Does Intensity Matter?

The effect of cardiovascular high-intensity interval training and moderate-intensity continuous training on neuroplasticity and psychosocial responses to exercise in individuals with chronic stroke

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ABSTRACT

Neuroplasticity is an important therapeutic target in stroke rehabilitation. Cardiovascular exercise (CE) has been proposed as a cost-effective method that may augment neuroplasticity to promote recovery. The impact of CE, however, may be dependent on the intensity of its performance. High intensity CE could potentially optimize benefits to neuroplasticity, relative to lower-intensity paradigms. Yet, CE is typically employed using moderate-intensity continuous training (MICT) protocols in stroke survivors. Conducting high-intensity exercise at similar durations to MICT may be challenging for post-stroke individuals to sustain.

High-intensity interval training (HIIT) may be a promising alternative to facilitate higher exercise intensities by utilizing repeated high intensity bouts interspersed with low-intensity recovery periods. Increasingly, evidence suggests that HIIT imparts benefits for cardiometabolic outcomes; however, its effect on neuroplasticity mechanisms essential for improving functional recovery in stroke is currently limited. In addition, irrespective of the potential benefits of HIIT, there is a limited understanding of psychosocial responses to HIIT that could influence its acceptability in stroke rehabilitation.

The objective of this thesis was to compare the effect of CE intensity on neuroplasticity and psychosocial responses to exercise in individuals with chronic stroke. This was accomplished by conducting a comparison of the effect of HIIT vs. MICT on these outcomes within the context of a randomized controlled trial. To provide context for the relevance of this objective, an introduction to the current literature pertaining to neuroplasticity and psychosocial responses to exercise in stroke rehabilitation, and important gaps in our current understanding, is presented in Chapter 1. The methodology and findings of the randomized controlled trial, pertaining to the objective of this thesis, are subsequently described in three separate manuscripts.

The first manuscript, in Chapter 2, is the published protocol of the randomized controlled trial that provides the rationale and study methodology. In Chapter 3, the effect of HIIT vs. MICT on markers of cortico-spinal excitability (CSE), a surrogate measure of neuroplasticity, is examined in individuals with chronic stroke using Transcranial Magnetic Stimulation. In this manuscript, we reveal novel findings that suggest HIIT and MICT equivalently augment excitability of the ipsilesional brain hemisphere and modulate the interhemispheric balance between ipsilesional and contralesional hemispheres. The effect of HIIT vs. MICT on motivation and enjoyment, two key intrapersonal psychosocial responses, which may influence the sustainability of exercise in stroke recovery, is examined in Chapter 4. In this manuscript we showed that HIIT and MICT elicit equivalent motivation, and post-exercise enjoyment, despite less positive affective responses elicited by participants in the HIIT program.

In Chapter 5, we propose potential mediators and mechanisms that may play a role in the effect of HIIT and MICT on neuroplasticity markers of ipsilesional cortico-spinal excitability in individuals in the chronic phase of stroke recovery. We also discuss potential explanations for the participants' psychosocial responses to HIIT, and how its implementation should consider factors that support HIIT's tolerability. In addition, we examine the limitations of the studies within this thesis and discuss their implications for future research. Lastly, a summary of findings of the collected manuscripts with respect to this thesis' objectives and potential direction for future research is presented in Chapter 6.

Taken together, this thesis addresses important questions concerning the effect of exercise intensity on neuroplasticity and psychosocial responses in stroke survivors. These findings should encourage the use of HIIT to take advantage of higher exercise intensities to promote neuroplasticity in stroke rehabilitation.

ABRÉGÉ

La neuroplasticité est une cible thérapeutique importante dans la rééducation après un accident vasculaire cérébral. L'exercice cardiovasculaire (EC) a été proposé comme une méthode rentable susceptible d'augmenter la neuroplasticité pour favoriser la récupération. L'impact de l'EC peut toutefois dépendre de l'intensité de son exécution. L'EC à haute intensité pourrait potentiellement optimiser les bénéfices pour la neuroplasticité, par rapport aux paradigmes d'intensité plus faible. Pourtant, l'EC est généralement utilisé dans des protocoles d'entraînement continu d'intensité modérée (MICT) chez les survivants d'accidents vasculaires cérébraux. La réalisation d'exercices de haute intensité à des durées similaires à celles de l'entraînement continu d'intensité modérée peut s'avérer difficile à maintenir pour les personnes ayant subi un AVC.

L'entraînement par intervalles de haute intensité (HIIT) peut être une alternative prometteuse pour faciliter des intensités d'exercice plus élevées en utilisant des épisodes répétés de haute intensité entrecoupés de périodes de récupération de faible intensité. De plus en plus de preuves suggèrent que le HIIT apporte des avantages sur le plan cardiométabolique, mais son effet sur les mécanismes de neuroplasticité essentiels à l'amélioration de la récupération fonctionnelle en cas d'AVC est actuellement limité. En outre, indépendamment des avantages potentiels de l'HIIT, les réactions psychosociales à l'HIIT, qui pourraient influencer son acceptabilité dans le cadre de la réadaptation post-AVC, sont mal comprises.

L'objectif de cette thèse était de comparer l'effet de l'intensité de l'EC sur la neuroplasticité et les réponses psychosociales à l'exercice chez les personnes souffrant d'un AVC chronique. Cet objectif a été atteint en comparant l'effet de l'HIIT par rapport au MICT sur ces résultats dans le contexte d'un essai contrôlé randomisé. Afin de mettre en contexte la pertinence de cet objectif, le chapitre 1 présente une introduction à la littérature actuelle sur la neuroplasticité et les réponses

psychosociales à l'exercice dans la réadaptation post-AVC, ainsi que les lacunes importantes dans notre compréhension actuelle. La méthodologie et les résultats de l'essai contrôlé randomisé, relatifs à l'objectif de cette thèse, sont ensuite décrits dans trois manuscrits distincts.

Le premier manuscrit, au chapitre 2, est le protocole publié de l'essai contrôlé randomisé qui fournit la justification et la méthodologie de l'étude. Dans le chapitre 3, l'effet du HIIT par rapport au MICT sur les marqueurs de l'excitabilité cortico-spinale (CSE), une mesure de substitution de la neuroplasticité, est examiné chez des personnes ayant subi un AVC chronique à l'aide de la stimulation magnétique transcrânienne. Dans ce manuscrit, nous révélons de nouveaux résultats qui suggèrent que le HIIT et le MICT augmentent de manière équivalente l'excitabilité de l'hémisphère cérébral ipsilésionnel et modulent l'équilibre interhémisphérique entre les hémisphères ipsilésionnel et contralésionnel. L'effet du HIIT par rapport au MICT sur la motivation et le plaisir, deux réponses psychosociales intrapersonnelles clés, qui peuvent influencer la durabilité de l'exercice dans la récupération de l'AVC, est examiné au chapitre 4. Dans ce manuscrit, nous avons montré que le HIIT et le MICT suscitent une motivation équivalente et un plaisir post-exercice, malgré des réponses affectives moins positives de la part des participants au programme HIIT.

Dans le chapitre 5, nous proposons des médiateurs et des mécanismes potentiels qui peuvent jouer un rôle dans l'effet du HIIT et du MICT sur les marqueurs de neuroplasticité de l'excitabilité cortico-spinale ipsilésionnelle chez les personnes en phase chronique de récupération d'un accident vasculaire cérébral. Nous discutons également des explications potentielles des réactions psychosociales des participants au HIIT et de la manière dont sa mise en œuvre devrait prendre en compte les facteurs qui favorisent la tolérance au HIIT. En outre, nous examinons les limites des études menées dans le cadre de cette thèse et la manière dont elles peuvent être liées à

des recherches futures. Enfin, le chapitre 6 présente un résumé des conclusions des manuscrits recueillis en ce qui concerne les objectifs de cette thèse et l'orientation potentielle de la recherche future.

Dans l'ensemble, cette thèse aborde des questions importantes concernant l'effet de l'intensité de l'exercice sur la neuroplasticité et les réponses psychosociales chez les survivants d'accidents vasculaires cérébraux. Ces résultats devraient encourager l'utilisation du HIIT pour tirer profit des intensités d'exercice plus élevées afin de promouvoir la neuroplasticité dans la réadaptation post-AVC.

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CONTRIBUTIONS OF AUTHORS

Lynden Rodrigues, doctoral candidate, and author of this thesis, conducted the review of literature, contributed to the development of the study methodology, data collection and data analysis for all studies under the supervision of Dr. Marc Roig (School of Physical and Occupational Therapy, McGill University). For all manuscripts, Dr. Roig and other contributing authors (see below) provided critical review and editing.

Chapter 2: Mr. Rodrigues and Dr. Kevin Moncion prepared this manuscript describing the study methodology of the randomized controlled trial from which the following manuscript chapters are based on. The first manuscript, in Chapter 2, was prepared by Mr. Rodrigues and co-first author, Dr. Kevin Moncion (McMaster University). The inclusion of this manuscript in this thesis was agreed upon by Mr. Rodrigues and Dr. Moncion. A signed letter attesting to this agreement is provided in the **Appendix**.

Dr. Roig and Dr. Ada Tang (McMaster University) developed the concept of this trial and obtained grant funding for its implementation. They and other co-authors reviewed and edited the manuscript prior to its publication.

