Priming the Brain for Recovery from Stroke: The Role of Aerobic Exercise as an Adjunct to Upper-Limb Therapy

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
Graduate Department of Rehabilitation Science
University of Toronto

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Abstract

Following a stroke, the majority of individuals are left with residual deficits and there is a need to continue to improve strategies to augment recovery. This dissertation explores the approach of optimizing central nervous system conditions using aerobic exercise prior to task training. In healthy individuals a single session of aerobic exercise influences arousal and attention however, it is unknown if these effects translate to a stroke population. Further, little is known about the effect of a single bout of aerobic exercise on subsequent skill adaptation. Therefore, the main objectives of this thesis were to investigate the effect of a single bout of aerobic exercise on: (1) CNS arousal and attention in a stroke population; and, (2) short-term skill adaptation in healthy individuals and those who have suffered a stroke. Overall, for individuals recovering from a stroke, CNS arousal may be augmented as indicated by faster reaction times in some conditions and consistently faster movement times across conditions following exercise. However, attention did not appear to be influenced by the exercise bout as reaction time variability was unchanged in study 1 and absolute change was comparable across tasks with differing attentional demands in study 2. While exercise positively enhanced short-term adaptation in healthy individuals, for individuals recovering from stroke the exercise bout did not appear to benefit upper-limb movement adaptation compared to a control condition. This dissertation highlights the potential
for using exercise to influence CNS state after stroke, though results revealed significant between
and within-subject variability in this population. Future work should progress to evaluating the
longitudinal multi-session effects of pairing aerobic exercise with ecologically valid task training
to determine if the observed single session benefits augment neurorehabilitation and aid long-
term recovery from stroke.
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<tr>
<td>5-HT, Serotonin</td>
<td>GABA, Gamma-aminobutyric Acid</td>
</tr>
<tr>
<td>Ach, Acetylcholine</td>
<td>HR, Heart Rate</td>
</tr>
<tr>
<td>ANOVA, Analysis of Variance</td>
<td>LTD, Long-term Depression</td>
</tr>
<tr>
<td>ANS, Autonomic Nervous System</td>
<td>LTP, Long-term Potentiation</td>
</tr>
<tr>
<td>BDNF, Brain Derived Neurotrophic Factor</td>
<td>M1, Primary Motor Cortex</td>
</tr>
<tr>
<td>BMI, Body Mass Index</td>
<td>MS, Millisecond</td>
</tr>
<tr>
<td>BPM, Beats per Minute</td>
<td>MT, Movement Time</td>
</tr>
<tr>
<td>CIMT, Constraint-Induced Movement Therapy</td>
<td>MVC, Maximal Voluntary Contraction</td>
</tr>
<tr>
<td>CMSA, Chedoke-McMaster Stroke Assessment</td>
<td>NE, Norepinephrine</td>
</tr>
<tr>
<td>CNS, Central Nervous System</td>
<td>RPE, Rating of Perceived Exertion</td>
</tr>
<tr>
<td>DA, Dopamine</td>
<td>RPM, Revolutions per Minute</td>
</tr>
<tr>
<td>EEG, Electroencephalography</td>
<td>RT, Reaction Time</td>
</tr>
<tr>
<td>EMG, Electromyography</td>
<td>SAS, Sympathoadrenal System</td>
</tr>
<tr>
<td>iEMG, Integrated Electromyography</td>
<td>SPM, Steps per Minute</td>
</tr>
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1 Introduction
1.1 Overview

Stroke is currently the leading cause of adult neurological disability and with the combination of an aging population and advances in acute stroke care, the number of people surviving strokes is expected to rise. Since the majority of individuals do not make a complete recovery (Koton et al., 2014), the search for new or improved rehabilitation strategies is paramount to optimize recovery. This dissertation explores the approach of using aerobic exercise to optimize the central nervous system (CNS) conditions prior to traditional rehabilitation to either improve performance during or the impact of rehabilitation. Under such a model, aerobic exercise is proposed as a method to prime the CNS as it has been shown in healthy individuals to transiently augment CNS arousal, cognitive function, and neurotrophic factors critical to promoting neuroplasticity. Little is currently known about the influence of a single session of aerobic exercise among individuals recovering from a stroke and whether this may be a useful strategy to optimize neurorehabilitation in this population. This thesis has two main areas of focus. First, it explores the influence of aerobic exercise on CNS state, with a focus on individuals recovering from a stroke. This follows from previous work that has revealed arousal and attention to be modified by exercise in healthy individuals (Chang et al., 2012; Kamijo et al., 2004a; McMorris et al., 2009b). Secondly, this dissertation investigated the proposed idea that exercise could augment short term skill adaptation in both healthy individuals and people recovering from a stroke. Specifically, two studies explored the ability of a single bout of exercise to influence rate of adaptation and the final outcomes of a subsequent training session. To address these objectives a strategy of using lower-limb driven aerobic exercise and measuring upper-limb motor performance was employed to isolate the central effects of exercise in limbs not specifically involved in movement associated with the exercise bout. The first two studies address the first objective and attempt to dissociate the influence of an exercise bout to CNS arousal (study 1) and focused attention (study 2). Studies 3 and 4 address the second objective using within-subject designs comparing an exercise and control condition. Healthy young adults are evaluated in study 3 using a visuomotor learning task while the fourth study utilizes individuals in the chronic stage of stroke recovery and employs an upper-limb training task. This dissertation represents one of the first attempts at exploring the potential for aerobic exercise to augment the state of the CNS prior to training for individuals recovering from a stroke.
1.2 The Problem of Stroke

Recent estimates suggest that every 40 seconds an individual in North America suffers a stroke and it is the leading cause of neurological disability in adults (Go et al., 2013). While stroke rates may be in decline (Koton et al., 2014), mortality rates are in similar decline and the number of individuals living with the effects of a stroke is expected to rise in the coming years as the population ages. While increased survival displays excellent advances in acute care, the majority of stroke survivors do not make a complete recovery and experience residual neurological deficits (Bonita et al., 1997; Mayo et al., 1996). Therefore, this combination of increased survival and an aging population is expected to translate into a rise in the number of individuals living with the lingering effects of stroke.

1.3 Post-Stroke Impairment

Following a stroke, individuals may be left with a wide-range of functional impairments depending on the location and severity of the stroke. Sensorimotor impairment is one area in particular that has profound influence on the ability to perform activities of daily living and health-related quality of life (Nichols-Larsen et al., 2005). After the sub-acute stage of recovery (3-6 months), upper-limb sensorimotor impairment persists in 55 to 75% of stroke survivors (Lai et al., 2002). Upper-limb control issues are multi-faceted and include compensatory involvement of the trunk (Cirstea & Levin, 2000), movement segmentation (Cirstea et al., 2003a), and a small range of motion (Cirstea et al., 2003a; Michaelsen et al., 2001). In terms of function, these deficits may leave an individual unable to feed or clothe themselves and represent a major hindrance to independent living. However, stroke survivors do maintain the capacity for motor learning and with practice and training can alleviate upper-limb sensorimotor control issues (Boyd & Weinstein, 2006; Boyd et al., 2010; Wolf et al., 2006).

1.4 Upper-limb Neurorehabilitation

Effective neurorehabilitation techniques exist that alleviate functional impairment and increase use of the upper-limb after stroke. Adaptation of upper-limb end-point control after limited practice over a single-session with reach to point and reach to grasp type tasks has been demonstrated in stroke patients (Cirstea et al., 2003b; Michaelsen & Levin, 2004). Over repeated
sessions, focused task-specific therapies such as constraint-induced movement therapy (CIMT) have been shown to reduce upper-limb post-stroke impairment at all stages of recovery (Wolf et al., 2010; Wolf et al., 2006). Together, these findings indicate that after a stroke, individuals retain the capacity for improvements in function within a single training session and over multiple training sessions. These are two critically important capabilities for post-stroke recovery as neurorehabilitation is aimed at recovering function by inducing lasting change through repetitive practice. Unfortunately, task-specific training strategies such as CIMT require a significant number of repetitions of focused training to induce neural recovery. Thus, there is a need for adjunct strategies to augment the benefits of neurorehabilitation therapies. One such strategy is to augment conditions in the CNS prior to neurorehabilitation. Under such a model, CNS conditions would be primed for improved performance during training or faster adaptation in response to training in order to optimize the benefits of a single session of therapy.

Pharmacologic adjuncts such as amphetamines (Gladstone et al., 2006) as well as the application of electrical stimulation have shown promise as adjuncts to post-stroke training (Edwardson et al., 2013). One unique possibility is the use of aerobic exercise as an adjunct to physical rehabilitation as exercise has been shown to have a profound neurophysiological influence (Colcombe et al., 2006; McMorris et al., 2009b). It is anticipated that long term benefits arise in part from the accumulation of single-session effects so any opportunity to optimize a single session could translate to improvements to long term recovery. This dissertation aims to understand if a single session of aerobic exercise may be such a tool to influence CNS state to benefit subsequent therapeutic intervention among stroke survivors.

1.5 Benefits of Regular Exercise in Stroke

Aerobic exercise is an important element of post-stroke rehabilitation as it positively influences a number of outcomes. Following a stroke many individuals do not have sufficient aerobic capacity for independent functioning (Tang et al., 2006). However, participation in aerobic exercise programs has consistently improved physical fitness and functional capacity in this population (Pang et al., 2006; Potempa et al., 1996; Quaney et al., 2009; Shaughnessy et al., 2012; Tang et al., 2009a). Regular aerobic exercise also reduces risk factors such as diabetes and hypertension associated with secondary stroke (Yung et al., 2009), likely mitigating the risk, or severity of a recurrent stroke (Middleton et al., 2013). Further, neurological impairment is
reduced and cognition is improved following aerobic exercise participation (Potempa et al., 1995; Quaney et al., 2009). Finally, participation in exercise programs is associated with improved sensorimotor function (Shaughnessy et al., 2012), particularly gait and balance outcomes following walking or treadmill training exercise programs (Dean et al., 2012; Duncan et al., 2003; Mayo et al., 2013). Importantly for the current dissertation, the vast majority of research, and current best practice guidelines (Lindsay et al., 2010) support the use of a moderate aerobic exercise intensity to improve a wide range of post-stroke outcomes. Therefore, this dissertation employs a similar model of exercise intensity with the target of augmenting CNS conditions for subsequent task training while maintaining the benefits to cardiovascular health.

Targeted neurorehabilitation involving repetitive task-specific training is current best practices for improving functional recovery. The question is whether there is any opportunity to combine aerobic exercise and task-specific training to augment the known benefits of both. One example is to conduct moderate aerobic exercise prior to task-specific training with the idea that conditions in the CNS could be optimized and the benefits of training may be augmented while maintaining cardiovascular health benefits of exercise. In fact, animal models of stroke have shown that a training program which delivered aerobic exercise immediately prior to targeted upper-limb sensorimotor training did provide added benefit to the therapy (Ploughman et al., 2008). While a similar study has not been completed in humans, even a single session of aerobic exercise has a profound neurophysiological effect for healthy individuals and may be beneficial for individuals recovering from a stroke.

1.6 Benefits of a Single Session of Aerobic Exercise in Stroke

Evidence is emerging about the potential benefits of aerobic exercise on CNS function after stroke recovery. While many have speculated about the potential benefit of exercise to prime targeted therapy (Mang et al., 2013) only a single study has evaluated the effect of a single session of exercise in a stroke population. Ploughman et al. (2008) demonstrated upper-limb motor function improvements but no change to cognitive function following a single bout of body-weight supported treadmill training in a chronic stroke population (Ploughman et al., 2008). This study was particularly interesting because of the lack of change to cognitive function and an unexpected and relatively large benefit to upper-limb motor function. The authors were
uncertain if the cognitive tasks chosen were ideal to reveal exercise effects and whether the exercise was intense enough to trigger increased neurotransmitter availability (i.e. the arousal hypothesis discussed below). Additionally, during the exercise training, participants were encouraged to use their arms to support their body and the rhythmical trunk motion around stationary arms may have led to warm-up effects such as reduced tone. This could have been the mechanism for improved motor function rather than CNS augmentation induced by the exercise bout (Ploughman et al., 2008). While this study provides an initial base for the potential of a single session of exercise to augment the CNS and alter sensorimotor function in a stroke population, more research is needed to confirm these findings. There is, however, a plethora of research examining the single-session effects of exercise on brain function in healthy individuals that suggests it may be a viable strategy to influence the CNS in stroke.

1.7 Neurobiological Mechanisms Linking a Single Session of Aerobic Exercise and Central Nervous System Function

The idea of using aerobic exercise to prime the CNS extends from the many neurobiological mechanisms that are activated by aerobic exercise. Priming the CNS refers to influencing global neurophysiological conditions rather than task-specific or localized effects. Behavioural change in response to exercise has been shown in conjunction with increased levels of important hormones and neurotransmitters associated with generalized arousal systems. Aerobic exercise has been shown to increase levels of norepinephrine (NE), dopamine (DA), Acetylcholine (Ach) and other neurotransmitters (McMorris et al., 2009b). Importantly, increased levels of metabolites of these neurotransmitters have been found which indicates that aerobic exercise leads to increased production, release, and use of neurotransmitters involved in these arousal systems (McMorris et al., 2008). While this neuroendocrinological link between aerobic exercise, general CNS arousal and function is critically important for the proposed model of exercise as a prime it is not the only benefit of aerobic exercise. While the mechanisms whereby aerobic exercise influences global neurological function are not the focus of the current dissertation an understanding of these mechanisms is prudent as the model follows the notion that augmenting global CNS neurophysiology may be used to influence subsequent task training. Thus, the following section will provide a brief introduction to the mechanisms of how a single session of aerobic exercise influences brain function (the arousal hypothesis). Additionally, it
will briefly outline important exercise effects including its influence on neurotrophic factors and neurophysiology important for neuroplasticity before finishing with a brief discussion of the additional benefits of a single session of aerobic exercise which may impact stroke rehabilitation.

1.7.1 Arousal Hypothesis

The arousal hypothesis outlines one mechanism whereby a single session of aerobic exercise influences global CNS arousal and this neuroendocrinological link was first suggested over 40 years ago (Cooper, 1973). During a bout of aerobic exercise, and even immediately preceding the exercise, the autonomic nervous system (ANS) initiates activity of the sympathoadrenal system (SAS). One of the crucial components of this connection is that the ANS continues to provide feedback to the SAS regarding the stress on the body induced by the exercise to trigger physiological responses such as heart rate and respiration rate increases. The hypothalamus receives this ANS feedback via the limbic system, thalamus and reticular activation system. Ultimately, the hypothalamus triggers the release of catecholamines, including norepinephrine (NE) and dopamine (DA) from stored vesicles. Continued feedback from the body during exercise, particularly the cardiorespiratory system and peripheral musculature, continues to exacerbate this process and leads to increased levels of a number of arousal related neurotransmitters such as serotonin (5-HT), NE and DA (McMorris et al., 2009b). While increases in peripheral plasma concentrations of these neurotransmitters has been confirmed to occur in the brain of rodent models (Meeusen et al., 1997) it was generally assumed that peripheral concentration was correlated with CNS use in humans. Importantly, an examination of the concentrations of NE and DA metabolites confirmed that during exercise concentration of the metabolites increases, confirming that increased use of these neurotransmitters is occurring in the CNS (McMorris et al., 2008).

CNS arousal is governed by both ascending and descending arousal systems. The ascending arousal system is primarily responsible for activating the cerebral cortex, while the descending arousal system is responsible for preparing the body for action by activating autonomic systems and reticulospinal neurons important for movement (Pfaff & Banavar, 2007). Commonly, arousal systems are separated based on the neurotransmitter involved, which for the ascending arousal system includes NE, DA, serotonin, and acetylcholine (ACh) among others. The NE system (or
noradrenergic) projects to the posterior cerebral cortex but not occipital cortex and is associated with sensory alertness. The DA nuclei project to the anterior, frontal cortex and are involved in directed motor acts. The 5-HT system projects to the limbic system and hypothalamus and is involved in emotional and autonomic behaviors. Aneurons are located in the basal forebrain and have widespread projections throughout the cortex (Pfaff & Banavar, 2007). One of the most important components of these arousal systems are the nucleus reticularis gigantocellularis (NRGc) neurons in the medullary reticular formation. These large neurons are master cells for arousal due to their bifurcating axons which influence both the ascending and descending arousal systems (Martin et al., 2010). NRGc neurons respond to a wide range of sensory stimuli and activity in these neurons is associated with CNS arousal measured with electroencephalography (EEG) and electromyography (EMG) in rodents (Wu et al., 2007). Of additional importance for the current dissertation, increased voluntary motor activity was associated with increased firing in these neurons (Martin et al., 2010). Thus, a single session of aerobic exercise is coupled with CNS arousal via the ANS and SAS and has the potential for profound influence due to the widespread connections across the cortex.

1.7.2 Neurotrophic Factors

The relationship between long-term aerobic exercise and neuroplastic change has long been established in healthy and diseased populations. However, only relatively recently has there been a neurobiological approach to understanding the mechanisms whereby physical activity induces neurological change (Cotman & Berchtold, 2002). A number of proteins and growth factors have received particular research interest including vascular-endothelial growth factor (Cotman et al., 2007) which is involved in blood vessel growth and insulin-like growth factor (Ploughman et al., 2005) which has roles in cell growth. However, significant research focus has been applied to understanding the link between neurotrophic factors and aerobic exercise, particularly brain-derived neurotrophic factor (BDNF) as it is a contributor to many common neuroplasticity pathways (Cotman & Berchtold, 2002; Cotman et al., 2007). BDNF plays important roles in neurogenesis, neuronal differentiation, neural survival and synaptic plasticity (Huang et al., 2014; Monteggia et al., 2004) Of particular interest for the current dissertation is the role of BDNF in synaptic plasticity, which refers to the creation and strengthening of neural connections and cortical pathways (Vaynman & Gomez-Pinilla, 2005; Vaynman et al., 2004). Since,
 therapeutically intervention is focused on repetitive practice to strengthen neural pathways, augmenting synaptic plasticity via increases in neurotrophins and other critical proteins may lead to more impactful therapy. Importantly, these growth factors and neurotrophic factors such as BDNF are up-regulated and released in response to a single bout of aerobic exercise.

Given the invasive nature of this research, animal models have primarily been used to investigate the effects of exercise on neurotrophic factors. Animal models have consistently displayed central increases in BDNF (and other proteins and neurotrophic factors) following multi-session forced and voluntary running paradigms (Ploughman et al., 2005; Vaynman & Gomez-Pinilla, 2005). More pertinent for the current dissertation however, is the influence of a single session of aerobic exercise on neurotrophic factor availability for subsequent therapeutic intervention. BDNF levels were increased (not statistically significant) after only a single day being housed with access to a running wheel in rats compared to sedentary housing (Adlard et al., 2004). Others have found 14 days of exercise daily or on alternating days was needed to significantly increase BDNF levels in rodent models (Berchtold et al., 2005). However, it is important to note that these studies are focused on basal levels of BDNF in animal models rather than transient changes from a single session of exercise as animals were not sacrificed immediately following their exercise bout. However, evidence does support transient increases in BDNF as following a single 30 minute session of walking in rats BDNF levels in the contralateral hippocampus and sensorimotor cortex were higher than sedentary animals (Ploughman et al., 2005). While effects seen in animal models are not always applicable to humans, it has been speculated that using aerobic exercise to increase the availability of BDNF and other neurotransmitters prior to active motor rehabilitation has been speculated to be an effective strategy (Mang et al., 2013). Human evidence does support the potential for a single-session of exercise to transiently increase BDNF availability. Moderate exercise for 30 minutes led to increased serum BDNF levels in healthy individuals and those with multiple sclerosis (Gold et al., 2003). Following a single session of high intensity running, serum BDNF levels were increased and this was correlated with greater immediate learning success (Winter et al., 2007). Further, a recent review found 14 of 15 studies found increased peripheral BDNF levels following a wide variety of single session aerobic exercise protocols (Huang et al., 2014) which remain elevated for 10 to 60 minutes after exercise (Knaepen et al., 2010). Thus, a single session of aerobic exercise increases BDNF availability in
animals and humans, which is an important facilitator of neuroplasticity, and may have profound impact on subsequent task training.

1.7.3 Neurophysiologic Adaptations to a Single Session of Aerobic Exercise

Evidence is accumulating which highlights neurophysiological changes following a single session of aerobic exercise. Specifically, following exercise, excitability within the primary motor cortex (M1) is modulated. Transcranial magnetic stimulation (TMS) paradigms allow for non-invasive evaluation of M1 excitability and have recently been used to probe intracortical inhibition and excitation. Delivering two stimulations in close temporal proximity over the motor cortex induces short-interval intracortical inhibition (SICI). Interestingly, after only 7 minutes of stationary cycling SICI was reduced in the leg representation area of M1 which is indicative of a reduction in intracortical inhibition. More importantly for the current thesis, intracortical inhibition has been shown to be reduced following exercise in hand regions of M1 that were not involved in the movement during the exercise bout. Following low and moderate intensity cycling exercise protocols SICI has been shown to be reduced for up to 15 (Smith et al., 2014) or 30 minutes (Singh et al., 2014a). Suppression of intracortical networks is thought to be modulated by the action of gamma-aminobutyric acid (GABA) (Singh & Staines, 2015).

Reducing intracortical inhibition may be a critical benefit to stroke as individuals commonly display altered interhemispheric inhibition (Honaga et al., 2013). However, just as critical may be the impact of exercise on GABA as lower levels of GABA are associated with functional recovery following a stroke (Singh & Staines, 2015). The above findings suggest that aerobic exercise may exert a global influence on M1 excitability as change is not limited to the limbs directly involved in the exercise. Interestingly, these findings extend to more targeted evaluation of plasticity using TMS protocols thought to induce long-term depression (LTD) or long-term potentiation (LTP)-like plasticity. Low-intensity exercise enhanced the response to TMS theta-burst stimulation which is thought to induce LTD-like effects (McDonnell et al., 2013). Further, both moderate (Singh et al., 2014b) and high-intensity (Mang et al., 2014) exercise bouts have displayed an augmented response to TMS paired-associative stimulation which is thought to reflect LTP-like plasticity. Unfortunately, the mechanisms leading to these effects are not well understood but are speculated to be related to neurotransmitters and neurotrophic factor release.
(as discussed above) as well as cerebral blood flow (Singh & Staines, 2015). Taken together, these results display the effects of exercise on global modulation of intracortical networks which may be particularly relevant for individuals recovering from a stroke.

1.7.4 Additional Neurobiological Benefits of a Single Session of Exercise

Acute effects of exercise are generally attributed to increased release of neurochemicals including neurotransmitters and neurotrophic factors. However, it is unlikely that these mechanisms work in isolation and are combined with additional exercise influences including cerebrovascular changes and improved mood. Delivery of oxygen and nutrients to cortical tissue is critical for optimal brain function. Novel MRI techniques including arterial spin labelling are able to provide a detailed picture of regional perfusion changes after an exercise bout. This technique has shown that a single-session of aerobic exercise increases cerebral blood flow (Smith et al., 2010). However, single-session exercise effects may be dependent on tissue type as gray matter perfusion was decreased 10 minutes after exercise while white-matter perfusion was increased at 40 minutes after exercise in young healthy adults (MacIntosh et al., 2014). These white matter findings match with the robust finding of faster information processing discussed below and further support an increased CNS arousal effect following aerobic exercise. While a full understanding of the cerebrovascular effects of exercise has yet to be reached this may be an important effect of exercise for a stroke population which has altered cortical blood flow from their infarct. Depression is a common challenge for individuals post-stroke and approximately one third of individuals suffer with depression following a stroke (Alajbegovic et al., 2014).

Long-term aerobic exercise has been linked to increased mood and is an effective treatment of depression (Cooney et al., 2013). Importantly, a single session of aerobic exercise is an effective strategy to transiently improve mood in healthy individuals (Yeung, 1996) and those with depression (Bartholomew et al., 2005). Part of this emotional response to a single session of exercise may be through increased neurotransmitter release including 5-HT and DA related to the arousal hypothesis discussed above; however, an important mediator is increased endorphin release (Ekkekakis & Petruzzello, 1999). Improved mood from increased endorphin and neurotransmitter release, may result in participants more willing to engage in or persevere through challenging sensorimotor therapy. While aerobic exercise is not unique in its ability to facilitate CNS arousal or alter neurotrophic factor expression, these additional benefits to
cerebrovascular function and mood are an added benefit of exercise as a prime for stroke neurorehabilitation.

These neurobiological mechanisms of exercise’s influence on global CNS function do not work in isolation, rather these exercise effects are likely additive and represent the many potential avenues for exercise to benefit the unique CNS challenges following cortical insult. Additionally, it is worth noting that the exercise effects on the CNS discussed above are in addition to well established cardiovascular and musculoskeletal benefits of aerobic exercise. Finally, it is pertinent to highlight that uncovering or confirming these mechanisms is beyond the scope of this dissertation, they are highlighted to provide a basic overview of global exercise effects and provide further context for specific objectives and hypotheses about the proposed effects of exercise on CNS state and behaviour among individuals recovering from a stroke.

