immediately after a single session of physical therapy for the hand, the activated cortical motor area on the affected side was significantly larger compared to baseline and not statistically different from the activated area on the unaffected side. These improvements were only partially reversed one day after the intervention.

The case report by Linder and colleagues (2015) remains the only published evidence regarding the effects of ACT at fast cadences on upper extremity function. Following eight weeks of ACT, a 46-year old male with stroke-related motor impairments displayed clinically important improvements on the functional ability scale of the Wolf Motor Function Tests, the 9-Hole Peg Test, and the Fugl-Meyer Assessment. Following each ACT session, he also completed 45 minutes of repetitive task practice with the paretic upper extremity. Thus, we cannot conclude with confidence that ACT benefited upper extremity motor control. Therefore, the effects of assisted lower extremity exercise such as ACT on upper extremity motor function after stroke remain unknown. In addition, we do not know whether ACT is more beneficial than VC in regards to the function of the paretic upper extremity because Linder et al. (2015) only tested ACT.

Upper Extremity Function Assessment Tools

The box and blocks test (BBT) was used as the outcome measures of upper extremity function because it has been associated with overall upper extremity motor function ($r = 0.35$ -

0.80) as well as the amount and quality of use of the paretic arm and hand (Lin, Chuang, Wu, Hsieh, & Chang, 2010). Performance on the BBT is also related to the overall functional status (strength, hand function, ADL, instrumental ADL, mobility, communication, emotion, memory and thinking, participation and role function; (Lin et al., 2010). Additionally, performance on the BBT is correlated with performance on the 9-hole peg test (Lin et al., 2010) which is in turn strongly associated the motricity index, a measure of functional strength ($r = 0.82$; Parker, Wade, & Hewer, 1986).

Aerobic Exercise and Executive Function

In older adults, aerobic exercise seems to precipitate chronic and acute benefits in executive function (Blumenthal et al., 1991; Kamijo et al., 2009; Kramer et al., 2003). There are at least four mechanisms explaining the causal pathway between exercise and improved cognitive function:

1. Increased blood flow and cerebral vascularization (angiogenesis) mediated through vascular endothelial-derived growth factor (Cotman, Berchtold, & Christie, 2007; Kleim, Cooper, & VandenBerg, 2002; Pereira et al., 2007)
2. Increased cortical excitability and the upregulation of neurotransmitters including dopamine and norepinephrine (arousal hypothesis; Hillman, Snook, & Jerome, 2003; Kubesch et al., 2003)
3. Upregulation of neurotrophic factors such as brain-derived neurotrophic factor (BDNF), glial-derived neurotrophic factor (GDNF), and insulin-like growth factor (IGF3) which promote neuroplasticity (Alberty et al., 2011; Ploughman et al., 2005; Schinder & Poo, 2000)
4. Improved mood and reduced depression (Kubesch et al., 2003; Russo-Neustadt, Beard, & Cotman, 1999)

Kamijo et al. (2009) found acute improvements in response time during the Flanker task in older adults after a 20-minute bout of moderate intensity stationary cycling at 60 rpm and 74% of maximal heart rate (Kamijo et al., 2009). However, there is a dearth of research on the effects of aerobic exercise on cognitive functions during the post-stroke period. The eight-week cycle ergometer intervention by Quaney et al. (2009) did not yield improvements in measures of

executive function such as set shifting and inhibitory control (Wisconsin Card Sorting Test, Stroop Test, TMT A & B). In this study, participants with stroke cycled at 70% of their age-predicted maximal heart rate for 45 minutes, three days per week. The cadence was not reported. Ploughman et al. (2008) did not find improvements in executive function either (TMT A & B, Symbol Digit Substitution Test, Paced Auditory Serial Addition Test) following a single 20-minute bout of body weight-supported treadmill walking. The authors postulate that the lack of improvement of executive function in people after stroke may be attributable to the cause of the cognitive impairment (i.e., ischemic apoptosis) being different from the cause of cognitive decline in healthy elderly (i.e., reduced gray and white matter volume; Ge et al., 2002) who have shown improvements. Additionally, the short duration and insufficient intensity (~70% of age-predicted maximal heart rate) of the exercise bout and the insufficient complexity of the tasks which may have resulted in a ceiling effect have been implicated (Ploughman et al., 2008).

A combined aerobic and resistance training intervention study of nine chronic stroke patients did produce improvements in working memory (digit span backwards) while improvements in attention and inhibition (Flanker Task) approached significance (Kluding, Tseng, & Billinger, 2011). Participants completed three training sessions per week for 12 weeks. Training sessions consisted of 30 minutes of total body recumbent stepping, with a five-minute warm-up, 20 minutes at 50% of VO_{2peak} , and a 5 minute cool down. This was followed by 30 minutes of resistive band exercise targeting lower extremity musculature important for gait. The improvements in working memory resulted in an effect size of Cohen's $d \approx 0.8$. The improvements on measures of accuracy during the Flanker task approached $d \approx 0.6$. Interestingly, improvements in accuracy on incongruent Flanker task items correlated significantly with improvements in VO_{2peak} ($r = 0.74$). The authors do not offer an interpretation of this findings, but it goes hand in hand with reports of positive relationships between executive function and aerobic fitness in healthy older adults and a slower decline in cognitive function in aerobically fit individuals (Barnes, Yaffe, Satariano, & Tager, 2003).

Rand et al. (2009) investigated the effects of 6 months of a combined exercise and recreation program on executive and motor function and dual tasking in 11 people with chronic

stroke. The participants completed two hours of exercise, which included 20 minutes of moderate to vigorous aerobic activities as well as stretching, balance, and mobility exercises, and one hour of recreational activities per week. Baseline deficits in executive function were apparent in all participants. Short term memory, inhibitory control (Stroop Test), set-shifting (Trail Making Test), dual-tasking, and walking speed were improved after the intervention. However, most improvements occurred within the first three months. Working memory did not improve.

A 12-week study of individuals who had a stroke and were not admitted to a hospital revealed that greater frequencies and durations of physical, occupational, and speech therapy than what is provided during standard rehabilitation therapy did not result in improvements in cognitive function as measured with the MMSE (Wolfe, Tilling, & Rudd, 2000). However, these participants had an average baseline MMSE score of 24, which indicates normal or close-to-normal cognitive function. Additionally, their lower and upper extremity function and ADL scores did not improve by more than the usual care group (Wolfe et al., 2000). A meta-analysis of all post-stroke exercise intervention studies up to 2011, which evaluated aspects of cognitive function, revealed a small but significant effect favoring exercise over control interventions (standardized mean difference = 0.20, $p = 0.015$). The nine studies included in the analysis differed considerably in their methods, with samples ranging from adults in the acute to chronic post-stroke period and interventions ranging from an acute 20-minute bout to a 12-month intervention (Cumming et al., 2012). The three studies which included participants in the chronic post-stroke period were discussed above.

The lack of executive function improvements is in line with the finding that only ACT and not VC appears to benefit executive function in persons with DS or PD (Holzapfel et al., 2016; Ridgel et al., 2011; Ringenbach et al., 2016; Ringenbach et al., 2014; Ringenbach et al., 2015). In agreement with those results, Linder et al. (2015) reported a large improvement in the set-shifting ability of their participant with chronic stroke following eight weeks of ACT. It is hypothesized that the increased cadence during ACT elicits greater afferent sensorimotor stimulation of the central nervous system than cycling at a preferred voluntary cadence. While it has been demonstrated that aerobic exercise can improve executive function (Davis et al., 2011), it seems that

cardiovascular stress in the form of traditional moderate to vigorous intensity aerobic exercise may not be an effective way of improving cognitive function in certain populations with reduced cognitive function. In those cases, a sensorimotor-based exercise modality (i.e., mechanism #2 & #3) with a low cardiorespiratory demand such as ACT may be more effective than a cardiovascular-based exercise modality (mechanism #1) such as VC.

In fact, intense aerobic exercise can lead to anxiety-like behavior in rodents (Leasure & Jones, 2008) and to increased cortisol levels in humans post-exercise (Duclos et al., 1998; Rojas Vega et al., 2006). Elevated corticosterone levels due to stress have been shown to downregulate BDNF levels (Adlard & Cotman, 2004) and it seems plausible that exercise-induced stress due to high intensity or duration counteracts the positive effects of exercise on executive function (Kamijo et al., 2004; Kamijo, Nishihira, Higashiura, & Kuroiwa, 2007). It has been shown that forced exercise bouts in rats with focal ischemia induced through the middle cerebral artery produces higher heart rates, corticosterone levels, and shorter periods of elevated BDNF levels compared to less intense, voluntary exercise bouts (Ploughman et al., 2007). The stress response may be specific to acute bouts and diminish with repeated exercise, nevertheless, frequent, lower intensity exercise bouts are indicated for post-stroke recovery (Ploughman et al., 2007). Similarly, Kamijo and colleagues (2004) showed in adult men that reaction time and brain activation were only improved after medium intensity stationary cycling, but not after high or low-intensity cycling. This evidence supports the inverted U-shaped hypothesis which posits that moderate intensity exercise benefits cognitive functions more than light or vigorous intensities. Nevertheless, both voluntary and forced exercise in rodents have been shown to reduce infarct volume and improve function regardless of whether exercise was only done before or after the infarct (Ding et al., 2005; Luo et al., 2007).

Executive Function Assessment Tools

Executive function tests, including the Stroop Test, the Flanker Task, the TMT A & B, and the Digit Span Test served as outcome measures. Attention deficits are common post-stroke (Cicerone et al., 2000; Hyndman & Ashburn, 2003; Park & Ingles, 2001; Tatemichi et al., 1994) and therefore, measures which include attention as an executive function domain (Flanker Task)

are used as outcome measures. Attention as an outcome measure is important because persons with chronic stroke with better attention had significantly better balance, ADL scores, and fewer falls than those with poorer attention (Hyndman & Ashburn, 2003). As mentioned in the introduction, impairments in processing speed are also common post-stroke and contribute to delayed neuromotor rehabilitation as well as difficulties with fast, sequential movements (Almkvist et al., 1993; Dancause et al., 2002; Lafosse et al., 1997; Mendez & Ashla-Mendez, 1991; Padovani et al., 1995; Villardita et al., 1992; Walker et al., 2004; Zinn et al., 2007).

The executive function domains measured by the Stroop Test include selective attention, inhibition, and processing speed (Jensen & Rohwer Jr., 1966; MacLeod, 1991; Siegrist, 1997). The Flanker Task is a measure of sustained selective attention, inhibition, and processing speed (Colcombe & Kramer, 2003; Fenske & Eastwood, 2003; Kopp, Rist, & Mattler, 1996). The Digit Span Test was chosen because working memory deficits are common after acquired brain injuries (Cicerone et al., 2000, 2005; Park & Ingles, 2001; Robertson & Murre, 1999). The Digit Span Test assesses short-term and working memory and has been associated with prefrontal cortex function (Aleman & Van't Wout, 2008; Baddeley, 1992; Engle, Tuholski, Laughlin, & Conway, 1999; Iverson & Franzen, 1994; Reynolds, 1997). Scores on the forward (short term memory) and backward (working memory) Digit Span Test have been shown to be reduced in persons with brain lesions (Black, 1986). The TMT A & B is a measure of processing speed, set-shifting ability, and fluid intelligence, the latter being a measure of reasoning and spatial visualization (Arbuthnott & Frank, 2000; Salthouse, 2011).

Chapter 3

METHODS

Participants

Adults aged 18 years or older who were in the chronic post-stroke period (i.e., time since the last stroke ≥ 6 months) were recruited from stroke support groups, outpatient rehabilitation centers, and newspaper ads in the greater Phoenix metropolitan area. Inclusion criteria consisted of at least one unilateral ischemic or hemorrhagic stroke, approval for exercise participation from the primary care physician, a MMSE score of ≥ 24 (to rule out significant cognitive impairment, i.e., dementia), a Modified Ashworth Spasticity Scale (MAS) score of ≤ 3 (to rule out severe spasticity), a Beck Depression Inventory (DBI) score of ≤ 29 (to rule out severe depression), and the ability to sit in any seat independently for an unlimited time. Exclusion criteria included subarachnoid hemorrhage, severe stenotic or regurgitant heart disease, uncontrolled arrhythmias, third degree heart block, acute progressive heart failure, acute aortic dissection, acute myocarditis or pericarditis, acute pulmonary embolus or pulmonary infarction, deep venous thrombosis, dissecting aneurysm, angina at rest and/or during exercise, uncontrolled hypertension (systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg), uncontrolled diabetes, resting heart rate of >100 bpm, other neurological conditions (e.g., ataxia, PD, Huntington's disease, etc.), orthopedic conditions which preclude leg cycling, acute infections, uncontrolled visual or vestibular disturbances, recent injurious fall without medical assessment, and pregnancy.

Design

Crossover trials are a preferred design when adequate washout periods between interventions are included to prevent carryover effects. The most common design for three interventions is a 3 x 3 design consisting of three periods and three sequences. An intervention sequence consists of three periods, each consisting of either one session of ACT (Assisted Cycling Therapy), one session of VC (voluntary cycling), or one session of NC (no cycling). The three intervention sequences include 1) ACT-VC-NC 2) VC-NC-ACT 3) NC-ACT-VC. Twenty-four participants were to be randomized in equal numbers to these three sequences. The design for

this trial is illustrated in Table 1. The randomization schedule for up to 24 participants was computer generated (Table 2). This means that a maximum of eight participants could be randomized to each sequence.

Intervention sessions were spaced five to 10 days apart and always took place during the same time of day within participants and they were preceded and immediately followed by administration of the outcome measures. Five to ten days prior to the first of the three intervention sessions, participants visited the lab for screening, informed consent, and the collection of descriptive variables. Thus, participants completed four study visits total.

Sample Size Calculations

An online sample size calculator for crossover trials (http://hedwig.mgh.harvard.edu/sample_size/js/js_crossover_quant.html) provided by the Massachusetts General Hospital Biostatistics Center, Boston, MA, was used. To perform sample size calculations for the upper extremity function outcome measure (BBT) a minimal detectable change value rather than a minimal clinically important difference/meaningful change value had to be used due to a lack of literature on the latter. The reported minimal detectable difference for the BBT is 5.5 blocks per minute and the reported standard deviation of the difference between two repeated measures is 3.9 blocks per minute (Chen, Chen, Hsueh, Huang, & Hsieh, 2009). The required sample size to detect this difference with a power of 0.9 and a two-sided α level of 0.05 is $N = 8$ for the entire sample not considering attrition rate. The BBT was considered the primary outcome measure and the study was adequately powered to detect the minimal detectable difference. The smallest real difference for the LEMOCOT is about 6.0 with a within-participant standard deviation of 1.2 (Pinheiro, Scianni, Ada, Faria, & Teixeira-Salmela, 2014). The required sample size to detect this difference with a power of 0.9 and a two-sided α level of 0.05 is $N = 4$.

A one-way ANOVA analyses with post-hoc tests on change scores (pre-test – post-test) from Time 1 were to be conducted should a significant carryover effect between interventions have occurred. This meant that the data from Time 2 and 3 would be discarded and the study would be treated as a between-subjects design. Based on the reported within-group standard

deviation for the BBT of 12.2 blocks and an improvement of 5.5 blocks (Chen et al., 2009) an effect size of $f = 0.27$ was calculated. These parameters yielded a total sample size of $N = 177$. Power analyses for the executive function measures were not completed because they were secondary outcome measures and because minimal clinically important differences or minimal detectable changes have not been established for these tests. There is also a lack of data about feasible changes in the measures that can be expected as a result of interventions. Moreover, there are no standardized test parameters or administration procedures for these tests. This makes cross-study comparisons of effect sizes problematic.

However, Kluding et al. (2011) did find improvements of promising magnitude ($d \approx 0.6$ - 0.8) in working memory, attention, and processing speed in people with chronic stroke following a 12-week aerobic and resistance exercise intervention, as previously described. Based on a change of 0.56 digits on the backwards digit span test, a standard deviation of 0.90 for this change (Kluding et al., 2011), a power of 0.9, and a two-sided significance level of $\alpha = 0.05$, the required sample size would need to be $N = 30$ to detect the same magnitude of change. To detect an increase of 2.2% (SD = 4.3%) and 11.4% (SD = 24.9%) in correct responses during the congruent and incongruent conditions of the Flanker task, respectively, the sample size would need to be $N = 43$ and $N = 53$ using the same parameters as above for the power calculation. Thus, this study may be underpowered to detect changes in executive function.

As mentioned, the BBT was the primary outcome measure and only required a sample size of 8 for adequate power. However, we aimed to enroll up to 24 participants to have a better chance of detecting changes in secondary measures (measures of executive function) and to accommodate participant attrition.

Interventions

During cycling sessions, the participants' feet were placed in a specialized pedal which stabilizes the legs in the sagittal plane and minimizes movements in the other planes. The bicycle for the intervention was stationary and recumbent which eliminated balance requirements and minimized fatigue as less postural control was required.

ACT sessions began with a five-minute voluntary warm-up followed by 5 minutes of ACT at the voluntary cadence plus 50% of the differences between the target cadence and the voluntary warm up cadence. This was termed the familiarization cadence ($Cadence_{fam} = Cadence_{VC} + 0.5 \times (Cadence_{target} - Cadence_{VC})$). Then, 15 minutes of ACT at the target cadence followed, which was 1.8 times faster than the voluntary cadence or at least 80 rpm. These guidelines for the assisted cadence are based on Ridgel et al. (2009) and our recently completed randomized control trial where persons with DS cycled at approx. 80 rpm or 1.8 times faster than their voluntary cadence (Holzapfel et al., 2016). If a participant was unable, for any reason, to do ACT at a minimum of 80 rpm, then the cadence was reduced in increments of 5 rpm until the fastest sustainable cadence was found. The electrical motor in the bicycle was programmed to maintain that target cadence. This means that the crank arms turned at the target cadence regardless of the power contribution by the participant. A SRM power meter (Schoberer-Rad Messtechnik, Jülich, Germany) built into the bike sampled heart rate and cadence at 5 Hz during cycling sessions. Disenrollment from the study resulted when orthopedic problems presented a limitation to cycling at the prescribed cadence. This was the case for one participant (see Figure 1 for study flow diagram).