Chapter 3: Mr. Rodrigues and Dr. Roig designed this study, Mr. Rodrigues and other co-authors collected data, and Mr. Rodrigues and Dr. Roig analyzed this data. Mr. Rodrigues prepared this manuscript, working with Dr. Roig. Other co-authors reviewed and provided comments and approval for this manuscript prior to its submission.

Chapter 4: Mr. Rodrigues and Dr. Roig designed this study, Mr. Rodrigues collected data, and Mr. Rodrigues, Dr. Roig and Dr. Shane Sweet (McGill University) analyzed data. Mr. Rodrigues prepared the manuscript. Other co-authors reviewed and provided comments and approval for this manuscript prior to its submission.

CONTRIBUTION TO ORIGINAL KNOWLEDGE

This PhD thesis is a work of original scholarship and that provides a distinct contribution to the existing body of knowledge. This thesis follows a manuscript-style format, in which three chapters (2, 3 and 4) consist of manuscripts that have been published (Chapter 2); and two which have been submitted for publication (Chapter 3 and 4).

Chapter 2 (manuscript #1) is the protocol paper, in *Trials*, which describes the study methodology of the randomized controlled trial which serves as the basis for the subsequent chapters, 3 and 4, and their respective manuscripts. This manuscript describes the novel multi-site randomized controlled trial study developed by Mr. Rodrigues and fellow co-authors. As part of this study design, the methodology of outcome data collection, design of exercise interventions, and statistical analyses are presented.

Chapter 3 (manuscript #2) is a manuscript submission for the *Journal of Physiology*. The novel study described within this manuscript is the first study to compare the effects of high-intensity interval training (HIIT) vs. moderate-intensity continuous training (MICT) in chronic stroke individuals within the context of a chronic exercise program. This manuscript reports novel findings of exercise-induced modulation of ipsilesional cortico-spinal excitability (CSE) measures using Transcranial Magnetic Stimulation in individuals with chronic stroke. In addition, we also report novel findings that describe a modulation of interhemispheric balance of CSE measures which may have significant impact on motor functioning.

Chapter 4 (manuscript #3) is a manuscript submission to Archives of Physical Medicine and Rehabilitation. This manuscript describes a novel secondary analysis of motivation and enjoyment outcomes in response to the HIIT vs. MICT interventions described in Chapter 2. This is the first study of its kind to compare the effects of HIIT and MICT exercise interventions in a

stroke population. Findings from this study provide important new knowledge concerning psychosocial determinants of exercise engagement and provides further support for the implementation and sustainability of HIIT as an exercise modality in stroke rehabilitation.

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LIST OF ABBREVIATIONS

10mWT – 10-meter walk test

6MWT – Six-minute walk test

BDNF – brain-derived neurotrophic factor

BP – blood pressure

BREQ-3 – Behavioural Regulation in Exercise Questionnaire-3

CE – cardiovascular exercise

CI – confidence interval

CLH – contra-lesional hemisphere

CPET – cardiopulmonary exercise test

CSE – cortico-spinal excitability

CSP – cortical silent period

CST – cortico-spinal tract

CT – computed tomography

ECG – electrocardiogram

EMG – electromyography

FDI – first dorsal interosseus muscle

FS – Feeling Scale

GABA – γ-aminobutyric acid

HIIT – high-intensity interval training

HR – heart rate

HRR – heart rate reserve

ICF – intracortical facilitation

ILH – ipsilesional hemisphere

JRH – Jewish Rehabilitation Hospital

LMM – linear mixed model

LTP – long-term potentiation

M1 – primary motor cortex

MEP – motor evoked potential

MICT – moderate-intensity interval training

MoCA - Montreal Cognitive Assessment

MRI – magnetic resonance imaging

MVC – maximal voluntary contraction

NMDA – N-methyl-D-aspartate

PACES – Physical Activity Enjoyment Scale

PWV – pulse wave velocity

RCT – randomized controlled trial

rMT – resting motor threshold

RPE - rate of perceived exertion

SICI – short-interval intracortical inhibition

T0 – baseline assessment

T1 – post-intervention assessment

T2 – follow-up assessment

TMS – transcranial magnetic stimulation

VEGF – vascular endothelial growth factor

$\dot{V}O_2$peak – maximal oxygen uptake

CHAPTER 1: INTRODUCTION

1.1 Stroke: Impact on society and the individual

In the latest estimates of stroke prevalence, over 100 million people worldwide currently live with stroke-related symptoms, making it the leading cause of disability[1] and second leading cause of death. In Canada alone, approximately 878,000 persons live with stroke, with approximately 90,000 stroke-events occurring each year. Post-stroke neurological and cardiovascular complications contribute to the burden of disability and death, costing $3.6 billion per year to the Canadian economy annually[2]. Stroke rehabilitation interventions have been demonstrated to improve outcomes of recovery, but only a partial return to pre-stroke functioning may be expected[3]. Effective interventions are needed to address complex post-stroke sequelae, and given its positive effects on neuroplastic, cardiorespiratory and metabolic benefits[4], cardiovascular exercise has shown great promise for stroke survivors.

1.2 Neuroplasticity in stroke recovery

Stroke pathophysiology

Stroke events, classified as either ischemic (caused by a blockage of blood supply to an area of the brain) or hemorrhagic (bleeding into the brain due to blood vessel rupture), result in injury to brain tissue. Following the initial lesion, a cascade of processes occurs, including a disruption of the blood-brain-barrier[5], inflammatory responses[6,7,8], disruption in cellular homeostasis[9] and apoptotic cell death[10]. Depending on the stroke location, the cumulative effect of these processes impacts neuronal and synaptic function in the brain and its projections, such as the cortico-spinal tract (CST)[11], which may lead to impairment of cognitive, sensory, and motor functioning[3, 12]. Motor tasks, such as those involving upper-limb movements of reaching and

grasping, are important for performing essential activities of daily living and have significant impact on the quality of life and well-being of stroke survivors.

The severity of impairment is dependent on several factors, including the location and size of the initial stroke lesion, and progression of recovery is dynamic following the initial event. The timeline following the stroke event has been characterised into hyper-acute (0-24 hours post-stroke), acute (1-7 days post-stroke), early subacute (7 days – 3 months post-stroke), late subacute (3-6 months post-stroke), and chronic (> 6 months post-stroke)[12].

Stroke survivors may experience some spontaneous recovery of post-stroke motor functioning, with little or no therapy[3, 12, 13], due to the innate capacity of the human brain to repair and re-wire existing neural circuitry. The physiological, structural, and functional change that produces these adaptations is collectively termed *neuroplasticity*. Animal and humans studies suggest that these mechanisms are particularly heightened during the subacute phase of recovery, and plateau as an individual transitions to the chronic phase[14].

Neuroplasticity and the excitatory-inhibitory balance post-stroke

The loss of neurons and corresponding synaptic and axonal connections in peri-infarct and ipsilateral areas (i.e., same brain hemisphere of stroke lesion), along with post-stroke neuro-regenerative processes and the formation of new connections, contribute to a reorganization of brain function. For a stroke injury affecting motor control, this may result in a transfer of cortical activity to adjacent and contralateral (i.e., opposite brain hemisphere of stroke lesion) areas of the brain. Effective recovery of post-stroke motor function may manifest as a return of activity to the ipsilateral regions; however, cooperating regions that govern motor control will be fundamentally altered post-stroke.

The underlying physiological processes of post-stroke neuroplasticity that manifest in motor recovery are also expressed through changes in the excitability of neuronal circuits in the brain and cortico-spinal tract (cortico-spinal excitability, -CSE-). Post-stroke enhancement of excitatory synaptic transmission between neurons, long-term potentiation (LTP), is an essential component of motor learning positively associated with motor recovery[15].

The balance between excitatory and inhibitory activity[11, 16] is primarily mediated by neurotransmitters glutamate, and γ-aminobutyric acid (GABA), respectively[11, 16, 17]. Glutamate and GABA constitute the major excitatory and inhibitory neurotransmitters of the brain, and their regulation is essential for motor functioning[17]. The regulation of these neurotransmitters is dynamic over the course of stroke recovery, as the hyper-acute phase is characterized by excessive glutamate-mediated excitotoxic activity, the acute-to-subacute phases exhibit increased GABA-mediated inhibition[16], which continues to persist into the chronic phase[11]. Elevated GABA-mediated inhibition in the subacute phase, may be an impediment to motor recovery post-stroke[18].

Therefore, the excitatory-inhibitory balance is a potentially important therapeutic target for the improvement of post-stroke motor outcomes, and Transcranial Magnetic Stimulation (TMS) is widely used to elucidate its mechanisms. Reviews by Shanks et al., and others[19-21] provide an excellent overview of TMS measures of CSE and post-stroke motor recovery[22] , as well as CE-mediated effects[20, 21]. In the following section, a brief review of TMS measures of CSE and their relevance to post-stroke motor recovery will be introduced.

Measuring neuroplasticity post-stroke with Transcranial Magnetic Stimulation

In stroke and neurotypical trials examining motor control, TMS is applied on the primary motor cortex (M1), to elucidate the electrophysiological biomarkers of functional integrity of the

and cortico-spinal tract (CST) that are associated with post-stroke motor recovery[19, 20, 23]. M1 is an important therapeutic target area for post-stroke motor recovery[24] and increased excitability in this area is predictive of improved motor function outcome[25].