1.8 Linking Observational Evidence with Underlying Neurobiological Effects: Potential Priming Targets for a Single Session of Aerobic Exercise

The wide range neurobiological effects of exercise display the broad potential for aerobic exercise to influence global CNS function. However, the most robust effects observed of a single session of aerobic exercise are underscored by augmented CNS state. CNS state refers to global neurophysiological modulation of neural activity and is influenced by factors including arousal, motivation, and attention. Given the neurobiological links outlined above, particularly the arousal hypothesis, and evidence to be outlined below, it appears that exercise has the greatest potential to augment CNS state by influencing arousal and attention. This dissertation will extend this line of inquiry by investigating the effects of a single bout of exercise on arousal and attention factors investigated using stimulus-response tasks among individuals recovering from stroke. Additionally, evidence suggests that the motor system may be preferentially augmented by aerobic exercise with limited evidence suggesting motor control may be influenced by exercise. Since the majority of neurorehabilitation is spent on targeted task-specific sensorimotor training this dissertation will investigate the influence of a bout of exercise on corticomotor activation using EMG during stimulus-response tasks as well as upper-limb motor control. Finally, little is known about the influence of exercise on short-term skill adaptation. Thus, this dissertation explores short-term adaptation in healthy individuals using a visuomotor association
task and those recovering from a stroke using an upper-limb movement training paradigm following a single-session of aerobic exercise. The following sections outline the evidence for the effects of a single-session of aerobic exercise that have the strongest association to the neurobiological mechanisms discussed above. Specifically, this dissertation investigates the effect of a single bout of aerobic exercise on CNS arousal, attention, corticomotor activation, motor control, and short-term learning.

1.8.1 Arousal

Understanding of exercise-induced changes to CNS arousal comes primarily from stimulus-response tasks focused on information processing time. Simple stimulus-response paradigms, which involve stimulus recognition and response execution, have been consistently reduced both during and following aerobic exercise, indicating that a single bout of aerobic exercise facilitates information processing during and after the exercise bout (Chang et al., 2012; Davranche et al., 2006; McMorris et al., 2009b). These findings extend to shorter response times during choice response tasks (Davranche et al., 2005) which adds a decision making step to the pathway and further supports faster information processing. However, choice response paradigms will primarily be discussed in the next section as they have generally been used to investigate the effect of exercise on executive function.

Response time includes all processing stages from stimulus presentation to movement completion while reaction time (RT) is the time from stimulus presentation until the onset of EMG activity in the primary muscle and movement time (MT) is the time from onset of EMG activity until movement completion. Faster reactions are associated with faster information processing but this requires measurement of RT without the confound of MT (e.g. use of EMG). Studies that have used EMG to dissociate response time into RT and MT have shown preferentially augmented MT or response execution (Davranche et al., 2005, 2006; McMorris et al., 2009b). Thus, faster responses appear to be driven by a reduction in MT or the motor components of a response. Of further interest, EMG measures suggest that during lower-limb driven aerobic exercise, upper-limb corticomotor commands are enhanced as indicated by a steeper initial slope of EMG activity (Davranche et al., 2005, 2006) which furthers the proposition of augmented arousal within the corticomotor system. Further, it is important to note
that RT was also reduced in these experiments which suggests faster information processing, due at least in part to augmented central CNS arousal from the exercise bout (Davranche et al., 2005, 2006). Conversely, TMS measures of excitability within the corticomotor tract have not displayed a significant change following a single session of exercise (McDonnell et al., 2013; Singh et al., 2014a). Taken together, this evidence indicates that a single session of aerobic exercise augments CNS arousal displayed through faster responses resulting from both shorter RT (faster information processing) and MT (augmented corticomotor command).

Additional support for exercise induced augmentation of CNS arousal is derived from neuroelectric markers of cortical excitability. Resting state electroencephalography (EEG) power, which is a measure of cortical neuronal activity at rest, is increased during and after exercise and this indicates heightened arousal and cortical excitability (Crabbe & Dishman, 2004; Moraes et al., 2011; Moraes et al., 2007). Importantly, this increased power is not restricted to the alpha frequency band which is indicative of fatigue but has been shown in the beta (Moraes et al., 2007) and higher frequency bands (Crabbe & Dishman, 2004) which suggests increased cortical activation and CNS arousal. Further, increased intracortical excitability in the primary motor cortex has been found following a session of aerobic exercise which was probed in muscles not actively involved in the aerobic exercise bout (Singh et al., 2014a). Together, these findings suggest enhanced CNS arousal during and after a bout of aerobic exercise in young healthy individuals. However, it is unknown if this exercise induced augmentation would occur for individuals recovering from a cortical insult.

Augmented CNS arousal is important for individuals recovering from a stroke. In the sub-acute period following a stroke, motor cortex excitability is imbalanced and characterized by hyperexcitability on the non-affected hemisphere and hypoexcitability on the affected hemisphere (Butefisch et al., 2008; Shimizu et al., 2002). Further, persistent hypoexcitability of the ipsilesional cortex is the strongest predictor of motor impairment in the chronic stage of stroke recovery (Volz et al., 2014). Therefore, increasing CNS arousal prior to therapy may have profound impact on this population and has potential to improve function during therapy. Given the relationship between aerobic exercise, information processing, cortical excitability, and CNS arousal outlined above, it may be the optimal strategy to prime CNS arousal prior to neurorehabilitation for individuals recovering from a stroke.
1.8.2 Attention

In addition to focusing on information processing time, consideration has been paid to understanding the influence of exercise on higher cognitive functions, with a particular focus on attention. Similar to CNS arousal-related outcomes discussed above, attention-related outcomes have generally been evaluated using stimulus-response tasks. Thus, it is important to recognize that faster responses in these tasks are in part likely due to faster information processing and CNS arousal as discussed above and not entirely due to improved attention. However, additional data analyses and the use of neuroelectric measures has suggested that aerobic exercise augments attention through improved allocation of attentional resources. For example, while exercising sub-maximally, attentional refocusing was improved as demonstrated by faster RT when attention was switched as compared to a rest condition (Pesce et al., 2003). Modified Flanker tasks have also commonly been used to evaluate the effects of exercise on attention-demanding tasks. The Flanker task (Eriksen & Eriksen, 1974) presents a central target which indicates the response while flanking stimuli which can be congruent or incongruent to the central target surround the central target (i.e. <<< or >>>, both indicate a left response). Thus, the task has a decision making component and requires attention as participants must focus on the central target while avoiding the visual interference created by the flanking stimuli. Additionally, time locking an EEG signal to stimulus presentation and then averaging the data across trials provides a robust event-related P3 potential whose amplitude and latency relate to the allocation of attentional resources and information processing speed respectively (Polich & Kok, 1995). Such studies have displayed faster responses without a decrement to accuracy with corresponding increases in P3 amplitude and decreases in P3 latency immediately following a single bout of aerobic exercise (Kamijo et al., 2009; Kamijo et al., 2004b; Kamijo et al., 2007) and after heart rate returns to baseline levels (Hillman et al., 2003; Magnie et al., 2000).

Thus, a single bout of aerobic exercise augments attention, which is generally exhibited through faster responses and enhanced neuroelectric markers in healthy individuals. Enhanced attention may be a critical priming benefit of exercise since attentional capacity is one of the strongest determinants of post-stroke functional recovery (Barker-Collo et al., 2010a; Robertson et al., 1997). Attentional capacity refers to a range of attention constructs including sustained, selective, focused, and divided attention. The benefits of a single session of exercise outlined
above have commonly utilized a modified Flanker task which mainly evaluates selective and focused attention. While an enhancement to all attention domains would likely benefit subsequent training, selective and focused attention, which refer to the ability to avoid distraction and respond to specific stimuli are particularly relevant (Posner & Petersen, 1990). During a therapy session, the ability to focus on the specific task and avoid distractions from extraneous stimuli is critically important for training success. Thus, using a session of aerobic exercise to augment attention, particularly selective and focused attention, may significantly improve an individual’s performance during therapy.

1.8.3 Motor Control

While considerable research has focused on the effects of a single session of aerobic exercise on cognitive outcomes, much less has focused on motor outcomes. However, if the proposed model of using aerobic exercise as a prime for subsequent therapy is to be utilized it is prudent to understand the influence of exercise on the motor system. Upper-limb sensorimotor dysfunction persists in 55 to 75% of individuals recovering from a stroke (Lai et al., 2002) and is a major hurdle for independent living. As a result, significant time during neurorehabilitation is spent on focused task-specific training to overcome specific sensorimotor deficits (Langhorne et al., 2011). Thus, a focus of the current dissertation is to evaluate the influence of a single session of aerobic exercise on the motor system. Specifically, we will utilize lower-limb driven exercise and evaluate the upper-limb to investigate the global effects of aerobic exercise (i.e. in limbs not involved in the exercise). As discussed above, a single session of aerobic exercise augments movement time during stimulus-response tasks and enhances EMG activity in healthy individuals. Exercise is also associated with increased activity in the sensorimotor cortex as motor commands are delivered and sensory input is received. It has been speculated that this increased cortical activity is an important component of exercise effects on the sensorimotor system (Ridgel et al., 2011). Together, these findings display positive effects of exercise on motor outcomes; however, it is unclear if this augmentation of motor processes in stimulus-response tasks extends to more complex motor control.

Interestingly, after an exhaustive exercise bout of lower-limb cycling, upper-limb control on a visuomotor tracking task was improved despite participant fatigue (Mierau et al., 2009). This
improved control was in the upper-limb which was not involved in the exercise and accompanied by altered brain activity suggesting a global effect of exercise on motor control (Mierau et al., 2009). Further, work by Ploughman (2008) displayed that a single bout of body-weight supported treadmill exercise in a chronic stroke population improved upper-limb motor function as measured by the action research arm test which assesses ability to handle objects of varying size, weight and shape (Ploughman et al., 2008). While this study lacked the ability to isolate the locus of these changes as participants partially utilized their upper-limbs for support during the exercise bout, it was novel in that it highlighted the potential for exercise to augment functional movements in a stroke population (Ploughman et al., 2008). While the support for exercise induced alteration to motor control is limited, a single-session of aerobic exercise interacts with the motor system and has potential to influence the motor system beyond excitation of the corticomotor command. Thus, the current dissertation will evaluate the effects of exercise on the corticomotor command but also undertake a preliminary evaluation of the effects of exercise on motor control through the analysis of movement kinematics (velocity, displacement) during goal-directed tasks.

1.8.4 Short-term Skill Adaptation

The exercise effects on arousal, attention and the motor system outlined above primarily benefit subsequent performance during therapeutic intervention. While clearly beneficial, the question remains whether a single session of aerobic exercise enhances the immediate impact of the therapeutic intervention (i.e. short-term adaptation). Since the overall aim is to utilize these acute benefits of aerobic exercise to augment subsequent motor and cognitive learning in stroke it is prudent to evaluate the influence of exercise on short-term skill adaptation. Short-term skill adaptation refers to tracking the rate of improvement over a period of minutes to hours and may be influenced by CNS arousal and attention which, as discussed above, are influenced by exercise. Improving the rate at which an individual is able to improve skill performance, even within a single-session, following a stroke is critical as the window of rapid improvement limited to weeks following the stroke and improvement outside this window requires a more significant investment of time and training (Langhorne et al., 2011).
While aerobic exercise augments CNS state and neurophysiology as discussed above, few studies have directly evaluated its effect on short-term skill adaptation. A short bout of high intensity running was shown to improve immediate acquisition of a new language by 20% compared to moderate intensity exercise and a resting condition (Winter et al., 2007). Conversely, exercise either before or after visuomotor skill training did not influence immediate acquisition compared to non-exercising participants (Roig et al., 2012). Interestingly, in both these studies, retention (> 24 hours after training) was superior following the exercise condition compared to the resting condition (Roig et al., 2012; Winter et al., 2007). Further, this upper-limb sequence-specific implicit learning has been shown to be augmented immediately following a bout of high intensity aerobic exercise which was maintained 24 hours later compared to a non-exercising condition (Mang et al., 2014). These studies suggest a link between more rapid adaptation following an exercise bout and improved retention. These findings are likely underscored in part by enhanced synaptic plasticity. Interestingly, long-term potentiation (LTP)-like mechanisms have been shown to be augmented following a single session of exercise (Mang et al., 2014; Singh et al., 2014b). Further, moderate aerobic exercise improves working memory in young healthy adults (Pontifex et al., 2009a) and memory consolidation among healthy elder individuals and those with mild cognitive impairment (Segal, Cotman, & Cahill, 2012) which indirectly supports exercise’s influence on short-term skill adaptation. Overall, these studies generally support a positive benefit of aerobic exercise; however, the majority of work has focused on retention (Roig et al., 2012; Winter et al., 2007). Thus, a focus of the current dissertation is the influence of a single bout of aerobic exercise on subsequent short-term skill adaptation.

1.9 Summary

This dissertation will use moderate intensity aerobic exercise immediately prior to task performance or task training. As stated above (section 1.5), moderate intensity exercise is recommended as part of best practice for stroke recovery (Lindsay et al., 2010). This dissertation is investigating whether the timing of the moderate exercise bout relative to task training may influence CNS state in addition to providing the well known cardiovascular benefits. Additionally, there appears to be an inverted U relationship between exercise intensity and information processing (Kamijo et al., 2004b). Thus, a moderate intensity target for the exercise
bout may be ideal for augmenting CNS arousal and attention which is the target of this dissertation. Following this reasoning, timing the exercise bout immediately prior to task performance or task training was done to maximize the exercise-induced CNS augmentation linked to the arousal hypothesis which lasts approximately 15-20 minutes after the exercise bout (Chang et al., 2012) but may extend further (Hillman et al., 2003). Finally, this dissertation focuses on within-session change in performance (short-term skill adaptation) which is likely a necessary precursor to relearning following a stroke. While the influence of exercise on CNS arousal and attention has been well documented in healthy individuals little is known about the effect of exercise on a stroke population. Additionally, little is known about the effect of a single bout of aerobic exercise on short-term adaptation in healthy or diseased populations. Given the potential for aerobic exercise to augment the CNS, while still providing cardiovascular benefit for individuals recovering from a stroke, aerobic exercise will be explored for its ability to prime the CNS prior to therapeutic intervention.

1.10 Objectives

This dissertation investigates the short-term effects of aerobic exercise on CNS arousal, attention, the corticomotor system and motor control (velocity profile and movement error) as well as short-term skill adaptation. Specifically, it examines the potential benefit of using a bout of lower-limb aerobic exercise prior to evaluating the upper-limb among individuals recovering from a stroke.

The overall objectives of this dissertation are to:

1. Explore the influence of aerobic exercise on CNS state in individuals recovering from a stroke with a focus on potential influences on arousal and attention.

2. Investigate the effect of exercise on short-term skill adaptation in healthy individuals and individuals recovering from a stroke.

These objectives are designed to determine if effects of exercise observed in healthy individuals translate to individuals recovering from a stroke. Additionally, the dissertation attempts to address gaps in the literature surrounding the effect of exercise on short-term skill adaptation in both healthy individuals and those recovering from a stroke. The following four experiments
address these objectives. The first two experiments attempt to focus on exercise induced effects on CNS arousal and attention. While the second objective is primarily addressed with the third and fourth experiments which focus on short-term adaptations in healthy individuals and those who have had a stroke.
The Influence of a Single Bout of Aerobic Exercise on Speed of Processing and Muscle Activity in Stroke
2.1 Abstract

**Background:** Aerobic exercise may be an effective adjunct to traditional neurorehabilitation to prime central nervous system state and facilitate neurological recovery. The objective was to examine the influence of a single session of lower-limb aerobic exercise on upper-limb reaction time (RT) and amplitude of muscle activity within a stroke population.

**Methods:** Fourteen stroke participants performed 20 minutes of lower-limb aerobic exercise. Upper-limb simple and choice RT was evaluated pre-, during and immediately post-exercise using electromyography (EMG). The RT task presented arrows on a computer screen which indicated the appropriate limb and participants responded with a wrist extension or bicep flexion depending on their functional ability. RT, EMG activity and RT variability outcomes were subjected to repeated measures ANOVA.

**Results:** At the group level, simple RT was slower during exercise (291ms, SD=90) and not different at post-exercise (240ms, SD=65) compared to pre-exercise (257ms, SD=105). Conversely, peak EMG amplitude during the simple RT task was maintained during exercise (p=.65) and smaller post-exercise (p=.02) compared to pre-exercise. RT variability was increased during exercise but not changed post-exercise. Choice RT displayed an interaction between limb and session as the affected limb was longer and the non-affected limb was unchanged during and post-exercise relative to pre-exercise. Finally, single-subject analyses performed for simple RT revealed 12 participants with a significant effect of session. Relative to pre-exercise, 9 had longer and 3 had shorter RT during exercise, while 4 had shorter, 1 had longer and 7 were unchanged post-exercise.

**Conclusions:** Exercise does not appear to facilitate information processing for individuals recovering from a stroke. However, for a few individuals aerobic exercise induced alterations to central nervous system state are possible. Future work should continue to investigate exercise induced alterations to sensorimotor processing in greater detail and focus on variability of performance in this population.
2.2 Introduction

Despite gains in post-stroke rehabilitation, the majority of individuals are left with residual deficits in physical function (Koton et al., 2014). Additionally, the majority of recovery gains are made within the first weeks to months after a stroke (Langhorne et al., 2011). Outside of this window, further functional gains are possible but take significantly more time and training (Wolf et al., 2010; Wolf et al., 2006). Therefore, strategies to expedite recovery of function are important across all stages of stroke recovery.

Aerobic exercise is an important strategy to improve post-stroke recovery as it positively impacts a wide range of important stroke outcomes. The benefits include improved cardiovascular function (MacKay-Lyons & Howlett, 2005; Tang et al., 2009a), balance and gait (Dean et al., 2012; Mayo et al., 2013), cognitive function (Quaney et al., 2009) and neurological recovery (Potempa et al., 1995). Similarly positive evidence has shown that exercise increases brain volume in healthy older adults (Colcombe et al., 2006) and animal models have consistently shown that exercise positively up-regulates many important neurotrophic growth factors related to neuroplasticity and synaptogenesis (Ploughman et al., 2005; Ploughman et al., 2009). Thus, there is considerable support for physical aerobic exercise to directly influence post-stroke recovery and indirectly influence conditions for neuroplastic recovery. However, despite these benefits of exercise, the majority of individuals recovering from stroke do not engage in sufficient activity to meet minimum recommended guidelines (Prajapati et al., 2013). This lack of engagement in aerobic exercise is troubling since a single bout of aerobic exercise also has profound influence on neurophysiology in healthy individuals and may be an effective tool to augment neurorehabilitation (Hillman et al., 2008).

Aerobic exercise may have a potentially important role in priming or preparing the central nervous system (CNS) state prior to traditional therapies. This proposition is supported by exercise-induced increases in catecholamines including dopamine and norepinephrine which augment arousal of the CNS (McMorris et al., 2008; McMorris et al., 2009b). Increased CNS arousal has commonly been evaluated behaviorally through shorter response times (especially movement time) and elevated muscle activity measured through electromyography (EMG) (Davranche et al., 2005, 2006). Further, neurophysiological evidence has displayed augmented information processing (Hillman et al., 2008; Kamijo et al., 2009) and cortical excitability
These exercise-induced effects may be a critical benefit to the stroke population which exhibits altered motor cortex excitability (Butefisch et al., 2008; Shimizu et al., 2002) in addition to a general slowing of psychomotor processes and information processing exhibited in tasks that evaluate reaction time (RT), visual inspection and finger tapping (Godefroy et al., 2010). Thus, aerobic exercise may be an effective tool to prime the CNS and facilitate subsequent performance during neurorehabilitation to augment post-stroke recovery of sensorimotor function.

Unfortunately, the transient influence of aerobic exercise on central sensorimotor processes (i.e. in limbs not involved in the exercise) is not well understood within the stroke population as only a single study has investigated the single session effects of exercise in stroke. Ploughman et al. (2008) observed functional upper-limb improvements following a single bout of body-weight supported treadmill training in a chronic stroke population (Ploughman et al., 2008). However, the participants were partially supporting their weight with their arms during the exercise and the authors concluded that the positive effects were likely due to the use of the arms during exercise rather than CNS augmentation. Thus, the influence of exercise on general motor processes in a stroke population remains largely speculative.

An important consideration of the current project is the focus on between- and within-subject variability of RT. Commonly, only group means are reported which does not consider individual differences in response to exercise or how exercise may influence consistency of performance. Inter-individual variability will be addressed by focusing on individual change and will provide greater detail about the influence of exercise between individuals. Intra-individual variability will provide an indication of consistency of performance which has been argued to be a function of neurological integrity, lapses of attention and deterioration within neurotransmitter systems (Anstey et al., 2005; Zahn & Mirsky, 1999). Together, evaluating variability of performance may provide a more targeted evaluation of the influence of exercise on outcomes related to CNS state (i.e. arousal and attention) and assist in identifying specific stroke characteristics that identify responders and non-responders to exercise. The main objective of this study is to evaluate the influence of a single session of lower-limb aerobic exercise on speed of processing and muscle activity evaluated using upper-limb reaction time in stroke. Shorter mean RT and increased muscle activity were hypothesized both during and post-exercise relative to pre-exercise likely reflecting augmented CNS arousal. Further, the variability of RT was hypothesized to be reduced
post-exercise relative to pre-exercise likely reflecting enhanced attention (more consistent RT). A secondary objective was to investigate the side-related effects of the involved and/or non-involved hemisphere since stroke is commonly lateralized to one cortical hemisphere. It is hypothesized that larger effects (faster reaction time and augmented response amplitude) will be observed on the more affected side of the body likely reflecting augmented arousal in the stroke affected hemisphere relative to the unaffected hemisphere.

2.3 Methods

2.3.1 Participants

Fourteen participants were recruited from both in-patient and out-patient stroke neurorehabilitation programs at the Toronto Rehabilitation Institute. Inclusion criteria included a diagnosis of stroke (>3 weeks prior), sufficient lower-limb function to exercise using a recumbent stepper and sufficient upper-limb function to voluntarily extend wrists or flex biceps. Participants were excluded if their medical chart or treating physiotherapist noted an inability to provide informed consent or any contraindications to exercise such as uncontrolled hypertension, acute cardiovascular morbidities, or musculoskeletal impairments limiting the ability to complete the study procedures.

2.3.2 Study Procedures

Testing consisted of pre-, during-, and post-exercise evaluation. Prior to beginning the pre-exercise evaluation, participants performed three maximal voluntary contractions (MVC). During MVC contractions participants were instructed to contract the target muscle maximally for 1-2 seconds. From the MVC, the largest peak EMG amplitude and the largest integrated EMG (iEMG) activity for a 100ms period of the three trials was extracted and used to standardize individual peak amplitude and iEMG values respectively. Following the MVC contractions, participants were provided with standard instructions and practiced the RT task. The practice session was identical to the evaluation session with half the number of reaction time trials. Following the practice session, the participant rested for a minimum of 10 minutes and then pre-exercise evaluation began. During the exercise session, reaction time evaluation began after 8 minutes of exercise and the post-exercise evaluation began 5 minutes after the end of the
exercise session (Figure 2-1). The study was approved by the Toronto Rehabilitation Institute research ethics board and all participants signed informed consent before enrolling in the study.

![Timeline of experimental procedures](image)

**Figure 2-1** – Timeline of experimental procedures. Black arrows represent time points where reaction time testing was performed (pre-, during, and post-exercise).

### 2.3.3 Exercise

Participants performed lower-limb exercise using a recumbent stepper (NuStep Inc., Ann Arbor, MI) for 20 minutes plus a 3-minute warm-up and 2-minute cool-down. Four participants were unable to achieve 20 minutes of exercise but completed at least 15 minutes of exercise; however, their response to exercise was comparable to individuals that completed the full exercise protocol and all participants were grouped for statistical analysis. Each participant exercised at a self-selected cadence and resistance was adjusted by the investigator to maintain heart rate (HR) between 50-70% of age-predicted maximum (208-[0.7*age]) (Tanaka et al., 2001). HR was sampled every five seconds using a chest transmitter and watch (Polar Electro Inc., NY). Steps per minute and watts were recorded at the end of each minute and rating of perceived exertion (RPE) was sampled after the first, 10th and 20th minutes of the exercise session using the Borg CR-10 scale (Borg, 1982). Blood pressure was monitored pre- and post-exercise.

### 2.3.4 Reaction Time Task

The main outcome measures were simple and choice reaction time measured prior to exercise, in the middle of exercise and 5 minutes after the end of the exercise session. The order of testing was simple reaction time (SRT) followed by a 2-choice reaction time (CRT). The starting limb for SRT was maintained within a testing session and then randomized between participants. A
custom program (LabVIEW, National Instruments Corp, Austin, TX) was used to present the targets on a computer screen mounted in front of the exercise equipment. The targets were arrows which pointed only left or right for SRT and randomly left or right for CRT (i.e. 2 choices). Participants were instructed to respond as quickly as possible by moving the appropriate limb (bicep flexion or wrist extension depending on functional ability). Each trial consisted of a fixation dot presented for a random time interval of 2-5 seconds. This was followed by the target arrow which was presented for 250 ms and indicated the appropriate arm for the response. Thus, each RT protocol took approximately 2 minutes (6 minutes total for SRT of both limbs and CRT). To evaluate a wider range of patient motor severity, the response was tailored to each patient’s functional ability (and the ability to measure a sufficiently large EMG signal) and involved either wrist extension or bicep flexion. Participants rested their arms on the supports of the exercise equipment approximately 90 degrees of elbow flexion. The time from target presentation to EMG onset was used to define reaction time. The SRT paradigm involved 20 trials per limb, while CRT involved a minimum of 40 trials (each trial had a 50% chance of being left or right and program was run until minimum of 20 trials were collected for each limb).