VC sessions consisted of a 5-minute warm-up followed by 20 minutes of cycling at a voluntary cadence and minimal resistance (~ 0.5 kp). During VC sessions the motor of the bicycle was not turned on. Periodic breaks during cycling sessions were allowed as necessary as long as they did not exceed 10 minutes cumulatively. Heart rate was monitored throughout each cycling session. For participants who are not taking β -blocker medication, age-predicted maximal heart rate was estimated using the equation $208 - 0.7 \times age$ developed by (Tanaka, Monahan, & Seals, 2001) which has been shown to be more valid in older adults than the conventional formula of $220 - age$ (Fox, Naughton, & Haskell, 1971), which tends to underestimate maximal heart rates in older adults (Tanaka et al., 2001). However, as most individuals post-stroke take blood pressure lowering medication such as β -blockers, heart rates may not be an accurate indicator of exercise intensity (American College of Sports Medicine, 2013). In fact, β -blocker therapy lowers heart rates at rest and in response to exercise (Chaloupka, Elbl, Nehyba, Tomaskova, & Jedlicka,

2005). Hence, the following formula was used for those undergoing β -blocker therapy: $164 - 0.72 \times \text{age}$ (Brawner, Ehrman, Schairer, Cao, & Keteyian, 2004). However, due to large interindividual variability in maximal heart rates of people who have had a stroke (Eng, Dawson, & Chu, 2004), ratings of perceived exertion (RPE) were also monitored with the Borg RPE scale (6-20; Borg, 1970). Brachial artery blood pressure measurements (on the less impaired arm) were taken at rest before the intervention session, twice during the intervention session (10 minutes apart) and one to two minutes after the conclusion of the intervention session. Exercise was discontinued if diastolic blood pressure exceeded 110 mmHg, if systolic blood pressure exceeded 250 mmHg, or if systolic blood pressure decreases by more than 10 mmHg during exercise (American College of Sports Medicine, 2013).

NC sessions consisted of sitting on the seat of the bicycle for 25 minutes without pedaling while engaging in a conversation about physical activity behaviors with a member of the research staff. During this conversation, the researcher asked standardized questions about their exercise habits and made standardized recommendations during the last 5 minutes of the conversation based on the answers from the participant and current exercise guidelines from the American Stroke Association. Participants were instructed not to change their normal physical and leisure activity habits during the 1-week intervals between intervention sessions. The administration of outcome measures began within five minutes after the conclusion of the intervention session.

Descriptive and Outcome Measures

On the first day, prior to randomization to a sequence, participants completed a brief cycling familiarization session to allow for the identification of potential problems during cycling and to assess eligibility. This was followed by the administration of the MMSE, the Physical Activity Scale for Individuals with Physical Disabilities (PASIPD), the Beck Depression Inventory (BDI), The Fugl-Meyer Assessment (FMA), and the Modified Ashworth Spasticity Scale (MAS) which served the purpose of descriptive and covariate measures.

During the intervention sessions, which were the second to fourth visits, the following outcome measures were administered in random order. The BBT assessed unilateral gross manual dexterity and arm function, and had adequate to excellent psychometric properties (Chen

et al., 2009; Lin et al., 2010). This test was the primary outcome measure and it was hypothesized that ACT would lead to improvements in global motor function (i.e., BBT). The LEMOCOT was used to assess changes in lower extremity function. The test was performed in a seated position. It required participants to tap two dots alternately with their big toe. The dots were spaced 30 cm apart and fixed proximally and distally in front of them on the floor at the intersecting line of the sagittal and transverse planes. The proximal dot was placed under the participant's heel when the knee was flexed to 90 degrees. The test was performed with one leg at a time. The LEMOCOT has adequate to excellent test-retest reliability in people post-stroke (ICC: 0.83–0.88) and it is a valid test of lower extremity function as it correlates with the Lower Extremity Fugl-Meyer Assessments (LEFMA; $r = 0.79$), the Berg Balance Scale ($r = 0.67$), and the Five Minute Walk Test ($r = 0.67$; Desrosiers et al., 2005).

The executive function tests were administered on an iPad or computer, and the index finger of the less impaired hand was used to respond, unless otherwise indicated. The Stroop Test is primarily a measure of selective attention and inhibitory control which has adequate to excellent psychometric properties (Jensen & Rohwer Jr., 1966; MacLeod, 1991; Siegrist, 1997). The TMT A & B primarily measure set-shifting ability (Salthouse, 2011). This test has excellent psychometric properties (Fals-Stewart, 1992; Sánchez-Cubillo et al., 2009; Smith et al., 2008). The Flanker Task is a measure of sustained selective attention, processing speed, and inhibitory control (Colcombe & Kramer, 2003; Fenske & Eastwood, 2003; Kopp et al., 1996). Specific psychometric properties for this test are not available due to methodological diversity. However, it has been used in people with stroke by Kluding, Tseng, & Billinger (2011). We used a similar version of the Flanker Task. The Digit Span Forward and Backwards Test is also a measure of prefrontal cortex function, specifically short-term and working memory as discussed previously (Aleman & Van't Wout, 2008; Black, 1986; Reynolds, 1997). We used a revised version of the forward and backward Digit Span Test with excellent test-retest reliability (Blackburn & Benton, 1957).

Statistical Analyses

A linear mixed model analysis was used with three main effects: sequence as a between-subjects factor, time or period as a within-subjects factor, and intervention as a within-subjects factor. Assignment to one of the three possible intervention sequences was coded as 1, 2, or 3. Time/period was coded as 1 (1st visit), 2 (2nd visit), and 3 (3rd visit) and intervention was coded as 1 (ACT), 2 (VC), and 3 (NC). Outcome measures were entered as the difference between pre- and post-scores. Recall that each outcome measure was administered before (pre) and immediately after (post) each intervention session. Least-square means, which adjusts for randomly missing values, was computed for each group at each time point. Two-tailed type I error probability was set to $\alpha = 0.05$. Tukey's HSD post-hoc analyses were used to test differences in change scores among the three interventions. The analyses were completed with a customized univariate general linear model in SPSS v.22. The sequence was entered as a random effect, time and intervention were entered as fixed effects, and sequence x subjects was entered as an interaction. The sequence x subjects interaction was entered specifically to use as the error term (denominator) to calculate the F statistic for the sequence effect. The p-value for the sequence effect was computed using an online p-value calculator (www.graphpad.com/quickcalcs/PValue1.cfm). If the sequence term was significant, indicating a carryover effect, then the intervention effect at time 1 was to be analyzed as a between-subjects factor using a one-way ANOVA which means that we would disregard time 2 and 3. BDI, months since stroke, LEFMA, UEFMA, and MAS scores were entered into the model as covariates for the LEMOCOT and BBT outcome measures. BDI, caffeine consumption, and months since stroke were entered into the model as covariates for EF outcome measures. As follow-up analyses, paired t-tests were used to test pre- to post-test differences within interventions in order to assess whether the changes in a given intervention were statistically significant.

Chapter 4

MANUSCRIPT #1: ASSISTED CYCLING THERAPY ACUTELY IMPROVES POST-STROKE UPPER AND LOWER EXTREMITY MOTOR FUNCTION

Abstract

Background: Stroke is the most common cause of long-term disability in the United States (US). Assisted Cycling Therapy (ACT) at relatively fast cadences of about 80 rpm has been associated with improvements in motor and clinical function in persons with Parkinson's disease and persons with Down syndrome. However, the acute effects of ACT on motor function of persons with stroke induced motor deficits have not been investigated.

Purpose: The purpose of this study was to compare the effects of ACT, voluntary cycling (VC), and no cycling (NC) on upper (Box and Blocks Test) and lower extremity motor function (Lower Extremity Motor Coordination Test) in adults with chronic stroke (age: 60 ± 16 years; months since stroke: 96 ± 85).

Methods: Twenty-two participants (female = 6, male = 16; ischemic = 12, n hemorrhagic = 10; left lesion = 15, n right lesion = 7) completed one session each of ACT, VC, and NC on separate days in counterbalanced fashion.

Results: ACT lead to greater improvements in lower and upper extremity function on the paretic and non-paretic side than VC or NC (all $p < 0.05$), except in the non-paretic lower extremity where ACT and VC produced similar improvement (both $p < 0.05$). Trend analyses revealed a positive relationship between ACT cadences and improvements in paretic lower and upper extremity function ($p < 0.05$). A positive relationship between voluntary cycling cadences and paretic and non-paretic lower extremity function was also revealed ($p < 0.05$).

Conclusion: ACT appears to benefit paretic and non-paretic motor function globally whereas the benefits of voluntary cycling are more task specific. Faster cycling ACT cadence are associated with greater improvements in global motor function which indicates a facilitating effect of faster movement rates on voluntary motor control.

Introduction

Post-stroke neuromotor deficits are the leading cause of long-term disability in adults (Dobkin, 2005). Arousal is a primary mechanism in the recovery of motor function during neurorehabilitation (Goldfine & Schiff, 2011). Exercised-induced arousal activates trophic and growth factor cascades that ultimately facilitate neuroplasticity and motor recovery (Goldfine & Schiff, 2011; Knaepen, Goekint, Heyman, & Meeusen, 2010; Mang, Campbell, Ross, & Boyd, 2013; Piepmeier & Etnier, 2015). Acute effects of exercise on arousal often indicates the efficacy of an exercise intervention. For instance, exercise-induced arousal can lead to the acute upregulation of Brain-Derived Neurotrophic Factor (Knaepen et al., 2010), which plays a facilitating role in neuroplasticity (Mang et al., 2013).

The kinematic similarities between cycling and walking, such as the cyclical and reciprocal agonist and antagonist activation patterns in the lower limbs, make cycling a viable mode of exercise for the post-stroke recovery of lower extremity function and walking ability (Barbosa, Santos, & Martins, 2015; Raasch & Zajac, 1999). Furthermore, the body weight support during cycling makes it an ideal therapeutic modality for people with severe hemiparesis, sensorimotor impairments, and muscular weakness that do not allow for dynamic body weight support (Barbosa et al., 2015). Cycling exercise has been shown to improve lower extremity function and mobility in the chronic post-stroke period (≥ 6 months post-stroke; Kamps & Schuele, 2005; Katz-Leurer, Carmeli, & Shochina, 2003). Increased muscular activation of the paretic leg has been reported in non-ambulatory participants during and within the first five to 30 minutes after cycling exercise (Fujiwara, Liu, & Chino, 2003; Seki, Sato, & Handa, 2009). Cycling facilitates the use of the paretic leg in people with hemiparesis as the paretic leg is aided by the non-paretic leg through coupling of the pedals (Barbosa et al., 2015). However, this may also encourage compensation by the non-paretic leg and perpetuate asymmetries in the use of the legs (Chen, Chen, Chen, Fu, & Wang, 2005; Ferrante et al., 2011).

Assisted Cycling Therapy (ACT), whereby an electric motor transmits torque to the pedals to facilitate the pedaling motion, may encourage more symmetric use of the lower extremities as the pedal motion does not rely on the torque contribution of the non-paretic leg

(Ferrante et al., 2011). ACT at low cadences (30-50 rpm) is typically used in the acute phase after a stroke for patients with impaired motor function and insufficient active muscular contractions for aerobic exercise (Barbosa et al., 2015), but ACT may also have potential benefits in regards to walking speed and distance during the chronic post-stroke period (Lee et al., 2008). In addition, ACT has shown to stimulate blood flow and neural activity bilaterally in the sensorimotor cortices, premotor cortices, and supplemental motor areas to the same degree that active cycling does in persons post-stroke, with the exception of the sensorimotor cortex on the unaffected side (Lin, Chen, & Lin, 2013).

ACT may be particularly useful for people with low cardiorespiratory fitness levels. Maximal aerobic capacities can be reduced by 50% post-stroke (Kelly, Kilbreath, Davis, Zeman, & Raymond, 2003) and this may limit the ability to sustain a movement rate and duration that optimizes neuroplastic effects and motor recovery (Christova et al., 2011; Linder et al., 2015). For instance, voluntary cycling at 50 rpm did not increase excitability or neuroplasticity in people with chronic stroke (Murdoch, Buckley, & McDonnell, 2016). However, a positive correlation between ACT cadences and changes in functional connectivity between the thalamus and primary motor cortex has been reported in persons with Parkinson's disease (PD; Shah et al., 2015). On average, the assisted cadence was 43% faster than the voluntary cadence and there was no evidence of diminishing returns at assisted cadences up to 95 rpm in regards to functional connectivity. During ACT, an electric motor integrated into a stationary recumbent bicycle powers the pedals and maintains a pre-programmed cadence regardless of the power contribution by the cyclist (for more details see Holzapfel, Ringenbach, Ganger, Gomez, & Parker, 2016; Holzapfel et al., 2015)

ACT may be most beneficial at fast cadences (e.g., 80 rpm) as it is in line with massed practice paradigms. The number of repetitions seems to be a crucial variable in the rehabilitation of motor function (Lang, MacDonald, & Gnip, 2007; Linder et al., 2015; Mark & Taub, 2004). Generally, a greater number of task specific repetitions are associated with greater improvements in motor function (Sterr et al., 2002). ACT at a fast cadence is a way to complete more repetitions in a given amount of time.

Evidence in support of the efficacy of ACT at greater than voluntary cadences (~80 rpm) has been mounting in recent years. ACT interventions have been shown to improve tremor (Ridgel, Peacock, Fickes, & Kim, 2012), bradykinesia (Ridgel et al., 2009; Ridgel et al., 2012), active range of motion in the lower and upper extremities (Corbett, Peer, & Ridgel, 2013), gait parameters (Corbett et al., 2013; Stuckenschneider, Helmich, Raabe-Oetker, Froböse, & Feodoroff, 2015), functional bimanual dexterity (Ridgel et al., 2009), clinical motor function (Beall et al., 2013; Mohammadi-Abdar et al., 2016; Ridgel et al., 2009; Ridgel, Phillips, Walter, Discenzo, & Loparo, 2015), and mobility (Ridgel et al., 2015) in people with PD. Thus, ACT may not only benefit the function of the lower extremities but also of the upper extremities. Similar evidence has been published about the effects of ACT in persons with Down syndrome (DS). Improvements in walking speed have been found after 8 weeks of ACT in adolescents and adults with DS (Holzapfel et al., 2016). ACT also seems to benefit manual dexterity acutely and chronically in adolescents with DS (Holzapfel et al., 2015; Ringenbach, Albert, Chen, & Alberts, 2014).

The only evidence regarding ACT at a relatively fast cadence in people post-stroke comes from a case report (Linder et al., 2015). A 46-year old male who had experienced a stroke 10.5 months prior to the study, completed 8 weeks of three 45-minute ACT sessions per week at approximately 80 rpm. Following each ACT session, they also completed 45 minutes of repetitive task practice with the paretic upper extremity. The pre- to post-test changes met or exceeded the threshold of minimal clinically important differences for the functional ability scale of the Wolf Motor Function Tests and the Fugl-Meyer Assessment. Improvements on the 9-Hole Peg Test and the 6-Minute Walk Test were also recorded. Due to the upper extremity repetitive task practice, we cannot conclude that ACT benefited upper extremity motor control, but the improvements in lower extremity function are most likely attributable to ACT.

To inform clinical practice, it is important to investigate dose response relationships between intervention parameters such as intensity, duration, or rate of movement and the degree of change in outcome measures (Cooke, Mares, Clark, Tallis, & Pomeroy, 2010). For instance, Sullivan and colleagues (2011) found a positive dose-response relationship between exercise

intensity and performance on a finger-to-nose task. Additionally, faster cycling cadences increase the frequency of mechanical stimulation and afferent sensory feedback, which may have a positive effect on cortical activation and excitability (Christensen et al., 2000; Corbett et al., 2013; Fisher et al., 2008) and in turn benefit motor control and output. For instance, mechanically induced vibrations of the hand appear to enhance corticospinal excitability (Christova et al., 2011). Christensen et al. (2000) reported positive correlations between active cycling cadences and activation of the cerebellum ($r = 0.66$), sensory cortex ($r = 0.72$), and motor cortex ($r = 0.75$) in young, healthy adults. Little is known about the influence of aerobic exercise intensity or movement rate on the degree of post-stroke motor rehabilitation.

In addition to exercise intervention metrics, one of the most powerful predictors of motor recovery after stroke is the time since the stroke (Jørgensen, Nakayama, Raaschou, & Olsen, 1995; Page, Gater, & Bach-y-Rita, 2004). Most of the post-stroke motor recovery takes place during the acute phase after a stroke but can continue during the chronic phase (Page et al., 2004). It is therefore important to investigate the relationship between the time since the last lesion and the effectiveness of ACT.

The primary purpose of this study was to compare the acute effects of ACT, VC (voluntary cycling), and NC (no cycling) on upper and lower, paretic and non-paretic extremity motor function in people during the chronic period after stroke. We hypothesized that global motor function would benefit more from ACT than from VC or NC. A secondary purpose was to explore the association of intervention parameters (ratings of perceived exertion [RPE], heart rate, and cadence) and months since stroke with the amount of change in motor function.

Methods

Participants

Participants were recruited through newspaper ads, from outpatient rehabilitation clinics, and from stroke support groups in the Phoenix metropolitan area. Twenty-two participants completed this study (see Figure 1 for flow-diagram). Participants had suffered at least one unilateral hemorrhagic or ischemic stroke at least six months ago, had residual hemiparesis, were at least 18 years of age, were medically stable, had controlled blood pressure levels (resting

blood pressure < 140/90 mmHg), scored at least 24 on the MMSE, and scored no higher than three on the Modified Ashworth Scale (MAS). Persons with severe aphasia that precluded comprehension and completion of tests and persons with other neurological conditions were excluded. See Table 3 for participant characteristics.

Design

Every participant completed four visits to our research laboratory spaced five to 10 days apart. The first visit consisted of the informed consent process, screening procedures, and the collection of descriptive measures. The following three visits consisted of a session of ACT, a session of VC, or a session of NC. The order in which participants completed these sessions was counterbalanced across participants (see Figure 1). Motor function testing was completed before (i.e., pre-testing) and immediately after each session (i.e., post-testing). Post-testing commenced within five minutes after completion of the given intervention session.

Descriptive Measures

The following measures were collected during the first visit. Height and weight were measured with a vertical stadiometer and a calibrated balance-beam scale. Body mass index (BMI) was calculated as the weight (kg) divided by the square of the height (m). Resting blood pressure and heart rate were measured after five minutes in a seated position. The MMSE (Tombaugh & McIntyre, 1992), Physical Activity Scale for Individuals with Physical Disabilities (PASIPD; Washburn, Zhu, McAuley, Frogley, & Figoni, 2002), Beck Depression Inventory (BDI; Beck, Steer, & Carbin, 1988), Fugl-Meyer Assessment for the lower (LEFMA) and upper extremity (UEFMA; Fugl-Meyer, Jääskö, Leyman, Olsson, & Steglind, 1975), and the Modified Ashworth Scale (MAS; Gregson et al., 1999) were administered according to standard procedures. The age-predicted maximal heart rate of participants was calculated using the following formula which was developed by Tanaka et al. (2001): $208 - 0.7 \times \text{age}$. For the 16 participants on beta-blocker medication a formula developed by Brawner, Ehrman, Schairer, Cao, and Keteyian, (2004) was used to predict maximal HR: $164 - 0.72 \times \text{age}$.