One measure in particular, motor-evoked potential (MEP), has been frequently described as a biomarker for upper-limb motor recovery post-stroke[19, 26]. For example, in the hyperacute phase of stroke, individuals exhibiting an MEP in the ILH, have a better prognosis for motor recovery than those who do not[25]. The amplitude of MEP waveforms, in response to single and paired-pulse TMS protocols, allows for an estimate of the excitability within the brain and CST (i.e., CSE), and the balance between excitability and inhibition of cortical networks. These TMS measures of excitability, facilitation and inhibition are obtained through single and paired-pulse TMS protocols and their mechanisms are described in **Figure 1**.

Single-pulse TMS measures (**Figure 1**) are used to evaluate cumulative excitability of the CST including resting and active MEP amplitude, and resting and active motor threshold (rMT and aMT)[27]. These measures also assess inhibitory mechanisms, such as cortical silent period (CSP). Paired-pulse TMS protocols (**Figure 1**) are used to determine CSE markers of intracortical facilitation (ICF) and short-interval intracortical inhibition (SICI), which determine the net excitability and inhibition of neuronal cortico-cortical circuitry, respectively. Collectively, these measures can help provide an understanding of glutamate and GABA neurotransmitter-receptor systems underlying motor learning processes[28, 29] that may predict post-stroke motor recovery[30].

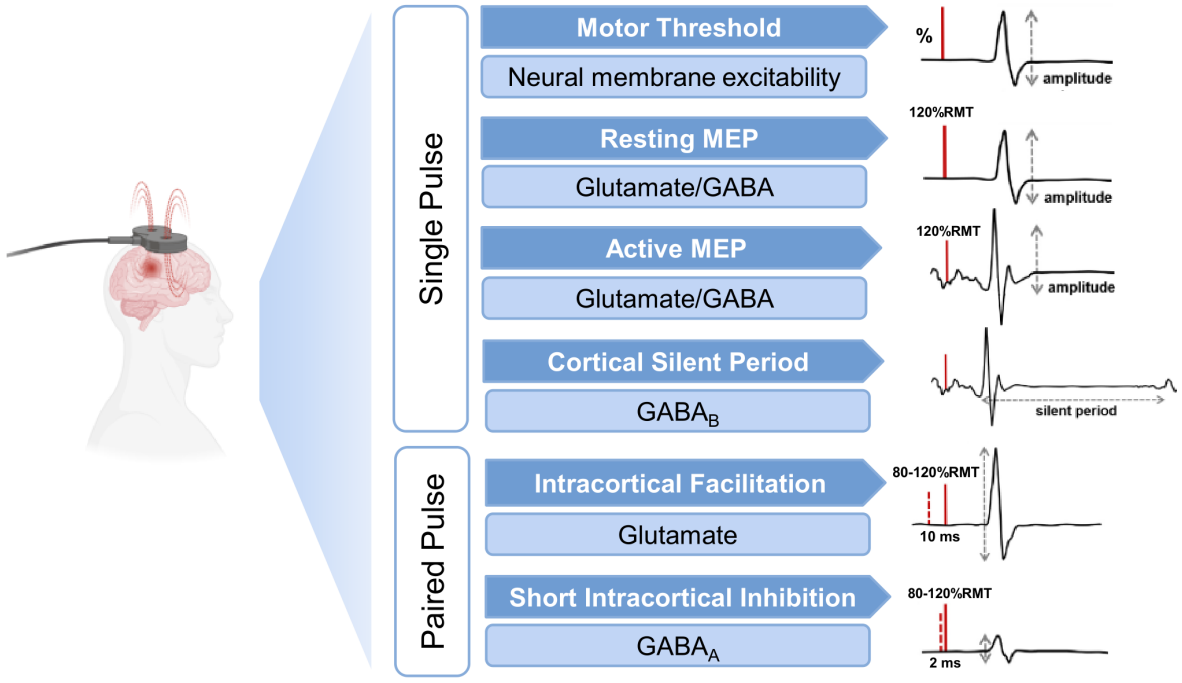

Figure 1. The amplitude of motor-evoked potentials in response to single and paired pulse Transcranial Magnetic Stimulation protocols and representative electromyographic signals. Image adapted from De Las Heras et al (2024), with permission. Motor threshold is representative of voltage-gated, sodium-channel mediated neuronal membrane excitability; Resting and active motor-evoked potential (MEP) Amplitude represents trans-synaptic activation of cortico-spinal neurons regulated by glutamatergic, GABAergic, and other neuromodulating neurotransmitters; Cortical silent period is representative of inhibition mediated by activation of $GABA_B$ receptors; Intracortical facilitation represents net facilitation of excitatory cortical circuits primarily mediated by glutamate and N-methyl-D-aspartate (NMDA) receptors; Short-interval intracortical inhibition assesses inhibition mediated by $GABA_A$ receptors.

From acute to chronic phases of stroke, measures of ILH resting MEP amplitude and rMT are typically lower and higher, respectively, than those of the CLH[31], indicating diminished excitability. Higher MEP amplitudes and reductions in rMT, upper-limb representational areas of ILH M1 have been associated with improved motor outcomes in post-stroke recovery[25]

Excessive ILH inhibition post-stroke impedes motor recovery, and reducing inhibition is a target for improving functional recovery[18]. For example, elevated ILH SICI in the chronic phase

of stroke is negatively associated with functional recovery[30]. ILH ICF, indicative of the net-excitability of intracortical circuitry (**Figure 1**), incorporating GABAergic and glutamatergic activity, is typically unaffected relative to the CLH or neurotypical comparisons throughout post-stroke recovery[31]. In the CLH, in contrast, there are typically no marked differences in excitability and inhibition measures, relative to neurotypical individuals[31]. Importantly, asymmetry in CSE between ILH and CLH is commonly observed after stroke[32]. This imbalance itself may be a potential marker of poorer post-stroke motor prognosis[23, 33].

These measures of CSE provide insight into mechanisms that govern the excitatory-inhibitory relationship during recovery. Change in these CSE measures can serve as benchmarks for the potential for motor recovery. Therapies that augment mechanisms of neuroplasticity, thereby inducing beneficial changes in CSE measures, are needed to optimize motor recovery outcomes. In recent years, cardiovascular exercise has been examined as an intervention to promote beneficial outcomes of CSE[20, 34].

1.3 Promoting neuroplasticity with cardiovascular exercise in stroke

Cardiovascular exercise in stroke rehabilitation: Intensity Matters

Cardiovascular exercise (CE), defined as a rhythmic physical activity involving major muscle groups and stressing the cardiorespiratory system, is a recommended component of stroke rehabilitation[35, 36] . CE has been demonstrated to be a safe and feasible method to mitigate the risks of stroke recurrence and to reduce the burden of stroke-related morbidity by improving cardiorespiratory, metabolic, and functional outcomes[35, 37]. In neurotypical and stroke rehabilitation contexts, CE interventions are categorized by several factors, namely frequency, intensity, time and type of exercise, collectively termed the FITT principle[38]

Increasingly, intensity of exercise is of particular interest, as this modifiable characteristic of exercise has significant impact on cardiovascular and functional recovery outcomes[38-41]. Intensity of exercise is typically described as low, moderate, high, near maximal-to-maximal intensity (**Table 1**). In stroke rehabilitation, CE is typically implemented as moderate-intensity continuous training (MICT)[36], which typically ranges from 20-60 minutes per sessions, held three to five times per week[35, 36]. However, emerging evidence suggest that high-intensity exercise modalities such as high-intensity interval training (HIIT) can further optimize the benefits of CE[38, 40, 41].

Recently, a meta-analysis by Moncion et al.[40], demonstrated that high-intensity exercise produces superior improvements in key cardiometabolic and functional indicators such as peak oxygen uptake ($\dot{V}O_2$peak), systolic blood pressure and gait speed. HIIT, in particular, was described as being the overall superior modality compared to high-intensity continuous exercise, and lower intensity exercise modalities such as MICT[40].

Table 1. *Classification of exercise intensity parameters in cardiovascular exercise*

Intensity	% HRR	% of HR_{max}	% VO_2max	Perceived Exertion
Very Light	< 30	< 57	< 37	< Very light (RPE < 9)
Light	30-39	57-63	37-45	Very light – fairly light (RPE 9-11)
Moderate	40-59	64-76	46-63	Fairly light to somewhat hard (RPE 12-13)
High	60-89	77-95	64-90	Somewhat hard to very hard (RPE 14-17)
Near-maximal to maximal	≥ 90	≥ 96	≥ 91	≥ Very hard (RPE ≥ 18)

Table adapted from Garber et al., (2011)[42]. *Abbreviations*: % HRR: percentage of heart rate reserve; % of HR_{max}: percentage of maximal heart rate; % VO_2max: percentage of maximal oxygen uptake; RPE: rating of perceived exertion

There remains, however, an important need to address neurological sequelae post-stroke. Encouragingly, multiple studies and reviews suggest that CE has considerable potential as an intervention to potentiate neuroplasticity mechanisms[4, 9, 20, 34, 39, 43] and potentially improve post-stroke motor recovery outcomes[44-46]. Once again, an important factor for CE-mediated benefits to neuroplasticity in post-stroke recovery is exercise intensity. The next section will introduce how CE impacts mechanisms of neuroplasticity, and how intensity may play a significant role in optimizing outcomes.