2.3.5 Electromyography recording and processing

EMG was recorded bilaterally (Noraxon Inc., Scottsdale, AZ) from either the wrist extensors (extensor carpi radialis longus) or the biceps brachii using paired surface Ag-AgCl electrodes. Muscle activity was amplified at a gain of 1,000, digitized at 1000Hz and saved for offline processing. Post-processing used customized software (LabVIEW, National Instruments Corp, Austin, TX). The raw EMG signal was band-pass filtered from 20 to 500 Hz (Butterworth filter, 2nd order) and full wave rectified prior to detection of EMG onset. Peak EMG amplitude was extracted from smoothed EMG activity that had been further processed with a 6Hz low-pass filter. EMG onset was marked using an automatic detection algorithm as the point at which the EMG amplitude crossed a threshold of 3 standard deviations above the mean of baseline activity (75 ms before stimulus presentation) and remained elevated for 50 ms. EMG onset was manually confirmed and adjusted if necessary by visual inspection of each trial which is equal or superior to computer algorithms (Van Boxtel et al., 1993).
2.3.6 Error Processing

For SRT trials, if EMG onset was greater than 1 second after stimulus presentation the trial was considered an error and removed from further processing. CRT trials were processed without knowledge of the target arrow direction and if EMG activity was detected for both limbs the trial was considered an error and removed from further averaging. EMG onsets were first marked by one of the study authors who was not blinded to the condition (MS). This analysis was repeated by two individuals not involved in the study who were blinded to the EMG recording parameters, and the different rater’s revealed identical results, with an absolute mean difference of only 3.9 ms.

2.3.7 Data Processing

Three variables were extracted from the EMG activity. Reaction time (RT) was defined as the time in milliseconds from stimulus presentation to EMG onset. Peak EMG amplitude was the maximal amplitude of the smoothed EMG signal and was standardized to each individual’s maximal peak amplitude from their MVC contractions. The total iEMG activity for 100ms following EMG onset was calculated from the full-wave rectified EMG activity and was standardized to the largest 100 ms of iEMG activity from the MVC contractions. To evaluate the distribution and consistency of reaction times, two variables were calculated from reaction time data. RT variability was calculated as the absolute mean difference between each trial’s RT and the mean for that individual (millisecond units). Trial to trial variability was calculated as the between trial variation in reaction time for each individual and testing session (i.e. trial 2 – trial 1; trial 3 – trial 2).

2.3.8 Statistical Analysis

Prior to statistical analysis, practice effects were evaluated using repeated measures ANOVA with session (practice vs pre) and limb (affected vs non-affected) as within subject factors. Both the SRT and CRT condition were then subjected to a group analysis using repeated measures ANOVA with testing session (pre vs during vs post) and limb (affected vs non-affected) as within subject factors for the mean of the five dependent variables (RT, EMG amplitude, iEMG, RT variability, and trial to trial variability). Planned comparisons with paired t-tests were used compare during and post-exercise values to pre-exercise for significant ANOVAs. Finally, exploratory single subject repeated measures one-way ANOVAs were performed separately for
each participant to compare RT for the SRT condition with the same effects as the group analysis. Results were then compiled according to the number of participants that significantly improved, worsened, or did not change due to exercise. This strategy was adopted as high variability in this sample was potentially reducing the ability to detect relatively large group effects of exercise and visual inspection suggested simple RT had the smallest within-subject variability compared to other outcome measures.

2.4 Results

Three participants were unable to complete 20 minutes of exercise and therefore did not complete CRT testing during the exercise bout. An additional three participant’s EMG data did not produce a clearly identifiable onset in the majority of CRT trials. Thus, all 14 participants completed the SRT testing, while a subset of 8 participants also completed the full CRT protocol. Table 2-1 provides a breakdown of participant characteristics. Overall the group of participants’ was of moderate to high function with median CMSA scores of 5 (mean=4.8, SD=1.2) and 6 (mean=5.7, SD=0.8) for the arm and leg respectively. However, there was a wide range of characteristics as age ranged from 18 to 78 years old and days post-stroke ranged from 22 to 1025 days. Importantly, comparing percent change from pre to during exercise and pre to post-exercise for time post stroke (<3 months, n=9 vs >3 months, n=5) and response muscle (biceps, n=4 vs forearm extensors, n=10) revealed comparable change between the groups.
Table 2-1 – Participant characteristics. Values are mean (standard deviation) or frequency counts. (BMI, Body Mass Index; CMSA, Chedoke-McMaster Stroke Assessment; HR, Heart Rate; RPE, Rating of Perceived Exertion)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD) or Frequency Count</th>
<th>Range</th>
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</thead>
<tbody>
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<td>Age (years)</td>
<td>54.9 (16.2)</td>
<td>18 – 78</td>
</tr>
<tr>
<td>Sex</td>
<td>F=6, M=8</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>28.3 (5.7)</td>
<td>23.7 – 42.3</td>
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<tr>
<td>Stroke Affected Side of Body</td>
<td>L=4, R=10</td>
<td></td>
</tr>
<tr>
<td>Days Post-Stroke (days)</td>
<td>239.9 (332.9) (Median 56 days)</td>
<td>22 – 1025</td>
</tr>
<tr>
<td>CMSA Arm</td>
<td>4.8 (1.2)</td>
<td>3 – 6</td>
</tr>
<tr>
<td>CMSA Leg</td>
<td>5.7 (0.8)</td>
<td>4 – 7</td>
</tr>
<tr>
<td>Exercise Duration (min)</td>
<td>18.4 (2.6)</td>
<td>12 – 20</td>
</tr>
<tr>
<td>Mean HR (% age-calculated max)</td>
<td>54.4 (6.6)</td>
<td>43 – 68.2</td>
</tr>
<tr>
<td>Peak RPE</td>
<td>2.9 (1.5)</td>
<td>0.5 – 5</td>
</tr>
</tbody>
</table>

2.4.1 Practice Effects

Practice trials were compared to pre-exercise trials and no significant differences between testing sessions were found for either simple or choice RT. However, significant effects of session indicated that peak EMG amplitude was significantly smaller at pre-exercise than practice in both the SRT (F(1,13)=9.83, p=.008) and CRT (F(1,7)=9.22, p=.02) conditions. Additionally, for the CRT condition, RT variability was smaller at pre-exercise than practice F(1,7)=7.27, p=.03).
Table 2-2 – Group mean (standard deviation) for: A) simple reaction time and B) choice reaction time tests. (ms, milliseconds; iEMG, integrated electromyography).

A) Simple Reaction Time (n=14)

<table>
<thead>
<tr>
<th></th>
<th>Affected Side</th>
<th></th>
<th></th>
<th>Non-Affected Side</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>During</td>
<td>Post</td>
<td>Pre</td>
<td>During</td>
<td>Post</td>
</tr>
<tr>
<td>Reaction Time (ms)</td>
<td>289 (137)</td>
<td>320 (105)</td>
<td>268 (77)</td>
<td>226 (45)</td>
<td>262 (63)</td>
<td>211 (34)</td>
</tr>
<tr>
<td>Peak Amplitude (% max)</td>
<td>41 (13)</td>
<td>39 (14)</td>
<td>36 (12)</td>
<td>48 (17)</td>
<td>51 (19)</td>
<td>44 (15)</td>
</tr>
<tr>
<td>iEMG (% max)</td>
<td>49 (22)</td>
<td>52 (23)</td>
<td>45 (21)</td>
<td>65 (37)</td>
<td>68 (40)</td>
<td>61 (32)</td>
</tr>
<tr>
<td>Reaction Time Variability (ms)</td>
<td>51 (21)</td>
<td>67 (32)</td>
<td>50 (23)</td>
<td>43 (13)</td>
<td>55 (32)</td>
<td>36 (15)</td>
</tr>
<tr>
<td>Trial to trial Variability (ms)</td>
<td>67 (26)</td>
<td>96 (46)</td>
<td>66 (32)</td>
<td>56 (23)</td>
<td>76 (47)</td>
<td>50 (19)</td>
</tr>
</tbody>
</table>

B) Choice Reaction Time (n=8)

<table>
<thead>
<tr>
<th></th>
<th>Affected Side</th>
<th></th>
<th></th>
<th>Non-Affected Side</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>During</td>
<td>Post</td>
<td>Pre</td>
<td>During</td>
<td>Post</td>
</tr>
<tr>
<td>Reaction Time (ms)</td>
<td>433 (100)</td>
<td>442 (127)</td>
<td>454 (97)</td>
<td>444 (112)</td>
<td>403 (91)</td>
<td>401 (85)</td>
</tr>
<tr>
<td>Peak Amplitude (% max)</td>
<td>29 (11)</td>
<td>34 (11)</td>
<td>29 (9)</td>
<td>43 (17)</td>
<td>47 (22)</td>
<td>41 (17)</td>
</tr>
<tr>
<td>iEMG (% max)</td>
<td>35 (18)</td>
<td>44 (20)</td>
<td>37 (20)</td>
<td>55 (39)</td>
<td>59 (40)</td>
<td>55 (37)</td>
</tr>
<tr>
<td>Reaction Time Variability (ms)</td>
<td>138 (147)</td>
<td>134 (152)</td>
<td>163 (152)</td>
<td>84 (42)</td>
<td>85 (24)</td>
<td>100 (51)</td>
</tr>
<tr>
<td>Trial to trial Variability (ms)</td>
<td>104 (45)</td>
<td>107 (31)</td>
<td>114 (20)</td>
<td>122 (60)</td>
<td>88 (16)</td>
<td>95 (25)</td>
</tr>
</tbody>
</table>

2.4.2 Group Results

2.4.2.1 Simple Reaction Time

Significant effects of limb were found for RT, RT variability and trial to trial variability but not peak EMG amplitude (F(1,13)=4.16, p=.06) or iEMG (F(1,13)=3.83, p=.07). These effects displayed longer RT, lower EMG amplitude (both peak and iEMG) and increased variability for the affected limb than the non-affected limb. Additionally, no limb by session interactions were found for any variables. Thus, the following results outline the significant effects of session for the five outcome variables for the SRT condition, see table 2-2A for all SRT data.
The grand averaged simple RTs were 257 (SD=105), 291 (SD=90), 240 (SD=65) ms across all subjects for the pre-exercise, during exercise and post-exercise conditions respectively. There was a significant effect of session (F(2,26)=6.88, p<.004) such that RT during exercise was longer (p=.03) while post-exercise RT was not significantly different (p=.22) than pre-exercise; Figure 2-2. Both variability measures revealed identical results as RT variability (F(2,26)=4.77, p=.02) and trial to trial variability F(2,26)=6.39, p=.006) were significantly larger during exercise and not different at post-exercise compared to pre-exercise levels.

Overall, the levels of muscle activity measured by peak EMG amplitude were 44.5% (SD=15.7), 45.2% (SD=17.4), and 40.2% (SD=13.8) of maximum for pre-exercise, during exercise and post-exercise respectively (iEMG followed same pattern). There were significant effects of session for both peak EMG amplitude (F(2,26)=5.47, p=.01) and iEMG (F(2,26)=4.53, p=.02). The general pattern was for EMG activity to be maintained during exercise (peak: p=.65; iEMG: p=.23) and decreased post-exercise (peak: p=.02; iEMG: non-significant, p=.10) relative to pre-exercise levels, Figure 2-3.

**Figure 2-2** – Simple reaction time (RT) across the three testing sessions and collapsed for limb. RT was significantly longer during exercise compared to pre-exercise (F(2,26)=6.88, p<.004). *Indicates significant difference between pre-exercise and during-exercise (p=.03). (ms, milliseconds)
Amplitude was unchanged during exercise but was significantly smaller post-exercise compared to pre-exercise levels (F(2,26)=5.47, p=.01).

*Indicates significant difference between pre-exercise and post-exercise (p=.02)

### 2.4.2.2 Choice Reaction Time

A subset of 8 participants completed the full CRT protocol. As expected, mean choice RT was longer than simple RT at all testing points (438 vs 257, 423 vs 291, 427 vs 240 for pre-during and post-exercise respectively). The percent correct were 86.1% (±8.6), 82.6% (±14.2), and 87.3% (±11.9) for pre-, during, and post-exercise respectively which were not different from each other F(2,17)=0.39, p=.68). In contrast to the SRT condition data there was no effect of limb (affected vs non-affected) for any variables in the CRT condition. Overall, few statistically significant results were found which are outlined below, see table 2-2B for all CRT data.

A significant interaction between session and limb was found for RT (F(2,14)=6.75, p=.009) which was driven by the non-affected limb which had shorter RT during (p=.008) and post-exercise (p=.005) relative to pre-exercise while the affected limb did not have a significant change in RT between testing sessions. Peak EMG amplitude also revealed a significant effect of session (F(2,14)=7.65, p=.006) as amplitude was larger during exercise (p=.01) and unchanged post-exercise relative to pre-exercise. Additionally, RT variability was unchanged during
exercise (p=.85) but larger at post-exercise (p=.02) compared to pre-exercise (F(2,14)=4.50, p=.03).

2.4.3 Single-subject Analysis (Simple Reaction Time)

Due to high variability a single-subject analysis was also conducted by comparing differences within each subject for simple RT. Single-subject analyses revealed significant effects of limb for 7 of 14 participants (p<.045 for all), all of whom had longer simple RT on the affected side. Significant effects of session were identified in 11 of 14 participants (p<.04 for all) with one additional individual approaching significance (p=.07). Among those 12, 9 had longer and 3 had shorter simple RT during exercise compared to pre-exercise. Conversely, at post-exercise 4 participants had shorter, 1 had longer, and 7 were not significantly changed compared to pre-exercise. Finally, 5 participants revealed significant session by limb interactions (p<.04 for all). RT decreased over testing session (pre- to during to post-exercise) for the affected limb only (n=2) or the non-affected limb only (n=2), while the opposite limb displayed longer RT during exercise with no change or shorter RT post-exercise. The final significant interaction was driven by no RT change during exercise for the non-affected limb while all other testing points had longer RT compared to pre-exercise for both limbs. See Figure 2-4 for the distribution of individual RT change for each limb relative to pre-exercise.
A) Simple reaction time (RT) during exercise subtracted from pre-exercise; group mean is the topmost point on the y-axis. Among the 12 individuals with a significant effect of session, 9 had significantly longer RT (negative difference), 3 had significantly shorter RT (positive difference) and 3 did not have significantly different RT during exercise.

B) Simple reaction time post-exercise subtracted from pre-exercise; group mean is the topmost point on the y-axis. Among the 12 individuals with a significant effect of session, 4 had significantly shorter RT (positive difference), 1 had significantly longer RT (negative difference) and 7 were unchanged post-exercise.

**Figure 2-4** – Individual mean reaction time differences for the simple condition. Values are the difference relative to pre-exercise. The group mean is provided at the top of the y-axis. Positive values indicate a faster reaction time. 11 participants revealed significant effects of session and another individual had a trend towards significance (p=.07).
2.5 Discussion

This study evaluated the influence of aerobic exercise on RT and muscle activity in a stroke population. While we did observe significant effects of exercise in simple RT and choice RT at the group level, results were in the opposite direction to our hypotheses. For example, in the simple RT condition, we observed longer RT during exercise and no change at post-exercise while EMG activity was unchanged during exercise and smaller post-exercise. Additionally, only choice RT displayed a side-related effect of exercise, however, this was also opposite to our hypotheses as the non-affected limb had shorter RT during and post-exercise while the affected limb had longer RT during and post-exercise. However, some individual participants were characterized by significant reductions in simple RT in response to the exercise bout.

The absence of group differences in the pre to post-exercise comparison in the current study may have been associated with high between-subject variability, as compared to observations from healthy adults. In this study the mean difference for simple RT was approximately 21 ms for the affected side and 15 ms for the non-affected side. These changes are greater than a commonly cited paper using healthy controls which reported statistically significant benefits with only 8 ms improvement in SRT during exercise (Davranche et al., 2006). In relative terms, our stroke sample improved by approximately 7.0%, while healthy young adults improved by only 3.5%. Applying a 3.5% threshold to the current results indicates that 5/14 (affected side) and 7/14 (non-affected side) participants improved by at least this amount. However, what is striking in this comparison is the variability differences as our stroke sample displayed standard deviations of 137 and 77ms for the affected limb and 45 and 34ms for the non-affected limb at pre- and post-exercise respectively. In healthy young adults, the standard deviations were 17ms and 20 ms for the two evaluations (Davranche et al., 2006). Thus, despite comparable mean RT change in our sample, our statistical analysis may have suffered due to high variability. Additionally, the non-affected side displayed the hypothesized results for the choice RT condition as RT was shorter during and post-exercise by 41 and 43ms compared to pre-exercise respectively. Even with a significant group effect, variability remained large relative to the mean as SD ranged from 85-112 ms compared to group means of 401-444 ms (table 2-2B) for the non-affected limb. One interpretation of these findings is that the influence of exercise on speed of processing may be specific to individual characteristics (i.e. infarct location, sensorimotor dysfunction, etc.) and the
heterogeneous sample in the current study increased between subject variability and reduced the ability to detect statistical significance despite seemingly large mean change.

During exercise both RT variability and trial to trial variability were larger and RT was longer for the simple RT condition. Simultaneously exercising and performing the task placed individuals in a dual-task situation and the increased cortical load associated with dual-tasking may be the cause of the observed longer and more variable RT. Interestingly, this is the opposite finding of previous research which has commonly found an improvement in RT during exercise; however, these studies have focused on healthy individuals with exercise experience (Davranche et al., 2006; Joyce et al., 2014). After a stroke greater cortical resources are required to perform everyday movements such as walking compared to healthy individuals (Zamparo et al., 1995). The increased challenges in control may have revealed a greater dual task cost compared to previous research on healthy adults. However, it is interesting that the choice RT task did not display these same effects as the only significant effects during exercise were a larger peak EMG amplitude and shorter RT on the non-affected limb. This is likely due to the fact that only 8 participants completed the full CRT protocol compared to 14 for the SRT protocol and there was less power to detect the effects of exercise in the CRT protocol. Further, this study did not evaluate the dual-task effects on the exercise. It is possible that evaluating stepping rate with and without the RT task may provide further insight into dual task costs with exercise among individuals recovering from stroke.

Interestingly, muscle activity and RT had seemingly opposite results as RT tended to slow during exercise and was not statistically different at post-exercise to pre-exercise levels. Conversely, the amplitude of muscle activity was maintained or increased during exercise and then lower post-exercise than pre-exercise. This finding is counter-intuitive as motor components of stimulus-response tasks have typically displayed greater change in response to exercise compared to pre-motor components (Davranche et al., 2005, 2006). This difference could be due to several factors but may be due to the specific task conditions. The task did not have a clear end goal as the response was to contract the appropriate muscle as quickly as possible with no requirement for the amplitude of contraction (i.e. maximal contraction). Thus, participants may have been grading their response to a minimal muscle contraction required to indicate a response. This prospect is suggested by the significant decrease in EMG peak amplitude from the practice trials to the pre-exercise evaluation. A task with a defined end point (i.e. consistent movement across
repeated evaluation) we may have been better suited to evaluate the effects of exercise on the motor components of the response and should be incorporated into future work.

We hypothesized that the effects of exercise would be lateralized such that the stroke affected hemisphere and contralateral side of the body would receive greater benefits than the non-affected side. This hypothesis was based on the observation of altered cortical inhibition and hypoarousal of the affected hemisphere post-stroke (Butefisch et al., 2008; Shimizu et al., 2002). However, our simple RT findings did not indicate any lateralization of effects of exercise on any of the variables tested at the group level. Additionally, the single subject evaluation highlighted 5 participants with lateralized effects. However, effects were variable with the affected side displaying a greater effect for 2 individuals while 2 individuals had a greater benefit on the non-affected side and 1 individual had longer RT for both sides with a greater increase on the affected side. This unanticipated finding suggests that the potential effect of exercise may be isolated to common processes. Conversely, the choice RT findings displayed faster RT on the non-affected side (both during and post-exercise) while RT on the affected side was unchanged. This was opposite to the hypothesis, however, with fewer participants (n=8) that completed the CRT paradigm we may have been underpowered for the CRT paradigm. Further complicating the analysis of the lateralization of effects, the sample was heterogeneous and we did not have a sensitive measure of stroke location or degree of lateralization of the stroke which may have concealed any true lateralized effects. Of additional interest, we did not include a timed measure of the motor components (i.e. movement time) of the response as our task did not have a defined end-point of the movement. The influence of aerobic exercise has been shown to be greater for the motor components (movement time) than pre-motor (reaction time) components of a response in healthy individuals (Davranche et al., 2006; McMorris et al., 2009b). Thus, it is plausible that movement time, rather than the pre-motor reaction time used in the current study, may display lateralized effects among individuals recovering from a stroke.

Our hypotheses were based on the assumption that the exercise bout would be sufficiently challenging to influence CNS neurophysiology but not overly taxing to the individual to induce fatigue and impair performance. Unfortunately, evaluating exercise intensity is a challenge that is magnified in the stroke population which is often deconditioned and inexperienced with exercise (Ivey et al., 2005). Additionally, heart rate modifying medications are common post-stroke and relying solely on heart rate to monitor intensity is unsuitable. Further, rating of perceived
exertion (RPE), which is recommended when heart rate response to exercise is unreliable, can be confounded in stroke patients with cognitive and sensorimotor deficits (Sage et al., 2013). Functional deficits in the stroke population further complicate evaluating exercise intensity and likely increase the cortical resources and attentional demands required to control the limbs to perform the exercise. Given the intricate relationship between exercise intensity and task performance (Kamijo et al., 2007), this relationship is an important consideration for the current study. Additionally, the potential benefit of aerobic exercise to CNS arousal and information processing may be confounded among individuals recovering from a stroke due to inexperience with exercise, aerobic deconditioning, and sensorimotor dysfunction. Exercise experience and differing fitness levels likely contributed to the high between-subject variability, while stroke specific factors such as sensorimotor dysfunction may be the main contributors to the highly variable individual response to exercise as witnessed in the single-subject analysis, where a single individual had a large post-exercise benefit for the affected limb while the majority of individuals witnessed relatively little change (Figure 2-3B). Future research should aim to disentangle these potential confounders and identify specific patient characteristics that preclude the potential impact of aerobic exercise.

Unfortunately, with our small sample, we were unable to identify any clear stroke or patient specific characteristics that were related to the influence of exercise. Additionally, the range on our clinical measures was limited, making it difficult to observe the effect of exercise across a range of functional deficits. One important consideration however, is the influence of medications such as beta-blockers that affect the noradrenergic system. This is important as the benefits of exercise are mediated in part through increased activity of the noradrenergic system which increases CNS arousal. However, beta blockers interfere with the binding of epinephrine and reduce the effect of arousal related hormones (Segal et al., 2012). Thus, the influence of exercise on CNS arousal may be muted or blocked altogether by the beta blocker medication. In our sample, 3 participants were taking beta-blocker medication and all outcome measures remained unchanged or worsened in response to exercise. Therefore, medication use is an important factor to consider in the stroke population if we propose to utilize exercise as a prime to alter CNS conditions prior to therapy.

Interestingly, with the exception of RT variability in the CRT condition, the variability outcomes were larger during exercise and unchanged post-exercise. Variability measures were included as
a secondary outcome to provide further information about the specific benefits of aerobic exercise to information processing and attempt to disentangle the potential arousal and attentional factors influenced transiently by an exercise bout. While arousal and attention are related, mean RT may be more reflective of CNS arousal, while attentional factors (i.e. increased focus, sustained attention) would be evidenced by a more consistent RT (less variability). Given that we had relatively few trials, and mixed results statistically, dissociating arousal and attentional factors is beyond the scope of this paper. As discussed above, the increase in variability during exercise is likely due to the dual-task effects of simultaneously exercising and performing the task and may reflect increased demands on attention to perform both tasks. Conversely, the post-exercise effects suggest that arousal may be augmented in some individuals displayed through a faster mean RT in the single-subject analysis while attention may be less directly influenced by exercise as variability was unchanged at the group level (not analyzed as single-subject). However, further research is needed to definitively address the effects of exercise on arousal and attention in a stroke population.

2.5.1 Conclusions

Exercise did not appear to facilitate information processing at the group level for individuals recovering from a stroke. However, some individuals displayed a potential post-exercise benefit to information processing as displayed through faster reaction time after a bout of aerobic exercise. These findings suggest that aerobic exercise induced alterations to CNS state may be possible in the stroke population. However, high between- and within-subject variability and differential responses to aerobic exercise in this population make it difficult to make definitive conclusions about the use of exercise to prime the CNS in this population. Future work should investigate exercise induced alterations to sensorimotor processing in greater detail by utilizing movement time and focusing on variability of performance in this population.
3 Single-Session Effects of Aerobic Exercise on Focused Attention in Stroke
3.1 Abstract

**Background:** Attention is an important predictor of post-stroke recovery and has been shown to be augmented after a single session of aerobic exercise in healthy individuals. Thus, aerobic exercise may be able to prime the central nervous system and improve attention prior to task training for individuals recovering from a stroke.

**Methods:** 15 participants in the chronic stage of stroke recovery performed 20 minutes of moderate lower-limb aerobic exercise. Pre- and post-exercise evaluation utilized a stimulus-response task which required participants to match a stimulus shape to target shapes with a motor response. Task difficulty was altered with visual distractors to vary demands on focused attention. Participants performed the task using their non-affected limb with a stylus on a touchscreen monitor and reaction time, movement time, velocity and path trajectory (velocity peaks and movement error) were extracted from the trace of the stylus position.

**Results:** Reaction time was slightly shorter in all task conditions (RT reduced by 28 ms in simple; 92 ms in choice; 21 ms in modified Flanker) but only reached statistical significance in the choice condition (p=.024) and trended towards significance in the modified Flanker condition (p=.06). Conversely, movement time was significantly shorter post-exercise relative to pre-exercise by 98, 79, and 56 ms in the simple (p=.001), choice (p=.005) and modified Flanker conditions (p=.002) respectively.

**Conclusions:** Results suggest augmented information processing and arousal of the motor system while the influence of exercise on focused attention was less clear. Future work should aim to dissociate the influence of exercise on arousal and attention and to determine if these effects of exercise influence task-training for individuals recovering from a stroke.
3.2 Introduction

Stroke is the leading cause of adult neurological disability and as the population ages incidence of stroke are expected to rise. Positive advances in medicine have increased survival rates, however, the majority of individuals do not completely recover (Koton et al., 2014; Langhorne et al., 2011). Thus, strategies to improve neurorehabilitation outcomes are critical.