Outcome Measures

Paretic and non-paretic upper extremity motor control was assessed during pre- and post-testing with the Box and Blocks Test (BBT; Chen et al., 2009; Lin et al., 2010; Platz et al., 2005). This test required participants to move wooden cubes (16.39 cm³) from one box (25.4 cm x 25.4 cm) to another box of equal size across a barrier that was 15.2 cm in height (Mathiowetz, Volland, Kashman, & Weber, 1985). Tossing cubes over the barrier was not allowed. Instead, a part of the participant's hand (i.e., finger tips) had to pass over the barrier and the cube was to be dropped into the box. Participants were instructed to move as many cubes as possible within 1 minute. This test was completed first with the non-paretic arm and then with the paretic arm. A 10-second practice trial was given for each arm before the 1-minute test. The number of cubes that were transported per minute was used as the outcome measure.

Lower extremity motor control was tested with the Lower Extremity Motor Coordination (LEMOCOT) test. The test was administered in accordance with (Desrosiers et al., 2005). This test was completed in a seated position and required participants to alternately touch two red dots with their big toe on a board that was placed on the floor in front of the participant. The dots were spaced 30 cm apart and arranged proximally and distally on the intersecting line of the sagittal and transverse plane in front of the participant with the proximal dot placed directly under the participant's heel when the knee was flexed to 90 degrees. Participants were required to alternately touch the dots with their big toe as fast as possible. This task required cyclical knee extension and flexion, slight ankle plantar and dorsi flexion, and very slight hip flexion and extension, similar to the musculoskeletal requirements of cycling. Participants completed a 5-10 second practice trail and then three 20 second test trails with a one minute break between trials. This was first completed with the non-paretic leg and then with the paretic leg. The average of the second and third trails was used as the outcome measure (Pinheiro et al., 2014).

Interventions

All cycling sessions lasted 20 minutes and were completed on a stationary, recumbent research prototype cycle ergometer (Theracycle) that was built by the Exercycle Company (Franklin, MA). The electric motor that was built into the bicycle could turn the pedals at up to 95

rpm regardless of the power contribution by the participant. The pedals were specialized platform pedals with metal cuppings and Velcro straps that prevented the feet from slipping off the pedals in any direction. For a thorough description of the bike, see Holzapfel, Ringenbach, Ganger, Gomez, and Parker (2016) and Holzapfel et al. (2015).

ACT sessions began with a five-minute voluntary warm-up without the help of the motor. The target ACT cadence was determined to be 1.8 times greater than the average warm-up cadence as previous research with persons with DS has shown that an ACT cadence which is 80% greater than the voluntary cadence may be beneficial for motor control and cognitive function (Holzapfel et al., 2015, 2016; Ringenbach et al., 2016). However, the minimum target cadence was 80 rpm because an assisted cadence of at least 80 rpm has been shown to be beneficial for clinical, motor, and cognitive function of persons with PD (Alberts et al., 2011; Ridgel, Vitek, & Alberts, 2009; Ridgel et al., 2011) and persons with DS (Holzapfel et al., 2015; Ringenbach et al., 2016). The maximum target cadence was 95 rpm due to the limit of the motor. After the five minute warm up, the motor was turned on and the cadence was set to the average of the warm-up and the target cadence to allow participants to become familiar with ACT. Subsequently, the motor was programmed to maintain the target cadence for 15 minutes. If participants were uncomfortable at the prescribed target cadence, then the cadence was lowered in 5 rpm increments until the participant felt comfortable. Participants were not encouraged to pedal slower or faster than the target cadence.

For VC sessions, participants were instructed to complete a five-minute warm-up by cycling at their own preferred cadence and then to continue cycling for 15 minutes at their preferred cadence. The motor was not turned on and participants were not encouraged to pedal faster or slower at any point. The resistance that participants were cycling against was 0.5 kp.

During NC sessions, participants also sat on the bicycle with their feet strapped into the pedals but they did not cycle. Participants were allowed to turn the pedals by 180 degrees every few minutes to change the position of their legs. During the 20 minute NC session, participants engaged in a conversation about their physical activity habits with the researcher which always

concluded by the researcher informing the participant of the post-stroke physical activity recommendations (Gordon et al., 2004).

Statistical Analyses

The outcome measures were converted into change scores by subtracting the pre-test scores from the post-test scores. Thus, a positive change score indicates an improvement. Numerous change scores were not normally distributed depending on the condition as indicated by Shapiro-Wilk tests. Therefore, all change scores were transformed as an inverse unit ($1/x$). Inverse transformations have the effect of making a very large number small and a very small number large. Thus, all values were first multiplied by -1 and then 1 was added to all values before inversion as there cannot be a 0 in the denominator. Once the transformation was completed the ordering of the data was identical to the original data. The transformed change scores were normally distributed within each intervention as verified with Shapiro-Wilk tests. Variances in change scores did not differ between interventions as shown by Levene's tests. The assumptions of homoscedasticity (visual inspection of the distribution of residuals by predictor), normal distribution of residuals (Shapiro-Wilk tests), and normal probability of residuals (visual inspection of Q-Q plots) did not appear violated for the regression analyses.

Linear mixed model (LMM) analyses were used with transformed change scores as the dependent variable(s) and with three main effects: sequence, time, and intervention. Assignment to one of the three possible intervention sequences was coded as 1 (ACT-VC-NC), 2 (VC-NC-ACT), or 3 (NC-ACT-VC). Time was coded as 1 (1st visit), 2 (2nd visit), and 3 (3rd visit) and intervention was coded as 1 (ACT), 2 (VC), and 3 (NC). Tukey's HSD post-hoc analyses were used to test differences among the change scores of the three interventions. The models were computed with and without the following covariates: BDI, months since stroke, and MAS scores. In addition, LEFMA scores were entered as a covariate for the LEMOCOT change scores and UEFMA was entered for the BBT change scores. BDI was included as a covariate because the treatment of post-stroke depression has been shown to accelerate motor recovery, potentially by improving mood, but also by acting on the serotonergic system which facilitates motor output (Chollet et al., 2011). Caffeine consumption has been shown to benefit gross motor performance

and potentially impair fine motor performance (Smith, 2002; Spriet, 2014) and it was therefore included as a covariate. Months since stroke was included as a covariate because motor recovery is fastest during the acute post-stroke period and approaches an asymptote with the potential for continued recovery for many years post-stroke (Jørgensen et al., 1995; Page et al., 2004).

As a follow-up to LMM analyses and to test whether within intervention pre- to post-test changes were significant, paired samples t-tests were conducted, separately for each intervention. Next, linear ordinary least squares (OLS) regression models were computed to analyze the trend and associations of RPE, percent of heart rate reserve (%HRR), cycling cadence, and months since stroke with change scores. These linear trends were analyzed separately for each intervention. All β values listed are unstandardized. Analyses were completed with SPSS v. 22. Two-tailed type I error probability was set at $\alpha = 0.05$.

Results

Treatment Fidelity

No adverse events occurred during or as a result of the interventions. All 22 participants completed all three intervention sessions and no session was terminated prematurely. Intervention parameters are summarized in Table 4. The mean ACT cadence was $83.8 \pm 23.9\%$ (mean \pm SD) faster than the voluntary warm-up cadence. However, three participants were not comfortable cycling the minimum prescribed 80 rpm. Their maximum cadences during ACT were 66 rpm, 70 rpm, and 74 rpm, which was still faster than their VC cadence. The mean VC cadence was significantly slower than the mean ACT cadence, but the heart rates did not differ between ACT and VC (see Table 4).

Main and Intervention Effects

The results of the LMM and post-hoc analyses are summarized in Table 5. The models did not differ whether covariates were included or not, and none of the covariates were significant. Thus, we are only reporting the statistics from the models without covariates. There was no main effect of sequence indicating that there were no carryover effects. There was also no main effect of time. There was a main effect of intervention for LEMOCOT-P change scores.

Post-hoc analyses revealed a significantly greater improvement for ACT compared to NC, but VC did not differ from ACT and NC. There was also a main effect for LEMOCOT-NP. Change scores were greater for ACT and VC compared to NC. There was a significant main effect for BBT-NP. Change scores for ACT and VC were greater compared to NC. There was no main effect of intervention for BBT-P.

Paired sample t-tests revealed significant pre- to post-test changes in all outcome measures for the ACT intervention. A significant improvement also occurred in the LEMOCOT-NP for the VC intervention. A negative change occurred in BBT-NP for the NC intervention. The results of the t-tests are listed in Table 6.

Trend Analyses

The trend analyses indicated the following for the ACT intervention (Table 7). A negative linear trend was found for RPE and BBT-NP change scores. A positive linear trend was found for cadence and LEMOCOT-P as well as BBT-P. Regarding the VC intervention (Table 8), the trend analyses revealed a negative linear association between RPE and LEMOCOT-P and a positive linear association for cadence and LEMOCOT-P and for cadence and LEMOCOT-NP.

Discussion

Main Effects of the Interventions

The results partially support our hypothesis. The main intervention effects and post-hoc analyses indicated a favorable effect of ACT and to a lesser degree VC on upper and lower extremity non-paretic motor control. Lower extremity paretic control appeared to benefit most from ACT. Follow-up analyses with the paired samples t-tests showed a significant positive effect of ACT on upper and lower extremity control on the paretic and non-paretic side (see Figure 2 through 5). The only other significant pre- to post-test improvement was present in the VC intervention on the non-paretic lower-extremity (see Figure 2). Thus, our results show more salient effects of ACT compared to VC on upper and lower extremity non-paretic and paretic motor control. The improvement in function of the paretic upper extremity following lower extremity exercise is consistent with other studies (Ploughman et al., 2008).

Specifically, our results are consistent with the case study by (Linder et al., 2015) which documented upper and lower paretic extremity benefits following eight weeks of ACT combined with upper extremity repetitive task practice. However, our study remains the first to provide evidence of the acute effects of ACT on upper extremity function in people with chronic stroke. Due to the chronic nature of Linder's study, this is also the first account of the acute effects of ACT at high cadences on lower and upper extremity function in people after stroke.

The ACT intervention in our study appears to have been more beneficial than VC. Other studies have also found ACT to be more effective than VC in regards to the motor control of persons with PD (Corbett et al., 2013; Ridgel et al., 2009; Ridgel et al., 2012, 2015) or persons with DS (Chen et al., 2014; Holzapfel et al., 2016; Holzapfel et al., 2015; Ringenbach et al., 2014). Compared to resting levels, ACT has been shown to increase blood flow and neural activity in areas of the motor cortex (Lin et al., 2013). It has been hypothesized that the benefits of ACT stem from the faster than voluntary cycling cadence and associated augmented afferent corticospinal stimulation rather than the cardiovascular stress or arousal (Alberts et al., 2016, 2011; Corbett et al., 2013). Across many studies, similar heart rates during ACT and VC but superior therapeutic effects of ACT have been found (Alberts et al., 2011; Corbett et al., 2013; Holzapfel et al., 2016; Holzapfel et al., 2015; Ridgel et al., 2015; Ringenbach et al., 2014).

Dose Response Relationships

Much of the evidence for the augmented effects of ACT on corticospinal activation and excitability comes from studies in persons with PD. ACT has repeatedly been shown to improve cortical and subcortical activation and clinical motor function (Alberts et al., 2016, 2011; Beall et al., 2013). ACT may also acutely improve functional connectivity of the primary motor cortex and ipsilateral thalamus following ACT (Beall et al., 2013), and, as mentioned, these changes in functional connectivity are positively related to cycling cadence (Shah et al., 2015). Further evidence for the cortical benefits of fast cycling cadences comes from (Christensen et al., 2000), who reported positive correlations between voluntary cycling cadences and activation of the cerebellum ($r = 0.66$), sensory cortex ($r = 0.72$), and motor cortex ($r = 0.75$) in young, healthy adults. The dose-response relationship between cycling cadence and cortical and subcortical

activation is even generalizable to the relationship between upper extremity mechanical stimulation and corticospinal excitability (Christova et al., 2011).

The results of the present study support these positive dose-response relationships. We found positive linear relationships between the ACT cadence and changes in the paretic lower and upper extremity (see Table 7 and Figures 6 and 7). We also found a positive relationship between the VC cadence and changes in paretic and non-paretic lower extremity control (see Table 8 and Figures 8 and 9). The positive relationships between cadence and paretic motor control in our study are especially encouraging and may be an indication of the potential for organizational changes and structural remodeling of ipsilesional and contralesional motor cortices during the chronic post-stroke period as evidenced by studies of constraint-induced movement therapy (Gauthier et al., 2008; Hallett, 2001; Liepert et al., 1998; Liepert, Bauder, Miltner, Taub, & Weiller, 2000; Rossini, Calautti, Pauri, & Baron, 2003). It appears that cadences close to or over 80 rpm are necessary for changes in paretic motor control to occur (see Figures 6, 7, and 8). This is consistent with the lack of effect of cycling at 50 rpm on post-stroke motor cortex excitability and neuroplasticity (Murdoch et al., 2016). The relationship of ACT but not VC cadence with paretic upper extremity control indicates that faster than voluntary cadences may be necessary for sufficient cortical activation that manifests in global and non-task specific motor control changes. Similarly, a positive relationship between cycling exercise intensity and motor cortex activation has been reported (Brümmer, Schneider, Strüder, & Askew, 2011). Motor cortex excitability, in turn, has been shown to relate positively to paretic hand function (Hummel et al., 2005).

Future studies should investigate whether ACT at fast cycling cadences increases motor cortex excitability similarly to transcranial magnetic stimulation and whether ipsilesional or contralesional excitability is associated with improvement in motor control on the paretic side. We have reason to speculate that changes in motor cortex excitability occurred bilaterally and globally after ACT at relatively fast cadences as both upper extremities exhibited task non-specific improvements. To shed more light on interindividual variability of motor recovery in response to ACT or VC, future research should investigate the effect of leg cycling on

contralateral sensorimotor cortex activation. The degree of activity of the contralateral sensorimotor cortex in response to passive movement may be predictive of motor recovery (Jang et al., 2004).

In contrast to our results, (Ploughman et al., 2008) reported an acute negative relationship between maximum treadmill speed and function of the paretic upper extremity in persons with chronic stroke. A difference between cycling and walking in computational demand on reticular formations, including motor cortex areas, could account for the contrasting results. According to (Dietrich & Audiffren, 2011) Reticular-Activating Hypofrontality (RAH) Model, motor activities involving large muscle groups place an enormous computational demand on reticular formations. The magnitude of the computational demand is directly related to the amount of muscle mass involved and the intensity of the exercise. According to this framework, walking would require a greater amount of computational resources than recumbent cycling as it involves postural and upper body musculature. The faster the walking speed, the greater the demand and the higher the chance that exercise could lead to central fatigue (Dietrich & Audiffren, 2011). This mechanism may have compromised post-exercise upper extremity control in those who walked at relatively fast speeds. Additionally, differences between the Action Research Arm Test that (Ploughman et al., 2008) used and the BBT may partially account for the differing results. If the Action Research Arm Test is more cognitively demanding than the BBT, maybe due to more complex instructions, then it may require a greater amount of executive control. The executive control processes of the prefrontal cortex may have been acutely impaired after treadmill walking at relatively fast speeds because the limited metabolic resources available to the brain were diverted to the reticular formations for the task of walking (Dietrich & Audiffren, 2011). This may have led to the impaired performance during the Action Research Arm Test following treadmill walking at fast speeds relative to slow speeds.

A significant negative linear association was present between RPE and change in BBT-NP for the ACT intervention and between RPE and change in LEMOCOT-P for the VC intervention. These trends indicate that higher levels of exertion may not be beneficial for acute motor control changes. This is in accordance with a negative relationship between perception of

effort and central motor drive in persons with chronic fatigue syndrome (Sacco et al., 2013). Relatively high RPE during exercise can lead to central fatigue (Dietrich & Audiffren, 2011; MacKay-Lyons & Makrides, 2002b; Michael et al., 2006; Riley & Bilodeau, 2002) which in turn may have compromised cortical and sub-cortical output (Benwell et al., 2006; Sacco et al., 2013). Locomotor activities are thought to tax a large portion of the computational capacity of reticular formations, subcortical, and cortical areas (Dietrich & Audiffren, 2011). This demand could be exacerbated in persons with stroke-induced hemiparesis because of difficulties with paretic extremity control (Riley & Bilodeau, 2002). In fact, we found a negative relationship between LEFMA scores and RPE ($R^2 = 0.24$, $\beta = -0.11$, $p = 0.022$) which indicates that persons with more impaired lower extremity motor function had higher RPE during ACT. However, emphasis must not be placed on the negative relationship between RPE and changes in motor control because only two out of eight possible relationships (see Tables 4.5 and 4.6) were significant. Additionally, (Ploughman et al., 2008) reported no relationship between RPE during treadmill walking and acute changes in paretic upper extremity function.

It should also be mentioned that we found no relationship between UEFMA scores and BBT change score. We also did not find a relationship between LEFMA and LEMOCOT change scores. This indicates that persons with varying degrees of stroke-induced motor impairments have similar potentials for acute motor improvements.

Limitations

The trend analyses were based on cross-sectional data instead of the experimental manipulation of predictor variables (i.e., cadence, RPE, heart rate, and months since stroke). Thus, the reported trends are a very limited piece of evidence needed to establish causality. Future studies should actively manipulate and control predictors of motor function that are of clinical interest. The primary purpose of this study, however, was not to examine intervention characteristics that predict improvements in motor function, but rather to compare the efficacy of ACT, VC, and NC in regards to the motor function of people during the chronic post-stroke period.

The acute effects of exercise do not serve the purpose of predicting chronic changes that may result from long-term interventions. For instance, participants who did not experience acute

improvements, maybe due to central fatigue, may still benefit from a long-term intervention as an adequate amount of rest between cycling sessions can allow for neuroplastic changes and structural remodeling to occur (Gauthier et al., 2008; Ploughman et al., 2005; Schinder & Poo, 2000) because the mechanisms that precipitate neurobehavioral changes differ between acute and chronic effects (Cotman et al., 2007; Hillman, Snook, & Jerome, 2003b; Kubesch et al., 2003; Molteni, Ying, & Gómez-Pinilla, 2002; Ploughman et al., 2005). Thus, the investigation of chronic effects of ACT on post-stroke paretic motor function is warranted. However, the acute improvements in motor function following ACT and, to a limited extent, VC, indicate increased arousal as the BBT and LEMOCOT are most likely highly implicit tasks (Dietrich & Audiffren, 2011). This increased arousal could be a positive predictor of the beneficial chronic effects that ACT may have on neuroplasticity and motor recovery (Goldfine & Schiff, 2011), but more research is necessary.

The BBT and LEMOCOT tests both suffered from a floor effect. For each test there were six participants who could not complete even one successful block transfer or toe touch either on the pre- or post-test. Thus, these tests were unable to detect any changes in participants with very poor motor function. Tests that can detect very small changes, such as range of motion tests, should be incorporated in future studies. However, the significant pre- to post-changes speak for the efficacy of the intervention despite six participants who experienced no detectable change.