Cardiovascular exercise and neuroplasticity in stroke rehabilitation

Animal and human studies, utilizing acute (single-bouts of exercise) and chronic (long-term or multiple bouts of exercise) CE, demonstrate that it is capable of modulating cellular, structural, and functional adaptations that promote neuroplasticity[7, 9, 47, 48]. Throughout the cellular and structural adaptations induced by CE, exercise intensity is a critical factor. In animal models, CE paradigms have been reported to confer neuroprotective benefits immediately post-stroke, by reducing lesion size, suppressing oxidative damage, and improving inflammatory responses[7]. Likewise, CE stimulates mechanisms of neurogenesis and synaptogenesis that may potentiate neuroplasticity during stroke recovery, through the upregulation of neurotrophins such as brain-derived neurotrophic factor (BDNF), insulin-like growth factor (IGF-1) and vascular-endothelial factor (VEGF). Moderate-to-high intensity exercise is required to upregulate these cellular factors of neuroplasticity[43]. CE-mediated cellular mechanisms of neuroplasticity may lead to changes in brain structure, such as increased brain volume, and gray and white matter integrity. In individuals with chronic stroke, acute CE paradigms, using HIIT, have been shown to elicit increases in blood serum concentrations of BDNF[49], IGF-1[50] and VEGF[50], demonstrating a capacity to augment

molecular factors of neuroplasticity. Both acute and chronic CE have also demonstrated potential for improving behavioural measures of motor functioning[44, 46].

Improvement in motor functioning in post-stroke individuals may be mediated by neuroplastic adaptations in brain function, such as the excitatory and inhibitory activity of neurons and synapses. Multiple studies using acute CE paradigms have demonstrated that exercise can elicit changes in CSE measures, reflecting the excitatory:inhibitory activity associated motor learning processes critical for functional recovery[44-46, 51]. To non-invasively examine the effects of CE and the role of intensity on CSE, TMS has been used to assess the effects of acute and chronic paradigms[20, 34]. In the following section we will review pertinent studies of CE interventions, and their effects on TMS measures in both neurotypical and stroke populations.

Acute cardiovascular exercise and TMS CSE measures

In studies using TMS in neurotypical and post-stroke individuals acute and chronic CE has been demonstrated to modulate CSE measures[52-62]. Previous studies in neurotypical individuals have established that a minimum of moderate intensity exercise is required to modulate CSE measures[54, 63]. For example, MacDonald et al.[54] reported that there was no effect of a 20-minute bout of continuous low-intensity cycle-ergometer CE (30% of heart rate reserve, -HRR-) on CSE measures, whereas 20 minutes of moderate-intensity (40-50% HRR) elicited an augmentation of resting MEP amplitude. Similar null effects of low-intensity exercise on CSE were also reported by Murdoch et al.[63].

High-intensity exercise protocols, like HIIT, have also been described to modulate measures of excitability, facilitation, and inhibition in neurotypical individuals[52, 57-59, 61]. Mang et al. described that cycle-ergometer HIIT training (20 minutes of exercise with alternating 1-minute

intervals at 90% $\dot{V}O_2$peak) combined with a paired associated stimulation protocol, elicits amplified resting excitability in M1[59]. Comparisons between acute HIIT and MICT reveal that high-intensity exercise also has the potential can further enhance neuroplasticity mechansisms[57]. For instance, Andrews et al.,[57] compared an acute HIIT bout (20 minutes, alternating between 50% HRR and 90% HRR), MICT (20 minutes at 50% HRR) and rest control, in conjunction with an LTP-inducing intermittent theta burst TMS protocol post-exercise. They reported that HIIT elicited greater resting MEP amplitude in comparison to MICT and control[57], while also equivalently reducing SICI[57].

Similar to neurotypical individuals, the current literature describes that moderate-intensity and high-intensity protocols can also modulate CSE markers of excitability[49, 64-68], and inhibition[44] in individuals with stroke. High-intensity exercise protocols, like HIIT, have therefore been utilized to optimize intensity-dependent mechanisms of neuroplasticity thereby modulating TMS measures of CSE associated with motor recovery[39, 69].

Excellent reviews and critical perspectives of the current literature on CE-based studies using TMS in stroke have been conducted by De Las Heras et al.[20] and others[34]. In general, modulation of CSE measures varies across studies, but most acute CE stroke studies have reported exercise-induced changes in CSE that occur primarily in the ILH[20]. For example, Li et al [64]., using an acute CE treadmill exercise paradigm in chronic stroke individuals, reported that 5 minutes of high-intensity exercise significantly ($p<0.001$) increased excitability (increased resting MEP amplitude) of the extensor carpi radialis muscle of the affected hand.

Forrester et al.,[68] also reported, in a cross-sectional analysis, that participants (> 6 months post-stroke) engaged in 3 months of treadmill exercise exhibited greater resting MEP amplitudes of the paretic quadriceps, compared to untrained individuals. Nepveu et al.,[44] using a graded

maximal exercise test as a high-intensity exercise bout, found no significant changes in CSE measures directly, but did observe reductions in the ratio between ILH and CLH SICI post-exercise. They also reported that motor learning improved post-HIIT, in comparison to the rest control condition[44].

Chronic cardiovascular exercise and TMS CSE measures

Chronic exercise interventions, utilizing TMS in both neurotypical and stroke populations, particularly those examining high intensities, have not been extensively studied and report contrasting results. For example, Nicolini and colleagues[70] utilized a six-week HIIT protocol in sedentary neurotypical males, conducted 3 times per week for 17.5 minutes on a cycle ergometer. Their HIIT protocol consisted of 1 minute high-intensity bouts (at 105%-135% workload peak) interspersed with 1.5-minute low intensity periods (30% workload peak). They reported no significant change in resting excitability or SICI, yet there was a reduction in ICF, which contrasts[71] and corresponds[53] with previous acute studies in neurotypical individuals. However, Moscatelli et al.,[56] reported that 12-weeks of moderate-intensity continuous training (30 mins at 60-75% of HR_{max}) in neurotypical young adults was able to yield improvements in resting excitability and rMT[56].

The majority of TMS studies have used acute CE paradigms to examine exercise induced effects on CSE[20, 34], while there are only a few studies which have used a chronic paradigm[66, 67, 72]. For instance, Yen et al.[67] reported reductions in resting motor threshold of the non-affected tibialis anterior muscle after a 4 week body-weight supported treadmill intervention. A similar intervention by Yang et al.,[66], in individuals in the subacute and chronic stroke phase, reported that only subacute stroke individuals experienced a reduction of ILH rMT of the abductor hallucis

muscle. Madhavan et al.,[72] compared a 4-week HIIT-treadmill training paradigm with HIIT+brain stimulation protocols in individuals with chronic stroke and reported no change in CSE measures of excitability (active excitability and rMT). In the available studies, small sample sizes were examined by Yen et al.,[67] (n=18), Yang et al.,[66] (n=14) and Madhavan et al. (n =20, for the exercise-only group)[72].

In all available chronic paradigm studies, measures of exercise intensity or adherence to prescribed intensities are not described. Additionally, comparisons between differing exercise intensity protocols are also limited to only acute CE paradigm studies[49, 73], despite a critical need to determine the extent to which exercise intensity modulates CSE post-stroke. The exercise modalities in these studies were body-weight supported treadmill exercise interventions and critical information concerning intensity of exercise are not provided[66, 67, 72]. Furthermore, comparisons between differing exercise intensities have not been conducted[96, 97,72].

High-intensity interval training vs. moderate-intensity continuous training on cortico-spinal excitability in stroke?

Studies that have compared moderate and high-intensity protocols in stroke are limited to acute CE paradigms, and findings are also conflicting. For example, Boyne et al.,[49] reported that a short-interval HIIT-treadmill session elicited significant decreases in active motor threshold of the quadriceps in the ILH in comparison to the MICT-treadmill protocol. In contrast, Abraha et al.,[73] comparing acute HIIT vs. MICT using recumbent steppers, reported a lengthening of ILH MEP latency post-HIIT, which was attributed to increased fatigue or diminished spasticity. No changes in any CSE measures of excitability or inhibition were observed[73].

Heterogeneous or null findings reported in studies using acute CE paradigms, employing high-intensity vs. moderate-intensity or control designs, may stem from several factors such as small sample sizes, inconsistent exercise prescriptions[44] or differences in TMS methodology[73]. Additionally any changes elicited by acute CE paradigms were transient in nature[74], and measurements observed directly in response to exercise could have been influenced by factors such as fatigue[73]. Most importantly, as Abraha et al.[73] postulated, acute CE may provide an insufficient stimulus for eliciting adaptations, therefore requiring multiple bouts of CE[73].

To determine the effect of exercise intensity on long-term adaptations to exercise in stroke populations, high quality trials using chronic exercise paradigms are required. Currently, however, there is a lack of high-quality chronic exercise trials comparing HIIT vs. MICT in stroke.

1.4 Psychosocial responses to high-intensity interval training in stroke rehabilitation

Despite apparent benefits of high-intensity CE for cardiovascular and functional outcomes, and its potential for promoting aspects of neuroplasticity such as CSE, its implementation still poses significant challenges in the wider stroke population. An important consideration is the dynamic of psychological intrapersonal factors, such as low motivation, or lack of enjoyment towards physical activity could also be important factors limiting participation in high-intensity exercise[75, 76]. This is particularly relevant for clinical populations like stroke[77], who are typically sedentary[78] and may be reticent to engage in physically demanding exercise regimens. To take advantage of the benefits of high-intensity exercise interventions such as HIIT, compared to conventional MICT interventions, it is necessary to appraise the psychosocial responses to exercise in individuals with stroke.