One important determinant of post-stroke functional recovery is attentional capacity (Barker-Collo et al., 2010a; Barker-Collo et al., 2010b; Robertson et al., 1997). Greater attention during neurorehabilitation allows a participant to perform better and likely receive a greater impact from each rehabilitation session. Attention includes selective and sustained attention as well as divided and alternating attention. Two critical components of attention are the ability to focus on the task and avoid distractions (selective attention) for a long period of time (sustained attention). Thus, transiently augmenting attention prior to neurorehabilitation may be an effective strategy to improve existing neurorehabilitation strategies for individuals recovering from a stroke.

Attention has widespread cortical networks including the parietal cortex and the anterior cingulate; however one fundamental component is the locus coeruleus and noradrenergic system (Posner & Petersen, 1990). The locus coeruleus mediates cortical arousal, which underpins attention. Thus, increasing activity of the noradrenergic system may be a key target to alter the state of the central nervous system (CNS) and improve attention for subsequent performance. Interestingly, aerobic exercise increases activity of the noradrenergic system (McMorris et al., 2008; McMorris et al., 2009b) and may be an effective technique to prime the CNS.

Aerobic exercise is an effective component of post-stroke rehabilitation as it positively influences a wide range of outcomes from cardiovascular function (MacKay-Lyons & Howlett, 2005) to gait and balance (Tang et al., 2009a) and cognitive function (Quaney et al., 2009). Importantly for the current study, in healthy individuals, even a single session of aerobic exercise has profound behavioural and neurophysiological influence relating to arousal and attention. Behaviorally, faster responses during stimulus-response tasks that rely on attention have consistently been shown in response to an exercise bout (Hillman et al., 2003; Kamijo et al., 2007; Pesce et al., 2003). Importantly, neuroelectric markers of cortical activity underpinning
attention have been shown to be augmented post-exercise (Kamijo et al., 2004b; Kamijo et al., 2007). Thus, aerobic exercise has potential utility as a prime for the CNS to positively influence attentional capacity for individuals recovering from a stroke. Unfortunately, this evidence comes largely from young healthy adults and the limited evidence from individuals with stroke has not been as positive.

Ploughman et al. (2008) found that cognitive function was not changed after moderate intensity body-weight supported treadmill training (Ploughman et al., 2008). Additionally, the results of study 1 of this dissertation suggest that information processing as reflected by reaction time was not changed post-exercise and was longer during exercise in a simple reaction time (RT) task while a choice RT task was faster for the non-affected limb and slower for the affected limb (Sage et al., 2015b). However, both experiments used relatively simple timed tasks and more complex tasks, particularly those that require interference control, may be optimal to display the effects of exercise (Chodzko-Zajko, 1991; Kamijo et al., 2007). Thus, the lack of a clear benefit of exercise on information processing and cognitive function in stroke may be due in part to task selection. Additionally, high variability has been observed when using RT to probe the effects of exercise in stroke (Sage et al., 2015b) and methodological strategies to reduce variability and highlight differences associated with exercise are warranted. An eye tracker was used to ensure participant’s vision was appropriately fixated prior to each RT trial in an attempt to control one potential source of variability in a visual RT task.

In the context of exercise, attention has been evaluated using visual stimulus-response tasks that incorporate visual interference with distracting stimuli. The main outcome is response time which lengthens as visual interference increases reflecting the increased demands on attention required to ignore irrelevant task information and concentrate on task-relevant information. Utilizing such task conditions have displayed faster responses after a single bout of aerobic exercise suggesting augmented information processing and attention (Hillman et al., 2003; Kamijo et al., 2009; Kamijo et al., 2004a; Kamijo et al., 2004b). Further, neuroelectric markers of the allocation of attentional resources mirror these behavioural changes, indicating that these tasks are effective at challenging attention and that attention is influenced by aerobic exercise (Hillman et al., 2003; Kamijo et al., 2009; Pontifex & Hillman, 2008). While these tasks are effective at evaluating information processing and attention, they have not been used to
dissociate the response into reaction time (RT) and movement time (MT). This is important as the motor components appear to be preferentially augmented from aerobic exercise (Davranche et al., 2005, 2006). Whether these effects occur for individuals with stroke is unclear as the limited research either did not use a stimulus-response task to probe information processing (Ploughman et al., 2008), or did not have a timed measure of movement (Sage et al., 2015b). Thus, the current study utilizes a stimulus-response task with visual distractors and a motor response which allows for the separation of RT and MT across varying attention demands. Additionally, a simple RT task is included to further probe the effects of exercise on information processing with a goal-directed timed movement component.

A single session of aerobic exercise may improve attention and an individual’s performance during a subsequent rehabilitation session. However, little is known about the influence of aerobic exercise on attention in a stroke population. Therefore, the objective of the current study was to evaluate the influence of a single bout of aerobic exercise on information processing and attention among individuals in the chronic stage of stroke recovery. Specifically, we utilized a stimulus-response task with 3 conditions (simple, choice and modified Flanker) which varied attention demands to evaluate the influence of aerobic exercise on an individual’s ability to focus their attention and avoid distraction. It was hypothesized that both RT and MT would be shorter following the aerobic exercise bout in all task conditions with no change in errors, reflecting faster information processing. Further, it was hypothesized that the reduction in RT would be larger for the more complex tasks (i.e. modified Flanker condition) reflecting augmented focused attention. A secondary objective was to determine if path trajectory would be influenced by exercise. It was hypothesized that trajectory evaluated with the number of velocity peaks and deviation from a straight line would not be affected by exercise as task movements were small and participants utilized their upper-limb that was unaffected by the stroke.

3.3 Methods

3.3.1 Participants

Fifteen individuals in the chronic stage of stroke recovery were recruited through the Toronto Rehabilitation Institute out-patient neurorehabilitation program and research volunteer pool. All participants reported they were right-handed before they had their stroke. Inclusion criteria
included a diagnosis of stroke, sufficient lower-limb function to exercise using a recumbent stepper, ability to provide informed consent. Participants were excluded if they displayed spatial neglect or their treating physiotherapist or medical chart indicated any potential issues with the ability to complete study procedures such as impaired cognitive function or contraindications to exercise such as significant lower-limb musculoskeletal impairment, acute cardiovascular morbidities and uncontrolled hypertension.

3.3.2 Procedure

All study procedures were completed over a single visit. The visit began with task familiarization which involved 20 trials of each of the task conditions. This was followed by a 15 minute break during which demographical information was collected and equipment set up. Pre- and post-exercise evaluation surrounded a 25 minute exercise bout which included a 3 minute warm-up and 2 minute cool-down (Figure 3-1). During the task evaluation participants completed 20 trials of the simple RT condition, 20 trials of the choice RT condition and 120 trials of the main modified Flanker condition (6 blocks of 20 trials). The task required participants to use a stylus to interact with a touchscreen monitor with their upper-limb that was not affected by the stroke. The position of the stylus on the screen was recorded at 1000 Hz and stored for offline analysis. While performing the task (not worn during familiarization period), eye movements were tracked using a mobile eye tracking system (Applied Science Laboratories, USA). Relevant stroke details (type, spatial location, etc.) were abstracted from medical chart review.

Figure 3-1 – Timeline of experimental procedures. Black arrows represent time points where evaluation was performed (pre- and post-exercise).
3.3.3 Exercise

The exercise included a 3 minute warm-up, 20 minutes at a moderate steady state and 2 minute cool-down and was completed using a lower-limb stepper (NuStep Inc., Ann Arbor, MI). During the steady-state exercise period, participants maintained a self-selected cadence and researchers adjusted resistance to maintain a heart rate (HR) target between 50-70% of age-calculated maximum (208-[0.7*age]) (Tanaka et al., 2001). HR was recorded continuously using a chest transmitter and watch (Polar Electro Inc, NY) and sampled at the end of each minute. Additionally, watts and steps per minute were recorded from the exercise equipment at the end of each minute. Finally, rating of perceived exertion (RPE) was sampled at the beginning, middle and end of the exercise session using the Borg CR-10 scale (Borg, 1982, 1998).

3.3.4 Task

The task was designed to include varying attentional demands as well as an overt motor response to probe the effects of exercise on information processing and focused attention. Participants were required to match a stimulus shape to a target shape under three task conditions which varied the difficulty and attentional demands by adding multiple choices and visual distractors (Eriksen & Eriksen, 1974); Figure 3-2. The task was presented using a touchscreen computer monitor (HP Compaq L2206tm) with a black background and white task components. The task was controlled using custom software (Labview, National Instruments Corp, Austin, TX). Participants used a stylus with their hand that had been unaffected by the stroke.

Each trial began with a fixation dot for 1-3 seconds while participants held the stylus at a central home position. The fixation dot was replaced with one of four randomly selected stimulus shapes (circle, triangle, square and octagon). Simultaneously, a response target (simple condition) or targets (choice and modified Flanker condition) appeared which were placed 7 cm from the home position.

During, the simple condition a single target was placed in line with and between the home and stimulus shape. Participants were instructed to move to the target as soon as the stimulus appeared and once they reached the target to return to the home position as quickly as possible. The choice and modified Flanker conditions had 4 targets spread in an arc 7 cm from the home position. Above each target one of the 4 shapes (circle, triangle, square and octagon) was
positioned in a random order every trial. Participants were instructed to move to the target which matched the stimulus shape as quickly as possible and return to the home position. Finally, the main task condition was a modified Flanker condition which was based on the Flanker task (Eriksen & Eriksen, 1974) and placed a visual distractor on either side of the stimulus shape. The distractors were either the same shape as the stimulus (congruent) or one of the remaining shapes (incongruent). Each trial had an equal probability of being congruent or incongruent. Similar to the choice condition, participants moved to the target which matched the stimulus shape as quickly as possible.

Participants completed 20 trials of the simple condition followed by 20 trials of the choice condition and 120 trials of the modified Flanker condition which was broken into 6 blocks of 20 trials. This order was maintained at pre and post-exercise evaluation. The targets were circles 1.2 cm in diameter and participants were instructed to move as quickly as possible, and ensure they hit the target but not worry if they crossed through the target.
(A) The simple condition. No target shapes were provided, participants were required to move from home position to target dot when a stimulus shape appeared.

(B) The choice condition. Participants were required to match the stimulus shape to the appropriate target shape and move the stylus from the home position to the target dot below the matching shape. Target shapes were randomly ordered each trial.

(C) The modified Flanker condition. Participants had to match the center stimulus shape with the appropriate target shape and move to the appropriate target dot. The incongruent condition is displayed where the distractors flanking the stimulus are a different shape. During the congruent condition the distractors were the same shape as the stimulus. Target shapes were randomly ordered each trial.

**Figure 3-2** – Outline of the three task conditions. Participants began the task with the stylus on the home position (dot at the bottom of screen). A stimulus shape was displayed at the top of the screen (an octagon in the examples). Participants moved to the dot placed below the matching target shape. All movements were an equal distance from the home position.
3.3.5 Outcome Measures

The position of the stylus on the screen was recorded at 1000Hz and stored for offline processing custom software (LabVIEW, National Instruments Corp, Austin, TX). The stimulus position trace was first low-pass filtered at 5 Hz to smooth the trace before calculating timing and kinematic measures. Movement onset and peak displacement were identified automatically by the software program and confirmed manually from the trace of stylus position. The main outcome measures were reaction time calculated as the difference from the time of stimulus presentation to movement initiation and movement time calculated as the time from movement initiation to peak displacement. Errors were defined as movement towards the wrong target or the absence of movement which were determined manually on a trial to trial basis during the choice and modified Flanker tasks. Mean velocity was extracted from the derivative of the stylus displacement. Additionally, path trajectory was evaluated using a count of the velocity peaks and movement error which was calculated as the maximal perpendicular distance between the stylus position and a straight line connecting the initial and final positions.

While performing the task (not worn during familiarization period), eye movements were tracked at 30 Hz using a mobile glasses mounted camera system (Applied Science Laboratories, USA). Eye tracking video was analyzed frame by frame to ensure vision was fixated appropriately (on fixation dot) prior to stimulus presentation in an attempt to reduce trial to trial variability. Additionally, the eye tracker video was used to determine errors (movement to incorrect target, absence of movement) during the choice and modified Flanker conditions.

3.3.6 Data Processing

Trials where gaze was not directed to the fixation point prior to stimulus presentation were removed from analysis. Additionally, error trials (moved to wrong target, absence of movement) were not included in the analysis of reaction time (RT), movement time (MT), velocity or path trajectory (see table 3-2 for error rates).

Prior to statistical analysis, repeated measures ANOVA comparisons using RT and MT as the dependent variables were made for each task condition to assess the effects of practice, stimulus shape and target location. To evaluate potential effects of practice, trial (1 to 20) was analyzed as a within-subject factor for each evaluation period. The modified Flanker condition also used
block (1 to 6) as a within-subject factor to compare responses over the six blocks of trials. Additionally, stimulus shape and target location (choice and modified Flanker only) were compared as within-subject factors for each evaluation period to determine if stimulus shape and target position influenced participants’ response. No MT differences were found and the following is a summary of the RT differences.

3.3.6.1 Trial and Block

During the familiarization period, the first 3 trials were removed from the simple and modified Flanker statistical analysis while the first 2 trials were removed from the choice condition analysis as these trials were significantly longer than the remaining trials (p<.05). The first trial was removed from pre- and post-exercise statistical evaluation for each condition as it was consistently longer than the other trials (p<.05). A significant effect of block was found during the modified Flanker pre-exercise evaluation (F(5,70)=2.41, p=.045) that was not present at post-exercise (F(5,70)=0.68, p=.64). Thus, the first block of trials was removed from the pre-exercise modified Flanker evaluation, and analysis was collapsed across blocks in further statistical analysis.

3.3.6.2 Stimulus Shape and Target Location

Stimulus shape did not influence RT in the simple condition but had a significant effect at all evaluation time points during the choice and modified Flanker conditions (p<.001) such that the octagon had significantly longer RTs than the other shapes. Thus, stimulus shape was included as a within-subject factor in subsequent analysis. Target location had a significant effect for both the choice and modified Flanker conditions at all evaluation points which indicated that the outside target locations had significantly longer RTs than the inside locations. Subsequent statistical analysis collapsed the two inside and outside target locations.

3.3.7 Statistical Analysis

Error rates were analyzed using repeated measures ANOVA for the choice and modified Flanker conditions with stimulus shape (circle vs triangle vs square vs octagon), target location (inside vs outside) and session (pre- vs post-exercise) as within subject factors; congruency (congruent vs incongruent) was added for the modified Flanker condition. The main analysis utilized correct
trials only and subjected dependent variables to repeated measures ANOVA with stimulus shape (circle vs triangle vs square vs octagon) and session (pre- vs post-exercise) as within-subject factors. For the choice and modified Flanker conditions target location (inside vs outside) was added as a within-subject factor. Finally, for the modified Flanker condition, congruency (congruent vs incongruent) was added as a within-subject factor. Additionally, the familiarization session was compared to the pre-session using repeated measures ANOVA and the same within-subject effects listed above to evaluate practice effects.

3.4 Results

3.4.1 Demographics

Table 3-1 provides a full breakdown of participant demographics. There were 6 females and 9 males with a mean age of 59.3 years old. There was an even split of hemisphere affected by the stroke with 7 left sided and 8 right sided. During exercise, mean HR was 53.7 % of age-calculated maximum with a mean peak RPE of 3.6 which is between the word anchors of moderate and somewhat hard. Two participants were unable to complete the full 20 minutes of moderate steady state exercise and stopped after 15 and 17 minutes. Their task data was compared with the group and yielded comparable results and they were therefore included in the statistical analysis. Trials where an individual’s gaze was not directed towards the fixation target were removed from analysis. This led to the removal of 6 (2.1%) and 9 (3.2%) trials from simple condition and 17 (6.1%) and 18 (6.4%) from the choice condition for pre- and post-exercise respectively. For the modified Flanker condition, 76 (4.5%) and 88 (5.2%) trials were removed from pre- and post-exercise respectively.
Table 3-1 – Participant characteristics and exercise data. Group mean data and standard deviations (SD) or frequency counts are displayed. (m, meters; kg, kilograms; bpm, beats per minute; RPE, rating of perceived exertion)

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.3 (11.8)</td>
<td>37 – 80</td>
</tr>
<tr>
<td>Days Post-Stroke</td>
<td>537.5 (528.7)</td>
<td>82 - 1557</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.72 (0.10)</td>
<td>1.52 – 1.85</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.6 (20.1)</td>
<td>48.1 – 113.4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.8 (5.5)</td>
<td>18.3 – 36.5</td>
</tr>
<tr>
<td>Sex (Females/Males)</td>
<td>6/9</td>
<td></td>
</tr>
<tr>
<td>Stroke Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Stroke affected hemisphere (Left/Right)</td>
<td>7/8</td>
<td></td>
</tr>
<tr>
<td>Exercise HR (bpm)</td>
<td>89.6 (15.3)</td>
<td>66.9 – 129.2</td>
</tr>
<tr>
<td>Exercise HR (% max)</td>
<td>53.7 (7.4)</td>
<td>43.4 – 71.0</td>
</tr>
<tr>
<td>Peak RPE</td>
<td>3.6 (1.2)</td>
<td>1.5 – 5</td>
</tr>
</tbody>
</table>

3.4.2 Familiarization Period

There was no significant difference in mean RT between the familiarization and pre-exercise testing sessions for either the simple or choice conditions (Simple: F(1,13)=0.09, p=.77; Choice: F(1,13)=2.68, p=.13) (note, that one individuals practice RT data was not available). Conversely, in the modified Flanker condition, the familiarization session had a significantly longer mean RT than the pre-exercise session (F(1,13)=15.24, p<.002). However, it is worth noting that the
familiarization session was not significantly different than the first block of the modified Flanker condition at pre-exercise (F(1,13)=3.54, p=.08), which as outlined above, also had a longer mean RT than the remaining blocks and was removed from further statistical analysis. Thus, effects of practice on the modified Flanker task appear to have been mitigated by removal of the first block of trials during pre-exercise testing. MT, velocity, and path trajectory (velocity peaks and movement error) did not reveal any significant differences between the familiarization and pre-exercise testing sessions for any task conditions.

3.4.3 Simple Condition

Stimulus shape did not affect RT (F(3,42)=1.14, p<.34) or interact with exercise for any of the outcome measures. Simple RT non-significantly improved from pre- (420ms) to post-exercise (392ms) (F(1,14)=0.91, p=.36). MT was significantly faster post-exercise (486ms) than pre-exercise (584ms) (F(1,14)=21.29, p<.001) which was echoed by faster mean velocity post-exercise (F(1,14)=57.58, p<.001). The path trajectory revealed smaller movement error (F(1,14)=6.13, p=.027) and fewer velocity peaks (F(1,14)=7.56, p=.016) post-exercise compared to pre-exercise.

3.4.4 Choice Condition

There was an effect of stimulus shape such that the octagon had a slower mean RT (F(3,42)=9.79, p<.001) than the other shapes. Additionally, the inside target locations led to significantly slower mean RT than the outside target locations (F(1,14)=9.01, p<.01). However, these effects did not lead to any notable interactions with exercise for any of the outcome measures.

Errors were not influenced by stimulus shape nor target location and were not significantly different between the pre-exercise (88.3% correct, SD=9.4) and post-exercise (89.0% correct, SD=10.9) sessions (F(1,14)=.02, p=.90). RT was significantly faster post-exercise (850 ms) than pre-exercise (942ms) (F(1,14)=6.43, p=.024). Similarly, MT was faster post-exercise (489ms) than pre-exercise (568ms) (F(1,14)=10.87, p=.005), with mean velocity trending towards being faster post-exercise (F(1,14)=3.48, p=.08). Additionally, path trajectory trended towards fewer velocity peaks (F(1,14)=3.70, p=.075) and smaller movement error (F1,14)=2.85, p=.11) at post-exercise relative to pre-exercise.
3.4.5 Modified Flanker Condition

Similar to the choice condition, there were significant effects of stimulus shape (p<.001) and target location (P<.001) on mean RT such that the octagon led to longer mean RT than the other shapes and the inside target locations had faster mean RT than the outside locations. Additionally, there was no effect of congruency as the congruent and incongruent trials had comparable mean RT (F(1,14)=0.83, p=.38).

Errors were not influenced by stimulus shape or target location. Additionally, there was not a significant effect on errors from trial congruency (91.3% correct for congruent trials vs 90.3% for incongruent (F(1,14)=.21, p=.62); session (91.8% correct pre-exercise vs 89.7% post-exercise) (F(1,14)=0.01, p=.91); or a session by congruency interaction (F(1,14)=0.14, p=.71).

RT was faster post-exercise (875ms) compared to pre-exercise (896ms), however, this only approached statistical significance (F(1,14)=4.07, p=.06). Consistent with the other testing conditions, MT was significantly faster post-exercise (478ms) than pre-exercise (534ms) (F(1,14)=14.58, p<.002, supported by faster mean velocity post-exercise (F(1,14)=5.55, p=.03). Path trajectory had significantly fewer velocity peaks post-exercise compared to pre-exercise (F(1,14)=5.64, p=.03) while movement error was not changed pre- to post-exercise (F(1,14)=1.45, p=.25).
Table 3-2 – Reaction time, movement time, velocity and path trajectory (velocity peaks, movement error) for the three task conditions. Group means and standard deviation (SD) are shown. Trials removed indicates the number of trials removed form analysis due to visual attention not being directed to fixation target prior to stimulus presentation.

*Errors during familiarization were not calculated as participants were not wearing the eye tracker during the practice trials.

(ms, milliseconds; cm, centimetres; s, second)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Evaluation</th>
<th>Trials Removed</th>
<th>Errors (%)</th>
<th>Reaction Time (ms)</th>
<th>Movement Time (ms)</th>
<th>Mean Velocity (cm/s)</th>
<th>Velocity Peaks (count)</th>
<th>Movement Error (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple</td>
<td>Practice</td>
<td>-</td>
<td>-</td>
<td>430 (168)</td>
<td>596 (207)</td>
<td>5.9 (2.2)</td>
<td>1.6 (0.9)</td>
<td>0.16 (0.09)</td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>6 (2.1%)</td>
<td>-</td>
<td>420 (161)</td>
<td>584 (178)</td>
<td>5.7 (1.7)</td>
<td>1.7 (1.0)</td>
<td>0.15 (0.10)</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>9 (3.2%)</td>
<td>-</td>
<td>392 (125)</td>
<td>486 (113)</td>
<td>6.8 (1.7)</td>
<td>1.3 (0.6)</td>
<td>0.13 (0.08)</td>
</tr>
<tr>
<td>Choice</td>
<td>Practice</td>
<td>-</td>
<td>-*</td>
<td>1007 (331)</td>
<td>616 (197)</td>
<td>8.1 (5.0)</td>
<td>1.9 (1.2)</td>
<td>0.27 (0.22)</td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>17 (6.1%)</td>
<td>88.3 (9.4)</td>
<td>942 (304)</td>
<td>568 (201)</td>
<td>8.6 (5.5)</td>
<td>1.8 (1.0)</td>
<td>0.23 (0.17)</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>18 (6.4%)</td>
<td>89.0 (10.9)</td>
<td>850 (229)</td>
<td>489 (153)</td>
<td>9.8 (6.7)</td>
<td>1.5 (0.9)</td>
<td>0.20 (0.13)</td>
</tr>
<tr>
<td>Modified</td>
<td>Practice</td>
<td>-</td>
<td>-*</td>
<td>981 (298)</td>
<td>593 (199)</td>
<td>8.1 (5.1)</td>
<td>1.8 (1.2)</td>
<td>0.23 (0.20)</td>
</tr>
<tr>
<td>Flanker</td>
<td>Pre</td>
<td>76 (4.5%)</td>
<td>91.8 (4.1)</td>
<td>896 (270)</td>
<td>534 (177)</td>
<td>9.3 (5.7)</td>
<td>1.7 (1.1)</td>
<td>0.21 (0.17)</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>88 (5.2%)</td>
<td>89.7 (6.8)</td>
<td>875 (267)</td>
<td>478 (152)</td>
<td>10.1 (6.6)</td>
<td>1.5 (0.8)</td>
<td>0.20 (0.13)</td>
</tr>
</tbody>
</table>
A) Simple Condition

B) Choice Condition

C) Modified Flanker Condition

Figure 3-3 – Reaction time and movement time for the Simple, Choice and modified Flanker conditions. Group mean data and standard deviations are displayed. *p<.05, **p<.01, #p<.06
3.5 Discussion

The current study strove to evaluate the influence of a single bout of aerobic exercise on focused attention in a stroke population. In support of the hypotheses, RT was generally faster post-exercise in all task conditions (with no change in errors), however, it only reached statistical significance in the choice condition. In addition MT and velocity were faster after exercise in all task conditions. Additionally, in contrast to what was hypothesized, improvements were not larger for the more challenging task conditions as RT improvement on the modified Flanker was the smallest relative improvement and there was no interaction with congruency in this task. Finally, path trajectory outcomes (velocity peaks and movement error) tended to be reduced post-exercise; however, path trajectory improvements, while largely statistically significant, may not represent meaningful change as they were relatively small (less than a millimeter for movement error and 0.3 fewer velocity peaks). Together, results suggest augmented arousal as evidenced by shorter RT in some tasks and shorter MT in all tasks. Further, the absolute change in RT was comparable across task conditions suggesting attention may not have been influenced by exercise to the same degree.