Conclusion

ACT at a relatively fast cadence of about 80 rpm seems to carry greater acute benefits on paretic post-stroke motor function than VC or NC. The benefits in motor function following ACT appear to be global as the upper extremities also benefited even though they were not involved in the exercise. The most likely mediator of these improvements is enhanced corticospinal excitability produced through the augmented afferent sensory input during ACT. This hypothesis is supported by the positive association between cycling cadence and motor function improvements. The negative association between perceived exercise intensity and motor function

changes indicates that high exercise intensities may lead to central fatigue and acutely blunt the positive effects of exercise on motor output.

Chapter 5

MANUSCRIPT #2: THE ACUTE EFFECTS OF ASSISTED CYCLING THERAPY AND VOLUNTARY CYCLING ON POST-STROKE EXECUTIVE FUNCTION: EVIDENCE OF THE RETICULAR-ACTIVATING HYPOFRONTALITY MODEL

Abstract

Background: Thirty-five to 75% of people with chronic stroke present with impairments in cognitive or executive function. These impairments exacerbate limitations in regards to activities of daily living. To date, there is very little evidence regarding the effects of exercise on post-stroke executive function. Assisted Cycling Therapy (ACT) has produced promising benefits on executive function in persons with Parkinson's disease and persons with Down syndrome.

Purpose: The primary purpose of this study was to compare the acute effects of ACT, voluntary cycling (VC), and no cycling (NC) on executive function in adults with chronic stroke. The secondary purpose was to explore predictors of changes in executive function.

Methods: Twenty-two adults with chronic stroke (age: 60 ± 16 years; months since stroke: 96 ± 85 ; female = 6, male = 16; ischemic = 12, hemorrhagic = 10; left lesion = 15, right lesion = 7) complete one session of ACT (cadence = 79.5 ± 8.5 ; heart rate = 90.3 ± 17.5), VC (cadence = 51.5 ± 13.7 ; heart rate = 92.3 ± 21.3), and NC on separate days in counterbalanced fashion. Inhibitory control, sustained selective attention, and set-shifting were tested with the Stroop Test, Flanker Task, and Trail Making Test, respectively.

Results: ACT was associated with greater improvements in inhibitory control compared to NC ($p < 0.05$), but did not differ from VC which was associated also associated with improvements in inhibitory control ($p < 0.05$). No changes were found in other measures of executive function or processing speed. Ratings of perceived exertion shared an inverted-U shaped relationship with measures of processing speed ($p < 0.05$) and a negative linear relationship with measures of executive function, including inhibitory control ($p < 0.05$). Negative or inverted-U shaped relationships between cycling cadence and aspects of executive function also emerged.

Conclusion: ACT and VC seem to carry similar acute benefits in inhibitory control in people with chronic stroke. In accordance with the Reticular-Activating Hypofrontality Model, greater levels of exertion and faster movement rates may lead to resource depletion in the prefrontal cortex and central fatigue in the reticular formations.

Introduction

About 35% of people post-stroke exhibit chronic cognitive impairment (Patel et al., 2003). Cognitive post-stroke recovery is important as greater cognitive recovery is associated with a lower degree of disability and a lower risk of institutionalization (Patel et al., 2003).

Pharmacological treatments and supplements have produced mixed results in slowing the progression of cognitive impairment in older adults (Fenton, Dickerson, Boronow, Hibbeln, & Knable, 2001; Harvey, Rabinowitz, Eerdeken, & Davidson, 2005; Reading, Luce, & McKeith, 2001; Sacco et al., 2013) and pharmacological treatments are typically associated with side effects and require adjunctive medication (Harvey et al., 2005; Reading et al., 2001). Exercise interventions have shown moderately strong effects in slowing or halting the progression of cognitive impairment (Heyn, Abreu, & Ottenbacher, 2004) and exercise is often more cost-effective and associated with fewer side effects compared to pharmaceuticals (Herman et al., 2005). However, limited evidence exists for a beneficial effect of exercise on post-stroke cognitive function.

Studies have shown mixed effects of exercise on cognitive performance in people post-stroke. Quaney et al. (2009) reported an improvement in processing speed but not in set-shifting or inhibitory control after an eight-week cycling intervention. Ploughman et al. (2008) found no changes in set-shifting or working memory after a single 20-minute bout of body weight supported treadmill walking. Twelve weeks of combined aerobic and strength training were associated with improvements in working memory during the chronic post-stroke period (Kluding et al., 2011). A meta-analysis completed in 2011, which included nine studies, revealed a small but significant beneficial effect of exercise on cognitive function in people post-stroke (Cumming et al., 2012).

More research is necessary to identify the optimal characteristics of exercise for the treatment of cognitive deficits in people who are post-stroke. Assisted Cycling Therapy (ACT)

paradigms have produced promising neurocognitive benefits in persons with other neurological conditions, including Parkinson's disease (PD; Ridgel, Kim, Fickes, Muller, & Alberts, 2011) and Down syndrome (DS; Holzapfel et al., 2016; Ringenbach et al., 2016). In ACT interventions, the participant's cycling cadence is typically augmented to an average of about 80 rpm through the help of an electric motor or a tandem cyclist. For instance, Ridgel et al. (2011) reported acute improvements in inhibitory control of participants with PD following ACT at 60, 70, and 80 rpm. Acute and chronic improvements in various measures of executive function have been found in persons with DS following ACT at an average of about 80 rpm (Holzapfel et al., 2015, 2016; Ringenbach et al., 2016; Ringenbach et al., 2014). The ACT interventions often produce a cadence that is 35% to 80% faster than the voluntary, active cadence (Holzapfel et al., 2016; Ridgel et al., 2009; Ringenbach et al., 2014). It is therefore worth exploring the effects of ACT on cognitive function in people who have suffered a stroke. To date, the only study of the effects of ACT after stroke is a case report by Linder and colleagues (2015). A 46-year old male participant who was 10.5 months post-stroke showed vast improvements in set-shifting ability following eight weeks of ACT at approximately 80 rpm. That is a promising result, but clearly more research is needed regarding the effects of ACT on post-stroke cognitive function.

It is also important to investigate dose-response relationships in intervention studies. Significant intervention effects indicate that the intervention is associated with a mean improvement across participants, but it is unlikely that every participant experienced an improvement and that every participant experienced the same magnitude of improvement (Bouchard et al., 1999). Thus, intervention studies are more clinically informative and applicable when there are documented relationships between intervention parameters and the magnitude of benefit and when these relationships can be exploited to the client's advantage. Often, there are linear or quadratic dose-response relationship between the intensity of exercise and improvements in aspects of cognitive function (Arent & Landers, 2003; Chen & Ringenbach, 2016; Chmura & Nazar, 2010). For instance, Arent and Landers (2003) reported an inverted-U shaped relationship between percent of heart rate reserve (%HRR) and processing speed. An inverted U-shaped relationship between the intensity of resistance training and cognitive planning

ability in middle-aged adults has also been observed (Chang, Chu, Chen, & Wang, 2011). Ratings of perceived exertion (RPE) are a valid measure of physiological exercise intensity (Chen, Fan, & Moe, 2002) and could also affect cognitive control processes. In accordance with the strength model of self-control, RPE may be indicative of the degree of fatigue and the degree to which exercise taxes self-control resources (Eston, Faulkner, St Clair Gibson, Noakes, & Parfitt, 2007; Muraven, Tice, & Baumeister, 1998). Furthermore, fatigue is associated with the depletion of self-control and can have a negative effect on executive function (Audiffren & André, 2015; McEwan, Ginis, & Bray, 2013; Muraven et al., 1998). The association between cadence and changes in cognitive function was of interest because of reported dose-response relationships between the frequency of the mechanical stimulation of limbs and corticospinal excitability (Christova et al., 2011).

In addition to exercise intervention metrics, one of the most powerful predictors of cognitive recovery after stroke is the time since the stroke (Patel et al., 2003). The majority of the cognitive recovery process in the chronic post-stroke period seems to take place within the first three years after stroke (Patel et al., 2003). It is therefore important to investigate the relationship between the time since the last lesion and the effectiveness of an intervention.

The primary purpose of this study was to compare the acute effects of ACT, voluntary cycling (VC), and no cycling (NC) on aspects of cognitive function in people who are at least 6 months post-stroke. We hypothesized that ACT would be associated with greater improvements in cognitive function than VC or NC. The secondary purpose of this study was to explore the association of intervention metrics, including RPE, %HRR, and cadence, and months since stroke with the degree of change in aspects of cognitive function.

Methods

Participants

Participants were recruited through newspaper ads, from outpatient rehabilitation clinics, and from stroke support groups in the Phoenix metropolitan area. Twenty-two participants completed this study (see Figure 1 for flow-diagram). Participants had suffered at least one unilateral hemorrhagic or ischemic stroke more than six months ago, had residual hemiparesis,

were at least 18 years of age, were medically stable, had controlled blood pressure levels (resting blood pressure < 140/90 mmHg), scored at least 24 on the Mini Mental State Examination (MMSE), and scored no higher than three on the Modified Ashworth Scale (MAS). All participants had physician approval for light to moderate intensity exercise. Persons with severe aphasia that precluded comprehension and completion of tests and persons with other neurological conditions were excluded. See Table 3 for participant characteristics.

Design

A 3 x 3 cross-over trial was used to investigate the mean change in outcome measures by ACT and VC intervention and NC control (see Figure 1). All participant completed four visits to our research laboratory. Each visit was separated by at least five days, but no more than 10 days. The first visit consisted of the informed consent process, screening procedures, and the collection of descriptive measures. The following three visits consisted of one session of ACT, one session of VC, or one session of NC. The order in which participants completed these session was counterbalanced across participants (see Figure 1). Participants completed executive function testing before (i.e., pre-testing) and after each intervention session (i.e., post-testing). Post-testing commenced within five minutes after completion of the intervention session.

Descriptive Measures

The following measures were collected during the first visit. Height and weight were measured to calculate body mass index (BMI) values. Resting blood pressure and heart rate were measured after five minutes in a seated position. The MMSE (Tombaugh & McIntyre, 1992), Physical Activity Scale for Individuals with Physical Disabilities (PASIPD; Washburn, Zhu, McAuley, Frogley, & Figoni, 2002), Beck Depression Inventory (BDI; Beck, Steer, & Carbin, 1988), Fugl-Meyer Assessment for the lower (LEFMA) and upper extremity (UEFMA; Fugl-Meyer, Jääskö, Leyman, Olsson, & Steglind, 1975), and the Modified Ashworth Scale (MAS; Gregson et al., 1999) were administered according to standard procedures. The age-predicted maximal heart rate of participants was calculated using the following formula which was developed by (Tanaka et al., 2001): $208 - 0.7 \times \text{age}$. For the 16 participants on beta-blocker medication a formula

developed by Brawner, Ehrman, Schairer, Cao, and Keteyian (2004) was used to predict maximal HR: $164 - 0.72 \times \text{age}$.

Outcome Measures

We chose common tests of executive function as outcome measures for this study. The executive function tests, administered in random order, included the Flanker Task, Stroop Test, and Trail Making Test (TMT). We also included the Digit Span Forward and Backward Tests, as measures of short-term memory (STM) and working memory (WM), respectively. However, we are not reporting the results of the Digit Span Tests because of violations of the normality assumption, even after transformations, and because of violations of homoscedasticity, the normal distribution of residuals, and the normal probability of residuals. Outcome measures were administered in random order immediately before and after each intervention session.

The Flanker Task was chosen primarily as a measure of sustained and selective attention and inhibitory control (Colcombe & Kramer, 2003; Fenske & Eastwood, 2003; Kopp et al., 1996). The test was administered on a computer using a modified version of the available Flanker Task of the Psychology Experiment Building Language software (Mueller, 2013; Mueller & Piper, 2014). The Flanker Task used in this experiment included 40 trials in the incongruent condition, whereas the four flanker arrows pointed in the opposite direction of the center arrow, 40 trials in the congruent condition, whereas the flanker arrows pointed in the same direction as the center arrow, and 80 trials in a neutral condition without flanker arrows and a 50% chance of the single arrow pointing to the right or the left. When the flanker arrows were present the five arrows were arranged horizontally. The stimulus was presented for up to 500ms, followed by an interstimulus interval of 800ms, and a fixation interval of 500ms with a "+" centered on the location where the middle arrow appears. The five stimulus arrows subtended a visual angle of approximately 10.5 degrees. The stimuli were presented in white on black background. The response keys were the right and left arrow keys so that participants would respond with the non-paretic hand only. Participants rested their index finger on the left arrow key and their ring finger on the right arrow key, or vice-versa for the left hand, during the test when they were not responding. A practice trial of 8 incongruent, 8 congruent, and 16 neutral trials with response

feedback was given. Median as opposed to mean response times were used for the outcome variables to limit the influence of excessively slow response times. Outcome variables included the median response time of congruent trials as a measure of processing speed (FlankerPS) and the conflict cost, which is the difference in median response times between incongruent and congruent trials as a measure of selective attention and inhibitory control (FlankerCost).

The Stroop test was chosen as a more challenging measure of response inhibition (Jensen & Rohwer Jr., 1966; MacLeod, 1991; Siegrist, 1997). It was administered on an iPad with a commercially available application (Stroop Effect Test, Star Studio). The test consisted of three trials of increasing inhibitory cost. A practice trial was given before each test trial. The first trial was a simple measure of processing speed (StroopPS) without stimulus conflict. During this trial, a word that spelled out a certain color (red, yellow, blue, green, or white) would appear on the screen. The font color of the word would be same as the color that it spelled. On the bottom of the screen were five squares (2.5 cm x 2.5 cm), horizontally arranged. Each square was a solid color (red, yellow, blue, green, or white). As soon as the word appeared, participants had to tap the square on the screen that was the same color as the font color. Once a response was registered, the next word appeared without an interstimulus interval. Each trial lasted 30 seconds and the number of correct responses was recorded. The second trial introduced a stimulus conflict as the font color did not match the color that the word spelled. Participants still had to tap the square that was the same as the font color. The third trial required greater inhibitory control because the squares were colored in gray and had the color written on them in white letters. Participants were still required to tap the square that matched the font color of the word. Thus, this trial likely presented a stimulus and a response conflict. The stimulus conflict is due to the discrepancy between the meaning of the word and the font color of the word. The response conflict is due to the response options being mapped to the irrelevant stimuli (i.e., meaning of the word) instead of the relevant stimuli (i.e., font color; Szűcs & Soltész, 2010; Verbruggen, Notebaert, Liefooghe, & Vandierendonck, 2006; Wendelken, Ditterich, Bunge, & Carter, 2009; Zhao et al., 2015). The outcome variables included the number of successful responses during the first trial as a measure of processing speed (StroopPS) and two measures of conflict cost which included the

difference in the number of successful responses to the first and second trial (StroopCost1) and the difference in the number of successful responses between the first and third trial (StroopCost2). A greater difference (i.e., greater number) indicates greater conflict cost and greater taxation of inhibitory control.

The Trail Making Test (TMT) was used as a measure of set-shifting ability (Salthouse, 2011). This test was administered with a commercially available application (NeuRA, Neuroscience Research Australia) on an iPad. The test consisted of two parts. Part A (TMTA) required participants to connect 25 numbers (1-25) in ascending order as fast as they could. The numbers were scattered on the screen and participants used the index finger of their non-paretic hand to connect the numbers by tapping them. Part B (TMTB) introduced a set-shifting component by requiring participants to connect a total of 25 numbers and letters in alternating, numerical, and alphabetical order. Thus, the order in which participants had to connect the numbers and letters was 1-A-2-B-3-C-4-D-5-E-6-F-7-G-8-H-9-I-10-J-11-K-12-L-13. Prior to each part of the test, participants completed a practice trial that mimicked the test but presented only eight numbers or numbers and letters. The time to complete TMTA and TMTB was automatically recorded by the application. The outcome measure for the TMT was the set-shifting cost (TMTCost), which was calculated as the time difference between TMTA and TMTB. A larger differences indicated greater set-shifting cost.

Interventions

All cycling sessions lasted 20 minutes and were completed with a stationary, recumbent research prototype cycle ergometer (Theracycle) that was built by the Exercycle Company (Franklin, MA). The electric motor that was built into the bicycle could turn the pedals at up to 95 rpm regardless of the power contribution by the participant. The pedals were specialized platform pedals with metal cuppings and Velcro straps that prevented the feet from slipping off the pedals in any direction. The bike has been described in more detail elsewhere (Holzapfel, Ringenbach, Ganger, Gomez, & Parker, 2016; Holzapfel et al., 2015).

ACT sessions began with a five-minute voluntary warm-up without the help of the motor. The target ACT cadence was determined to be 1.8 times greater than the average warm-up

cadence as previous research with persons with DS has shown that an ACT cadence which is 80% greater than the voluntary cadence may be beneficial for motor control and cognitive function (Holzapfel et al., 2015, 2016; Ringenbach et al., 2016). However, the minimum target cadence was 80 rpm while the maximum target cadence was 95 rpm due to the limit of the motor. An assisted cadence of at least 80 rpm has been shown to be beneficial for clinical, motor, and cognitive function of persons with PD (Alberts et al., 2011; Ridgel, Vitek, & Alberts, 2009; Ridgel et al., 2011) and persons with DS (Holzapfel et al., 2015; Ringenbach et al., 2016). After the five minute warm up, the motor was turned on and the cadence was set to the average of the warm-up and the target cadence to allow participants to become familiar with ACT. Subsequently, the motor was programmed to maintain the target cadence for 15 minutes. If participants were uncomfortable at the prescribed target cadence, then the cadence was lowered in 5 rpm increments until the participant felt comfortable.

For VC sessions, participants were instructed to complete a five-minute warm-up by cycling at their own preferred cadence and then to continue with 15 minutes of cycling at their preferred cadence. The motor was not turned on and participants were not encouraged to pedal faster or slower at any point. The resistance that participants were cycling against was 0.5 kp.

During NC sessions, participants also sat on the bicycle with their feet strapped into the pedals but they did not cycle. Participants were allowed to turn the pedals by 180 degrees every few minutes to change the position of their legs. During the 20 minute NC session, participants engaged in a conversation about their physical activity habits with the researcher which always concluded by the researcher informing the participant about the post-stroke physical activity recommendations (Gordon et al., 2004).

Statistical Analyses

The normality assumptions for all outcome measures were tested using the Shapiro-Wilk tests. We transformed the outcome measures as an inverse unit, multiplying by -1 and adding 1 to avoid 0 in the denominator. Once the transformation was completed the ordering of the data was identical to the original data. The transformed change scores were normally distributed within each intervention as verified with Shapiro-Wilk tests except for the digit span change scores

(STM and WM). The assumptions for linear regression analysis were also tested by checking homoscedasticity for error variance and normality for response and error (ϵ) values.