Examining motivation for exercise through Self-Determination Theory

In stroke populations, motivation is an influential determinant of behaviour for engagement in exercise[75, 76, 79]. Intensity may also play a role in this relationship, as motivation for exercise in stroke survivors is associated with engagement in moderate-to-vigorous intensity exercise adherence.[79] Motivation is commonly examined using Self-Determination Theory (SDT)[80] and has examined in the context of HIIT feasibility[81] post-stroke rehabilitation[82] and exercise engagement[79]. SDT has been employed to examine motivation, with respect to exercise behaviours[83], along a spectrum of self-determined motivational types. This spectrum ranges from amotivation (absence of motivation) to intrinsic motivation (performing an activity because of its inherent satisfactory qualities)[80, 84] (Figure 2).

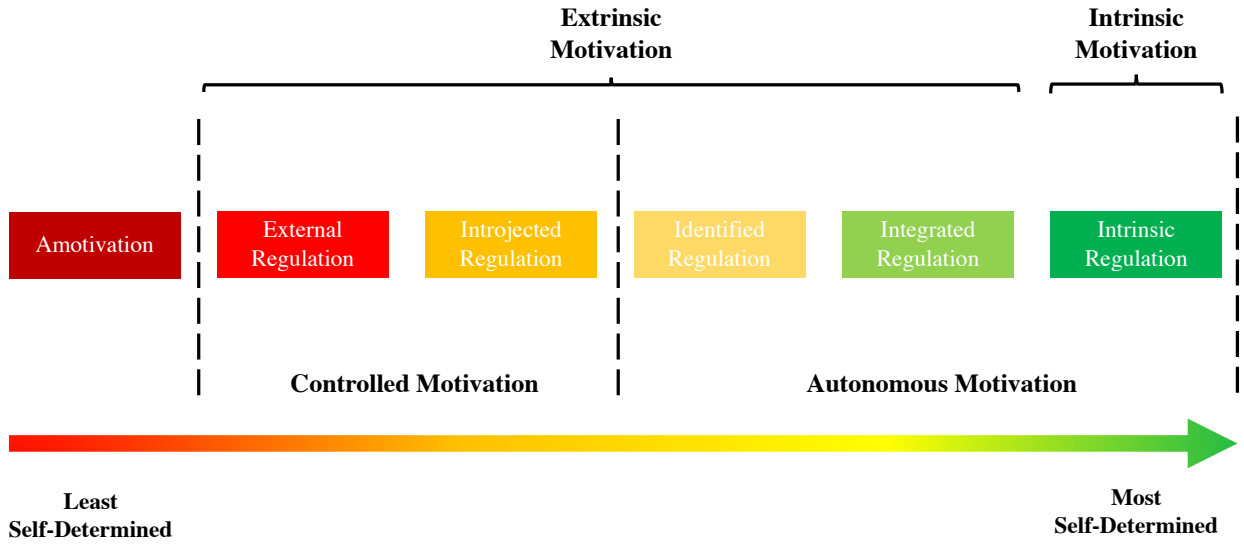

Figure 2. Spectrum of Motivation according to Self Determination Theory, adapted from Deci et al.[80].

Intrinsic motivation tends to be correlated with long-term adherence to exercise and is derived from activity that provides inherent enjoyment and self-satisfaction. Within it lies intrinsic regulation, the most self-determined of behavioural regulations. Extrinsic motivation is associated with initial or short-term adoption of exercise and consists of behavioural regulations ranging from

less self-determined (external and introjected regulation) to more self-determined (identified and integral regulation).

External regulation is the least self-determined form of regulation in which the behaviour is influenced by an external source (such as a physician or physiotherapist). Introjected regulation are behaviours that are performed to receive positive or negative reinforcement. Identified regulation is more self-determined, whereas a person is motivated to engage in exercise that are not inherently enjoyable but that are relevant to the person. For example, an individual with stroke may engage in exercise that they may feel is not enjoyable, but perceive it is necessary to recover fully. Finally, integrated regulation is the most self-determined form of extrinsic motivation, occurring when exercise is aligned with deeply held values and needs[84]. Those who exhibit more self-determined, i.e. "autonomous" motivation are more likely to engage and continue with physical activity, health and overall well-being[80], compared to those who primarily derive motivation from external sources, i.e. "controlled" motivation[83, 84].

Multiple reports in neurotypical populations have reported that self-determined motivation is positively correlated with continued exercise behaviour[85, 86]. In clinical populations, such as those undergoing cardiovascular rehabilitation,[87, 88] individuals with greater self-determination are more likely to engage in exercise behaviours post-rehabilitation. In community dwelling individuals post-stroke, greater autonomous motivation is associated with an increased propensity to engage in physical activity[79]. Autonomous motivations may also be linked to individuals with stroke experiencing their needs of autonomy, competence, and relatedness being met[89].

Motivation in response to HIIT and MICT

Understanding how exercise interventions like HIIT impact motivation along the spectrum of self-determined motivation is important for appraising the long-term sustainability of these interventions in stroke rehabilitation. However, it is important to note that studies examining motivational responses to HIIT are currently limited and none currently exist specifically for stroke populations.

In obese and diabetic populations, HIIT appears to elicit increases in autonomous motivation constructs[90, 91]. For example, Batrakoulis et al., reported that a 10-month HIIT program for young obese adults, increased "more-autonomous" identified, and intrinsic motivations while reducing "controlled" external motivation[90]. Alarcon-Gomez et al., reported that a 6-week HIIT program with sedentary neurotypical adults with diabetes, compared to a non-exercise control, significantly increased intrinsic motivation[91]. A comparison of a 10-month HIIT vs MICT with sedentary neurotypical adults by Thorgersen-Ntoumani et al., revealed no differences in motivational subscales. However, higher intrinsic motivation post-HIIT, was associated with greater adherence to the training program compared to MICT.[92]

Considering the potential relevance of motivation for exercise adherence[83, 92] high-intensity exercise protocols in stroke rehabilitation, such as HIIT, warrant an examination of this psychosocial determinant of exercise behaviour. HIIT appears to elicit changes in motivational responses in typically sedentary populations[90, 91]; however, this has yet to be addressed in individuals with stroke.

Enjoyment in response to HIIT and MICT

In addition to motivation, another intrapersonal factor that is critical to engagement in physical activity, and potentially the sustainability of HIIT in stroke populations is exercise enjoyment[39]. Enjoyment, i.e. subjective feelings of pleasure, during exercise is associated with adherence to physical activity in neurotypical and clinical populations[93], such as individuals in cardiac rehabilitation[88]. Examining this factor through the lens of SDT, enjoyment is associated with greater autonomous motivation, and particularly the construct of intrinsic motivation[93].

Enjoyment derived from exercise has been previously classified as either affective in-task responses *during* performance of exercise or reflective judgements *following* exercise participation[94-96], heretofore referred to as affective response and post-exercise enjoyment, respectively. Both measures have potential associations with adherence to exercise behaviour[93, 94], however, it is important to note that this relationship has only been described in response to moderate intensity exercise.[93, 94]

High-intensity exercise has been argued to be unsustainable because of negative affective responses experienced during physically demanding exercises which evoke unpleasant emotional states[77, 97]. However, studies with acute exercise paradigms and meta-analyses examining both affective responses and post-exercise enjoyment have indicated that, despite lower affective responses during exercise sessions, neurotypical and clinical subjects responded equivalently or more positively to HIIT post-exercise, compared to MICT[95, 96, 98, 99]. A recent meta-analysis by Niven et al.,[95] reported that acute CE HIIT paradigms, compared to MICT, were more likely to elicit a negative affective response, measured by the Feeling Scale[100]. However, post-exercise enjoyment measures such as the Physical Activity Enjoyment Scale (PACES)[101] remained more positive.

An example of this behavioural response was described by Jung et al.,[102] in sedentary neurotypical young adults performing continuous moderate and vigorous intensity exercises and HIIT, using a randomized, within-subject design. HIIT participants reported significantly lower affective response during training sessions, compared to MICT, yet also reported a non-significantly (p=0.08) greater post-exercise enjoyment.[102]. Significantly lesser affective response (p=0.004) and greater post-exercise enjoyment (p=0.013) in cycle-ergometer based neurotypical adults participating in HIIT and MICT, has also been reported by Thum et al.[103]. Additionally, 92% of their participants (n=12) preferred HIIT.

Multiple studies with chronic exercise paradigms have also indicated that post-exercise enjoyment in response to HIIT is either equivalent[104, 105] or greater[106-108] in comparison to MICT protocols in neurotypical and clinical populations. For example, Heisz et al.,[106] reported that 8 weeks of HIIT using cycle ergometery in neurotypical young adults elicited HIIT-specific increases in post-exercise enjoyment that were significantly than MICT after five weeks ($p < 0.05$), as measured by the PACES. Kong et al.,[107] in young obese women, also reported greater post-exercise enjoyment compared to MICT at every weekly time point of a 5-week intervention.

Greater post-exercise enjoyment in HIIT vs. MICT is not consistently described in the literature. For example, Vella et al.,[104] reported equivalent and stable high post-exercise enjoyment in obese young adults who participated in 8-weeks of HIIT or MICT. However, the modality of exercise they employed varied between treadmill, cycle ergometer and ellipticals, and sessions were initially supervised but then transitioned to unsupervised exercise. Bottoms et al.,[105] similarly reported equivalent post-exercise enjoyment and affective response in 12-week HIIT vs. MICT participants with Crohn's disease who exercise on cycle ergometers. In stroke populations,

however, there are currently no studies that examine affective and post-exercise enjoyment responses to HIIT vs. MICT.