In line with the results of study 1, simple RT was unchanged after the exercise bout while choice RT was reduced (for the non-affected limb). For simple RT, the mean change was over 6.5% which is similar to study 1 and larger than observed in healthy individuals (Davranche et al., 2006). However, similar to study 1, high between-subject variability may have negatively impacted the ability to detect statistical significance at the group level. Thus, strategies to reduce variability including using the non-affected limb and the eye tracker to ensure vision was properly focused prior to trial initiation did not appear to overcome high variability in this stroke sample. Conversely, MT was shorter post-exercise in the current study while EMG activity was found to be unchanged in study 1. These differences are likely due to task differences as the current study incorporated a goal-directed movements while study 1 only required a muscle contraction. The defined movement in the current study may have been better suited to reveal the effects of exercise on the movement of a response.

Further, the more difficult choice and modified Flanker conditions (non-significant trend) displayed faster RT post-exercise. This is also in line with the results of study 1 which witnessed
faster RT for the non-affected limb. These findings may corroborate research in healthy individuals which has suggested that more difficult tasks may be better suited to reveal the effects of aerobic exercise (Kamijo et al., 2007). However, it is interesting that the modified Flanker did not observe an even larger improvement compared to the simple and choice conditions as was hypothesized. Change in RT was 6.7, 10.0, and 2.2% for the simple, choice, and Flanker conditions respectively. This may suggest that information processing is influenced to a greater degree under more challenging task conditions (simple vs choice); however, this does not appear to be the case as adding distractors to challenge focused attention resulted in the smallest relative change in RT. Further, comparing absolute change in RT reveals comparable change on the simple and modified Flanker conditions of 28 and 21 ms respectively, while the choice condition improved by 92 ms. These findings are challenging to interpret and may be in part due to fewer trials in choice condition and practice effects, although none were observed from the familiarization to pre-exercise evaluations. Alternatively, these findings may indicate that the influence of exercise on individuals recovering from stroke are specific to processes common to these tasks such as faster information processing reflecting augmented arousal rather than changes to attention.

The differences in MT (greater than 10% improvement) in all task conditions may support a difference associated with increased arousal. This is consistent with previous research in healthy individuals where the motor components of a response were preferentially augmented in response to a single bout of aerobic exercise (Davranche et al., 2006; McMorris et al., 2009b). These large MT improvements which were consistent for all task conditions also suggests that common processes underscoring response execution such as general excitation of the motor system are augmented by aerobic exercise. Together, these results suggest that general CNS arousal, which underlies the speed of both response selection (RT) and response execution (MT), is likely a main contributor to these results as opposed to improved focused attention.

The influence of exercise on motor control was not the primary focus of the current study and the improvements to the path trajectory (number of velocity peaks and movement error) were unanticipated. However, it is important to note that participants were using their non-affected limb and the improvements were likely too small to represent meaningful change as the number of velocity peaks was reduced by approximately 0.3 peaks per movement and movement error
was reduced by less than half a millimeter. Nevertheless, the improvements may reflect less time making movement corrections (fewer velocity peaks) and an improved ability to maintain a straight line trajectory (less movement error, and indirectly fewer velocity peaks). Given that previous work has suggested that motor function may be improved following a single session of aerobic exercise in stroke (Ploughman et al., 2008), future work should continue to examine the effect of acute exercise on motor outcomes and determine if these changes extend to the stroke affected upper-limb and represent meaningful change.

While attention is generally linked to the right frontal lobe it does have wide spread cortical networks. This study had an equal distribution of left and right sided strokes and observed improvements in RT for the choice and modified Flanker (non-significant trend) conditions which require greater attention. This highlights the fact that the mechanisms for improved attention are diverse. Our results suggest that common processes such as faster information processing are likely the main contributors to the observed faster RT. Faster information processing may be due to augmented CNS arousal since in healthy individuals exercise increases activity of the noradrenergic system and production and release of arousal neurotransmitters such as norepinephrine and dopamine (McMorris et al., 2008). However, 5 of our 15 participants were currently taking beta-blocker medication which may reduce the effect of exercise on CNS arousal as it interferes with the binding of epinephrine (Segal et al., 2012). Thus, these individuals would be expected to display a muted effect of exercise on information processing (RT) which did not materialize. Thus, augmented CNS arousal from increased neurotransmitter release is likely not the sole contributor to the observed effects. Other contributors including mood alterations (Bartholomew et al., 2005), neurovascular change (MacIntosh et al., 2014) or neurotrophic factor release (Huang et al., 2014) may be mediating these post-exercise effects. Determining the mechanism for post-exercise benefit was not the focus of the current study, yet is an important focus for future research as the mechanisms may differ from what has been observed in young healthy individuals.

The eye tracker was used to quantify visual attention with greater detail. Unfortunately, it was unreliable in this sample for tracking eye movements during task performance and was therefore unable to provide detailed information about task performance. However, it did ensure that vision was directed at the fixation point prior to stimulus presentation and led to the removal of
approximately 5% of trials. Unfortunately, this did not appear to reduce either between or within-subject variability as expected. For example, compared to study 1 between-subject standard deviation for simple RT with the non-affected limb was between 34-63 ms for study 1 compared to a mean of 211-262 ms (i.e. coefficient of variation ranging from 0.16 to 0.24). Conversely, in study 2, standard deviation ranged from 125-168 ms compared to means of 392-430ms (i.e. coefficient of variation ranging from 0.32 to 0.39). These differences could be attributed to the different tasks, however, within-subject variability was only slightly lower in study 2.

Comparing simple RT (collapsed for pre and post-exercise evaluations), mean within-subject standard deviation was 64 ms (mean=279) for study 1, and 81 ms (mean=418 ms) for study 2. In relative terms, mean coefficient of variation (calculated for each participant and then averaged) was 0.23 for study 1 and 0.19 for study 2. Thus, while ensuring visual attention was focused on the fixation point may have modestly reduced within-subject variability, future work should strive to illuminate the remaining sources of variability.

The main modified Flanker task was designed and chosen to vary the demands on focused attention and incorporate visual distractors; unfortunately, no congruency effect was observed. Typical Flanker administration requires a yes/no response with a button press rather than a 4-choice response. By forcing participants to find the correct match for the stimulus shape from four target shapes, participants are required to extract features from the stimulus shape to aid in finding the matching shape. This may have increased their focus on the relevant stimulus and aided in avoiding the visual interference from the distracting stimuli, thereby reducing the usual delay in the incongruent condition. Such a proposition may be supported by reaction times that were almost twice as long as those observed in young healthy individuals (Hillman et al., 2003; Kamijo et al., 2007) and older adults (Hillman et al., 2002) suggesting more time may have been spent extracting features from the relevant stimulus. Thus, the task conditions may have been significantly altered such that any congruency effect was hidden by the variability created with multiple stimuli and targets.

3.5.1 Conclusions

Similar to study 1, we observed slightly faster RT across task conditions which did not reach statistical significance in the simple condition but was significant in the more difficult choice
condition and trended towards significance in the modified Flanker condition. This may suggest enhanced focused attention, but is more likely reflective of faster information processing as the change in RT was comparable across task conditions. In contrast to study 1 we observed augmented motor components as reflected in significantly faster MT among individuals recovering from a stroke, suggesting augmented arousal of the motor system. Together, results suggest augmented information processing and arousal of the motor system. Future work may benefit from neuroelectric evaluation during attentionally demanding tasks to dissociate the relative contributions of arousal and attention to the observed effects. Further, the potential to utilize these single-session effects of aerobic exercise to influence task-training for individuals recovering from stroke should be explored.
A Single Session of Aerobic Exercise as a Modulator of the Rate of Short-Term Performance Adaptation on a Visuomotor Association Task in Healthy Individuals
4.1 Abstract

**Background:** A single session of aerobic exercise is linked to faster motor responses; however, the effect on rate of short-term skill adaptation is less clear. The objective was to evaluate the influence of a single bout of aerobic exercise on the rate of performance adaptation of a shape-letter association task requiring a motor response.

**Methods:** 23 healthy young adults were evaluated before and after moderate (exercise) and light (control) intensity cycle ergometry. Participants performed 3 blocks each of alternating training and testing. During training, participants were tasked with learning 6 unique shape-letter associations. Subsequent testing required a key press response to a visually presented shape pattern. Response time and error rates were used to assess rate of adaptation over the 3 blocks of testing.

**Results:** Mean response time was not significantly faster post-exercise relative to the other evaluations (p<.07). However, no significant difference in the rate of response time reduction was identified between the four evaluations (pre and post the exercise and control conditions). Rate of error reduction (test block 1 minus test block 3) suggested that individuals had the smallest change in errors post-exercise (p<.05). Follow-up analyses revealed a trend towards fewer errors in test block 1 and test block 2 post-exercise (p=.06) suggesting near-perfect error levels were obtained after only 2 testing blocks post-exercise compared to 3 blocks in the other evaluations.

**Conclusions:** Support for augmentation of short-term rate of performance adaptation was mixed as errors were reduced post-exercise while the rate of response time reduction was not different between evaluations. Future work should include neurophysiological evaluation and a retention test to better elucidate the influence of aerobic exercise on rate of skill adaptation.
4.2 Introduction

The neurological benefits of regular aerobic exercise are well established and include protection against cognitive decline (Colcombe et al., 2006; Cotman & Berchtold, 2002) and improving recovery after neurological accident such as a stroke (Quaney et al., 2009). Since these chronic exercise benefits are likely the accumulation of acute effects, the influence of a single session of aerobic exercise on brain health is a burgeoning field and positive effects linked to information processing, cognitive function and neurophysiology are becoming apparent. Such studies provide support that exercise may be able to ‘prime’ the brain for subsequent performance, however, few studies have focused on how exercise may immediately influence rate of skill adaptation.

While acute exercise has displayed transient changes in cortical function the majority of studies have evaluated performance on specific cognitive tasks with less attention to how these improvements may influence learning. For clinical settings it would be advantageous to focus on evaluating exercise as a potential modulator of short-term adaptation if we aim to utilize these acute exercise benefits to cortical function to augment subsequent motor and cognitive relearning following cortical insult. Short-term skill adaptation refers to the rate of improvement or skilled performance improvement over a period of minutes to hours and is influenced by a variety of cognitive functions including information processing (stimulus evaluation and immediate recognition), as well as the allocation of attentional resources to task relevant stimuli; components which are all influenced acutely by exercise. Additionally, following an exercise bout, the rate of acquisition is proposed to be linked to improved retention as faster acquisition and retention has been observed (compared to a non-exercise control condition) across tasks such as learning a new language and visuomotor tracking performance (Mang et al., 2014; Winter et al., 2007).

Acute effects of exercise on neurophysiology and behaviour are likely mediated, at least in part, by increased central nervous system arousal driven by up-regulation of catecholamines including epinephrine and dopamine (McMorris et al., 2008; McMorris et al., 2009b; Sutoo & Akiyama, 2003). These changes have materialized in faster information processing reflected behaviorally using stimulus response tasks (Joyce et al., 2014; Lambourne & Tomporowski, 2010) and through augmentation of cortical neurophysiological markers of stimulus processing and
allocation of attentional resources (Chang et al., 2012; Hillman et al., 2003; Kamijo et al., 2004b; Kamijo et al., 2007). Additionally, neurotrophic factors, including brain-derived neurotrophic factor (BDNF), which related to synaptic plasticity and implicated in short- and long-term potentiation are acutely up-regulated following an exercise bout (Tang et al., 2008). This boost to catecholamines and other factors including neurotrophic growth factors after exercise are linked to faster rate of acquisition and learning evaluated 1 and 7 days later (Winter et al., 2007). However, these behavioural changes in cognitive function including attention (Hillman et al., 2003) and memory consolidation (Chang et al., 2012; Lambourne & Tomporowski, 2010; Roig et al., 2012) have generally relied on response time which is robustly decreased after exercise and may reflect general arousal as opposed to alterations in higher cognitive function. Thus, dissociating arousal effects (i.e. timed measures) from specific cognitive functions is critical to properly understand the influence of aerobic exercise on cognition.

While there is hypothetical support for the notion that acute aerobic exercise may augment short-term skill adaptation, few studies have directly evaluated this theory. A single session of intense aerobic exercise has been shown to improve immediate acquisition of a new language as well as retention (Winter et al., 2007). Further, sequence-specific implicit motor learning on a visuomotor tracking task was enhanced following a single-session of high intensity aerobic exercise which was maintained after 24 hours (Mang et al., 2014). Conversely, exercise either before or after visuomotor skill training did not influence immediate acquisition but did improve retention compared to non-exercising participants (Roig et al., 2012). Finally, exercise after training has also been linked to improved memory consolidation evaluated an hour post-exercise among healthy elder individuals and those with mild cognitive impairment (Segal et al., 2012). Overall, the findings have generally found a positive effect of aerobic exercise on retention but inconsistencies remain around the influence of aerobic exercise on immediate acquisition.

This study strove to further our understanding of post-exercise facilitation of timed responses separate from alterations in short-term adaptation. Tracking short-term skill adaptation requires a task where proficiency can be achieved over a relatively short time frame and evaluated simply and objectively. It has been advocated that such a task would ideally provide within-subject test-retest stability to evaluate short-term effects over multiple testing sessions while preserving task characteristics (Tang et al., 2009b). Following such a paradigm, a vibrotactile discrimination task
successfully displayed short-term adaptation via reductions in errors and speed of execution over training for a period of approximately 40 minutes (Tang et al., 2009b). Following these task principles we developed a visuomotor association task and measured response time and errors while participants were taught shape-letter associations over multiple blocks before and after a single session of moderate aerobic exercise and a control condition. Rate of short-term performance adaptation was assessed by the decrease in response time and errors over testing blocks. We hypothesized that mean response time would be fastest after the exercise session relative to all other testing sessions. Additionally, we hypothesized that acquisition of the shape-letter associations would occur faster after exercise as reflected by a larger reduction in both response time and errors over testing sessions.

4.3 Methods

4.3.1 Participants

Twenty-four healthy young adults volunteered to participate in this study. Participants signed informed consent forms prior to enrollment and the study received ethics clearance from the University of Waterloo’s research ethics board.

4.3.2 Procedure

Each participant took part in two sessions which were counter-balanced for the order of sessions between participants and separated by at least one day. The difference between the sessions was the intensity of the exercise component (very light or moderate intensity) which involved 25 minutes of semi-recumbent cycling, which included a 3 minute warm-up and 2 minute cool-down. Participants were evaluated using the visuomotor task described below before and 5 minutes after the end of the exercise bout.

4.3.3 Exercise

The moderate intensity exercise session (herein referred to as the exercise condition) required participants to exercise at a self-selected cadence while researchers adjusted resistance to achieve a target heart rate (HR) of 70% of their age-calculated maximum calculated as \([208-0.7*\text{age}]*0.7\) (Tanaka et al., 2001). The low intensity exercise session (herein referred to as the control condition) was designed to engage participants in a comparable movement frequency but
against low load to avoid a significant aerobic challenge and associated increase in heart rate. Thus, during the control session no resistance was placed on the exercise equipment and the cadence was controlled to ensure HR did not increase (approximately 30 revolutions per minute (RPM) which was estimated to be half the RPM during exercise). These constraints were designed to ensure participant’s HR remained within 10 beats per minute (BPM) of rest (approximately within 5%). HR was continuously monitored and if it approached 10 BPM above resting, the participant was instructed to slow down. Additionally, Borg’s rating of perceived exertion (RPE) was recorded at the end of the 1st, 10th and 20th minute of exercise using the CR-10 scale (Borg, 1982). During exercise HR was continuously monitored using a 3-lead ECG (EK-10, Burdick Inc., Milton, WI) and custom software (LabVIEW, National Instruments, Austin, TX) which stored the ECG trace for offline analysis. Additionally, RPM and watts were recorded manually from the recumbent cycle each minute.

4.3.4 **Visuomotor Task**

Participants were presented a shape-letter association task to learn and then were tested within 2 minutes to evaluate immediate retention. This process repeated for three alternating rounds of training and testing (T1, T2, T3). Six unique shape-letter associations were used during each evaluation period and these were changed during each evaluation to avoid carryover between the different days of testing. A pattern of six shapes was presented to represent each letter. The six shapes were a random assortment of 2 triangles, 2 squares and 2 circles. The shape combinations were balanced between the groups such that an equal number of combinations began and ended with the same shape and no group had more than 2 repeating sequences. There were 4 evaluations, each with six shape-letter associations, thus, all letters of the alphabet were used with the exception of Q and Z; see Table 1. Finally, there were four groups of shape-letter combinations which were quasi-randomized to ensure each participant had a unique order. The visuomotor task was controlled by custom software (LabVIEW, National Instruments, Austin, TX) and presented on a computer screen while the participant was seated on a standard office chair. Figure 1 outlines the visuomotor task procedures.
4.3.5 Task Training

Participants were required to learn 6 shape-letter associations over 24 trials in random order in a mass practice format during task training that lasted 132 seconds (2 minutes, 12 seconds). The number of training and testing trials were selected to allow for observation of change in performance over repeated blocks while not achieving peak performance. The protocol was based on pilot work that adopted a variation of a previously reported vibrotactile discrimination task used to measure short-term adaptation (Tang et al., 2009b). The 24 trials incorporated 4 trials of each of the 6 shape-letter combinations in a random order. Each individual trial began with a fixation dot presented for 1.5 seconds. The shapes were displayed in a horizontal row for 2.5 seconds followed by the matching letter which was displayed for 1.5 seconds. No response was required during training.

4.3.6 Testing

The testing period was used to evaluate short-term performance adaptation of the shape-letter associations. Similar to training, 24 trials were evaluated during each testing block with each shape combination being displayed 4 times in a random order. Each trial began with a fixation dot for a random interval of 1-2 seconds. A shape combination was then presented for 2.5 seconds followed by all 6 letters from training. All 6 letters were displayed in a horizontal row and always in the same order. Participants were instructed to respond as quickly and as accurately as possible by pressing the number keys 1 through 6 on a standard keyboard to indicate the matching letter. Participants began the task seated with their fingers resting on the number keys, which corresponded to the letters from left to right. No feedback was provided to participants.
(a) Example training presentation

\[\bullet \rightarrow \Box \Box \Delta \Box \Delta \Box \Rightarrow M\]

(b) Example testing presentation

\[\bullet \rightarrow \Box \Box \Delta \Box \Delta \Box \Rightarrow G\ B\ J\ A\ M\ S\]

1\ 2\ 3\ 4\ 5\ 6

**Figure 4.1** – Example of task training and testing parameters. A fixation dot was presented for 1.5 seconds followed by a row of 6 shapes for 2.5 seconds. During training (a) the matching letter was then presented for 1.5 seconds. During testing (b) all six letters taught during training were shown in a horizontal row and participants responded by pressing the appropriate number key (numbers 1 through six from left to right). In this case the correct response during testing would be the letter M, indicated by pressing the #5 key.

### 4.3.7 Outcome Measures

The primary outcome measures were response time (RT) and errors during the testing blocks. RT was measured as the time from presentation of the six letters until the participant pressed a number key. An error was defined as an incorrect keyed response to the presented shape combination. Response speed was assessed by calculating the mean RT over all three testing blocks. Short-term performance adaptation was assessed by calculating the change in RT and errors between testing blocks 3 and 1 (T3 and T1). Improved performance would be characterized by a reduction in reaction time and/or reduction in errors.

### 4.3.8 Data Processing

Trials were removed from analysis if RTs greater than 4 standard deviations from the mean for that participant and testing group were found. Additionally, trials with RT outliers less than 4 standard deviations were visually identified from frequency distributions and were removed from analysis a priori if independently identified by at least 2 of three study authors (MS, ML, CL). This processing removed 25 of 6624 total trials (19 outside 4 SD’s; 6 identified by study authors), which represented 0.4% of trials.

### 4.3.9 Statistical Analysis

To evaluate the efficacy of the task, a repeated measures ANOVA with testing block (T1, T2, T3) and letter group (1 through 4) as within-subject factors was used for both RT and errors as
dependent variables. Additionally, to confirm that rate of change over testing blocks was not different between the four groups of symbol-letter combinations a repeated measures ANOVA was used with the difference from testing block 1 (T1) to block 3 (T3) as the dependent variable and letter group as a within-subjects factor for both RT and errors.

To evaluate our specific hypotheses, repeated measures ANOVA were employed. To evaluate the first hypothesis that the fastest mean response time would be following the exercise session, a repeated measures ANOVA with mean RT collapsed across all three testing blocks as the dependent variable and order (pre vs post) and condition (exercise vs control) as within-subject factors was used. To assess hypothesis 2 and the rate of performance adaptation, the difference in RT and errors from T1 to T3 was used as the dependent variable. This was used rather than using testing block (T1, T2, T3) as a within-subject factor because individual performance was highly variable at T2 (based on visual inspection of individual plots) but consistently displayed improvement from T1 to T3. Separate repeated-measures ANOVA with condition (Exercise vs Control) and order (Pre vs Post) as within-subject factors and planned comparisons between the post-exercise and post-control testing sessions were used for both RT and errors. Statistical analysis was performed using SAS 9.3 and SAS Enterprise guide 5.1 (SAS Institute, Inc. Cary, NC).

4.4 Results

All 24 participants completed the full testing protocol, however, one individual’s data was unusable due to a technical issue and the following statistical analysis relates to 23 individuals. There were 11 females and 12 males with a mean age 20.8 (SD=2.7) years. Participants exercised at a mean HR of 128.4 (SD=6.5) bpm during the exercise session (66.4% of maximum) and 72.6 (SD=7.8) bpm during the control session (37.5% of maximum). See Table 4-1 for a full breakdown of participant characteristics.
Table 4-1 - Participant characteristics and exercise data (n=23). Values are mean (standard deviation) or frequency counts. (BMI, body mass index; kg/m^2, body weight in kilograms divided by height squared in meters; bpm, beats per minute; RPE, rating of perceived exertion)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD) or Percent (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>20.8 (2.7)</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>47.8% (11)</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>23.2 (4.0)</td>
</tr>
<tr>
<td>Education (years of formal schooling)</td>
<td>14.7 (2.4)</td>
</tr>
<tr>
<td>Time between sessions (days)</td>
<td>3.6 (3.2)</td>
</tr>
<tr>
<td>Mean heart rate (bpm)</td>
<td></td>
</tr>
<tr>
<td>Exercise session</td>
<td>128.4 (6.5)</td>
</tr>
<tr>
<td>Control session</td>
<td>72.6 (7.8)</td>
</tr>
<tr>
<td>Mean heart rate (% max)</td>
<td></td>
</tr>
<tr>
<td>Exercise session</td>
<td>66.4 (3.2)</td>
</tr>
<tr>
<td>Control session</td>
<td>37.5 (4.0)</td>
</tr>
<tr>
<td>Mean RPM</td>
<td></td>
</tr>
<tr>
<td>Exercise session</td>
<td>57.8 (8.2)</td>
</tr>
<tr>
<td>Control session</td>
<td>26.7 (5.5)</td>
</tr>
<tr>
<td>Mean RPE (range 0-10)</td>
<td></td>
</tr>
<tr>
<td>Exercise session</td>
<td>4.2 (1.3)</td>
</tr>
<tr>
<td>Control session</td>
<td>0.6 (0.7)</td>
</tr>
</tbody>
</table>

4.4.1 Efficacy of Task

The task was effective at demonstrating improved performance as mean RT (F(2,44)=56.77, p<.001) and errors (F(2,44)=129.69, p<.001) were consistently reduced from T1 to T2 to T3; Figure 4-2. Additionally, the task displayed stability over repeated administrations as the four groups of letters did not lead to statistically different mean RT (F(3,66) = 1.94, p=0.13), mean number of errors (F(3,66)=1.97,p=.13), or change from T1 to T3 of RT (F(3, 66)=2.32, p=0.08) or errors (F(3,66)=0.22, p=0.88). Table 4-2 provides a full breakdown of RT and errors.
A) Response times

![Graph showing response times over testing periods for different conditions.]

B) Errors

![Graph showing errors over testing periods for different conditions.]

**Figure 4-2:** Average response time and errors for the three testing blocks and the four evaluations (pre and post the exercise and control condition). (a) Collapsed for condition (exercise and control) and order (pre and post) response time was significantly shorter across testing blocks T1 to T2 to T3. (b) There were significantly fewer errors across testing blocks T1 to T2 to T3 collapsed for condition (exercise and control) and order (pre and post).
4.4.2 Hypothesis 1: Speed of Execution

There was a significant effect of order on mean RT indicating post-test had a shorter mean RT than pre-test (F(1,22) = 10.76, p=.003). The interaction of order (pre vs post) and condition (exercise vs control) was not significant (F(1,22)=1.68, p=.21). Planned comparisons revealed shorter post-exercise mean RT (1059 ms, SD=1022) than post-control (1169 ms, SD=1105) but this only approached statistical significance (t(22)=1.89, p=.07). However, it is worth noting that exploratory post-hoc testing revealed that pre-control (1418 ms) mean RT was significantly longer than pre-exercise (1203 ms) (t(22)=3.71, p=.01) which may have driven the differences between post-exercise and post-control mean RT. Figure 4-3 displays mean response time for the four testing sessions.

![Figure 4-3: Mean response time for the four evaluations. There was a significant effect of order indicating post-tests had shorter response time than pre-test (p=.003). Planned comparisons revealed a trend for faster responses post-exercise than post-control. *p=.07, planned comparison displayed trend for shorter response time post-exercise compared to post-control.](image)

4.4.3 Hypothesis 2: Short-term Performance Adaptation

No significant effects of condition (exercise vs control) or order (pre vs post) were observed for change in RT (p>.05). Additionally, the condition by order interaction did not reveal any
difference between the four evaluations for change in RT (F(1,22)=1.22, p=0.28). Further, planned comparisons did not reveal a difference between post-exercise (622ms, SD=394) and post-control (720ms, SD=502) for change in RT (t(22)=0.91, p=0.37).