Linear mixed models (LMM) were used to test main effects (sequence, time, and intervention) and interaction effects. Assignment to one of the three possible intervention sequences was coded as 1 (ACT-VC-NC), 2 (VC-NC-ACT), or 3 (NC-ACT-VC). Time was coded as 1 (1st intervention visit), 2 (2nd intervention visit), and 3 (3rd intervention visit) and intervention was coded as 1 (ACT), 2 (VC), and 3 (NC). Outcome measures (dependent variables) were entered as the difference between pre- and post-scores. All change scores were calculated so that a positive change score indicated an improvement (i.e., faster reaction time or higher score). Tukey's HSD post-hoc tests were used to test mean differences in the change scores among the three interventions. We separately tested intervention effects with and without adjustment for covariates, which included BDI, caffeine consumption, and months since stroke. The BDI was included as a covariate because post-stroke depression can blunt the effects of treatments aimed to improve cognitive function (Kimura, Robinson, & Kosier, 2000). Caffeine consumption has also been shown to affect aspects of cognitive function (Nehlig, 2010) and was therefore included as a covariate. Months since stroke was included as a covariate because the recovery from cognitive impairment seems to plateau after about two years post-stroke (Patel et al., 2003). As follow-up analyses, paired sample t-tests were completed separately for each intervention to test within intervention pre- to post-test changes.

Polynomial regression analyses were used to investigate the associations of ratings of perceived exertion (RPE), percent of heart rate reserve (%HRR), cycling cadence, and months since stroke with change scores in outcome measures by treating all variables as continuous scales. Linear and quadratic trends were analyzed separately for each intervention. All β values listed are unstandardized. Quadratic trends were tested because of substantial evidence for the inverted-U shaped hypothesis, whereas exercise intensity relates to changes in cognitive performance in a quadratic manner with a negative quadratic term (Arent & Landers, 2003). All analyses were completed with SPSS v.22. Two-tailed type I error probability was set at $\alpha = 0.05$.

Results

Treatment Fidelity

All 22 participants completed all three intervention sessions. No session was terminated prematurely and no adverse events occurred. Intervention parameters are summarized in Table 4. The ACT cadence was $83.8 \pm 23.9\%$ (mean \pm SD) faster than the voluntary warm-up cadence ($p < 0.001$) which was close to the goal of 80%. However, three participants were not comfortable cycling the minimum prescribed 80 rpm. Their maximum cadences during ACT were 66 rpm, 70 rpm, and 74 rpm. The mean VC cadence was significantly slower than the mean ACT cadence but the heart rates did not differ between ACT and VC ($p = 0.926$; see Table 4).

Main and Intervention Effects

No significant sequence effects occurred in the LMMs indicating that there was no carry-over effect of interventions. There was a significant effect of time on StroopCost2 change scores ($F(2,39) = 7.10, p = 0.002$). A Tukey's post-hoc analysis and line graphs of estimated marginal means revealed that change scores were greatest and positive on day one and then decreased linearly from day to day. There was also a significant effect of time for FlankerPS change scores ($F(2,39) = 5.59, p = 0.007$) which were greatest in day one and lower on day two and three. These time effects are not surprising as they most likely reveal a learning effect. But, they do not present a threat to the internal validity of the study as the interventions were counterbalanced across times.

The LMM analyses with or without covariates did not show any significant intervention effects (see Table 9). None of the covariates explained a significant amount of variance and, therefore, the unadjusted models are presented. Paired sample t-tests revealed a significant pre- to post-test change for the StroopCost1 (see Figure 10) and the StroopCost2 (see Figure 11) in both the ACT and the VC interventions (see Table 10).

Trend Analyses

We explored intervention parameters that could predict the failure and success of improving the measures of cognitive function. The trend analyses were completed separately for the ACT and VC interventions because of the differences in motor output and cadences. The

analyses were not completed for the NC intervention as the intervention parameters remained at or near resting levels during the NC intervention with minimal variance amongst intervention parameters. The results of the linear and quadratic trend analyses are listed in Table 11 and Table 12.

Discussion

Main Effects of the Interventions

Our hypothesis of a greater beneficial effect of ACT compared to VC on executive function was not supported. However, both ACT and VC were associated with improvements in inhibitory control, whereas NC was not. The pre- to post-test (main) effects of our interventions, as examined with paired t-tests, indicated improvements in the StroopCost1 (Figure 10) and StroopCost2 (Figure 11) measures following both the ACT and VC interventions. These results indicate an improvement in the inhibitory control aspect of executive function which is most likely controlled by explicit processing (i.e., prefrontal cortex; Dietrich & Audiffren, 2011). Thus, we found a general facilitating effect of cycling exercise on inhibitory control in people during the chronic post-stroke period. However, this is only true for the Stroop Test and not for the Flanker Task. No changes occurred in measures of processing speed or set-shifting. The acute improvements of inhibitory control but not processing speed following exercise are consistent with other studies in the general population (Chang et al., 2016; Chang, Labban, Gapin, & Etnier, 2012; Lambourne & Tomporowski, 2010; Tam, 2013).

The post-testing took place within minutes following exercise as opposed to during exercise. This means that the implicit computational demand of cycling had ceased and it may have allowed enough time for a shift of resource (i.e., blood flow, glucose, oxygen, etc.) from the reticular formations to other regions of the brain (i.e., prefrontal cortex) based on task demand. However, the FlankerCost also measured aspects of inhibitory control, but did not show improvements following the cycling sessions. The methodological differences between the Stroop Test and Flanker Task may be responsible for the discrepancy in the results. The three parts of the Stroop Test only took 30 seconds each with a small break in between. The Flanker Task took two to three minutes to complete without breaks. The Flanker Task therefore taxed the sustained

selective attention of participants more than the Stroop Test. Additionally, no improvements were found in set-shifting ability, which is an explicit process, as measured with the TMTCost.

However, the TMT also taxes working memory (Sanchez-Cubillo et al., 2009) which is often not improved by exercise (Smith et al., 2010). Thus, it seems that the benefits of ACT and VC may be specific to inhibitory control. Further research is necessary to investigate the differential effects of exercise on task characteristics such as duration, domain, and complexity.

Our results are not consistent with previous research on the effects of assisted cycling paradigms on executive function. For instance, Ringenbach et al. (2014) reported acute improvements in the cognitive planning ability of adolescents with Down syndrome following ACT but not VC and Ringenbach et al. (2015) found acute improvements in the inhibitory control of adolescents with Down syndrome after ACT but not VC. Furthermore, as opposed to Chang et al. (2016), we did not find improvements in processing speed using the Stroop Test or Flanker Task. One reason for the lack of change in processing speed may be the implicit computational changes and shift in metabolic processes following exercise. Measures of processing speed such as simple and choice reaction time tasks are considered implicit and the performance of these tasks is typically improved during exercise (Dietrich & Audiffren, 2011; Lambourne & Tomporowski, 2010). However, following the cycling exercise the activation of the reticular formations may have subsided to the point where no changes in processing speed were evident. This result is not entirely surprising as exercise interventions have often yielded mixed results in regards to measures of processing speed (Lambourne & Tomporowski, 2010). It is possible that the implicit computational centers experienced fatigue due to the computational demand of the sustained activity of large muscle groups, which in turn could impair tasks which rely on implicit processing such as tasks of processing speed (Dietrich & Audiffren, 2011). We are not implying that the cycling interventions were equally demanding for all participants or that every participant experienced central fatigue in the reticular formations and other brain regions. Rather, the cycling interventions probably led to fatigue in some participants, which then led to an insignificant main effect of the interventions. Our discussion of the trend analyses will shed more light on the results concerning processing speed.

The Reticular-Activating Hypofrontality (RAH) Model

We incorporated the Reticular-Activating Hypofrontality (RAH) Model into the discussion of the results as it is the most comprehensive model to date explaining the acute effects of exercise on aspects information processing and executive function (Dietrich & Audiffren, 2011). The RAH model rests on the following premises: 1) The brain receives a limited supply of metabolic resources that can be distributed to different regions based on demand; 2) Motor tasks, especially those involving large muscle groups, are a monumental computational task involving many areas of the brain and this computational demand is directly related to the muscle mass involved and the intensity of exercise; 3) The cognitive-computational processes of the brain can be dichotomized into implicit processes and explicit processes. Implicit processing takes place in the reticular formations of the brain stem, medulla, pons, cortical motor areas, cerebellum, basal ganglia, motor thalamus, substantia nigra and many other sensorimotor areas. Explicit processing is almost exclusively done by the prefrontal cortex. Implicit processes are subconscious and automated and they are not limited by working memory. These are most evident in the expert execution of complex motor skills such as butterfly swimming. The implicit processing allows an expert swimmer to swim butterfly in a smooth and efficient fashion with little or no cognitive effort. A beginner, on the other hand, uses explicit (i.e., conscious) processing and has to keep the components of the stroke in their working memory to piece the stroke together. This performance would most likely not look smooth and it would not be efficient. Another example would be the tennis serve where one is better served by the implicit processing because the skill is too complex and requires too many computational resources for the prefrontal cortex (explicit system) to handle. Thus, our performance in a specific sport suffers when we “think too much” about the execution of our movements; 4) When the brain is “overtaxed” by exercise, the supply of resources to the highest order brain centers, beginning with the prefrontal cortex, will be downregulated in order to sustain the implicit processing necessary for the task at hand. Thus, with increasing muscle mass and intensity, the implicit processing eats up more and more of the available resources, reducing the resources available to other brain centers such as the prefrontal cortex. This hypofrontality may explain the commonly observed impairment of executive function

during or after exercise (Dietrich & Audiffren, 2011; Lambourne & Tomporowski, 2010), especially after high intensity exercise (Bardsley, 2010); 5) Lastly, the RAH model applies best during exercise as opposed to after exercise as the implicit computational demands of the motor task stop when exercise stops. However, metabolic responses lag behind the computational demands, which means that the RAH may be observable within the first few minutes following the cessation of exercise (Ángyán & Czopf, 1998; Eich & Metcalfe, 2009; Ide, Schmalbruch, Quistorff, Horn, & Secher, 2000).

Dose-Response Relationships

Ratings of perceived exertion. Consistent with Arent and Landers (2003) and Chen and Ringenbach (2016) we found a curvilinear, inverted-U shaped relationship between exercise intensity, as indicated by RPE, and processing speed as measured by both the Stroop Test and the Flanker Task in the ACT intervention. The greatest improvements in processing speed seem to occur at an RPE of 10-11 on the 6-20 Borg scale in both the Stroop Test and Flanker Task and benefits of exercise appear to be absent or reversed at a RPE of 13 and higher (see Figures 12 and 13) which is consistent with Dietrich and Audiffren's (2011) RAH model.

Interestingly, Ploughman et al. (2008) also found that 20% body weight supported treadmill walking at an average RPE of 13 did not lead to any improvements in executive function, short-term memory, or working memory. It has been shown in rodents that forced exercise can lead to anxiety-like behavior, stress and elevated corticosterone levels, and blunted brain-derived neurotrophic factor levels (Adlard & Cotman, 2004; Ke, Yip, Li, Zheng, & Tong, 2011; Leasure & Jones, 2008; Ploughman et al., 2007). It may be that ACT induced heightened states of stress, psychological arousal, and maybe even anxiety in some participants compared to VC, due to the novel nature and rapid movement rate of this exercise modality. Optimal levels of arousal (Lambourne & Tomporowski, 2010; Sanders, 1983) and anxiety (Eysenck, Derakshan, Santos, & Calvo, 2007) have been associated with improved processing speed. However, supra-optimal levels of arousal or anxiety may have evoked RPE of 13 or greater and impaired processing speed by diverting and fatiguing attentional resources (Eysenck et al., 2007; McMorris & Graydon, 2000; Sanders, 1983).

Additionally, RPE usually correlates strongly with physiological measures of arousal such as heart rate, blood lactate levels, oxygen consumption, and ventilation (Borg, 1970; Chen et al., 2002; Hetzler et al., 1991). However, we did not find a relationship between RPE and HR for any of the interventions. Thus, the variability seen in RPE in our data does not seem to be associated with physiological arousal which is indirect evidence that it is associated with psychological factors. RPE can indicate mental fatigue during exercise, specifically a reduced state of activity in the frontal cortex (Marcora, Staiano, & Manning, 2009; Nybo & Nielsen, 2001). Thus, the inverted-U shaped relationship between RPE and processing speed may indicate the depletion of metabolic and self-control resources at greater exercise intensities (Audiffren & André, 2015; Dietrich & Audiffren, 2011; Marcora et al., 2009). Thus, when we apply the RAH model to these results, it appears that higher levels of exertion (i.e., $RPE \geq 13$) indicate that the reticular formations (i.e., implicit processing) are being taxed to the point of central fatigue (Dietrich & Audiffren, 2011). This central fatigue may be responsible for an impairment of processing speed in those who exercised at relative high RPE. It may seem unjustified to assume that the participants experienced central fatigue after only 20 minutes of cycling, but reduced exercise capacities and low exercise tolerance are common post-stroke (MacKay-Lyons & Makrides, 2002b; Michael, Allen, & Macko, 2006).

Next, our results indicate an inverse linear association of RPE with changes in inhibitory control (i.e., StroopCost2 and FlankerCost; see Figures 14 and 15). Again, this relationship was only evident for the ACT intervention. This result is consistent with the RAH framework and other studies. For instance, a negative relationship between the intensity of isometric hand grip exercise and Stroop test performance has been reported previously (Brown & Bray, 2015). It has been shown that enduring physical discomfort, as well as physical and mental exertion, require self-control (explicit) resources and self-regulatory capacity which are an integral part of executive function (Audiffren & André, 2015; Eysenck, 1960; Muraven et al., 1998). ACT was a novel exercise modality for all participants and most participants were not used to cycling at greater than voluntary rates. Thus, ACT may have demanded greater mental effort (i.e., attentional, explicit resources), similar to high intensity hand grip exercise, in order to stabilize the body

during cycling, especially in regards to the paretic side. ACT may also have placed a greater demand on implicit resources due to the fast cadence which would increase the demand on global neural resources compared to slower cadences (Dietrich & Audiffren, 2011). As mentioned, greater frequencies of mechanical stimulation appear to result in greater corticospinal excitability (Christova et al., 2011). These demands may have induced an over-taxation of the limited neural and metabolic resources in the brain, which ultimately led to central fatigue. For instance, cycling to exhaustion has been shown to induce very high RPE values and central fatigue that persists for at least 30 minutes post-exercise as evidenced by reduced central motor drive (Presland, Dowson, & Cairns, 2005). Thus, the relatively high RPE by some, maybe less fit participants in our study seems to indicate a metabolic overtaxation in the brain which could have resulted in the decrement of executive function following exercise. However, there was no relationship between RPE and resting heart rate or between RPE and the mean heart rate during cycling. This is further evidence that the psychomotor load rather than physiological exercise intensity may be responsible for the high RPE and relative decrement in cognitive function following ACT. This would be consistent with the RAH model (Dietrich and Audiffren, 2011).

The argument that the degree of depletion of self-regulatory resources moderates the relationship between ACT and changes in executive function also fits with the strength model of self-control as outlined by (Audiffren & André, 2015). In addition, an increased state of anxiety, affect, or perception of threat due to ACT may have further stripped prefrontal areas of resources by diverting them to other brain regions such as the amygdala (Eysenck et al., 2007; Perlstein, Elbert, & Stenger, 2002; Pessoa, 2008, 2009; Phelps, 2006), which may have further contributed to the decrement in inhibitory control following ACT at high RPE. On the other hand, there was no relationship between RPE and changes in inhibitory control in the VC intervention. It appears that VC was less likely to change levels of anxiety and psychological arousal as the movement rate and intensity was entirely under the participant's control.

Our argument that the cessation of cycling allowed for a shift in resources from the reticular formations to the prefrontal cortex which might explain the average improvement in inhibitory control after both the ACT and VC interventions may seem to contradict the argument

that high RPE may have led to central fatigue in prefrontal areas and prevented an improvement in inhibitory control. However, keep in mind that the improvement in inhibitory control after ACT is an average which is driven by those participants which reported low RPE values and are unlikely to have experienced central fatigue.

In contrast to our results regarding RPE as a predictor, Kamiyo et al. (2007) reported an inverted-U shaped association between RPE during cycling exercise and inhibitory control measured with the Flanker Task and a positive linear association between RPE and processing speed as measured with the Flanker Task. These contrasting findings may be the result of the different population used by Kamiyo et al. (2007), namely young (range: 22 to 30 years), healthy adults. Our sample was older (range: 28 to 82 years) and had suffered at least one stroke. These may be reasons as to why their processing speed did not continue to benefit from increasing RPE and why inhibitory control benefited most from exercise only at the low range of RPE.

The relationship between RPE and information processing in the ACT intervention may be the result of the increased demand for the motor control of the non-paretic and paretic side that ACT required. Persons with stroke-induced hemiparesis exhibit greater fatigue in the paretic arm than the non-paretic arm when exercising both arms equally and at least part of that fatigue is associated with central fatigue (Riley & Bilodeau, 2002). Additionally, the increased energy cost of walking is associated with fatigue in persons after stroke (Colle, Bonan, Gellez Leman, Bradai, & Yelnik, 2006). These studies and our current data indicate that ACT may have led to central fatigue and reduced processing speed and inhibitory control in those participants with high RPE. In fact, we found a significant negative relationship between LEFMA scores and RPE during ACT ($R^2 = 0.24$) but not during VC. This indicates that those with greater relative hemiparesis reported higher RPE during ACT.

Cadence. Ridgel et al. (2011) compared the effects of ACT at 60, 70, and 80 rpm on executive function in patients with PD and found no dose-response relationship. This result is consistent with the lack of relationship between cycling cadence and measures of processing speed or inhibitory control in our study. It has been proposed before that the neurocognitive

benefits of ACT may simply be due to the assisted nature of the cycling rather than the augmented cadence (Holzapfel et al., 2016; Ringenbach et al., 2016).

But, we found a significant negative relationship between the ACT cadence and changes in set-shifting ability (TMTCost; see Table 11). This relationship may be spurious as cadence did not relate to any other outcome variables in the ACT intervention. However, there was also a negative relationship between the VC cadence and inhibitory control (FlankerCost) and an inverted-U shaped relationship between the VC cadence and set-shifting (TMTCost). The RAH model fits well with the negative relationship of cadence with set-shifting and inhibitory control. According to the RAH model, a faster cadence would increase the implicit computational demand, which in turn would lead to the downregulation of activity in brain areas irrelevant to the motor task starting with the areas supporting the highest cognitive functions (i.e., prefrontal cortex; (Dietrich & Audiffren, 2011). In addition, as mentioned previously, cycling at fast cadences may be a novel and very demanding motor control challenge for persons with post-stroke hemiparesis, especially due to the impaired neuromotor control of the paretic leg, and it may therefore also require explicit processing which would involve areas of the prefrontal cortex. This would mean that the reticular formations and prefrontal regions are competing for metabolic resources and neither area may be receiving an optimal amount which could ultimately lead to central fatigue, and this would appear to affect the prefrontal cortex more than the reticular regions. (Dietrich & Audiffren, 2011) offer an evolutionary explanation for this finding. The prefrontal cortex is a brain region that developed much later than the reticular formations, and the latter are involved in the fight or flight mechanisms. Thus, after a bout of physical exertion, it would be detrimental to survival if the fight or flight and implicit motor control systems were impaired. Additionally, a downregulation of prefrontal areas may be beneficial in those situations, when fast and “instinctive” decisions have to be made. Our data fit this model showing an impairment of executive function (i.e., explicit processing) after exercise at high RPE or fast CAD, and a facilitating effect of exercise on implicit processes as long as the intensity was not too high, as shown by the inverted-U shaped relationships between processing speed and RPE. It may be important to mention that there was no relationship between cadence and RPE. Thus, these

factors acted independently which is also shown by their influence on different aspects of information processing (see Table 11).