The effect of HIIT vs. MICT on motivation and exercise in stroke?

Evaluating the effect of exercise on motivation and enjoyment (both affective response and post-exercise) in individuals with stroke requires a comparison of chronic paradigms. Drawing inferences from neurotypical and other clinical populations is also difficult because comparisons of HIIT vs. MICT on motivation and enjoyment are limited by heterogeneity of methodology and relatively small sample sizes. Variations in characteristics such as intensity of HIIT and MICT protocols, durations of exercise bouts and total sessions, and the modality of exercise training could contribute to heterogeneity in results. Study design considerations for interpersonal factors such as the influence of group training and trainer feedback[109], though acknowledged[106, 107], are also lacking.

An appraisal of motivation and enjoyment responses to HIIT, that accounts for these gaps in the available literature, could provide valuable information for the implementation of HIIT vs. MICT in stroke rehabilitation. To date, a comprehensive examination of psychosocial responses of motivation and enjoyment has not been conducted in stroke populations.

1.5 Gaps in the current state of literature

The introduction of this thesis has identified critical areas concerning the clinical relevance of CE in stroke rehabilitation, namely its effects on neuroplasticity and psychosocial responses to exercise. The intensity of CE may play an important role in its efficacy and sustainability in stroke populations. However, two gaps in the literature are present:

1. There are limited and small studies examining the effect of chronic exercise on neuroplasticity in individuals with stroke, and none comparing the effect of HIIT vs. MICT.
2. No studies have evaluated the effect of exercise intensity, during chronic exercise, on psychosocial responses to exercise in individuals with stroke.

In the following section, the objective of this thesis will be presented, and the structure and overview of its corresponding chapters will be described.

1.6 Thesis objectives

The aim of this PhD thesis was to examine the effect of a chronic cardiovascular exercise intervention, and specifically the effect of exercise intensity, on neuroplasticity and psychosocial responses to exercise in individuals with chronic stroke. This thesis addresses the understudied gaps in current knowledge on the efficacy of chronic exercise interventions, and the influence of exercise intensity, to produce adaptations in the primary outcome of neuroplasticity in individuals in the chronic phase of stroke. Additionally, this work also examined the effect of exercise intensity, in chronic cardiovascular exercise, on the secondary outcome of psychosocial responses of motivation and enjoyment in this population.

This manuscript-style thesis comprises three chapters that describe the methodology of the randomized controlled trial (**Chapter 2**), two separate studies that examine primary (**Chapter 3)** and secondary (**Chapter 4**) outcomes. The specific objective of these chapters are as follows:

Chapter 2: Intensity Matters: Protocol for a Randomized Controlled Trial Exercise Intervention for Individuals with Chronic Stroke.

This chapter comprises the published study protocol, in *Trials*, of a 12-week randomized controlled trial, comparing short-interval HIIT vs. MICT individuals with chronic stroke, and includes the rationale for the primary (neuroplasticity) and secondary (psychosocial responses to exercise) outcomes. Details on the study design, population of interest, primary and secondary outcomes and respective measurement tools, and the exercise interventions implemented will be described.

Chapter 3: Modulating Brain Excitability with High and Moderate-Intensity Cardiovascular Exercise in Chronic Stroke: A Randomized Controlled Trial.

In this chapter, the effect of 12-weeks of HIIT vs. MICT on measures of a surrogate of neuroplasticity, cortico-spinal excitability, in individuals with chronic stroke is examined. The findings are presented in a manuscript format, submitted to the *Journal of Physiology*. This chapter describes a novel study that examines the effect of chronic cardiovascular exercise at high (HIIT) or moderate (MICT) intensity on markers of excitability (resting and active excitability; rMT), inhibition (CSP; SICI) and facilitation (ICF) using TMS. This study is also the first to examine the effect of chronic HIIT vs. MICT on interhemispheric balance between these markers of CSE.

Chapter 4: Psychosocial Responses to a Cardiovascular Exercise Randomized Controlled Trial: Does Intensity Matter for Individuals Post-Stroke?

This chapter examines the understudied effect of HIIT vs. MICT on key potential indicators of exercise behaviour in stroke recovery, motivation, and enjoyment in response to exercise as part

of a submitted manuscript to the journal, *Archives in Physical and Rehabilitation Medicine*. This chapter describes a novel study of the effect of 12-weeks HIIT vs. MICT on motivation (BREQ-3) and enjoyment, specifically affective response (FS) and post-exercise enjoyment (PACES), in individuals in the chronic phase of stroke recovery.

Chapter 5 and 6: Discussion and Conclusion

Chapter 5 of this thesis will summarise the collective work of Chapter 2 to 4. Within this chapter, there will be a discussion pertaining to potential explanatory mechanisms that explain findings in Chapter 3 and 4, their potential limitations, and implications for future research. A conclusion and final remarks will be provided in **Chapter 6.**

CHAPTER 2: Intensity Matters: Protocol for a Randomized Controlled Trial Exercise Intervention for Individuals with Chronic Stroke

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2.1 Abstract

Rationale: Cardiovascular exercise is an effective method to improve cardiovascular health outcomes, but also promote neuroplasticity during stroke recovery. Moderate-intensity continuous cardiovascular training (MICT) is an integral part of stroke rehabilitation, yet it may remain a challenge to exercise at sufficiently high intensities to produce beneficial adaptations to neuroplasticity. High-intensity interval training (HIIT) could provide a viable alternative to achieve higher intensities of exercise by using shorter bouts of intense exercise interspersed with periods of recovery.

Methods and design: This is a two-arm, parallel group multi-site RCT conducted at the Jewish Rehabilitation Hospital (Laval, Québec, Canada) and McMaster University (Hamilton, Ontario, Canada). Eighty participants with chronic stroke, recruited at both sites and will be randomly allocated into a HIIT or MICT individualized exercise program on a recumbent stepper, 3 days per week for 12 weeks. Outcomes will be assessed at baseline, at 12 weeks post intervention, and at an 8-week follow-up.

Outcomes: The primary outcome is cortico-spinal excitability, a neuroplasticity marker in brain motor networks, assessed with transcranial magnetic stimulation (TMS). We will also examine additional markers of neuroplasticity, measures of cardiovascular health, motor function, and psychosocial responses to training.

Discussion: This trial will contribute novel insights into the effectiveness of HIIT to promote neuroplasticity in individuals with chronic stroke.

Trial registration: ClinicalTrials.gov NCT03614585. Registered 3 August 2018, https://clinicaltrials.gov/ct2/show/NCT03614585.

Keywords: Stroke, Neuroplasticity, Cardiovascular Health, Exercise, Clinical Trial.

2.2 Background and rationale

Exercise training is a recommended core component of comprehensive stroke rehabilitation programs [1, 2]. In the context of stroke, exercise is typically employed on the premise that the brain has a plastic capability (neuroplastic response) to repair itself from neurological damage [3]. A cost-effective method to promote this neuroplasticity, is the use of cardiovascular exercise [4]. One bout of exercise performed alone or in concert with non-invasive brain stimulation (e.g., Transcranial Magnetic Stimulation, TMS), may elicit neuroplastic responses that ameliorate motor learning, as studies have demonstrated in healthy individuals [5-7]. Studies in young adults, for instance, demonstrate that cardiovascular exercise can stimulate changes in the excitability of the primary motor cortex (M1) [5-7]. M1 is an important area to target for the promotion of motor function recovery post-stroke [8].

Studies on the acute response to cardiovascular exercise on neuroplasticity in healthy individuals demonstrate that the intensity of the exercise is an integral component in the improvement of neuroplasticity. A single bout of high-intensity interval training (HIIT), a cardiovascular exercise modality that utilizes short periods of high intensities, with interspersed periods of active recovery or rest during the exercise, has demonstrated effectiveness in stimulating neuroplasticity [9, 10] and improving motor learning [11]. Mang et al., reported that 20 minutes of HIIT at 90% of peak oxygen uptake ($\dot{V}O_2peak$) increased the response to a brain stimulation protocol, amplifying M1 excitability [12]. In contrast, a moderate intensity continuous (MICT) training protocol (performed at 60% of VO_2peak) resulted in no benefit to M1 excitability [13].

For individuals with stroke, cardiovascular exercise might also elicit improvement in neuroplasticity and motor recovery [14]. Experiments with animals that have been subjected to a brain lesion have shown that cardiovascular exercise reduces the size of the lesion and

inflammation and oxidative stress in perilesional areas [14, 15]. In healthy humans, a single bout of HIIT has been demonstrated to be more effective than MICT in stimulating the release of peripheral Brain Derived Neurotrophic Factor (BDNF) [16]. BDNF is a protein that is essential for the promotion of neuroplasticity and motor recovery post-stroke [17, 18]. In young healthy individuals, a single bout of HIIT performed after the practicing of a motor skill, can increase BDNF levels, which correlate positively with skill retention, even several days after motor practice [10]. In context of chronic stroke, acute high intensity exercise has been described to be associated with larger responses in increased serum BDNF, and additionally greater increases of cortico-spinal excitability [19, 20].