Change in errors did not reveal any significant effects of condition or order (p>.05). A significant condition by order effect was observed for change in errors (F(1,22)=5.03, p=.035) such that post-exercise (mean=6.1, SD=4.5 reduction in errors) had the smallest improvement of the four evaluations; Figure 4-4a. However, exploratory analysis using the difference in errors from testing block 2 to testing block 3 suggested that errors plateaued post-exercise at testing block 2 (mean=1.4, SD=2.4 reduction in errors post-exercise) while the other evaluations continued to improve (mean reduction in errors ranged from 3.1 – 5.5 from T2 to T3 for the other three evaluations) (F(1,22)=5.97, p=0.023); Figure 4-4b. Additionally, a repeated measures ANOVA with testing block (T1, T2, T3), order (pre vs post) and condition (exercise vs control) indicated a trend towards a significant interaction between the three factors (F(2,22)=2.98, p=0.061) which suggested that post-exercise had lower error rates at T1 and T2 compared to the other evaluations; Figure 4-4b.

Table 4-2: Group mean (standard deviation) for the three testing blocks and four evaluations (pre and post the control and exercise conditions).

A) Response times. Values are group mean (standard deviation) in milliseconds.

<table>
<thead>
<tr>
<th></th>
<th>Test 1</th>
<th>Test 2</th>
<th>Test 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>1695 (670)</td>
<td>1348 (644)</td>
<td>1213 (684)</td>
</tr>
<tr>
<td>Post</td>
<td>1546 (690)</td>
<td>1132 (577)</td>
<td>826 (490)</td>
</tr>
<tr>
<td><strong>Exercise</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>1468 (513)</td>
<td>1226 (478)</td>
<td>916 (381)</td>
</tr>
<tr>
<td>Post</td>
<td>1383 (508)</td>
<td>1035 (486)</td>
<td>760 (319)</td>
</tr>
</tbody>
</table>

B) Error rates. Values are group mean number of errors (standard deviation). There were 24 trials per testing block.

<table>
<thead>
<tr>
<th></th>
<th>Test 1</th>
<th>Test 2</th>
<th>Test 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>14.4 (6.2)</td>
<td>10.0 (7.0)</td>
<td>6.5 (6.2)</td>
</tr>
<tr>
<td>Post</td>
<td>10.9 (6.1)</td>
<td>6.4 (7.3)</td>
<td>3.3 (4.9)</td>
</tr>
<tr>
<td><strong>Exercise</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>13.8 (4.6)</td>
<td>9.7 (6.3)</td>
<td>4.3 (4.2)</td>
</tr>
<tr>
<td>Post</td>
<td>9.8 (5.5)</td>
<td>5.1 (5.7)</td>
<td>3.7 (4.5)</td>
</tr>
</tbody>
</table>
A) Change in errors from testing block 1 to testing block 3. (*p=.035, post-exercise had smaller reduction in errors compared to all other evaluations)

B) Change in errors from testing block 2 to testing block 3. (*p=.023, post-exercise had smaller reduction in errors compared to all other evaluations)

Figure 4-4: Mean change in errors between the four evaluations. Post-exercise had smallest reduction in errors compared to the other three evaluations. (a) Difference between testing block 1 and 3 revealed smaller reduction in errors for post-exercise relative to the other three evaluations (*p=.035). (b) The difference in errors between testing block 2 and 3 revealed a smaller reduction in errors post-exercise compared to the other three evaluations (*p=.023).
4.5 Discussion

The current study supported our hypothesis of shorter overall mean response time post-exercise. However, results only partially supported the main hypothesis of faster performance adaptation of the visuomotor association task. In this task, short-term performance adaptation was characterized by a reduction in response time and/or errors over successive testing blocks. Aerobic exercise positively influenced error reduction (evaluated as the mean difference between testing block 1 and testing block 3). Conversely, there was no difference on response time reduction (testing block 1 minus block 3) between the four evaluations (pre and post the exercise and control conditions). Thus, error reduction supported faster rate of performance adaptation post-exercise while response time did not display an effect of exercise. These findings may be due to the relative insensitivity of the task measures to evaluate rate of adaptation or reflect a dissociation between short-term performance adaptation and the benefits of a single session of moderate aerobic exercise.

A single bout of aerobic exercise has been shown to influence rate of acquisition and retention in healthy individuals across a variety of tasks. For example, high intensity exercise improved acquisition and retention of a novel language (Winter et al., 2007), greater retention (but not acquisition) of a visuomotor skill (Roig et al., 2012) and enhanced acquisition and retention of implicit sequence-specific motor learning (Mang et al., 2014). While the influence on retention has been consistent, acquisition has not been universally augmented by aerobic exercise. One possible explanation is that short term benefits of exercise may not contribute, immediately after exercise, to meaningful changes in behavioral measures of rate of short-term adaptation. The few studies in humans have utilized a variety of tasks that focus on different types of learning which may not be universally influenced by exercise. For example, Winter et al. (2007) focused on lexical learning using words from a new language (Winter et al., 2007), while Roig et al. (2012) utilized a visuomotor tracking task to focus on motor memory (Roig et al., 2012) and Mang et al. (2014) also used a visuomotor tracking task but focused on implicit sequence specific learning (Mang et al., 2014). Our task was closest in structure to learning a new language and it is interesting that our results mirrored Winter et al. (2007) as accuracy (error rates) improved faster after exercise but response time reduction was not different between conditions (although mean response time was shortest following exercise). This suggests that executive functions such as
working memory may be mediating these exercise benefits rather than arousal (reflected in faster mean response time). Additionally, it is possible that the immediate benefits from exercise are small relative to task variability and are thus difficult to observe using response time. Thus, quantifying learning (both acquisition and retention) may be best reflected in accuracy (i.e. errors) rather than timed responses.

Alternatively, the inconsistent findings between change in response time and change in errors could be linked to the intensity of exercise. Peripheral catecholamine levels, which contribute to the effects of exercise, increase linearly with increasing exercise intensity (McMorris et al., 2008). However, our moderate exercise prescription of 70% of maximum HR has also been shown to increase CNS arousal networks (McMorris et al., 2008) and was expected to be sufficient to augment processes important to short-term performance adaptation. It is likely that the exercise protocol did augment CNS arousal as mean response time trended towards being shortest post-exercise. However, no difference in change in response time over testing blocks was observed between the four evaluations (pre and post the exercise and control conditions). An alternate explanation may be that neurotrophic factor release was less than optimal. Intense exercise leads to greater peripheral brain-derived neurotrophic factor (BDNF) than moderate exercise (Winter et al., 2007), and peripheral BDNF levels during learning have been associated with greater immediate success in humans (Winter et al., 2007) and animal models (Vaynman et al., 2004); however, not universally (Mang et al., 2014). BDNF may be the critical component of rate of skill adaptation due to its important influence on both short and long-term potentiation (Vaynman & Gomez-Pinilla, 2005). Thus, while moderate aerobic exercise increases up-regulation and release of catecholamines and neurotrophic factors, which theoretically should benefit the rate of adaptation, future work is needed to elucidate their relative contributions to short-term performance adaptation and the intensity of exercise needed to augment these components.

The one specific design advantage in the current study was the use of a within-subject design exploring short term adaptation within an individual person and then being able to reconfigure the task so that is was not influenced by previous exposure. This approach was confirmed by the consistent change in performance curves for each of the four evaluations and compares well to previous work that has use a similar approach (Tang et al., 2009b). Our design reduced within-
subject variability compared to previous between-subject designs, but this did require the use of a novel learning task. It is possible that the task had a floor effect as participants were near optimal performance after only the second testing block post-exercise. A more difficult task (i.e. more repetitions needed for proficiency) may have been better suited to reveal differences in change in performance between the evaluations. This proposition is partially supported by animal models pairing aerobic exercise with upper-limb training which was only shown to be more beneficial than upper-limb training alone when training difficulty was increased (Ploughman et al., 2007). However, this was a longitudinal study and the differences appeared during the fifth (and final) week when upper-limb training provided daily was most difficult and may reflect the accumulation of the previous five weeks of the intervention rather than task difficulty. Nevertheless, the shape-letter association task was effective at displaying short-term change in performance over repeated administration and future work can utilize similar task characteristics but vary difficulty to further elucidate the influence of aerobic exercise on short-term performance adaptations.

An important consideration is whether the rate of acquisition is linked to long-term benefits. Animal models of exercise prior to upper-limb therapy suggests that short-term effects may not be linked to long-term benefits as there were no differences between an exercise plus training group and a training alone group until the fifth week of training (Ploughman et al., 2007). Thus, the accumulation of multiple sessions may be needed to reveal the benefit of pairing aerobic exercise with task training. Further, single-session studies in humans, including the current study have not universally displayed a benefit of aerobic exercise to the rate of acquisition. However, retention has consistently revealed a benefit of pairing aerobic exercise with training compared to training alone (Mang et al., 2014; Roig et al., 2012; Winter et al., 2007). Thus, the rate of adaptation may not be a critical factor to long-term success and the benefit of pairing exercise with training may not be to immediate success rather the increased release of neurochemicals from the exercise bout. Exercise increases availability of neurotransmitters including dopamine and norepinephrine as well as neurotrophic factors such as BDNF (McMorris et al., 2009b) which are associated with neuroplastic alteration. Further, neurophysiological evaluation of long-term potentiation (LTP) like neuroplasticity has shown increased LTP like effects following an exercise bout (Mang et al., 2014; Singh et al., 2014b). Thus, the real benefit of pairing exercise
with training may be to augment cortical mechanisms underlying the effect of exercise on learning and the effects may be revealed by a retention test rather than evaluating rate of acquisition. Unfortunately, our design did not include a retention test or neurophysiological evaluation and these should be targets for future work to clarify the influence of exercise on rate of adaptation and its relationship to learning.

4.5.1 Conclusions

While a single session of aerobic exercise led to faster mean response time, support for enhanced rate of performance adaptation was mixed as reduction in errors supported a benefit of exercise but response time reduction was no different than a control condition. A more difficult task may be better suited to reveal potentially small differences to rate of adaptation from an aerobic exercise bout. Future work may benefit from measures of underlying neurophysiology and a retention test to elucidate the influence of aerobic exercise on rate of short-term adaptation and retention, which has important implications relating to the potential usefulness of exercise as an acute modulator of relearning during rehabilitation in clinical populations.
Does Aerobic Exercise Augment Upper-Limb Movement Performance in Stroke?
5.1 Abstract

**Introduction:** Aerobic exercise may be an effective strategy to influence the central nervous system and influence sensorimotor function prior to neurorehabilitation for stroke patients. However, little work has been done to investigate the effect of exercise on motor function in a stroke population.

**Methods:** 10 stroke participants completed 2 sessions which both involved 20 minutes of recumbent stepping at a moderate (exercise session) or very light (control) intensity. Following the recumbent stepping, participants completed 20 minutes of upper-limb training focused on drawing a rectangle as fast as possible. Evaluation involved drawing a rectangle as large and as fast as possible in the same direction as training (pre and post-test) as well as in the opposite direction (transfer task).

**Results:** Participants had shorter movement time (p<.01) and faster velocity (p<.01) pre- to post-testing but no differences were found between the exercise and control conditions. Conversely, the transfer task revealed shorter movement time following the control session compared to the exercise session (difference = 158 ms for 1st segment of rectangle, p=.03). Finally, during arm training, an initial improvement period occurred in fewer trials in the control condition (mean=4.6m SD=1.8) compared to the exercise condition (mean=8.9, SD=3.6) (p=.005).

**Conclusions:** While performance improved from pre- to post-testing it was not different between the conditions. Between-condition effects suggested that adaptation was faster during training following the control activity. Future work should investigate the effects of various exercise intensities and the accumulated effects of multiple sessions of pairing exercise with task training.
5.2 Introduction

Stroke is the leading cause of neurological disability in adults (Go et al., 2013) and, unfortunately, the number of individuals suffering and surviving a stroke is expected to rise as the population ages and mortality rates decline. As such, there continues to be a need to advance approaches to improve post-stroke recovery. While task specific training is an essential therapeutic component there is evidence that adjuncts can improve the outcomes from such use-dependent training. For example, pharmacologic adjuncts such as amphetamines have shown some promise (Gladstone et al., 2006). In addition, the application of electrical stimulation has also appeared to augment the benefits of post-stroke training (Edwardson et al., 2013). These adjuncts appear to benefit rehabilitation by setting the CNS state into a more receptive state prior to and during training. The idea of ‘priming’ the CNS to augment the benefits of use-dependent training continues to be an important possible opportunity to improve post-stroke outcomes.

One unique possibility is the use of aerobic exercise as such a ‘prime’ prior to use-dependent training. Aerobic exercise has well documented benefits to stroke recovery including vascular health (Tang et al., 2009a), mobility (Dean et al., 2012; Duncan et al., 2003) and reducing risk factors associated with secondary stroke (Yung et al., 2009). As a result is part of the clinical practice guidelines (Lindsay et al., 2010) and should be routinely performed. Interestingly, aerobic exercise is also a potential adjunct to augment the conditions in the central nervous system prior to neurorehabilitation. A single session of aerobic exercise has consistently displayed improved performance on stimulus-response tasks indicating improved attention (Hillman et al., 2003; Kamijo et al., 2004b), executive function (Chang et al., 2012) and faster information processing (McMorris et al., 2009b). Importantly, these behavioural changes have been supported by augmented neurophysiology reflected in neuroelectric measures suggesting heightened cortical excitability (Hillman et al., 2003; Kamijo et al., 2004b). These changes begin immediately after exercise (Kamijo et al., 2007), persist for at least 20 minutes (Chang et al., 2012) and may continue beyond the time required for the cardiovascular system to return to baseline (Hillman et al., 2003). Thus, aerobic exercise may improve performance and underlying cortical neurophysiology prior to traditional rehabilitation.
Of further interest, a single bout of exercise has also shown to positively impact rate of skill acquisition and retention. A high intensity running bout resulted in participants acquiring a novel language 20% faster (based on error rates) than moderate exercise or a resting control condition (Winter et al., 2007). Similarly, we have shown improved error reduction but not response time in a visuomotor association task following an aerobic exercise bout compared to a control condition (Sage et al., 2015a). Interestingly, task adaptation on a visuomotor tracking task was faster following an exhaustive exercise bout compared to a control condition despite participant fatigue (Mierau et al., 2009). Importantly, this improved motor function was in the upper-limb which was not directly involved in the exercise and accompanied by altered brain activity suggesting a central effect of exercise (Mierau et al., 2009). However, the benefit of exercise prior to training has not been universal as rate of improvement on visuomotor tasks focused on motor memory were not enhanced (Roig et al., 2012). Conversely, sequence-specific implicit motor learning was augmented following an exercise bout which was combined with enhanced LTP like plasticity (Mang et al., 2014). However, it is still unclear if this potential augmentation of rate of improvement in performance extends to individuals recovering from a stroke.

Important for the current study, aerobic exercise appears to preferentially augment the motor system. This has been particularly evident when stimulus-response type tasks have been employed to evaluate exercise effects. When a response is broken into pre-motor and motor components, the motor components have consistently shown a robust improvement during and post-exercise compared to the pre-motor components (Davranche et al., 2006; McMorriss et al., 2009b). However, these tasks use simple motor responses such as a button press which suggests an augmented motor command but does not inform about the impact of aerobic exercise on movement control. Additionally, little work has been done in a stroke population.

Specific to stroke, visuomotor learning and motor function were enhanced following an 8 week chronic exercise intervention (Quaney et al., 2009). More relevant to the current study, a single session of body-weight supported treadmill training significantly improved motor function; however, the results were variable between participants and the exact cause of the change could not be isolated to the aerobic exercise versus the active involvement of the upper-limb in the exercise (Ploughman et al., 2008). Conversely, among individuals recovering from stroke, we have shown no post-exercise augmentation of the electromyography (EMG) signal (Sage et al.,
but augmented movement time (Sage et al., 2015c) during stimulus-response tasks. Thus, it appears that aerobic exercise may positively influence the motor system; however, it is unclear if this augmentation is simply a faster execution of a simple motor command or if it extends to control for more complex movements.

To evaluate the effects of exercise on performance during training and movement control, we investigated an arm training paradigm following an aerobic exercise bout or control condition. Change from pre to post arm training was compared between the conditions. The rate of change during arm training was also compared between the conditions. Additionally, a transfer test was performed to evaluate if the effects of each condition would extend to a different movement pattern. The overall objective of this study was to investigate the influence of a single session of aerobic exercise on adaptation of upper-limb movement control. We hypothesized that after the aerobic exercise bout, participants would exhibit faster movements but control outcomes (i.e. path trajectory evaluated with the number of velocity peaks and path deviation from a straight line) would not be different between the two conditions. This was evaluated using a pre- and post- test for the exercise and control conditions. We hypothesized faster movements based on consistent findings of faster timed responses following an exercise bout in both healthy individuals (McMorris et al., 2009b) and faster movements among those recovering from a stroke (Sage et al., 2015c). Conversely, motor learning but not motor control appears to be influenced by a single session of exercise in healthy individuals (Mang et al., 2014). Secondly, we hypothesized that any benefits of the training paradigm would extend to the transfer test of movement performance for a similar task that was not trained. Finally, we hypothesized that the rate of change associated with arm training would be greater following the exercise condition than the control condition.

5.3 Methods

5.3.1 Participants

Ten individuals in the chronic stage of stroke recovery were recruited through the Toronto Rehabilitation Institute out-patient neurorehabilitation program and research volunteer pool. Inclusion criteria included a diagnosis of stroke, sufficient lower-limb function to exercise using a recumbent stepper and the ability to provide informed consent. Participants were excluded if
they did not have sufficient upper-limb function to complete the task, or their treating physiotherapist or medical chart indicated impaired cognitive function or uncontrolled contraindications to exercise.

5.3.2 Procedure

Participants completed two conditions separated by 48 hours, an exercise and control condition. Conditions were randomly ordered and 6 participants completed the exercise condition first and 4 completed the control condition first. The two conditions were identical with the exception of the workload intensity of the lower limb movements performed. During the exercise condition participants had the goal of maintaining heart rate (HR) between 50-70% of their age-calculated maximum, while during the control condition workload was set to keep HR within 10 beats per minute (bpm) of rest. During both conditions, this exercise bout was immediately followed by an upper-limb training task. Participants also completed pre and post-testing which were completed prior to the exercise bout and 10 minutes after the upper-limb training. Finally, participants completed a transfer test consisting of the opposite movement pattern during training within 5 minutes of completing post-testing. Participant demographics, stroke characteristics and clinical measures were abstracted from medical chart review. Upper-limb function was characterized using the Chedoke-McMaster Stroke Assessment (CMSA) which was also extracted from medical chart or their treating physiotherapist. Participants were all in the chronic stage of recovery (minimum time since stroke was 242 days or approximately 8 months) and no participants had undergone significant rehabilitation therapy or upper-limb training between the time of CMSA measurement and the time of the study.

5.3.3 Exercise

The exercise included a 3 minute warm-up, 20 minutes at a moderate steady state and 2 minute cool-down and was completed using a lower-limb stepper (NuStep Inc., Ann Arbor, MI). HR was monitored continuously using a chest transmitter and watch (Polar Electro Inc, NY) and sampled at the end of each minute. Additionally, watts and steps per minute were recorded from the exercise equipment at the end of each minute. Finally, rating of perceived exertion (RPE) was sampled at the beginning, middle and end of the exercise condition using the Borg CR-10 scale (Borg, 1982, 1998).
During the steady-state movement during the exercise condition, participants maintained a self-selected cadence and researcher’s adjusted resistance to maintain heart rate (HR) and RPE targets. For the exercise condition the HR target was 50-70% of age-calculated maximum (208- [0.7*age]) (Tanaka et al., 2001) with an RPE of 3-4 (moderate-somewhat hard). For the control condition, which was designed to engage participants in a comparable movement frequency against low load, HR was maintained within 10 bpm of rest with an RPE less than 2 (very light). This was achieved by placing no resistance on the exercise equipment and adjusting participant’s cadence. If HR did increase participants were instructed to slow their cadence and if HR went over 10 bpm above rest than they were instructed to stop stepping and wait until HR lowered to within 5 bpm of rest (this situation occurred once for a single participant).

5.3.4 Upper-Limb Task: Training and Testing

Arm training and testing involved discrete upper-limb movements in the horizontal plane performed with the hemiparetic limb. While performing the upper-limb movements, participants were seated comfortably in front of a table which was approximately mid-chest height as per individual comfort. They rested their chin on a support, which was adjusted to individual comfort to isolate the upper-limb and reduce compensatory trunk movements. Training and testing movements were performed on a 21.5” touchscreen monitor (HP L2206 tm, Hewlett-Packard Development Company L.P.) which was centered on the participant’s chest and rested at a 10° angle to reduce glare from overhead lights. Functional reach was measured by having participants reach along the table top along their mid-line. The bottom edge of the monitor was placed at 25% of the distance reached, while the top edge of the monitor was approximately 70-75% of functional reach distance; Figure 5-1.
Figure 5-1 – Experimental setup from a bird’s eye view. Participants were seated with their trunk restrained by placing their chin on a rest. Functional reach along the midline was measured and the front edge of the computer monitor was placed at 25% of the functional reach. The far edge of the monitor was approximately 70-75% of functional reach. The monitor was angled up at 10° from the horizontal. The targets shown represent the upper-limb training task. Participants held a stylus and began in the ipsilateral bottom corner (bottom right in this example) and moved counter-clockwise with the right arm and clockwise with the left (displayed with arrows on the diagram). During testing only a single target was displayed in the bottom ipsilateral corner to provide a starting and end-point; however, participants were told they did not need to enter the target.

5.3.4.1 Upper-limb Training Task

Training involved 50 trials separated into 5 blocks of 10 trials with rest provided as necessary. This training paradigm and number of repetitions was selected as it has been shown to be sufficient to induce a within-session training effect (Cirstea et al., 2003b) but not produce stable between-session performance on upper-limb tasks (Michaelsen & Levin, 2004). Participants used a stylus to trace a rectangle on the computer monitor with their hemiparetic upper limb. Prior to arm training participants moved the stylus towards the four corners of the monitor to evaluate functional reaching space on the monitor. A rectangle was then fit to the smallest vertical and horizontal distances reached. Targets were placed in the four corners of the fitted rectangle to ensure movement amplitude remained consistent during training. The targets were 5 cm red squares that changed to green when participants moved the stylus over them to indicate the target had been hit.

Participants drew a single rectangle for each trial beginning in the bottom ipsilateral corner and was traced clockwise for the left hand and counter clockwise for the right hand to ensure
equivalent movement patterns between participants. Instructions were to draw the rectangle as quickly as possible while ensuring the stylus passed through all four targets. Following each trial participants received feedback relating to the timing of their movement in comparison to the previous trial. A green, yellow or red light was shown for 2 seconds to indicate faster, no change and slower time respectively. A threshold of either a 5% or 100 ms change in time to draw the rectangle was used to determine feedback. Additionally, participants received feedback about their relative trial to trial change in time to draw the rectangle as a percentage on a faded schedule. This feedback was given following every second trial for the 1st block, after trials 3, 6 and 9 for the 2nd block, and every fifth trial for the 3rd to 5th blocks. This equates to feedback on 28% of trials and a similar schedule has been successful in improving upper-limb control in stroke patients (Cirstea & Levin, 2007).

5.3.5 Upper-limb Testing

Testing involved drawing 10 rectangles in a similar pattern to training. The screen had a single green square (5cm x 5cm) in the bottom corner ipsilateral to the arm used. This square was provided as a start and end point for each rectangle; however, participants were explicitly instructed that they were not required to start or end their rectangle within the rectangle. No feedback was provided during testing. Pre- and post-testing was performed prior to the exercise training and 10 minutes following the upper-limb training to evaluate the influence of the intervention. This testing involved drawing 10 rectangles in an identical pattern to the arm training. Additionally, a transfer test was performed within 5 minutes of post-testing to evaluate whether any training effects extended to a different movement pattern. This testing involved drawing 10 rectangles in the opposite direction to training.

5.3.6 Outcome Measures

Custom software was used to control the task and record the position of the stylus at 1000 Hz for offline processing (LabVIEW, National Instruments Corp, Austin, TX). The stylus position was first low-pass filtered at 5 Hz to smooth the trace. A velocity trace was then calculated from the first derivative of the position trace. Positions of zero velocity were then automatically detected and confirmed manually to locate the position of the four corners of the rectangle. Task performance was quantified using the path length travelled and movement time from the initial to
end positions of each segment and summed for the whole rectangle. Mean velocity was calculated for each segment and the whole rectangle. Path trajectory was quantified as the number of velocity peaks in the velocity trace and the movement error measured as the maximum perpendicular distance between the stylus position and a straight line between the initial and end positions. These were calculated for each segment of the rectangle and summed for the whole rectangle.

5.3.7 Statistical Analysis

The first hypothesis compared pre- and post-testing between the two conditions. This was achieved using a repeated measures ANOVA with condition (exercise x control) and testing (pre- vs post-test) as within-subject factors. The second hypothesis compared the transfer task between the exercise and control conditions using a paired t-test. The third hypothesis compared the rate of change during arm training between the exercise and control conditions. First a plot of movement time per trial was constructed for each individual and visually inspected. Two distinct periods were noted, an initial period of rapid improvement followed by a stable period where movement time was relatively consistent. Thus, to evaluate rate of improvement we utilized the slope of the initial period of rapid improvement as well as the number of trials needed for movement time to stabilize. Movement time for the first segment of the rectangle was chosen for this analysis as it had the least variable performance within an individual and minimal loss of data. The end of the initial period of improvement was located using two methods to ensure accuracy and was performed with an automated custom software program (LabVIEW, National Instruments Corp, Austin, TX). The primary method began at trial 20 (chosen as the starting point based on visual inspection of individual data) and worked backwards through the trials until a movement time greater than 3 standard deviations above the mean of trials 31-50 was identified and then added one to that trial. If this method was unsuccessful at identifying the end of the initial period of improvement (determined by manual inspection, blinded to participant and condition) than a second method was employed. The secondary method began at trial 1 and stopped at the first trial that was longer than the preceding trial and was used if the primary method was unable to clearly identify the end of the initial period of improvement. The end of the initial period of improvement was confirmed by manual inspection (blinded to the participant and condition) and adjusted if necessary. The number of trials until the end of the initial period
of improvement and the slope of the linear fit of the initial period of improvement were used for statistical analysis by paired t-tests between the two conditions. See Figure 5-2 for an example of how the initial period of improvement was identified.