We need to mention that in line with other studies (Fornusek & Davis, 2008; Ridgel et al., 2011), we found no relationship between cadence and HR. This underlines the theory of reticular activation through afferent motor input and its role in the distribution of metabolic resources in the brain. Thus, the impairment of executive function at relatively high RPE or cadences is not due to high cardiovascular workloads, but rather, high neuromotor workloads. This is also supported by the lack of relationship between %HRR and changes in outcome measures (see Tables 11 and 12).

The inverted-U shaped relationship between cadence and TMTCost (i.e., set-shifting) in the VC intervention does not quite fit the rest of the data. This inverted-U shaped relationship suggests that medium intensities, relatively speaking, benefit the prefrontal cortex post-exercise. However, the relationship between cadence and TMTCost is linear and negative in the ACT intervention. Thus, the difference between voluntary control of movement and assisted rapid movements may account for some of the difference between the two interventions. During the VC intervention, the participants were told that the pedaling rate and intensity is self-selected. It seems plausible then that some participants did not pedal fast enough and did not reach a sufficient intensity to produce improvements in set-shifting ability, whereas others exercised at a more optimal rate and intensity and again others pushed too hard.

Months since stroke. Lastly, months since stroke related negatively to StroopCost1 and StroopCost2 for the ACT intervention (see Table 11). Numerous studies have found large improvements in cognitive function during the acute post-stroke period (Kimura et al., 2000; Särkämö et al., 2008; Simis & Nitrini, 2006; Wendelken et al., 2009), whereas most studies did not find any cognitive changes during the chronic post-stroke period (Ballard et al., 2003; Patel et al., 2003; Ploughman et al., 2008; Quaney et al., 2009). Our results show variation in the degree of cognitive change even in the chronic post-stroke period. Participants whose stroke was more recent experienced a greater improvement in inhibitory control compared to participants with a less recent stroke. This finding is in accordance with the theory of a critical period of

neuroplasticity following stroke (Murphy & Corbett, 2009; Nudo & Friel, 1998). The critical period is defined to be within the first two weeks following a stroke and thus the chronic post-stroke period falls outside of that window. However, our result suggests that after the critical period, the effects of the insult wear off gradually, over the years, and that the prefrontal cortex exhibits greater afferent feedback induced excitability the less time has passed since the stroke. Thus, interventions should occur sooner rather than later even in the post-stroke period when recovery has seemingly plateaued (Dobkin, 2005).

Limitations

It should be noted that the trend analyses were based on cross-sectional data instead of the experimental manipulation of predictor variables (i.e., cadence, RPE, heart rate, and months since stroke). For instance, instead of having every participant complete separate cycling sessions at different set cadences or RPE, as in a within-subjects design, the cadences and RPE within a single session of ACT or VC were individualized. Thus, the present results are merely associations which are just one piece of evidence needed to establish causality. The trends serve the purpose of informing future research which will hopefully inform clinical practice. Future, studies should actively manipulate and control predictors of cognitive function that are of clinical interest. The primary purpose of this study, however, was not to examine intervention characteristics that predict improvements in cognitive function, but rather to compare the efficacy of ACT to VC and NC in people during the chronic post-stroke period.

Conclusion

The results of this study indicate an acute benefit of ACT and VC, but not NC, on inhibitory control in people during the chronic post-stroke period. This shows that people after a stroke may be able to improve some aspects of cognitive function. More research is needed in regards to the chronic effects of exercise on cognitive function in people post-stroke. It is important to maximize the cognitive benefits of exercise during the post-stroke period as the prevalence of dementia after stroke is elevated relative to the general population (Pinkston, Alekseeva, & Toledo, 2009). ACT seems to induce physiological or psychological states at relatively high RPE (i.e., ≥ 13), such as central fatigue, increased affect, or mild anxiety, that can

have detrimental effects on information processing. This may be important to consider for clinicians in order to avoid excessive fatigue during rehabilitative therapy. In addition, relatively fast cycling cadences may also induce resource depletion and central fatigue which could impair inhibitory control or set-shifting abilities. Thus, it may be advisable for cycling interventions to start conservatively in regards to RPE and cadence. We also recommend the use of cadence and RPE to track relative intensities, rather than HR which showed no relationship to changes in cognitive function. Lastly, even during the chronic post-stroke period, the beneficial effects of exercise on cognitive function may be greater during the first few years post-stroke (0.5 to 5 years) than later.

Chapter 6

LIMITATIONS AND FUTURE DIRECTIONS

Despite the significant improvements in paretic motor function that occurred, the motor function tests that were used in this study have a floor effect that may have prevented the quantification of change in those with low LEFMA and UEFMA scores. Six participants were unable to do a single toe-tap in the LEMOCOT and six participants, but not necessarily the same participants, were unable to transfer a single block in the BBT. Thus, future studies should include active range of motion tests to quantify changes better. For instance, Corbett et al. (2013) reported improvements in active range of motion of hip flexion, hip extension, shoulder flexion, shoulder extension, and shoulder abduction of adults with Parkinson's disease following a single 30-minute bout of assisted cycling at about 80 rpm. Consistent with other studies, the effects of ACT on motor function appear to be global. The improvements following assisted cycling were generally greater than the improvements following biomechanical muscle stimulation. However, the cycling paradigm used by Corbett et al. (2013) differed from ACT because participants were only assisted by the motor when their cadence fell below 80 rpm. Thus, future studies need to compare the effects of ACT to VC at the same, relatively high cadence of about 80 rpm.

Additionally, future research could use a lower Modified Ashworth Scale score as an inclusion criterion. In the current study, a score of three or less was used as an inclusion criterion. A score of three may be too high to allow for the successful completion of the LEMOCOT or BBT with the paretic extremity by some participants. However, the significant main effects of the interventions on measures of paretic motor function in the current study point to the robustness of the interventions, specifically ACT. In fact, 59% of all participants scored a three on either elbow, knee, or ankle assessment of the Modified Ashworth Scale and 62% of those 59% were able to perform at least one toe touch during the LEMOCOT and 77% were able to transfer at least one block during the BBT. Thus, the inclusion of persons with a score of three on the Modified Ashworth Scale allows for greater applicability of the results as opposed to limiting the scores to two or less.

In the current study, participants were generally only given a short practice trial before performing the motor and executive function tests the first time for pre-testing. Thus, a learning effect probably occurred and mixed with intervention effects. However, the crossover design of this study balanced learning effects across the interventions. Nevertheless, future studies should incorporate more extensive familiarization and directly measure learning effects in order to quantify intervention effects better.

The TMT test may be especially prone to a learning effect and a diminishing demand on executive function with repeated test taking because the numbers and letters always appeared in the same positions on the tablet screen. This may explain the lack of intervention effect on the TMT, as participants may have started to memorize, consciously or subconsciously, the pattern in which numbers or numbers and letters were scattered. The improvements in the Stroop Test indicate that improvements only occurred in tasks that sufficiently taxed executive function. In the future, a version of the TMT A and B that randomly changes the positions of numbers and letters should be used so that set-shifting ability is taxed to the same degree each time the test is taken.

The trend analyses were based on cross-sectional data and not experimental data. The predictor variables (i.e., cadence, RPE, percent of heart rate reserve, months since stroke) were not controlled. For better causal inference, future research should test different levels of cadence, heart rate, and RPE as independent variables. When testing the acute effects, this could be done efficiently with cross-over design similar to the one in the current study. Our results do provide preliminary evidence that RPE is an important moderator of the effects of ACT on measures of executive function and that cadence is an important moderator of interventions effects on motor function. To our knowledge, Ridgel et al. (2011) were the first to systematically test the effects of passive cycling at 60 rpm, 70 rpm, and 80 rpm on executive function in persons with PD. They did not find a dose-response relationship.

Maybe greater variations of ACT and VC cadences need to be tested. ACT cadences only ranged from 66 rpm to 95 rpm. It is unknown if there is a cadence above 95 rpm at which the benefits on motor function plateau. It is also unknown if there is a cadence below 66 rpm at which executive function benefits can be maximized acutely. The same could be investigated for VC

where cadences ranged from 33 rpm to 79 rpm. Lastly, the effects of ACT and VC at equal cadences should also be compared. These questions concerning the dose response of cadence have not been addressed in regards to the stroke recovery process. The dose response regarding RPE should also be tested systematically as RPE seems to be an important moderator of intervention effects on executive function. In order to do this, it may be necessary to screen or stratify participants in regards to LEFMA scores as LEFMA scores share a negative relationship with RPE.

It is also important to uncover the neural mechanisms underlying the effects of assisted cycling. So far, Beall et al. (2013) have tested functional connectivity following assisted cycling and Shah et al. (2015) have tested the relationship of cycling cadence with functional connectivity between cortical and subcortical regions involved in motor control. However, the relationship of changes in functional connectivity with changes in motor control following assisted cycling paradigms has not been investigated. Cortical activation during cycling could be tested with functional Near Infrared Spectroscopy (fNIRS) and after cycling with functional Magnetic Resonance Imaging (fMRI). Changes in neural activation patterns and functional connectivity could then be correlated with changes in intervention parameters and changes in motor function.

Another question that remains largely unanswered is the extent to which ACT elicits active muscular control and efferent corticospinal output. Christensen et al. (2000) shed some light on this question. They reported minimal electromyographic activity in the soleus, tibialis anterior, quadriceps muscles, and hamstring muscles during passive cycling at 60 rpm. However, they found that the anterior cerebellum and primary motor cortex were activated in response to passive cycling, similarly to active cycling. The degree of activation correlated positively with cadence but not with load (i.e., resistance). This suggests that efferent corticomotor activation may be minimal during assisted cycling and that changes in corticospinal excitability and changes in motor output following exercise are the result of the afferent stimulation of cortical and cerebellar regions. However, the passive cycling cadence used by Christensen et al. (2000) was only 60 rpm and the participants were instructed to stay as relaxed as possible during passive cycling.

Lastly, the relatively high RPE in some participants in the current study may have been the result of the lack of familiarity with ACT and associated mild anxiety or negative affect. This could have impaired executive function following ACT (Eysenck et al., 2007; Perlstein et al., 2002; Pessoa et al., 2009). Future studies that investigate the acute effects of ACT in persons with stroke-related impairments should incorporate an ACT familiarization phase. During the familiarization phase, measures such as RPE, state anxiety, and affect should be measured. Chronic, multiple week interventions may allow for sufficient familiarization and allow for more salient effects of ACT to manifest. Future chronic intervention studies should measure markers of neuroplasticity such as Brain-Derived Neurotrophic Factor, other trophic and growth factors, and functional or organizational changes during motor tasks. Long-term intervention studies should further investigate the effectiveness of ACT by comparing changes in outcome measures to minimally clinically meaningful differences and by directly measuring Activities of Daily Living and quality of life. In this regard, ACT should be compared to traditional interventions such as over ground walking, body weight supported walking, repetitive task practice and constraint-induced movement therapy. The effectiveness of ACT as an adjunct therapy to traditional treatments should also be compared to the traditional treatments alone.

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APPENDIX A
TABLES

Table 1

Design for the 3x3 Crossover Trial

Sequence Number	Period 1	Period 2	Period 3
1	ACT	VC	NC
2	VC	NC	ACT
3	NC	ACT	VC

Note. Abbreviations: ACT = Assisted Cycling Therapy, NC = no cycling, VC = voluntary cycling

Table 2

Randomization Schedule for the 3x3 Crossover Trial

Participant Number	Sequence # from Table 1	Sequence		
01	2	VC	NC	ACT
02	1	ACT	VC	NC
03	2	VC	NC	ACT
04	3	NC	ACT	VC
05	1	ACT	VC	NC
06	1	ACT	VC	NC
07	3	NC	ACT	VC
08	1	ACT	VC	NC
09	2	VC	NC	ACT
10	3	NC	ACT	VC
11	2	VC	NC	ACT
12	1	ACT	VC	NC
13	3	NC	ACT	VC
14	1	ACT	VC	NC
15	3	NC	ACT	VC
16	2	VC	NC	ACT
17	2	VC	NC	ACT
18	3	NC	ACT	VC
19	3	NC	ACT	VC
20	1	ACT	VC	NC
21	2	VC	NC	ACT
22	1	ACT	VC	NC
23	2	VC	NC	ACT
24	3	NC	ACT	VC

Note. Abbreviations: ACT = Assisted Cycling Therapy, NC = no cycling, VC = voluntary cycling

Table 3

Descriptive Statistics

Gender (m/f)	16/6
Lesion side (r/l)	7/15
Type of stroke	
Ischemic (n)	12
Hemorrhage (n)	10
Age (years; mean \pm SD)	60.26 \pm 15.55
MSS (mean \pm SD)	95.70 \pm 85.26
Assistive device including AFOs (n)	16
Aphasia (n)	6
BB medication (n)	16
BMI (kg/m ² ; mean \pm SD)	30.17 \pm 6.18
MMSE (mean \pm SD)	26.90 \pm 3.09
BDI (mean \pm SD)	8.82 \pm 5.26
PASIPD (mean \pm SD)	37.5 \pm 21.16
LEFMA (mean \pm SD)	21.00 \pm 8.01
UEFMA (mean \pm SD)	34.63 \pm 18.15

Note. Abbreviations: AFO = ankle foot orthosis; BB = beta blocker; BDI = Beck Depression Inventory; BMI = body mass index; LEFMA = Lower Extremity Fugl-Meyer Assessment; MMSE = Mini Mental State Examination; MSS = Months Since Stroke; PASIPD = physical activity scale for individuals with physical disabilities; UEFMA = Upper Extremity Fugl-Meyer Assessment

Table 4

Mean Differences in RPE, HR, %HRR, and CAD Across Interventions.

	ACT	VC	NC		p	Post-hoc comparisons
RPE	11.9 ± 2.0	11.2 ± 1.7	7.5 ± 1.3	F(2,64) = 46.24	< 0.001	ACT, VC > NC
HR	90.3 ± 17.5	92.3 ± 21.3	74.3 ± 15.0	F(2,64) = 6.79	0.002	ACT, VC > NC
%HRR	27.8 ± 17.3	31.8 ± 25.2	4.8 ± 2.5	F(2,64) = 14.77	< 0.001	ACT, VC > NC
CAD	79.5 ± 8.5	51.5 ± 13.7		t(21) = 13.96	< 0.001	ACT > VC

Note. Abbreviations: %HRR = percentage of heart rate reserve; ACT = Assisted Cycling Therapy; CAD = cadence; HR = heart rate; NC = no cycling; RPE = rating of perceived exertion; VC = voluntary cycling;

Values are expressed as mean ± SD.

Table 5

Change in Outcome Measures by ACT, VC, and NC

	Change scores			F (2,41)	η^2	p	Post-hoc comparisons
	ACT	VC	NC				
LEMOCOT-P	2.16 ± 2.34	0.91 ± 3.05	0.33 ± 2.17	3.74	0.21	0.036	ACT > NC; ACT = VC = NC
LEMOCOT-NP	5.09 ± 4.24	4.48 ± 4.52	-1.74 ± 4.99	16.42	0.45	<0.001	ACT, VC > NC
BBT-P	1.55 ± 2.73	0.44 ± 3.27	0.44 ± 3.37	1.40	0.06	0.259	ACT = VC = NC
BBT-NP	3.73 ± 3.66	1.48 ± 4.98	-2.04 ± 3.53	11.13	0.35	<0.001	ACT, VC > NC

Note. Abbreviations: ACT = Assisted Cycling Therapy; BBT-NP (Box and Blocks Test - non-paretic): Number of successfully transported blocks in minute with the non-paretic arm; BBT-P (Box and Blocks Test - paretic): Number of successfully transported blocks in 1 minute with the paretic arm; LEMOCOT-NP (Lower Extremity Motor Coordination Test - non-paretic): Mean number of successful toe-touches in 20 seconds with the non-paretic leg; LEMOCOT-P (Lower Extremity Motor Coordination Test - paretic): Mean number of successful toe-touches in 20 seconds with the paretic leg; NC= no cycling; VC = voluntary cycling.

Values are expressed as mean ± SD.

Table 6

Means ± Standard Deviation for Pre- and Post-Tests in Each Intervention

	ACT		VC	
	pre	post	pre	post
LEMOCOT-P	16.47 ± 15.86	18.64 ± 17.11**	18.76 ± 17.03	19.67 ± 17.96
LEMOCOT-NP	45.61 ± 11.53	50.70 ± 11.72**	45.87 ± 10.73	50.35 ± 10.73**
BBT-P	16.77 ± 20.79	18.32 ± 22.34*	18.39 ± 21.82	18.83 ± 22.92
BBT-NP	56.68 ± 10.14	60.41 ± 10.62**	57.83 ± 12.26	59.30 ± 12.30
	NC			
	pre	post		
LEMOCOT-P	18.93 ± 17.45	19.26 ± 18.18		
LEMOCOT-NP	49.67 ± 12.62	47.93 ± 12.11		
BBT-P	19.74 ± 22.85	20.17 ± 22.65		
BBT-NP	60.57 ± 12.66	58.52 ± 11.97*		

Note. Differences between pre- and post-test means were tested with paired samples t-tests (df = 21): *p < 0.05, **p < 0.001. Abbreviations are listed in the legend of Table 5.

Table 7

Predictors of Change in Outcome Variables in the ACT Intervention

	RPE				CAD			
	R ²	F(1,19)	β_{RPE}	Trend	R ²	F(1,19)	β_{CAD}	Trend
LEMOCOT-P	0.06	0.85	-1.94	—	0.36	10.54*	0.19*	/
LEMOCOT-NP	0.08	1.65	-1.38	—	0.08	1.64	0.16	—
BBT-P	0.01	0.17	0.13	—	0.24	5.91*	0.16*	/
BBT-NP	0.23	6.01*	-0.91*	\	0.05	1.08	0.11	—
	%HRR				MSS			
	R ²	F(1,19)	$\beta_{\%HRR}$	Trend	R ²	F(1,19)	β_{MSS}	Trend
LEMOCOT-P	0.04	0.71	-0.03	—	0.11	2.17	0.02	—
LEMOCOT-NP	0.05	0.98	0.06	—	0.02	0.23	-0.01	—
BBT-P	0.10	2.13	0.05	—	0.08	1.18	-0.01	—
BBT-NP	<0.01	<0.01	<0.01	—	0.12	0.21	0.01	—

Note. Most abbreviations are listed in the legend of Table 4 and Table 5.