The importance of higher intensity of exercise is supported by studies which demonstrate the greater improvements in motor learning when motor practice is followed or preceded by a single bout of HIIT, compared to MICT [21]. For instance, studies in individuals with chronic stroke, have described that a single bout of MICT may have no effect on M1 excitability, while HIIT can potentially increase affected side excitability, reduce interhemispheric imbalance in excitability, increase neurotrophic factors like BDNF, and improve motor learning [19, 21, 22]. These studies describe a promising methodology of utilizing acute bouts of HIIT exercise, however, eliciting adaptations in brain plasticity that lead to long-term functional recovery (that include functional motor recovery) would require multiple bouts of exercise utilizing a long-term exercise regimen. Therefore, it would be imperative to determine whether multiple bouts of HIIT, in comparison to a MICT program, may result in greater and sustained benefits to neuroplasticity and resultant post-stroke recovery.

Cardiovascular Exercise can Improve Cardiovascular Health for Stroke Survivors

The most important preventative measure to reduce the risk of stroke is by maintaining ideal cardiovascular health [23-25]. However, amongst stroke survivors, cardiovascular comorbidities are highly prevalent. For example, heart disease and hypertension are present in almost 75% and 84% of this population, respectively [26, 27]. Exercise interventions that utilize cardiovascular exercise have been demonstrated to improve cardiovascular risk factors in individuals with stroke such as blood pressure (BP), an important risk factor for primary and secondary stroke [28, 29]. The challenge, however, is that individuals with stroke may be highly sedentary and likely not engage in activities or sustain levels of activity that reduce cardiovascular risk.

Our research group has demonstrated the use of conventional MICT is a safe and feasible method to improve mobility and cardiovascular fitness after stroke [30, 31]. However, like neuroplasticity and motor learning, the intensity of the exercise is a critical component for improving upon cardiovascular health. Our research group has reported greater benefit to cardiac function after 6 months of MICT, when compared to low-intensity exercise [32]. Also observed, were improvement in resting BP, amongst other risk factors, which are only attained when exercise is performed at higher intensities [33].

In order to attain higher intensities of exercise and subsequent benefit to cardiovascular health, HIIT could be a more efficient method than MICT, despite lower amounts of exercise volume. In young adults, for example, 6-12 weeks of HIIT, consisting of short (10-20 minutes) sessions, performed 3 times per week have been reported to be more effective in improving arterial stiffness, a measure of myocardial demand and coronary perfusion associated with occurrence of stroke and other cardiac events [34, 35]. A previous meta-analysis has demonstrated that HIIT has resulted in almost a two-fold improvement of VO_2peak compared to MICT [36]. Indeed, HIIT has

also been reported to be as or even more effective than MICT in reducing BP [37], for individuals with high BP, despite 20-30% less time devoted to exercise. HIIT could help individuals achieve high intensities that could result in the benefits to cardiovascular health in people post-stroke, which MICT cannot provide. However, a long-term comparison of HIIT vs, MICT for post-stroke individuals has yet to be conducted in a controlled exercise intervention study, in order to fully appraise the extent to which HIIT can yield greater benefit.

Psychosocial responses to high intensity exercise are unknown in stroke rehabilitation

While HIIT may provide significant benefits for those with chronic stroke, the adherence to such a physical activity regimen like a HIIT exercise program will depend on several factors such as lack of time [38], and psychosocial determinants such as level of enjoyment [39] and motivation [40]. HIIT may be able to address the prior, as the shorter time commitment has been reported, in healthy populations, as a factor in preference for HIIT in comparison to MICT [41]. Indeed, determinants such as enjoyment have been described to be at higher levels in response to HIIT, or similar in comparison to MICT [41-43].

Considering that in the stroke population, the intensities that are achieved may be psychologically demanding, due to heightened cardiovascular and neuromotor effort, it is surprising that an examination of psychosocial factors in HIIT or MICT training for stroke population is not currently available. An understanding of psychosocial indicators of exercise, like enjoyment and motivation, and how HIIT may affect such outcomes, would provide important information about the sustainability of HIIT and its applicability in stroke rehabilitation.

Objectives

The primary objective of this study is to compare the effects of 12 weeks of HIIT vs. MICT on neuroplasticity. Changes in neuroplasticity will be determined by examining different markers of excitability in upper limb representational areas of M1 with TMS. In addition, the secondary objectives of this study are to compare the effects of HIIT and MICT on measures of cardiovascular health, motor function and psychosocial responses to exercise. Change in cardiovascular health will be measured by assessing resting BP, arterial stiffness, cardiorespiratory fitness (VO_2peak) and waist-hip ratio. Psychosocial responses to exercise will examine the effect of HIIT vs. MICT on motivation and enjoyment in response to the respective exercise intervention. Motor function parameters of gait speed, walking capacity and upper limb motor learning will also be assessed. The exercise interventions of HIIT and MICT will be conducted using a whole-body paradigm, using recumbent steppers.

Hypotheses

We hypothesize that HIIT will be more effective in promoting neuroplasticity. HIIT will increase the excitability of upper limb representational areas on M1 of the lesioned hemisphere. This will lead to a reduction in the imbalances in M1 excitability that is typically observed in chronic stroke [44, 45]. Based on previous findings [22], we will also expect that the increases in M1 excitability in the lesioned hemisphere after HIIT will be partially mediated by a reduction in intra-cortical inhibition [46], which is a marker that has been described to increase post-stroke, negatively affecting recovery [8]. HIIT is also expected to be more effective in improving cardiovascular measures of resting BP, arterial stiffness and VO_2peak [33, 36]. We predict that after a period of 8-weeks post termination of the training program (T2), these improvements in neuroplasticity and

cardiovascular health will be maintained after a to a greater extent in the HIIT group, in comparison to the participants in the MICT group.

We also anticipate that greater improvement in walking speed [47], and motor learning post-HIIT, due to an increase in neuromuscular recruitment due to high intensity exercise, and aforementioned changes in neuroplasticity, respectively [22]. In contrast, we will also expect a similar improvement in walking capacity in response to either HIIT or MICT. Additionally, responses of motivation and enjoyment will be similar in both groups.

2.3 Methods

The following sections describe the current study protocol (version 1.0 – Dec 2021). This study protocol is presented in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines [48].

Study Design

This study is a two-arm, parallel group multi-site RCT (**Additional File 1**). Outcomes will be assessed at baseline (T0, week 0), at the end of the intervention period (T1, week 12), and at 8-week follow-up (T2, week 20) (**Figure 1**). T2 will allow us to evaluate the long-term effects of HIIT and MICT. Assessors will be blinded to group assignment prior to completion of T0. Due to limitations in staffing and resources, assessors and exercise instructors will not be blinded to group assignment.

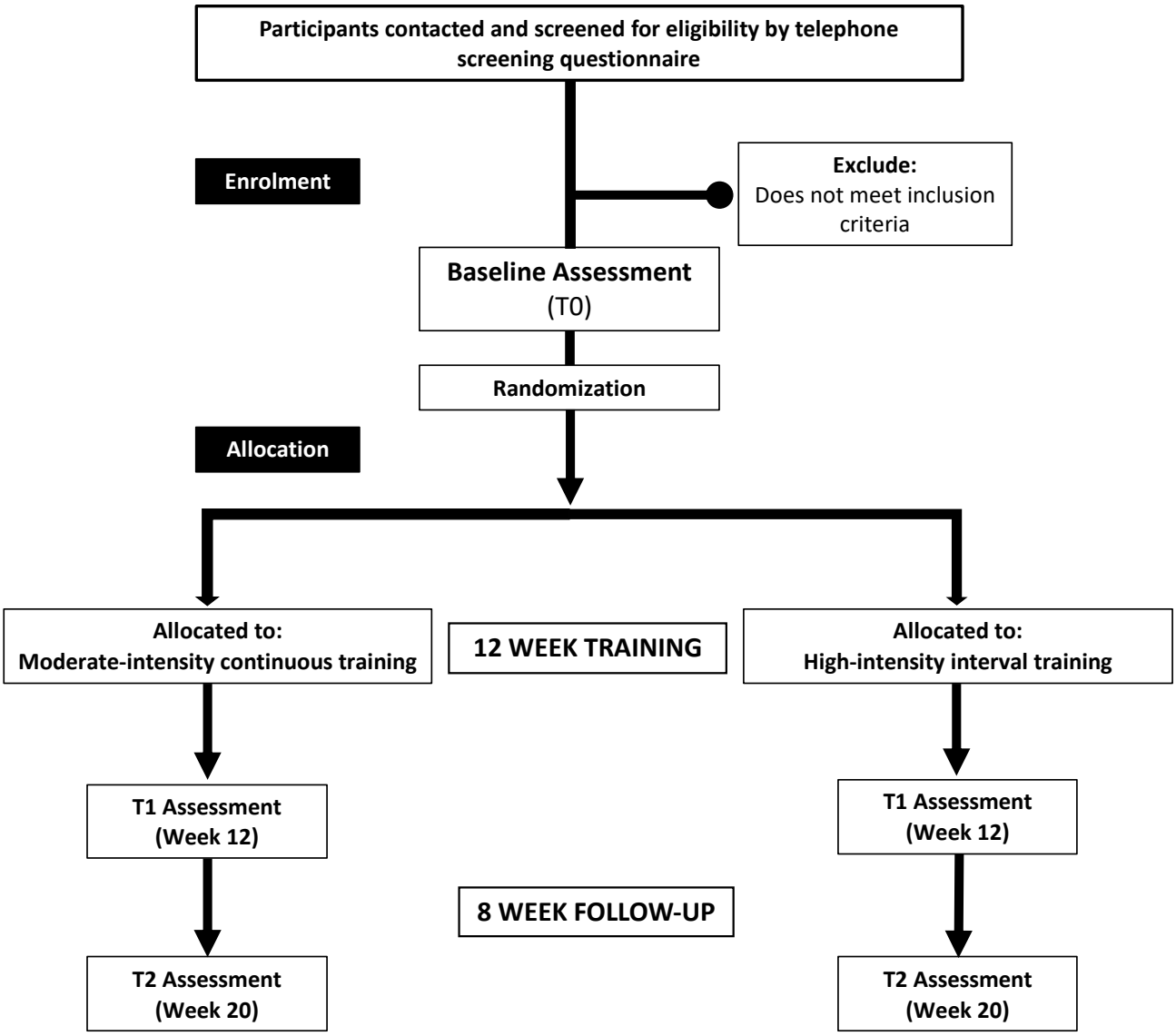


Figure 1. Study flow diagram

Sites

This study will be conducted at the Jewish Rehabilitation Hospital (Laval, Québec, Canada) and McMaster University (Hamilton, Ontario, Canada).