![Graph showing the identification of the initial period of improvement](image)

**Figure 5-2** – Example procedure to identify the end of the initial period of improvement (using movement time (MT) of the first rectangle segment) during arm training for the exercise session from a single representative participant (Chedoke-McMaster Stroke Assessment = 6 for the arm and hand). First, a threshold of 3 standard deviations above the mean (518.1 ms) was applied (horizontal dashed line, standard deviations=54.4 ms, threshold=681.3 ms). In this example, trial 13 (MT=731 ms) was the first trial larger than the threshold and trial 14 (vertical dashed line, MT=553 ms) was identified as the end of the initial period of improvement. A linear fit of the initial period of improvement was then applied and the slope of the line calculated (dashed line, slope = -123.4 ms/trial in this example).

5.4 Results

Statistical comparisons reported below are for the first segment of the rectangle as well as the total rectangle. Segments 2, 3, 4 were not used in isolation because the stylus position was sometimes marked incorrectly or lost by the computer monitor at the second corner (top contralateral corner) and thus data was inaccurate or lost for segments 2, 3 and 4. The most common reason was when an individual’s hand, arm or shirt came into contact with the screen.
and the cursor position was lost. Therefore, it was decided to statistically analyze the first segment of the rectangle as the primary outcome and the total rectangle as a secondary outcome (due to reduced trials). For hypothesis 1 (pre- and post-testing) one individual’s data was lost due to a technical issue. For segment 1, n=9. For the full rectangle an additional participant was removed due to significant data loss, n=8. For hypothesis 2 (transfer test), n=10 for the segment 1 analysis, n=8 for the full rectangle analysis due to significant data loss in two individuals. Finally, for hypothesis 3 (analysis of rate of change during arm training), movement time of segment 1 was used as it had the least data lost (n=8, control condition: 390/400 useable trials; n=8, exercise condition: 394/400) compared to the entire rectangle (n=8, control condition: 229/400 useable trials; n=8, exercise condition: 296/400). Two participants were not included in statistical analysis of rate of change during training. One had high variability and did not display an initial period of rapid improvement and one was missing trials 1 and 5 for the control condition making it impossible to clearly identify the initial period of improvement. It is worth noting that one individual was excluded from all full rectangle analyses and was also one of the individuals excluded from the rate of change during training analysis. Therefore, this individual was only included in the segment 1 analyses of pre- and post-testing and the transfer test. This individual was the lowest functioning of the group with a CMSA of 3 for both the arm and hand.

5.4.1 Demographics

Ten individuals (7 males, 3 females) with a mean age of 66.1 (SD=8.8) who all self-reported being right handed prior to their stroke completed study procedures. Six participants completed the exercise condition first and four completed the control condition second. Participants were 505 days (approximately 1.4 years) post-stroke on average with a wide range of upper-limb function measured with the CMSA (mean arm=4.95, range: 3-7; mean hand=5.25, range 3-7). A single participant had a right hemisphere stroke while the remaining 9 were left-hemisphere affected. Mean HR during exercise was 83.6 bpm (SD=16.3) compared to 67.4 bpm (SD=14.1) at rest. This represented 51.7% (SD=10.0) of age-calculated maximum HR. Peak RPE during exercise was 3.6 (SD=0.7) which corresponds to the word-anchors moderate-somewhat hard. Conversely, during the control condition mean HR was 73.2 bpm (SD=13.5) compared to 66.5 bpm (SD=12.5) at rest which represented 45.3% (SD=8.4) of age-calculated maximum HR. RPE
was 1.9 (SD=1.5) (word anchors of very light-light) during the control condition. See table 5-1 for group characteristics and 5-2 for exercise data.

Table 5-1 – Participant Characteristics. Group mean data and standard deviation (SD) or frequency counts are displayed. (CMSA, Chedoke-McMaster Stroke Assessment; m, meters; kg, kilograms)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD) or Count</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66.3 (8.8)</td>
<td>52 – 79</td>
</tr>
<tr>
<td>Sex</td>
<td>7-Male</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 Female</td>
<td></td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>26.1 (4.0)</td>
<td>20.4 – 32.3</td>
</tr>
<tr>
<td>Type of Stroke</td>
<td>9-Ischemic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1-Hemhoragic</td>
<td></td>
</tr>
<tr>
<td>Stroke Affected Hemisphere</td>
<td>9-Right</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1-Left</td>
<td></td>
</tr>
<tr>
<td>Time Post-Stroke (days)</td>
<td>505.3 (236.8)</td>
<td>242 – 1072</td>
</tr>
<tr>
<td>CMSA Arm</td>
<td>5.0 (1.5)</td>
<td>3 – 7</td>
</tr>
<tr>
<td>CMSA Hand</td>
<td>5.3 (1.4)</td>
<td>3 – 7</td>
</tr>
</tbody>
</table>
Table 5-2 – Group mean (standard deviation) heart rate (HR), rating of perceived exertion (RPE), and steps per minute (SPM) during the movement in the exercise and control conditions. Movement HR refers to the individual’s HR while on the recumbent stepper. During the control condition HR remained within 10 beats per minute (bpm) of resting HR. During the exercise condition, the HR target intensity was 50-70% of age-calculated maximum HR. (HR, Heart Rate; bpm, Beats per Minute)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting HR</td>
<td>66.5</td>
<td>12.5</td>
</tr>
<tr>
<td>Movement HR</td>
<td>73.2</td>
<td>13.5</td>
</tr>
<tr>
<td>Movement HR (%) max</td>
<td>45.3</td>
<td>8.4</td>
</tr>
<tr>
<td>Steps per Minute</td>
<td>63</td>
<td>16.4</td>
</tr>
<tr>
<td>Rating of Perceived Exertion</td>
<td>1.7</td>
<td>1.1</td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting HR</td>
<td>67.4</td>
<td>14.1</td>
</tr>
<tr>
<td>Movement HR</td>
<td>83.6</td>
<td>16.3</td>
</tr>
<tr>
<td>Movement HR (%) max</td>
<td>51.7</td>
<td>10.0</td>
</tr>
<tr>
<td>Steps per Minute</td>
<td>84.8</td>
<td>16.3</td>
</tr>
<tr>
<td>Rating of Perceived Exertion</td>
<td>3.6</td>
<td>0.7</td>
</tr>
</tbody>
</table>

5.4.2 Hypothesis 1: Pre vs Post Testing

One individual’s post-exercise testing data was lost due to technical difficulties and they were excluded from the pre vs post-testing statistical analysis. See table 5-3a and 5-3b for group results from pre vs post testing.

Segment 1 (n=9):

Movement time was shorter (F(1,8)=20.78, p=.002) and mean velocity was faster (F(1,8)=24.55, p=.001) at post-test than pre-test. However, neither MT nor mean velocity had a significant interaction with condition (exercise or control) (MT: F(1,8)=.01, p=.91, mean velocity: F(1,8)=.31, p=.59). Path length revealed a trend to be longer in the exercise condition than the control condition (F(1,8)=5.33, p=.05). Additionally, path length trended towards being shorter at post-test than pre-test (F(1,8)= 4.73, p=.06). Path trajectory revealed that there were fewer peaks in the velocity trace during post-testing relative to pre-testing (F(1,8)=16.23, p=.004); however, velocity peaks were not different between the exercise and control conditions. Conversely, movement error remained unchanged (p>.12 for all effects). Figure 5-3 displays the
individual change from pre-to post-test for each condition arranged by functional ability (not statistically analyzed).

Figure 5-3 – Average percent improvement from pre to post-test for the movement time of the first segment of the rectangle for each of the 10 participants. Columns are organized by condition order with the left bar representing the first condition and the right bar the second. The black column represents the exercise condition and the white column represents control condition. Participants are organized along the x-axis by upper-limb functional ability measured with the Chedoke-McMaster Stroke Assessment (CMSA). CMSA score is the mean of the arm and hand score for each individual. *Note, participant with CMSA=5 does not have a change score for the exercise condition and was not included in any pre vs post-test statistical analyses.

(CMSA, Chedoke-McMaster Stroke Assessment)

Full Rectangle (n=8):

Data for the full rectangle was unusable for one additional individual for the post-exercise testing due to loss of stylus position (n=8). Consistent with the segment 1 analysis, post-testing had shorter movement time (F(1,7)=13.28, p=.008) and faster velocity (F(1,7)=17.76, p=.004) than pre-testing which was not different between the exercise and control conditions. Path length of the rectangle was unchanged at all testing points. Path trajectory indicated that there were fewer velocity peaks at post-test than pre-test (F(1,7)=6.31, p=.04); however, movement error was
significantly larger at post-test than pre-test (F(1,7)=11.17, p=.01). Neither the number of velocity peaks nor movement error was different between the control and exercise conditions.

5.4.3 Hypothesis 2: Transfer Task

See table 5-3c for group results from the transfer test.

Segment 1 (n=10):

Movement time (t(9)=2.56, p=.03), was significantly longer while velocity (t(9)=2.12, p=.06) trended towards being slower after the exercise condition compared to the control condition. Conversely, path length was not different between the exercise and control conditions (t(9)=0.66, p=.52). Path trajectory analysis revealed a trend for more velocity peaks after the exercise condition than the control condition (t(9)=1.98, p=.079), while movement error was not different between the two conditions (t(9)=0.5, p=.623). Figure 5-4 displays the individual change for MT from the first segment of the rectangle for each condition arranged by functional ability and order of conditions (not statistically analyzed).

![Figure 5-4](image_url)

**Figure 5-4** – Average movement time (MT) and standard deviation during the transfer test from the first segment of the rectangle for each of the 10 participants. Columns are organized by condition order with the left bar representing the first condition and the right bar the second. The black column indicates the exercise condition and the white column indicates the control condition. Participants are organized along the x-axis by upper-limb functional ability measured with the Chedoke-McMaster Stroke Assessment (CMSA). CMSA score is the mean of the arm and hand score for each individual. (CMSA, Chedoke-McMaster Stroke Assessment; ms, millisecond)
**Full Rectangle (n=8):**

Two individuals were removed from this analysis due to significant data loss (n=8). Similar to the segment 1 analysis, movement time trended towards being slower after the exercise condition than the control condition (t(7)=2.08, p=.076). Conversely, mean velocity (t(7)=1.57, p=.16) and path length (t(7)=0.62, p=.55) were not different between the two conditions. There was a trend for more velocity peaks in the exercise condition than the control condition (t(7)=2.12, p=.07) while movement error was not different between the conditions (t(7)=0.36, p=.73).
Table 5.3 – Group mean (standard deviation) movement time (MT), velocity, path length and path trajectory (velocity peaks and movement error) for hypothesis 1 and 2. (a) Pre and post-testing for the first segment of the rectangle. (b) Pre and post-testing for the entire rectangle. (c) Transfer test for both the first segment of the rectangle and the entire rectangle. (cm, centimetre; ms, milliseconds; s, second)

A) Hypothesis 1: Pre vs post-testing for the first segment of the rectangle.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Movement Time (ms)</th>
<th>Mean Velocity (cm/s)</th>
<th>Path Length (cm)</th>
<th>Velocity Peaks (count)</th>
<th>Movement Error (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Pre-test</td>
<td>9</td>
<td>818 (400)</td>
<td>26.0 (12.9)</td>
<td>20.9 (4.3)</td>
<td>2.2 (1.4)</td>
<td>0.8 (0.25)</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>600 (200)</td>
<td>32.6 (11.9)</td>
<td>20.2 (4.1)</td>
<td>1.3 (0.5)</td>
<td>1.1 (0.5)</td>
</tr>
<tr>
<td>Exercise Pre-test</td>
<td>9</td>
<td>959 (393)</td>
<td>22.2 (9.0)</td>
<td>22.3 (1.9)</td>
<td>2.3 (1.6)</td>
<td>0.9 (0.3)</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>752 (289)</td>
<td>27.5 (10.3)</td>
<td>21.2 (4.0)</td>
<td>1.7 (1.1)</td>
<td>0.9 (0.3)</td>
</tr>
</tbody>
</table>

B) Hypothesis 1: Pre vs post-testing for the full rectangle.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Movement Time (ms)</th>
<th>Mean Velocity (cm/s)</th>
<th>Path Length (cm)</th>
<th>Velocity Peaks (count)</th>
<th>Movement Error (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Pre-test</td>
<td>8</td>
<td>3123 (1230)</td>
<td>44.6 (15.8)</td>
<td>122.5 (13.3)</td>
<td>8.6 (3.7)</td>
<td>5.6 (1.2)</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>2380 (613)</td>
<td>55.7 (15.4)</td>
<td>123.5 (8.8)</td>
<td>5.9 (1.7)</td>
<td>5.4 (0.8)</td>
</tr>
<tr>
<td>Exercise Pre-test</td>
<td>8</td>
<td>3836 (1113)</td>
<td>35.9 (9.1)</td>
<td>127.6 (10.6)</td>
<td>9.6 (4.4)</td>
<td>7.5 (2.5)</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>2687 (562)</td>
<td>49.1 (10.4)</td>
<td>126.0 (8.2)</td>
<td>6.6 (2.1)</td>
<td>6.7 (1.5)</td>
</tr>
</tbody>
</table>

C) Hypothesis 2: Transfer test for the first segment of the rectangle and the full rectangle.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Movement Time (ms)</th>
<th>Mean Velocity (cm/s)</th>
<th>Path Length (cm)</th>
<th>Velocity Peaks (count)</th>
<th>Movement Error (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Segment Control</td>
<td>10</td>
<td>787 (222)</td>
<td>33.8 (11.9)</td>
<td>39.1 (5.9)</td>
<td>1.6 (0.6)</td>
<td>1.9 (0.7)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>945 (280)</td>
<td>29.2 (8.6)</td>
<td>39.7 (4.2)</td>
<td>2.2 (1.3)</td>
<td>1.8 (0.2)</td>
</tr>
<tr>
<td>Full Rectangle Control</td>
<td>8</td>
<td>2975 (927)</td>
<td>47.8 (16.7)</td>
<td>127.9 (7.0)</td>
<td>7.4 (2.2)</td>
<td>7.4 (2.8)</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>3429 (1064)</td>
<td>41.4 (13.3)</td>
<td>128.6 (7.3)</td>
<td>9.1 (3.9)</td>
<td>7.2 (1.2)</td>
</tr>
</tbody>
</table>
5.4.4 Hypothesis 3: Rate of Change in Performance during Arm Training

Two participants were not included in the statistical analysis of improvement during training as one did not display an initial period of rapid improvement and one was missing trials 1 and 5 for the control condition making it impossible to identify the initial period of improvement. There was evidence of task improvement as movement time was shortened over successive trials before stabilizing. Thus, two periods were evident, an initial period of improvements and a period of relatively stable performance; see Figure 5-5 for individual training data. During the control condition (mean=4.6m SD=1.8), it took significantly fewer trials for the initial improvement period to end than the exercise condition (mean=8.9, SD=3.6) (t(7)=3.99, p=.005). Conversely, the slope of the initial improvement period was not significantly different (t(7)=1.32, p=.23) between the control condition (-75ms/trial) and the exercise condition (-50 ms/trial).
Figure 5-5: Movement time from the upper-limb training (first segment of rectangle) for each participant. Graphs are organized by functional ability measured as the average of the Chedoke-McMaster Stroke Assessment (CMSA) arm and hand inventories. Note that the y-axis is movement time in milliseconds and is scaled relative to each participant. The title of each graph is the mean CMSA score for that individual. The control condition is shown with the solid black line and the exercise condition is the dashed line. The vertical lines display the end of the initial period of improvement (solid=control condition, dashed=exercise condition). Note that the two participants represented by the top graphs without vertical lines displaying the end of the initial period of improvement (CMSA = 3 and 3.5) were not included in statistical analysis. The first (CMSA=3, top left graph) had high trial to trial variability and did not display a period of improvement for either condition. The second (CMSA = 3.5) was missing important trials (#1 and 5) for the control condition making it impossible to accurately identify an initial period of improvement for the control condition.
5.5 Discussion

The primary objective was to investigate upper-limb movement adaptation induced by arm training following either an exercise bout or control condition. The upper-limb training effectively demonstrated change in performance measures as improvements in MT at post-test compared to pre-test. However, we did not observe any differences in changes in movement performance between the exercise and control conditions as measured by movement time or peak velocity. Additionally, path trajectory outcomes (number of velocity peaks and movement error) were not different between the two conditions as hypothesized. Conversely, during the transfer test, the control condition displayed shorter MT and faster mean velocity compared to the exercise condition. Finally, our third hypothesis was also not supported as participants reached stable performance in fewer trials during training following the control activity compared to the exercise activity; however, the slope of the initial period of improvement was not different between the conditions.

Following arm training, movements were faster and path trajectory was smoother as shown through shorter movement times, faster velocity and fewer peaks in the velocity trace. However, these effects were not further enhanced by the exercise bout as hypothesized. One potential explanation is that the aerobic challenge from the movements during the exercise and control conditions were too similar to invoke different neurophysiological effects (i.e. CNS arousal). Heart rate was 51.7% of age-predicted maximum during the exercise condition compared to only 45.3% in the control condition. Thus, while the lower-limb stepping was designed to be a moderate and very light intensity during the exercise and control conditions respectively, cardiovascular response appears to have been modest and close in intensity between conditions. However, ratings of perceived exertion provided a sense of a large average difference between the two tasks as the exercise condition (mean RPE=3.6, ‘moderate to somewhat hard’) was perceived as more difficult than the control condition (mean RPE=1.9, ‘very light to light’). The perception of increased exertion in the exercise condition may have increased emotional stress. High stress is associated with poor cognitive performance (Vedhara et al., 2000) and increased competition for resources between the prefrontal cortex and the limbic system (Miller & Cohen, 2001). However, a moderate level of anxiety and stress would be expected to produce similar results to the moderate level of CNS arousal from the physical stress of the exercise bout which
form the basis of our hypotheses and these two influences are difficult to distinguish from each other. However, the risk to performance may come from passing a certain stress threshold to activate a biological response. For example, while catecholamine concentration increases linearly with increasing exercise intensity, stress related hormones including adrenocorticotropin and cortisol display increased concentrations at high intensity but not moderate intensity exercise (McMorris et al., 2009a). Thus, it appears that a high stress response may only be activated once a threshold is passed. If this threshold is passed, any increased physiological outcomes such as augmented CNS arousal in the exercise condition compared to the control condition may have been mitigated by an increased stress response in the exercise condition. Thus, the lack of a behavioural difference at pre- vs post-test between the two conditions may be attributable to comparable exercise intensities (i.e. physiological response) or different emotional responses (i.e. high stress response) to the two conditions. Future work may benefit from investigating the effects of varying exercise intensity on the emotional stress response using biological markers such as cortisol in conjunction with the neurophysiological response in stroke.

Conversely, the transfer test revealed differences between the exercise and control conditions as movement time was slower after the exercise condition for the first segment of the rectangle and was a trend for the whole rectangle. However, all other outcome measures were non-significant or trended towards better performance in the control condition (faster mean velocity, fewer velocity peaks). These findings may also be the result of similar neurophysiological responses to the lower intensity stepping activity as aerobic workloads were comparable in the two conditions. Alternatively, this may be related to participant fatigue following the exercise condition as the transfer test was conducted last. Thus, the combination of an exercise bout and 50 trials of upper-limb training as well as 20 trials of testing (pre and post-testing) may have induced fatigue that was observed as differences between the conditions during the final transfer test.

The second objective was to characterize the rate of adaptation during upper-limb training following the lower-limb stepping activity in the control or exercise conditions. Results suggest that adaptation was faster following the control condition than the exercise condition. However, it is worth noting that only the number of trials needed to reach a plateau in performance was different between the conditions and not the slope of the initial improvement curve. Further,
group mean peak performance was achieved within the first block (10 trials) of training in both conditions. Further, pre vs post-test effects were not observed between the two conditions indicating that the behavioural change from upper-limb training was comparable following both conditions. Thus, the differences during upper-limb training between conditions may not be meaningful and a more difficult task that required more trials to achieve peak performance may have amplified any potential difference between the conditions.

Conversely, it could be interpreted that the control condition may have been better suited for subsequent adaptation to task training than the exercise condition. This is disconcerting as one of the main reasons for pairing aerobic exercise with task training is for individuals recovering from a stroke to receive both the cardiovascular benefits of moderate exercise and the neurophysiological benefits to subsequent task training. If low intensity exercise is superior for immediate adaptation than the additional benefits of aerobic exercise including cardiovascular health (Tang et al., 2009a) and cognition (Quaney et al., 2009) may be muted or lost as moderate intensity exercise is optimal for these effects. One potential option is to explore alternative timing of the aerobic activity and task training as different mechanisms may have very different time courses. For example, in healthy individuals information processing is augmented for approximately 15-20 minutes following exercise (Chang et al., 2012) while augmented attention has been shown for up to 40 minutes post-exercise (Hillman et al., 2003). Conversely, BDNF levels are increased for 10 to 60 minutes post-exercise (Knaepen et al., 2010). Cerebrovascular response is also altered for up to 40 minutes post-exercise (MacIntosh et al., 2014). Together these suggest that subsequent performance may benefit from a close pairing of exercise and training as information processing and cognitive function (particularly attention) appear to have a shorter time course post-exercise of 15-20 minutes. Conversely, long-term adaptation may not be influenced by a delay between exercise and task training as BDNF and cerebrovascular effects may last for up to 40-60 minutes. Thus, a moderate exercise bout followed by a short rest period may be optimal to reduce fatigue from the exercise bout but still receive benefit from increased neurotrophic factor availability. Future work should explore the timing of aerobic exercise paired with task training.

Of further interest, is whether single-session behavioural adaptation is an indicator of long-term outcomes. The combination of aerobic exercise and task training in rats that had a stroke induced
was not better than training alone until 5 weeks of training had been completed suggesting that it may require multiple sessions to reveal a benefit of exercise to task training (Ploughman et al., 2007). Further, evidence of augmented neurophysiology (Hillman et al., 2003; Kamijo et al., 2004b) and cerebrovascular function (MacIntosh et al., 2014) have been shown without behavioural differences following aerobic exercise. Thus, if we reframe our interpretation of the behavioural data it may be a positive that the exercise condition did not negatively impact (i.e. longer MT, slower velocity) the upper-limb training. The benefit of the exercise condition may be linked to neurophysiological influence of the exercise bout rather than observable behavioural change. If true, multiple sessions pairing exercise and task training may be required before overt behavioural change is observed compared to task training alone. Thus, future work should investigate the model of pairing of aerobic exercise and task training over multiple sessions compared to task training alone to further elucidate the influence of aerobic exercise. 

The main limitation to the current study was the relatively small sample size, which was further impacted due to the removal of participants for portions of the statistical analysis from loss of stylus position for the entire rectangle. However, it is important to note that participants successfully completed all study procedures and the stylus position was primarily lost during arm training as opposed to testing for the full rectangle. Thus, the first segment of the rectangle was used as the primary outcome while the full rectangle was a secondary outcome. The small sample size did represent a range of upper-limb motor function which afforded an opportunity to observe the interaction of exercise and arm training across the spectrum of upper-limb function. Unfortunately, response to task training evaluated with pre- vs post-testing and the transfer test was variable between participants. For example, all participants improved at post-test compared to pre-test; however, the range of improvements ranged from less than 5% to over 50%. Further, it did not appear from the current data that any effect of exercise was related to upper-limb functional ability or the order of evaluation. Future work should strive to identify individual characteristics that are linked with large responses to training following an exercise bout (i.e. responders).
5.5.1 Conclusions

This study sought to investigate the impact of a single session of aerobic exercise on subsequent upper-limb task training. While performance improved following training there were no differences between the exercise and control conditions. However, during training, task proficiency was reached in fewer trials following the control condition than the exercise condition. Future work should investigate the influence varying aerobic workload on subsequent performance and the accumulated effects of multiple sessions of pairing exercise with task training.
6 Discussion
6.1 Summary of Findings

This dissertation explored the use of aerobic exercise to influence CNS state in healthy individuals and stroke patients with a focus on using it to prime the CNS to improve task performance after exercise. Given the robust effect of exercise on CNS arousal, information processing, and attention in healthy individuals that has been documented in the literature the first two studies focused on understanding if these potential effects translated to the stroke population. The final two studies were focused on the influence of a single bout of aerobic exercise on rate of short-term skill adaptation in both healthy and stroke samples. Overall, there was evidence for a single bout of aerobic exercise to augment CNS arousal, particularly evident as increased motor activity (i.e. movement time) during stimulus-response tasks. However, exercise did not appear to influence attention as reflected by: 1) no change in trial-to-trial variability after exercise in study 1; and, 2) a lack of difference between tasks with varying attentional demands in study 2. With respect to exercise effects on short term adaptation there was some evidence of an improvement following an exercise bout as evidenced by fewer errors in study 3. However, among individuals recovering from a stroke, movement adaptation during upper-limb training was not enhanced by a bout of aerobic exercise compared to a control condition.