MSS = months since stroke.

\ = significant negative linear trend, / = significant positive linear trend

*p < 0.05, **p < 0.001

Table 8

Predictors of Change in Outcome Variables in the VC Intervention

	RPE				CAD			
	R ²	F(1,19)	β_{RPE}	Trend	R ²	F(1,19)	β_{CAD}	Trend
LEMOCOT-P	0.26	5.66	-6.30*	\	0.45	16.02**	0.16**	/
LEMOCOT-NP	0.01	0.19	0.67	—	0.17	4.64*	0.16*	/
BBT-P	0.02	0.48	-0.29	—	0.03	0.55	0.04	—
BBT-NP	<0.01	0.02	0.09	—	0.03	0.61	0.07	—
	%HRR				MSS			
	R ²	F(1,19)	$\beta_{\%HRR}$	Trend	R ²	F(1,19)	β_{MSS}	Trend
LEMOCOT-P	0.12	2.74	0.04	—	0.14	2.64	0.08	—
LEMOCOT-NP	0.14	3.36	0.07	—	<0.01	<0.01	>-0.01	—
BBT-P	<0.01	0.07	0.01	—	<0.01	0.05	<0.01	—
BBT-NP	0.06	1.34	0.05	—	<0.01	0.02	>-0.02	—

Note. Most abbreviations are listed in the legend of Table 4 and Table 5. MSS = months since stroke.

\ = significant negative linear trend, / = significant positive linear trend

*p < 0.05, **p < 0.001

Table 9

Change in Outcome Measures by ACT, VC, and NC

	Change scores			F (2,39)	η^2	p
	ACT	VC	NC			
StroopPS (%)	1.38 ± 6.40	0.41 ± 8.37	1.70 ± 10.11	0.13	0.01	0.878
StroopCost1 (%)	17.52 ± 22.32	17.43 ± 21.36	12.99 ± 33.35	0.08	>0.01	0.924
StroopCost2 (%)	15.99 ± 18.77	11.69 ± 22.32	6.29 ± 24.18	1.68	0.08	0.200
FlankerPS (%)	3.13 ± 9.36	3.68 ± 8.56	3.28 ± 8.71	0.09	>0.01	0.917
FlankerCost (%)	-23.69 ± 94.17	2.48 ± 48.29	-5.46 ± 108.02	0.49	0.02	0.619
TMTCost (%)	7.58 ± 32.43	-13.62 ± 50.82	-0.05 ± 46.15	1.36	0.06	0.269

Note. Abbreviations: ACT = Assisted Cycling Therapy; FlankerCost: Median response time of the incongruent condition - median response time of the congruent condition; FlankerPS (Flanker processing speed): Median response time of the congruent condition; NC = no cycling; StroopCost1: Number of correct responses in the no-interference condition - number of correct responses in the light interference condition; StroopCost2: Number of correct responses in the no-interference condition - number of correct responses in the heavy interference condition; StroopPS (Stroop processing speed): Number of correct responses in the no-interference condition in 30 seconds; TMTCost (Trail Making Test cost): Mean time to completion of TMTB - mean time to completion of TMTA; VC = voluntary cycling
Values are expressed as mean ± SD

Table 10

Means ± Standard Deviation for Pre- And Post-Tests in Each Intervention

	ACT		VC	
	pre	post	pre	post
StroopPS (raw score)	31.24 ± 4.55	31.67 ± 4.95	31.18 ± 6.65	31.14 ± 6.42
StroopCost1 (raw score)	10.28 ± 6.21	8.86 ± 6.80*	12.05 ± 9.34	9.95 ± 8.07**
StroopCost2 (raw score)	17.10 ± 5.67	14.29 ± 5.72**	15.91 ± 7.35	14.05 ± 5.30*
FlankerPS (millisec.)	613.76 ± 229.21	558.81 ± 197.88	592.82 ± 157.41	572.43 ± 172.45
FlankerCost (millisec.)	65.19 ± 39.14	83.10 ± 59.04	71.11 ± 49.79	64.63 ± 41.22
TMTCost (sec.)	61.42 ± 41.35	54.80 ± 45.97	55.16 ± 48.08	52.20 ± 43.36
	NC			
	pre	post		
StroopPS (raw score)	30.50 ± 5.14	30.91 ± 5.30		
StroopCost1 (raw score)	10.18 ± 7.09	9.05 ± 7.57		
StroopCost2 (raw score)	16.50 ± 5.06	15.18 ± 5.79		
FlankerPS (millisec.)	590.34 ± 159.55	569.75 ± 170.22		
FlankerCost (millisec.)	80.98 ± 91.97	59.55 ± 29.85		
TMTCost (sec.)	56.87 ± 39.75	49.68 ± 33.33		

Note. Differences between pre- and post-test means were tested with paired samples t-tests (df = 21):

*p < 0.05, **p < 0.001.

Abbreviations are listed in the legend of Table 9.

Table 11

Predictors of Change in Outcome Variables in the ACT Intervention

	RPE					CAD				
	R ²	F(1,19)	β_{RPE}	β_{RPE^2}	Trend	R ²	F(1,19)	β_{CAD}	β_{CAD^2}	Trend
StroopPS (%)	0.52	9.73 ^{a,*}	18.96 ^{**}	-0.84 ^{**}	∩	0.13	2.94	0.31		—
StroopCost1 (%)	0.11	2.36	-10.94		—	0.01	0.27	-0.96		—
StroopCost2 (%)	0.17	3.34 [*]	-4.75 [*]		\	0.15	3.40	-1.17		—
FlankerPS (%)	0.56	11.48 ^{a,**}	31.01 [*]	-1.47 ^{**}	∩	<0.01	<0.01	-0.02		—
FlankerCost (%)	0.19	4.48 [*]	-20.91 [*]		\	0.09	1.90	3.73		—
TMTCost (%)	0.01	0.10	-1.68		—	0.16	3.62	-2.27 [*]		\
	%HRR					MSS				
	R ²	F(1,19)	$\beta_{\%HRR}$	$\beta_{\%HRR^2}$	Trend	R ²	F(1,19)	β_{MSS}	β_{MSS^2}	Trend
StroopPS (%)	0.01	0.22	0.04		—	0.16	2.38	0.03		—
StroopCost1 (%)	0.01	0.16	-0.12		—	0.58	17.63 ^{**}	-0.28 ^{**}		\
StroopCost2 (%)	0.01	0.14	-0.10		—	0.24	3.74 [*]	-0.11 [*]		\
FlankerPS (%)	<0.01	<0.01	0.01		—	0.01	0.08	-0.01		—
FlankerCost (%)	0.10	2.18	-1.79		—	0.04	0.48	0.22		—
TMTCost (%)	0.02	0.41	0.29		—	0.01	0.12	-0.04		—

^aThe degrees of freedom for quadratic trends are 2 and 18 for the numerator and denominator respectively.

Note. Most abbreviations are listed in the legend of Table 4 and Table 9. MSS = months since stroke

\ = significant negative linear trend, ∩ = significant inverted-U shaped trend

*p < 0.05, **p < 0.001

Table 12

Predictors of Change in Outcome Variables in the VC Intervention

	RPE					CAD				
	R ²	F(1,19)	β_{RPE}	β_{RPE^2}	Trend	R ²	F(1,19)	β_{CAD}	β_{CAD^2}	Trend
StroopPS (%)	0.01	0.17	0.84		—	0.01	0.17	0.11		—
StroopCost1 (%)	0.05	1.02	-7.01		—	0.01	0.13	-0.33		—
StroopCost2 (%)	<0.01	0.07	2.19		—	0.01	0.15	0.42		—
FlankerPS (%)	0.01	0.14	0.42		—	0.06	1.22	0.16		—
FlankerCost (%)	0.01	0.26	-36.67		—	0.21	5.16*	-3.52*		\
TMTCost (%)	<0.01	0.02	-1.29		—	0.22	2.65 ^a	20.98*	-0.19*	∩

	%HRR					MSS				
	R ²	F(1,19)	$\beta_{\%HRR}$	$\beta_{\%HRR^2}$	Trend	R ²	F(1,19)	β_{MSS}	β_{MSS^2}	Trend
StroopPS (%)	0.01	0.11	-0.03		—	0.05	0.91	-0.04		—
StroopCost1 (%)	0.08	1.70	-0.31		—	0.04	0.58	-0.11		—
StroopCost2 (%)	<0.01	0.01	0.02		—	0.07	1.13	0.20		—
FlankerPS (%)	0.01	0.17	0.03		—	0.04	0.60	0.02		—
FlankerCost (%)	<0.01	<0.01	-0.01		—	0.01	0.16	-0.68		—
TMTCost (%)	0.05	0.99	-0.45		—	0.04	0.58	0.15		—

^aThe degrees of freedom for quadratic trends are 2 and 18 for the numerator and denominator respectively.

Note. Most abbreviations are listed in the legend of Table 4 and Table 9. MSS = months since stroke

\ = significant negative linear trend, ∩ = significant inverted-U shaped trend

*p < 0.05, **p < 0.001

APPENDIX B
FIGURES

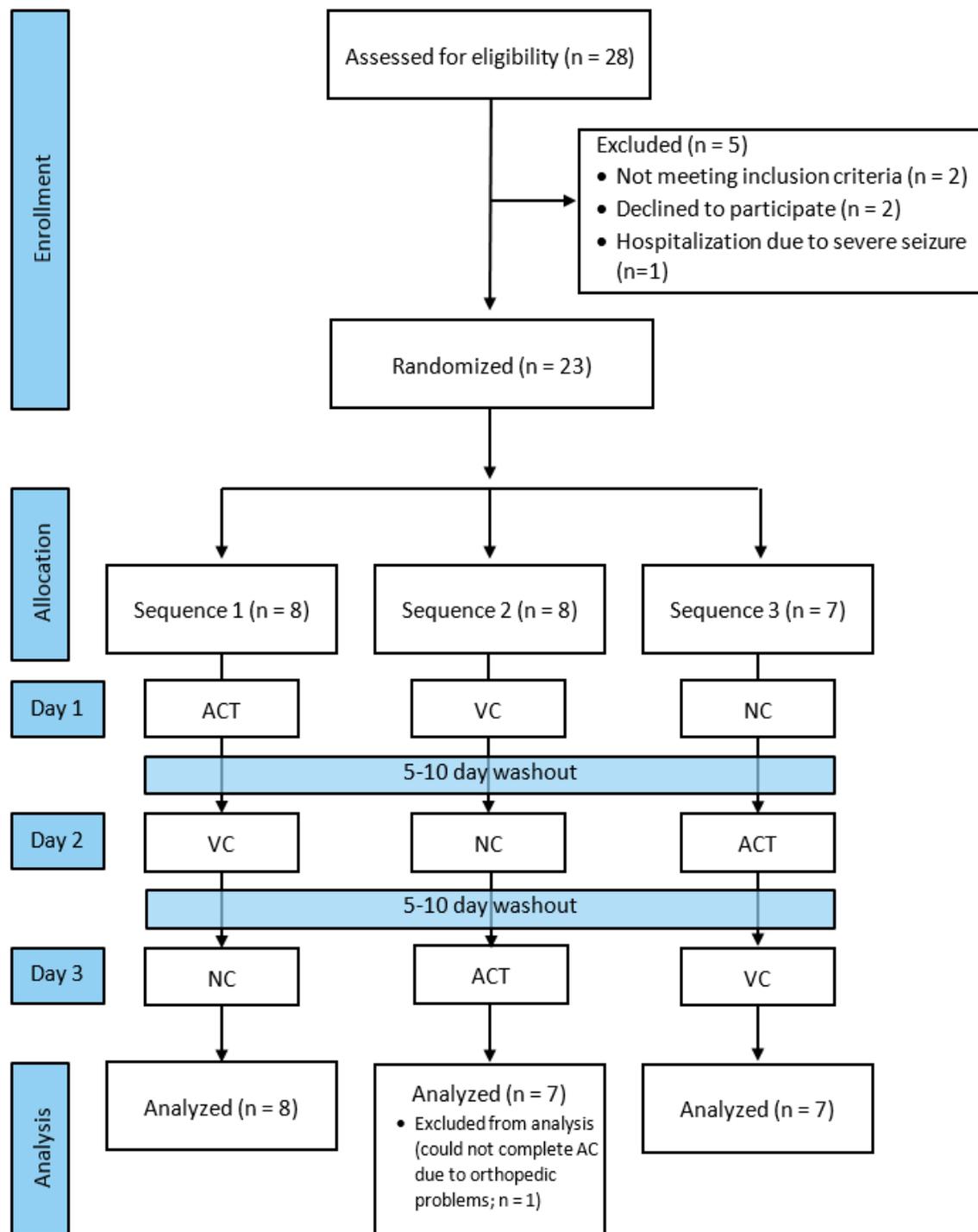


Figure 1. Study flow diagram indicating inclusion, exclusion, and randomization.

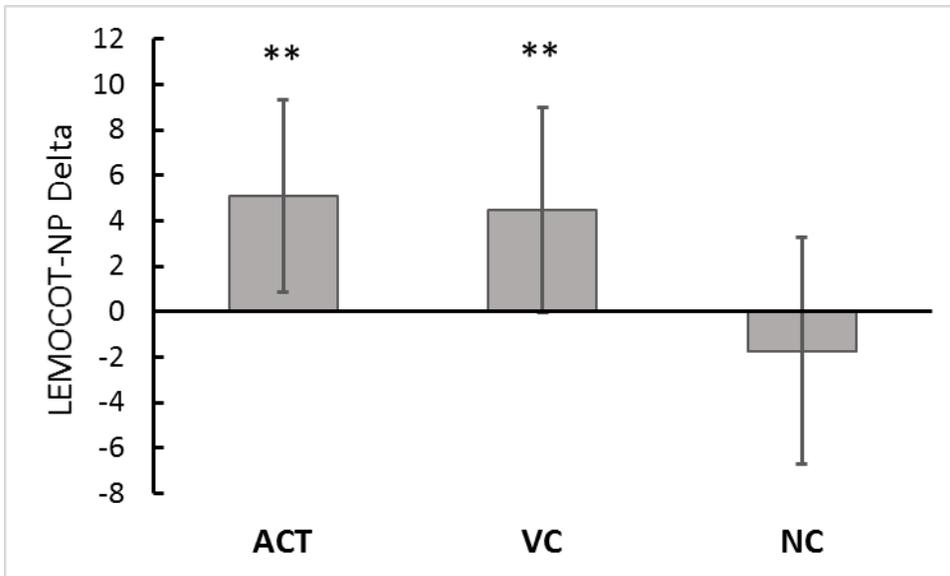


Figure 2. Change scores of LEMOCOT-NP by intervention.
 Abbreviations: ACT = Assisted Cycling Therapy, LEMOCOT-NP = Lower Extremity Motor Coordination Test - non-paretic, NC = no cycling, VC = voluntary cycling.
 Error bars represent ± 1 standard deviation.
 Significant pre- to post-test change at * $p < 0.05$, ** $p < 0.001$.

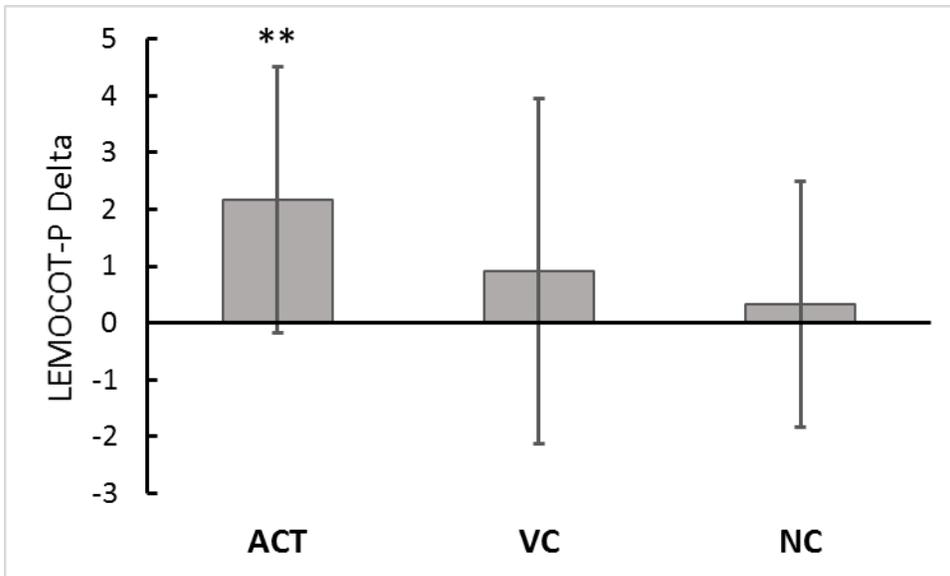


Figure 3. Change scores of LEMOCOT-P by intervention.
 Abbreviations: ACT = Assisted Cycling Therapy, LEMOCOT-P = Lower Extremity Motor Coordination Test - paretic, NC = no cycling, VC = voluntary cycling.
 Error bars represent ± 1 standard deviation.
 Significant pre- to post-test change at * $p < 0.05$, ** $p < 0.001$.

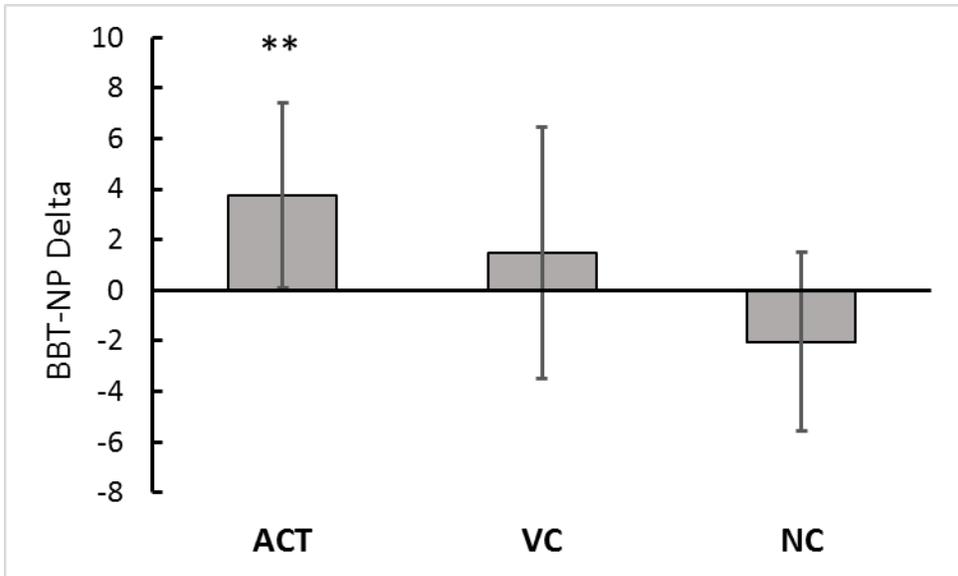


Figure 4. Change scores of BBT-NP by intervention.
Abbreviations: ACT = Assisted Cycling Therapy, BBT-NP = Box and Blocks Test – non-paretic, NC = no cycling, VC = voluntary cycling.
Error bars represent ± 1 standard deviation.
Significant pre- to post-test change at * $p < 0.05$, ** $p < 0.001$.