6.2 Variability of Performance & Response among Stroke Patients

Consistent with many studies was the high between subject variability among the individuals recovering from a stroke. The current studies adopted a within subject design in order to reduce the potential challenges with high between subject variability. However, the current results also revealed high within subject differences associated with the influence of a single bout of exercise. The cumulative impact of high between and within subject variability likely impacted the ability to detect statistical significance at the group level despite mean differences that were comparable or larger than statistically significant findings in healthy individuals. For example, in study 1 individuals with a stroke improved their simple RT by approximately 7% from pre to post-exercise which was not statistically significant. By comparison, statistical significance has been shown with approximately 3.5% improvement in healthy individuals (Davranche et al., 2006). The real difference between these two studies was between-subject standard deviation
which was approximately 4 times larger in the stroke individuals compared to healthy individuals despite similar mean RT. It was believed that one significant contributor to this variability was attention (i.e. participants not focusing on the task) which in the case of visual reaction time studies could be influenced by where individuals were directing their gaze at the time the stimulus was presented. Thus, study 2 attempted to address this variability by utilizing an eye tracker to ensure participants were visually attending to the fixation point prior to stimulus presentation (approximately 5% of trials were excluded from analysis based on this criteria). However, this did not appear to meaningfully reduce either between or within subject variability compared to study 1. For example, comparing simple RT (collapsed for pre and post-exercise evaluations), mean within-subject standard deviation was 64 ms (mean=279) for study 1, and 81 ms (mean=418 ms) for study 2. In relative terms, mean coefficient of variation (calculated for each participant and then averaged) was 0.23 for study 1 and 0.19 for study 2. Thus, while ensuring visual attention was focused on the fixation point in study 2 may have modestly reduced within-subject variability, significant sources of variability remain and should be taken into consideration for future work.

Increased variability poses a challenge to group analysis but may also afford some opportunity to address the potential sources of within and between subject variability. Typical analysis strategies of stimulus-response tasks compare measures of central tendency, however, reaction time distributions are not normally distributed and are characterized by a positive skew (Ratcliff, 1979). While the mean can indicate differences attributable to the intervention (i.e. exercise), the distribution can assist in dissociating the difference between alterations to CNS arousal or attention related factors. If the reaction time distribution within an individual shifts to the left (i.e. gets faster) then it is more likely that augmented CNS arousal was the mediator as all trials were influenced. However, if the characteristics of the distribution are changed, namely the long slow trials are reduced while the fast trials remain unchanged this may indicate augmented attention. Within subject variability has been used as an indication of consistency of performance which has been argued to be a function of neurological integrity, lapses of attention and deterioration within neurotransmitter systems (Anstey et al., 2005; Zahn & Mirsky, 1999). Additionally, in older adults, reaction time variability coincides with lapses in attention (Bunce et al., 1993; Hultsch et al., 2002), thus, a more normalized distribution of RT suggests improved attention. Future work would benefit from a focus on within subject variability, including
utilizing a greater number of trials to adequately compare central tendency with individual distributions to further dissociate the specific effects of aerobic exercise.

A potentially important aspect of between subject variability in responses to aerobic exercise may be the differentiation of individuals who respond versus those who do not respond to the benefits of exercise. Classifying individuals on the basis of their responses to exercise, rather than as a homogeneous group expected to have a typical response to exercise, may well be a more appropriate approach to explore exercise related effects. Importantly, a better understanding of individual determinants of response to exercise may be a more appropriate focus among heterogeneous groups such as stroke (Tang et al., 2013). In the current dissertation variability on response to exercise could lead one to the view that there were individuals who may be classified as responders or non-responders. For example, in study 4, all participants improved movement time from pre to post intervention; however, the range of improvements varied from less than 5% to almost 50% between individuals. Thus, while all improved, there appear to be responders that have a large positive benefit and non-responders that have a smaller benefit. The challenge would be the determination of the threshold of responders and to ensure other, non-exercise effects, were not accounting for the between subject differences. Additionally, this further highlights the benefits of presenting individual responses to exercise within the stroke population. Unfortunately, the current dissertation was unable to identify any characteristics related to an individual’s response to exercise; however, this was beyond the scope of this dissertation. Future work, to focus on characteristics of responders or non-responders should first establish the stability of any exercise induced effects within individuals possibly through repeated testing, in part to exclude the possibility that between subject variability might be associated with state or task-specific factors.

Possible sources of between-subject variability after stroke may include stroke specific characteristics (i.e. infarct size, location) and physical fitness. Small differences in the size and location of a stroke can lead to very different functional disabilities. Unfortunately, this thesis relied on clinical notes for stroke location and there was no clear link between stroke location and the influence of exercise. Future work may benefit from better infarct localization to determine if the effects of exercise are specific to stroke location. For example, following a stroke individuals require a higher energy expenditure to complete activities of daily living (Ivey et al., 2005). Thus, individuals with greater deficits in movement control may find the exercise
bout overly taxing and subsequent performance may deteriorate due to fatigue. Conversely, individuals with primarily cognitive deficits may have a greater effect of exercise for certain tasks as exercise has been shown to improve executive function in healthy & older adults (Colcombe et al., 2006; Cotman & Berchtold, 2002). Further, the state of cerebrovascular health may be a determinant of the influence of exercise. It appears that post-exercise perfusion of cortical tissue is not universal and was larger in white matter opposed to grey matter in healthy individuals (MacIntosh et al., 2014). However, in stroke, it is possible that a bout of aerobic exercise may increase cerebral perfusion in hypoperfused areas and the potential vascular effects may be of greater importance and underpin the influence of aerobic exercise in this population.

An additional source of between-subject variability is the use of medication, particularly beta blockers among the stroke participants. Beta blockers interfere with the binding of epinephrine (Segal et al., 2012) and likely reduce the exercise induced increases in CNS arousal. We chose not to exclude individuals based on medication use as there are multiple mechanisms whereby aerobic exercise influences CNS function. However, it is possible that medication use muted the arousal related effects of exercise in some individuals in this dissertation, increasing the between-subject variability observed. While identifying specific stroke related characteristics that are related to the effects of exercise was beyond the scope of the current dissertation this is a worthwhile avenue for future research as this is likely a significant source of the variable responses to exercise observed in this dissertation.

A variable response to exercise could also arise from differences in participant’s cardiovascular fitness. Relatively large differences between individuals with high and low physical fitness have been observed without an exercise bout (Hillman et al., 2002; Kamijo et al., 2010; Pontifex et al., 2009b). Unfortunately, we did not evaluate physical fitness and cannot comment on the effects of physical fitness on the studies in this dissertation; however, it is plausible that some of the variability may be attributed to individual fitness levels. Future work should investigate the effects of physical fitness on the individual response to an exercise bout. Ideally, with the use of graded exercise testing to evaluate peak VO$_2$ which is the gold standard for evaluating aerobic capacity and is safe and feasible in this population (Tang et al., 2006). Graded exercise testing may also aid in appropriate exercise intensity prescription rather than relying on age predicted maximal HR.
A theme throughout the research studies was that exercise intensities may not have been optimal to maximize the benefits of exercise. Challenges to prescribing and monitoring exercise intensity are discussed in more detail in future sections, however, they are worth briefly discussing here as they may influence variability. An inverted U model has been proposed to explain the observed influence of exercise on CNS arousal and cognition (Kamijo et al., 2004b). Under this model, moderate aerobic exercise at 70% of maximal intensity is optimal while light and intense exercise are suboptimal. In stroke, moderate intensity exercise targets have typically been 60-70% of maximum capacity for long-term exercise programs (Macko et al., 2005; Tang et al., 2009a); however, initial training was at lower intensities of 57% (Tang et al., 2009a) or 40-55% (Macko et al., 2005) of maximum capacity. In the current work, exercise intensity evaluated using HR from age-predicted maximums, was approximately 50-55% of age-predicted maximum for the stroke participants which would be considered light for the inverted U hypothesis (Kamijo et al., 2004b). Similarly, Ploughman et al. (2008) aimed for a moderate intensity of 70% of age predicted maximum HR to examining the single-session effects of exercise (Ploughman et al., 2008). However, HR achieved during exercise was not reported but RPE (on a different scale from this dissertation) was comparable to the RPE in this thesis as mean ratings were associated with word anchors “somewhat hard” (Borg, 1982). Thus, while HR response to exercise is variable in this population, secondary measures of intensity from individual ratings of perceived exertion (RPE) suggest that participants were exercising at a moderate intensity comparable to previous work in stroke.

While some variability may be attributed to different exercise intensities between participants, the emotional response of exercise also influences individual response. High stress is associated with poor cognitive performance which may be in part to competition for cortical resources between the limbic system and prefrontal cortex (Miller & Cohen, 2001). The emotional stress response to the exercise bout may be exacerbated among individuals recovering from stroke as they are in a deconditioned state (Tang et al., 2006). Thus, behavioural performance post-exercise on the tasks in the current dissertation may have been variable between participants due to individual emotional responses. Following this reasoning, it is possible that as an individual improves their cardiovascular fitness over multiple exercise bouts their emotional response to a single bout of aerobic exercise may be reduced and cognitive benefits may improve. Changes in perceived exertion may be linked to improved tolerance to exercise after stroke in the same
manner as cardiovascular fitness evaluated with VO$_2$ improves over repeated testing (Tang et al., 2006). If true, this would suggest that repeated exposure to exercise may improve the overall response to the same workload largely due to the individual’s familiarity with the task challenge.

Variable responses to the aerobic exercise bout may have been limiting the ability to detect statistical significance at the group level in the studies in this dissertation. Future work should explore the potential sources of this variability including stroke specific characteristics (i.e. location, functional ability) and exercise intensity (including emotional response to an exercise bout). If specific factors can be identified that are linked with a positive benefit of aerobic exercise (i.e. responders) it will aid in understanding the potential utility of pairing aerobic exercise with neurorehabilitation for individuals recovering from a stroke.

6.3 Arousal vs Attention

This dissertation attempted to understand the influence of exercise on arousal and attention. Study 1 results suggested that the exercise bout augmented CNS arousal in some individuals but did not influence attention as mean RT was faster in some participants (not statistically significant at the group level) but RT variability measures were unchanged post-exercise. However, study 1 likely lacked power to dissociate these effects and study 2 strove to isolate the effects of exercise on attention, specifically focused attention and distractibility. Again, results suggested that CNS arousal was augmented as RT (only statistically significant in choice condition and a non-significant trend in modified Flanker condition) and MT were faster after exercise. However, focused attention did not appear to be influenced as the absolute change was comparable across task conditions despite increasing visual interference. Together, this dissertation provides evidence for an exercise induced augmentation to CNS arousal rather than attention among individuals recovering from a stroke. These findings both confirm and contradict results from healthy individuals. Augmented arousal reflected in faster information processing and amplified cortical excitability are robust effects of exercise displayed in behavioural data from stimulus-response tasks (Chang et al., 2012; McMorris et al., 2009b) and in neuroelectric markers (Crabbe & Dishman, 2004; Kamijo et al., 2004b; Kamijo et al., 2007). Contradictory to this dissertation, enhanced attention post-exercise has been revealed in healthy individuals through faster responses on stimulus-response tasks that vary attention demands (Hillman et al., 2003; Pontifex & Hillman, 2008). While a portion of these faster responses can
be attributed to augmented CNS arousal it is important to note that neuroelectric measures have consistently shown augmented markers of the allocation of attentional resources (Hillman et al., 2003; Kamijo et al., 2004b; Kamijo et al., 2007; Pontifex & Hillman, 2008). While the current dissertation suggests CNS arousal but not attention benefits of aerobic exercise in a stroke population, neuroelectric markers may be more sensitive to the effects of exercise rather than overt behaviour (Kamijo et al., 2007). Thus, neuroelectric evaluation of task-specific cortical activity may aid in dissociating the effects of exercise on arousal and attention in this population.

However, it is equally important to address the potential interaction between the constructs of arousal and attention with the idea that these may not be independent. While physiologic definition of these contrasts can be dissociated (Fan et al., 2005; Pfaff & Banavar, 2007) the behavioral expression of differences in arousal and attention is more complex. Since reaction time is a commonly used metric of the response of the nervous system, essentially a final common path, it would be true that similar changes in reaction time (faster or slower) may single differences in arousal or attention. The speculation in the current study to distinguish average timing and variability of reaction time as indirect measures of arousal and attention respectively is not with its limitations. Certainly, augmenting measures of reaction time with complementary behavior, physiologic, and neuroelectric measures to dissociate the influence of exercise may be helpful. It is also true that changes in arousal are also likely to directly influence attention further confounding the interpretations. Thus, to address these challenges future work should continue to design tasks with the aim of isolating specific components of attention (i.e. focused attention, sustained attention) in concert with physiologic evaluation of arousal and neuroelectric evaluation of cortical activity underlying behaviour.

6.4 Prescribing and Monitoring Exercise Intensity

An inverted U function has long been used to describe the relationship between task performance and arousal level (Yerkes & Dodson, 1908). As arousal increases, task performance improves up to a peak. Performance begins to deteriorate as arousal levels rise above this peak. This relationship is mirrored in aerobic exercise as an inverted U relationship between exercise intensity and information processing has been displayed (Kamijo et al., 2004a; Kamijo et al., 2004b). With this in mind, the hypotheses in the current dissertation are based on the assumption that the exercise bout would be sufficiently challenging to activate the ANS and SAS but not too
challenging to induce fatigue. It has been proposed that the facilitative effects of exercise may be negated following intense exercise due to peripheral and central fatigue (Kamijo et al., 2007). In the stroke population, fatigue from exercise is likely as individuals are generally in a deconditioned state (Tang et al., 2006). Further, it is likely that peripheral fatigue in the affected limbs may occur even at low workload demands (i.e. low HR). This is one of the main reasons we utilized the lower-limbs to control the exercise bout while evaluating the unused upper-limbs. However, future work may benefit from limb-specific ratings of perceived exertion to determine if peripheral and/or central fatigue is an issue for some individuals and if it is related to the response to the exercise bout.

While moderate intensity aerobic exercise was the target, determining this intensity is challenging for individuals recovering from a stroke. Moderate intensity exercise paradigms in healthy and stroke populations commonly prescribe intensity from 50-70% of maximal capacity based on a graded exercise test. Oxygen consumption during a graded maximal exercise test is the gold standard for evaluating peak aerobic capacity (American College of Sports Medicine, 2013) and is safe and feasible in stroke patients (Ivey et al., 2005; Tang et al., 2006). However, during these graded tests, the majority of individuals do not achieve the criteria for maximal VO₂ and peak VO₂ becomes the surrogate for aerobic capacity (Tang et al., 2006). Additionally, sub-maximal exercise testing in replace of maximal testing may not be suitable as it overestimates maximal capacity (Kelly et al., 2003). While there are challenges to determining maximal capacity in this population, future work would benefit from graded exercise testing to better control exercise intensity prescription across participants. In this dissertation, age predicted maximal HR was used to prescribe exercise intensity in concert with ratings of perceived exertion. This method was applied because graded exercise testing is not feasible in all clinical settings and, based on previous results, it was anticipated that the effect size would have been large enough to overcome variability in exercise prescription between individuals. In the current study the effect sizes were much smaller than expected raising the important concern for better controlling sources of within and between subject variability including standardization of workload across subjects.

Similarly, measuring exercise intensity is challenging among individuals recovering from a stroke as relying on heart rate alone is inappropriate given the variable cardiovascular response to exercise from medication use, autonomic dysfunction, etc. in this population. When heart rate
is unreliable an individual’s rating of perceived exertion, is recommended as it has a strong relationship with physiological response to exercise (American College of Sports Medicine, 2013). However, this relationship is complicated in a stroke population and relying on perceived exertion may not be ideal as intensity increases (Sage et al., 2013). Thus, monitoring exercise intensity is challenging for this population which may lead to individuals exercising outside their target intensity. Further, moderate intensity assumes a moderate cardiovascular response to exercise and moderate emotional response to exercise. However, individuals that have suffered a stroke are often deconditioned (Tang et al., 2006) and may be inexperienced with exercise which may contribute to a larger emotional response to the exercise bout than healthy individuals. Additionally, following a vascular event, individuals may be reserved about their ability to safely exercise without causing another stroke. Together, inexperience and reservations about exercise may increase the emotional response to exercise which may increase HR and RPE leading to an inaccurate reflection of exercise intensity in some individuals. This may be overcome with multiple exercise sessions in a similar manner to VO2 increases with repeated testing within individuals (Tang et al., 2006). Thus, ensuring individuals are exercising within the optimal physiological intensity range is a challenge in this population and likely contributed to the variable response to exercise observed in this dissertation. Future work would benefit from graded exercise testing to prescribe exercise intensity and standardize workloads across participants and reduce variability from differing exercise intensities. Additionally, multiple exercise sessions, or practice exercise sessions may alleviate some concerns with prescribing and monitoring exercise intensities for those unfamiliar with aerobic exercise. Finally, multiple measures of exercise intensity beyond HR such as RPE are encouraged but should be individualized based on graded exercise testing (i.e. individual perceived exertion level at 70% of maximal physiological response).

6.5 Limitations and Future Directions

The findings of the current dissertation provided some support for the idea that aerobic exercise may be a viable prime for influencing movement time and speed but not task training for individuals recovering from a stroke. However, there are limitations to this dissertation which displayed highly variable results between individuals. One main remaining question is the long-term multi-session benefits of pairing exercise and task training remain as it may be that multiple
sessions are needed before the benefits of pairing exercise with task training diverge from training alone.

6.5.1 Outcome Measures

While the tasks in the current dissertation were designed based on established outcome measures they were customized in an attempt to isolate specific functions. Thus, it is possible that these tasks were inadequate to reveal the effects of exercise. This is particularly relevant for study 2 where the traditional Flanker effect of longer responses for incongruent compared to congruent trials was not observed. Typical Flanker administration requires a yes/no or left/right response rather than a 4-choice reaction time response. By forcing participants to find the correct match for the stimulus shape to the four targets, participants are required to extract features from the stimulus shape to aid in finding the matching shape. This may have increased their focus on the relevant stimulus and aided in avoiding the visual interference from the distractors, thereby reducing the usual delay in the incongruent condition. This proposition may be supported by RTs approximately twice as long as those observed in young (Kamijo et al., 2007) and older (Hillman et al., 2002) healthy adults which may suggest more time spent extracting features from the relevant stimulus. Thus, the task conditions in study 2 which were designed to vary demands on focused attention, may not have successfully isolated focused attention. Further, the effects of exercise were uniform across the task conditions in study 2 which was interpreted as exercise induced increases in arousal but not focused attention. However, as discussed above, dissociating arousal and attention constructs is a difficult proposition and future work should attempt to isolate focused attention, perhaps with a more traditional 2-choice Flanker task to confirm the effects of exercise on attention in a stroke population.

Faster responses during and following an aerobic exercise bout is a robust finding in healthy individuals that was hypothesized to translate to a stroke population. However, this was not the case as highly variable behavioural responses to exercise were observed. As discussed above, neuroelectric evaluation may have been a more sensitive measure of the effects of exercise and aided in overcoming variability concerns. For example, in the absence of behavioural improvements after an exercise bout, augmented cortical neurophysiology has been observed (Hillman et al., 2008; Kamijo et al., 2004b; Kamijo et al., 2007). The benefit of pairing aerobic exercise with therapy for stroke recovery may be the influence of exercise on neurophysiology
rather than overt performance. Unfortunately, neuroelectric evaluation was beyond the scope of the current dissertation but should be a target for future work to evaluate alterations to task-specific cortical processing following an exercise bout among individuals recovering from a stroke.

6.5.2 Do Short-term Gains Equal Long-term Change?

The immediate single-session benefits of pairing exercise with task training are likely small when compared to the longitudinal effects of repeated administration. This assumes that the single-session effects will be additive over repeated administration. The current dissertation focused on immediate change following an exercise bout and displayed improvements in arousal and immediate acquisition for some stroke patients. However, it is unclear if single-session effects ultimately lead to cumulative benefits following repeated administration. There is also the possibility that the benefits of pairing exercise with therapy may not be revealed following a single-session but after multiple sessions. For example, pairing exercise and upper-limb therapy in rats did not display a benefit over therapy alone until the fifth week of training (Ploughman et al., 2007). The findings of study 4 certainly raise some question that repeated administration may be required to display a benefit of exercise as following a single session of exercise and arm training, no differences were found between the exercise and control conditions despite the suggestion that training adaptation occurred faster in the control condition. In other words, faster adaptation during arm training did not translate to better post-test performance, but over repeated sessions differences between exercise paired with task training and training alone may be revealed. Therefore, longitudinal evaluation of the pairing of aerobic exercise with targeted training is an important step in understanding the value of using exercise to prime the CNS prior to targeted intervention.

6.5.3 Does Exercise Influence Functional Movements?

A worthwhile area for future consideration is whether aerobic exercise influences functional, ecologically valid movements that are routinely the focus of neurorehabilitation such as reach to grasp, pinch grip, etc. The results from this dissertation would suggest slightly improved motor control based on improved path trajectory outcomes, however, this was not a main focus of the dissertation and drawing a rectangle on the horizontal plane as in study 4 lacks ecological validity. Additionally, the suggestions of improved motor control come from fewer peaks in the
velocity profile and smaller path deviation from a straight line. The velocity profile may have become more normalized due to a larger initial movement burst from increased corticomotor arousal while path deviation was small at pre-test and improvements here do not likely represent meaningful change. Thus, concrete conclusions about motor control cannot be abstracted from this dissertation. However, Ploughman et al. (2008) found upper-limb function evaluated with the action research arm test which assesses the ability to handle objects of varying size, weight and shape, was improved following a single session of body-weight supported treadmill training in a stroke population (Ploughman et al., 2008). Alternatively, exercise may not influence motor function in limbs not directly involved in controlling the exercise bout. In healthy individuals sequence specific motor learning was enhanced by an exercise bout but not motor control (Mang et al., 2014). This may suggest that to influence motor control the limbs may need to be directly involved in controlling the exercise modality. Future work should explore the potential of using exercise modalities that utilize the limb to be trained (i.e. upper-limb ergometry prior to upper-limb task training) to evaluate exercise induced changes to motor control. Additionally, given the focus on using exercise to prime sensorimotor neurorehabilitation and the limited results from the literature and current dissertation, future work should investigate whether aerobic exercise positively influences motor control during ecologically valid movements.

### 6.5.4 What is the Optimal Timing of Exercise and Training?

This dissertation hypothesized that optimizing the state of the CNS prior to therapeutic intervention would have a positive impact on performance during therapy. It follows that aerobic exercise has the potential to be an effective modality to augment CNS state. However, the strategy of exercise immediately prior to therapy may not be the ideal approach. There is some debate about how long the arousal related influence of exercise lasts, but generally accepted that it is approximately 15-20 minutes (Chang et al., 2012; Joyce et al., 2014). However, there is evidence from neuroelectric markers to suggest that cortical excitability and allocation of attentional resources remain augmented after heart rate returns to pre-exercise levels or approximately 45 minutes after the exercise was completed (Hillman et al., 2003). Further, neurotrophic factors including BDNF remain elevated for 10 to 60 minutes post-exercise (Knaepen et al., 2010). Allowing a longer rest period post-exercise may benefit this population if it helps mitigate fatigue from the exercise bout which can negatively impact performance. Thus, if exercise prior to neurorehabilitation is the optimal strategy, investigating the ideal post-
exercise timing to deliver therapy is needed. Conversely, limited evidence supports the potential for simultaneous delivery of exercise and task training, or for the exercise to be delivered following task training. While evidence does support faster information processing during exercise in healthy individuals (McMorris et al., 2009b), a concern for individuals recovering from a stroke is the potential detriment of multi-tasking. Simultaneously performing exercise and targeted therapy creates a multi-tasking situation and after a stroke individuals have added difficulty in these situations (Lesniak et al., 2008). A viable strategy that warrants investigation is to target the exercise modality to a specific sensorimotor deficit. For example, gait training can be done by body-weight supported treadmill. This strategy effectively turns the exercise bout into task-specific training, which is currently the most effective strategy for stroke neurorehabilitation (Langhorne et al., 2011), with the added benefits of aerobic exercise. Finally, it has been suggested that exercise following training may be an effective strategy to augment memory consolidation (Segal et al., 2012). This strategy posits that NE is involved in memory consolidation and increasing NE availability during memory consolidation (i.e. after training) with aerobic exercise should benefit memory. Further, motor memory may benefit from an exercise bout after task training as retention of a visuomotor tracking task was better among individuals that performed exercise after task training compared to those that performed exercise before training (Roig et al., 2012). While using aerobic exercise as a prime prior to task training has been the most commonly employed strategy, there is value to evaluating the post-exercise timing of training as well as the order of exercise and training to ensure optimal benefit to post-stroke neurorehabilitation.

6.6 Summary and Conclusions

This dissertation had the main goals of understanding the influence of a single session of aerobic exercise on CNS state (arousal and attention) in stroke and subsequent short-term adaptation in both healthy individuals and those recovering from a stroke. Evidence suggests that CNS arousal is augmented but attention is not following an aerobic exercise bout. While exercise positively enhanced some aspects of the rate of short-term change in performance in healthy individuals, for individuals recovering from stroke the exercise bout did not benefit task training over a control condition. However, results were not as robust as comparable studies in healthy populations which highlights the significant between and within-subject variability in this population which likely impacted the ability to detect statistical significance at the group level.
Continued evaluation of the proposed model of pairing aerobic exercise with targeted therapeutic intervention is needed. A focus on evaluating underlying neurophysiology using neuroelectric markers of cortical excitability is critical to evaluate the effects of exercise on the CNS in this population. Further, an understanding of the optimal exercise intensity and how best to evaluate intensity is an important area for future work. These questions will help understand the optimal timing and pairing of exercise and therapeutic intervention. Finally, and most importantly, this dissertation focused on the immediate effects of a single session of aerobic exercise and task training. The logical progression is to evaluate the longitudinal, multi-session effects of pairing aerobic exercise with targeted therapy to determine whether the observed single session benefits augment neurorehabilitation and aid long-term recovery from stroke.
References