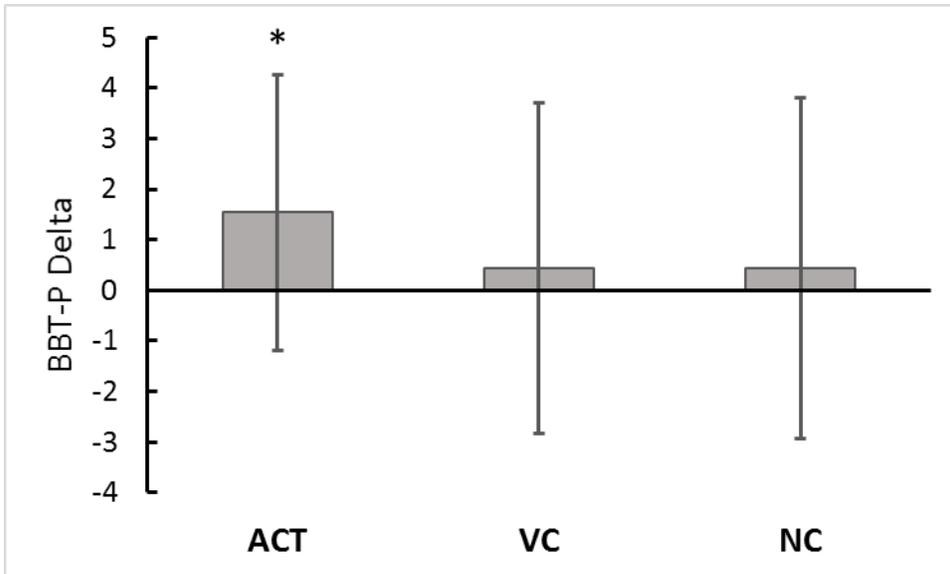


Figure 5. Change scores of BBT-P by intervention.

Abbreviations: ACT = Assisted Cycling Therapy, BBT-P = Box and Blocks Test – paretic, NC = no cycling, VC = voluntary cycling.

Error bars represent ± 1 standard deviation.

Significant pre- to post-test change at * $p < 0.05$, ** $p < 0.001$.

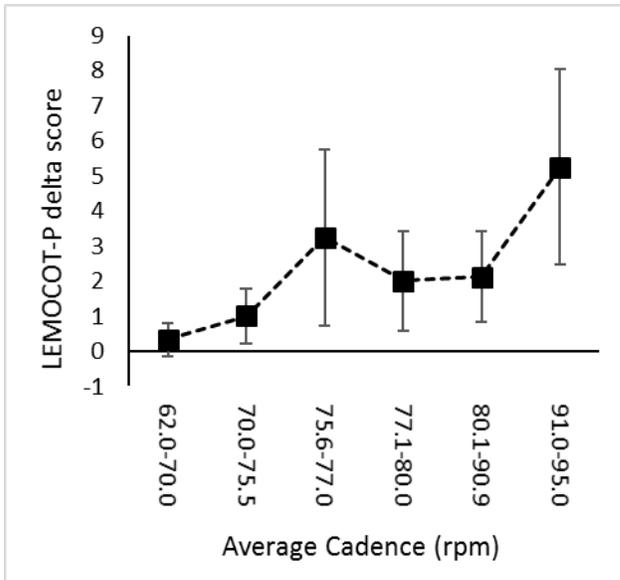


Figure 6. Significant positive linear trend ($p < 0.05$) between LEMOCOT-P delta scores and cadence during ACT. A positive delta score indicates improvement. Abbreviation: ACT = Assisted Cycling Therapy, LEMOCOT-P = Lower Extremity Motor Coordination Test – paretic. Error bars represent ± 1 standard deviation.

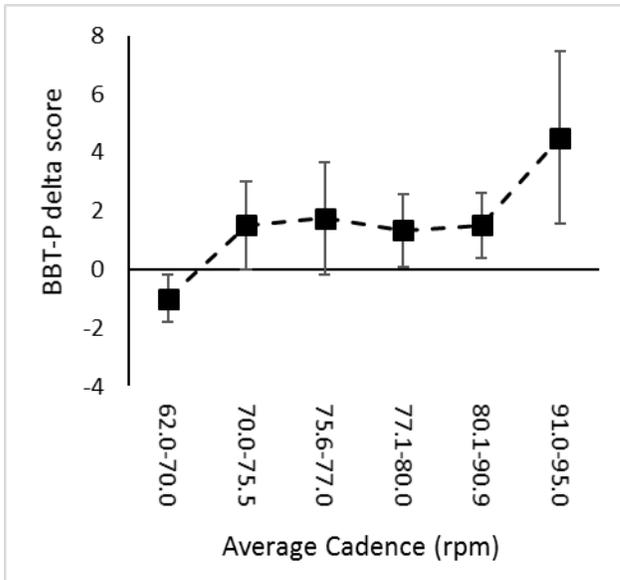


Figure 7. Significant positive linear trend ($p < 0.05$) between BBT-P delta scores and cadence during ACT. A positive delta score indicates improvement. Abbreviation: ACT = Assisted Cycling Therapy, BBT-P = Box and Blocks Test – paretic. Error bars represent ± 1 standard deviation.

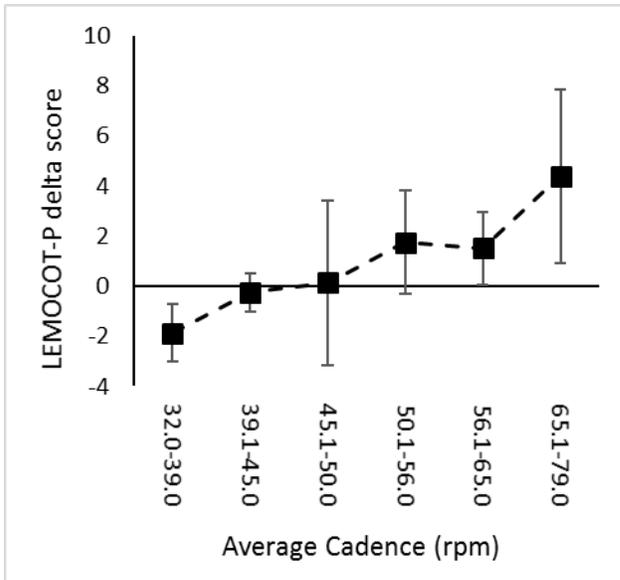


Figure 8. Significant positive linear trend ($p < 0.01$) between LEMOCOT-P delta scores and cadence during VC. A positive delta score indicates improvement. Abbreviation: LEMOCOT-P = Lower Extremity Motor Coordination Test – paretic, VC = voluntary cycling Error bars represent ± 1 standard deviation.

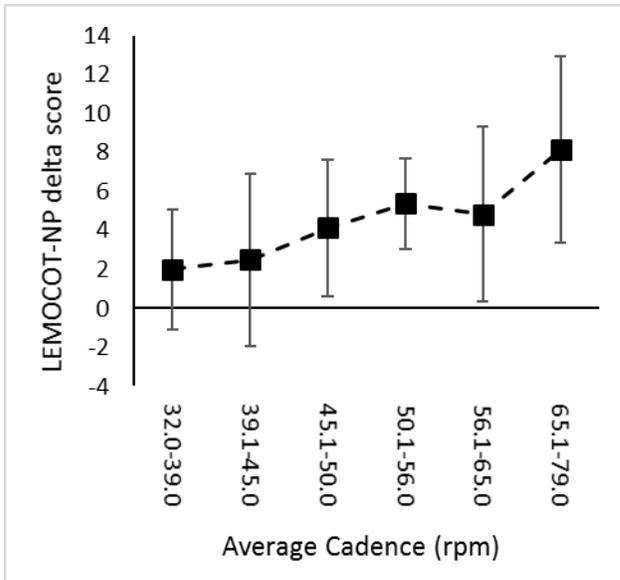


Figure 9. Significant positive linear trend ($p < 0.05$) between LEMOCOT-NP delta scores and cadence during VC. A positive delta score indicates improvement. Abbreviation: LEMOCOT-NP = Lower Extremity Motor Coordination Test – non-paretic, VC = voluntary cycling Error bars represent ± 1 standard deviation.

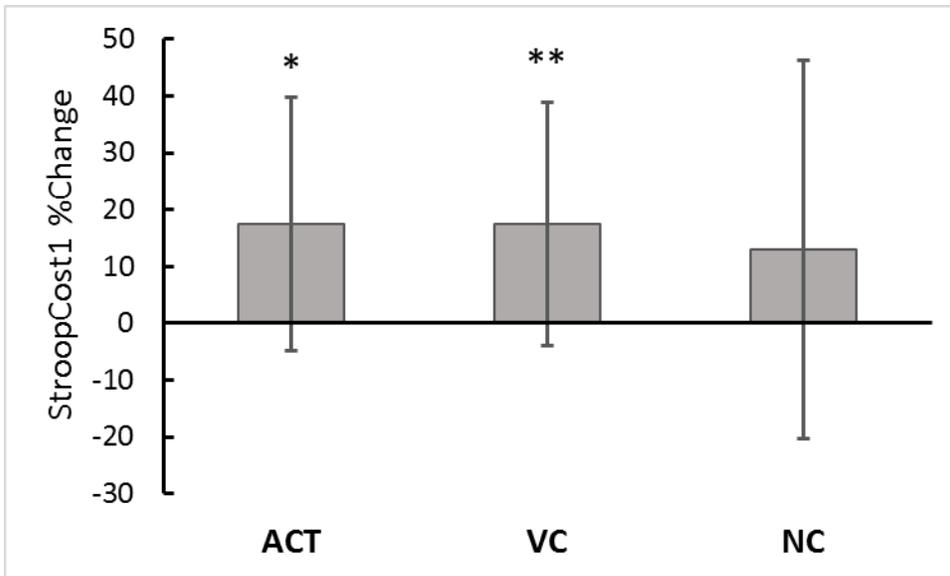


Figure 10. Percent change scores of StroopCost1 by intervention.
 Abbreviations: ACT = Assisted Cycling Therapy, NC = no cycling, StroopCost1: Number of correct responses in the no-interference condition - number of correct responses in the light interference condition, VC = voluntary cycling.
 Error bars represent ± 1 standard deviation.
 Significant pre- to post-test change at * $p < 0.05$, ** $p < 0.001$.

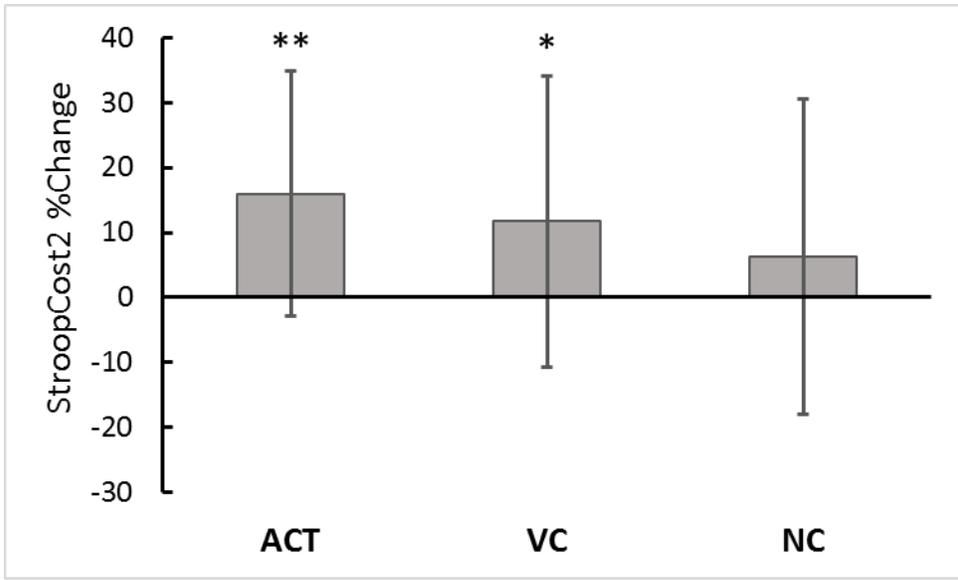


Figure 11. Percent change scores of StroopCost2 by intervention.
 Abbreviations: ACT = Assisted Cycling Therapy, NC = no cycling, StroopCost2: Number of correct responses in the no-interference condition - number of correct responses in the heavy interference condition, VC = voluntary cycling.
 Error bars represent ± 1 standard deviation.
 Significant pre- to post-test change at * $p < 0.05$, ** $p < 0.001$.

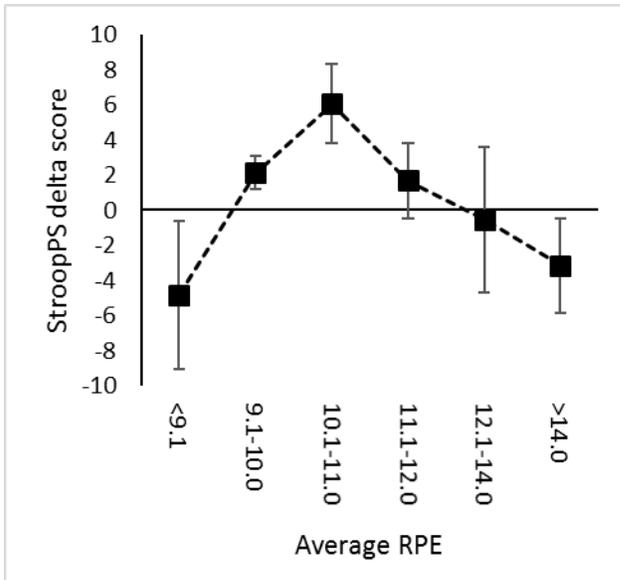


Figure 12. Significant inverted-U shaped trend ($p < 0.01$) between StroopPS delta scores and RPE during ACT. A positive delta score indicates improvement. Abbreviation: ACT = Assisted Cycling Therapy, RPE = Ratings of Perceived Exertion, StroopPS = Stroop Test processing speed. Error bars represent ± 1 standard deviation.

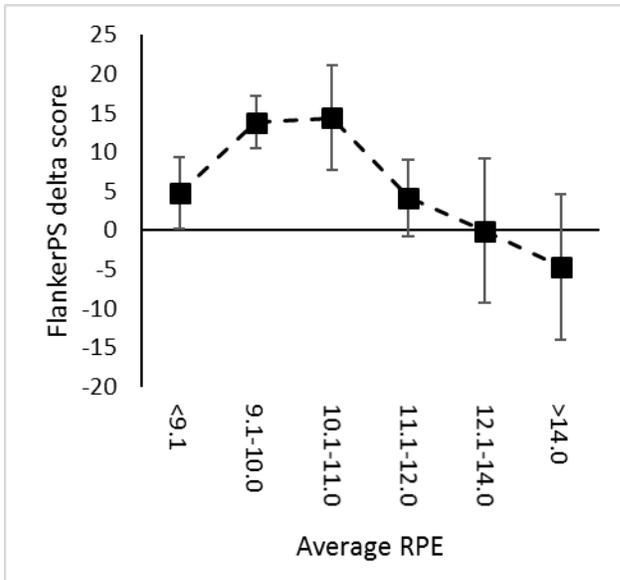


Figure 13. Significant inverted-U shaped trend ($p < 0.01$) between FlankerPS delta scores and RPE during ACT. A positive delta score indicates improvement. Abbreviation: ACT = Assisted Cycling Therapy, FlankerPS = Flanker Task processing speed, RPE = ratings of perceived exertion. Error bars represent ± 1 standard deviation.

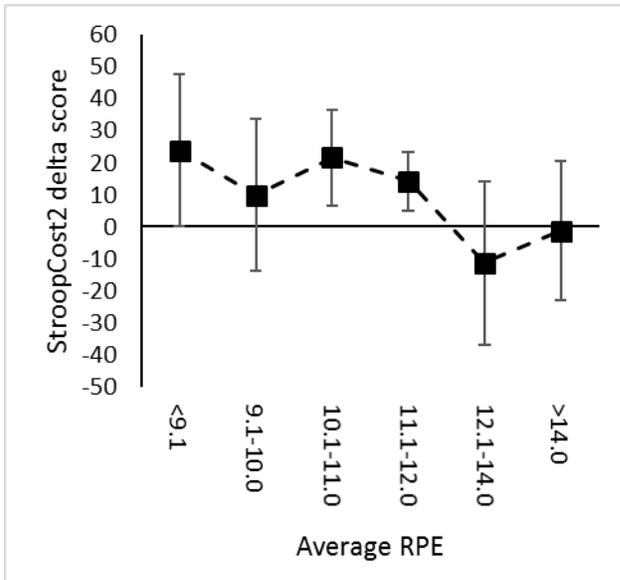


Figure 14. Significant negative linear trend ($p < 0.05$) between StroopCost2 delta scores and RPE during ACT. A positive delta score indicates improvement.

Abbreviation: ACT = Assisted Cycling Therapy, RPE = ratings of perceived exertion, StroopCost2 = Number of correct responses in the no-interference condition - number of correct responses in the heavy interference condition

Error bars represent ± 1 standard deviation.

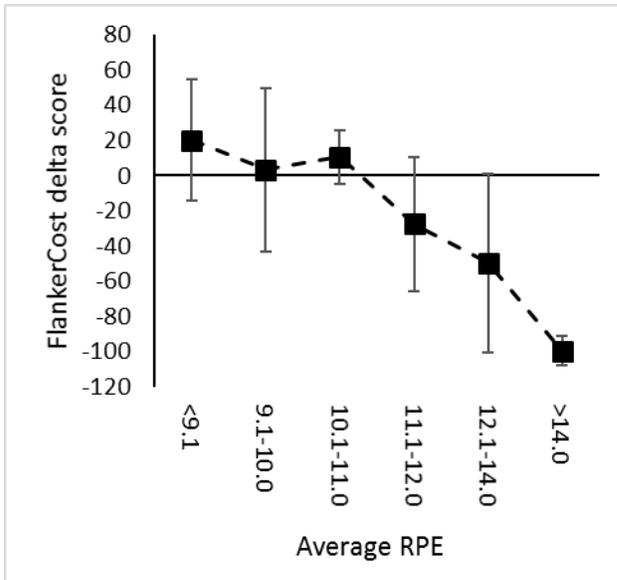


Figure 15. Significant negative linear trend ($p < 0.05$) between FlankerCost delta scores and RPE during ACT. A positive delta score indicates improvement.
 Abbreviation: ACT = Assisted Cycling Therapy, RPE = ratings of perceived exertion, FlankerCost = Flanker Task conflict cost
 Error bars represent ± 1 standard deviation.