Participant eligibility

Participants will be recruited from the Jewish Rehabilitation Hospital (JRH) and Ontario Central South Stroke Network (Hamilton, ON). We will recruit individuals who are in the chronic phase of stroke, which will allow us to test whether HIIT can promote neuroplasticity at later stages in recovery, where changes in neuroplasticity are potentially more difficult to achieve [3]. By recruiting individuals in chronic stage of stroke recovery, we will also reduce the inter-individual differences in brain excitability, that are observable in the subacute stage of stroke recovery. Participants will be contacted by telephone and screened for eligibility via screening questionnaire addressing the following inclusion/exclusion criteria:

Inclusion criteria: 40-80 years old; 6-60 months following first-ever, single stroke confirmed by MRI/CT; living in the community and able to independently ambulate at least 10 meters (the use assistive devices are permitted, as many individuals who do regain some ability to walk following stroke do so with some adaptation); and the ability to follow instructions in exercise and assessments. If individuals have communicative difficulty due to speech or language deficits (e.g., aphasia), admission into the study is to be done on a case-by-case basis based on judgement taken by the research group.

Exclusion criteria: Significant disability, as determined by a modified Rankin scale[47] score of > 2; actively engaged in stroke rehabilitation services or a structured exercise program in addition to the one provided by this study; class C or D American Heart Association Risk Criteria [49] ; other neurological or musculoskeletal comorbidities that will prevent safe exercise participation; pain

that is made worse with exercise; cognitive, communication or behavioral issues that may limit safe participation in the exercise program; contraindications to TMS [50].

Informed consent to participate in the study, prior to entry will be obtained from the participant by study coordinators, LR and KM, at JRH and McMaster sites, respectively.

Recruitment Strategy

At the JRH site, participants will be admitted from clinician referrals and access to participant databanks from patients who have consented to be contacted for participation in research projects. The JRH stroke program admits approximately 190 patients per year, and currently conducts a cardiovascular exercise program that will allow us to recruit individuals who have the most interest in exercise and will meet the inclusion criteria of our stroke study, like those conducted previously in at this site [22].

At the McMaster site, the Ontario Central South Regional Stroke Network and the Regional Rehabilitation Centre at Hamilton Health Science can provide access to the potential 600 new patients with stroke admitted per year. The Regional Rehabilitation Centre will serve as the primary source of recruitment for this site. The McMaster site has already utilized successful strategies for recruitment of such participants for large community-based exercise trials through these networks.

Randomization

The unit of randomization will be the participant. The randomization process will use a computer-generated group assignment (http://www.randomizer.org) with a 1:1 allocation ratio into either HIIT or MICT training groups. Participants will be stratified between both sites (JRH and

McMaster) and we will conduct the randomization with a variable block size unknown to each site. PI's MR and AT will conduct and conceal the allocation of their counterpart's site (MR for McMaster, AT for JRH). Upon obtainment of participant consent and completion of baseline assessments (T0), group allocation will be revealed to the participant and assessor.

Interventions

All interventions will take place at the JRH and McMaster site facilities. HIIT and MICT will consist of 12 weeks of training with three sessions per week performed on alternate days to avoid overtraining and maximize adaptations [51]. Initially, training was to be performed in a group training session on recumbent steppers with a 2:5 trainer-to-participation format, as group training may be an important facilitator for adherence to exercise in stroke [52]. However, to reduce risk of COVID-19 infection, we will be using a 1:1 trainer-to-participant format during training sessions. Recumbent steppers were chosen because they will 1) allow participants with wide range of functional abilities to exercise at high intensities [53]; 2) have been previously described as safe and effective for implementing HIIT [54] and MICT [55] training protocols in stroke populations and allow for exercise intensity to be controlled in an easier manner than using treadmill training; 3) reduce the risk of falls due to the seated position required during exercise; and 4) involve both upper and lower limbs, training muscles that are evaluated in TMS and motor function outcomes, facilitating an examination of relationships between upper and lower limb functions. Heart rate (HR), rate of perceived exertion (RPE), and if needed, BP, will be monitored continuously throughout each training session as individuals who take beta-blockers will exhibit a blunted HR response.

Exercise intensity will be determined using the HR reserve (HRR) method calculated as HRR = (max HR at peak VO_2peak – resting HR) x (% exercise intensity) + (resting HR), in

combination with RPE [56]. For participants taking HR limiting medication (e.g., beta-blockers), a modified HRR equation will be used (HRR = 0.8 x [max HR at peak VO_2peak – resting HR] + [resting HR])[57]. Both MICT and HIIT will involve 3-minute warm-up and 2-minute cool down periods at 30% of HRR.

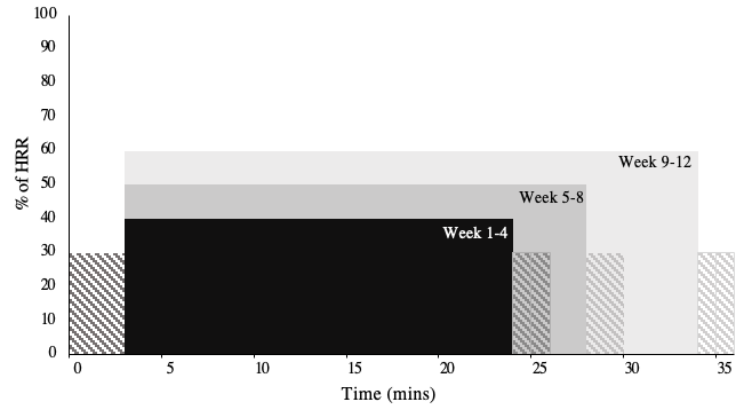
HIIT: We will use an adjusted HIIT protocol that has been described to ventilatory threshold in individuals with chronic stroke [58]. It will involve ten 60-second intervals of high intensity bouts interspersed with nine 60-second low-intensity intervals [58] (**Figure 2**). The high intensity workload will initially start at 80% of HRR and will be increased by 10% every 4 weeks. Low intensity bouts will be performed at 30% of HRR. To reduce sudden changes in BP and ensure that target intensity is achieved [59], the workload at the low intensity interval will increase gradually over 15 seconds prior to the next high intensity interval. The total duration of the HIIT session, will be 24 minutes.

MICT We will use a conventional MICT protocol typically employed in stroke rehabilitation programs. Initial intensity will start at 40% HRR and will progressively be increased by 10% HRR every 4 weeks up to 60% HRR and time (5 minutes) until the end of the intervention (**Figure 2**). If initial tolerance is low, to achieve 20 minutes of continuous exercise, initial intensity will be set at <40% HRR. Intensity will be increased by 5-10% HRR and/or 5 minutes per week until 30 minutes of continuous exercise at 40% HRR are achieved. The total duration for the MICT session will be 35 minutes.

Intensity will be determined using the HR reserve (HRR) method calculated as HRR = (max HR at peak VO_2peak – resting HR) x (% exercise intensity) + (resting HR), in combination with RPE. For participants taking HR limiting medication (e.g., beta-blockers), a modified HRR equation will be used (HRR = 0.8 x [max HR at peak VO_2peak – resting HR] + [resting HR])

Both MICT and HIIT will involve 3-minute warm-up and 2-minute cool down periods at 30% of HRR

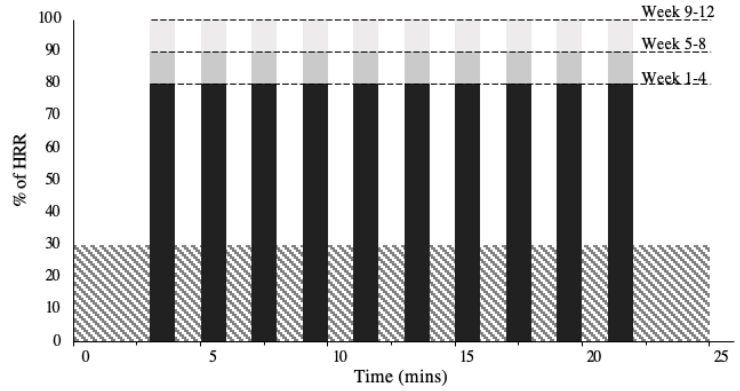
MICT Protocol (25 – 35 mins)



Initial intensity will start at 40% HRR and will progressively be increased by 10% HRR every 4 weeks up to 60% HRR and time (5 minutes) until the end of the intervention.

If initial tolerance is low, to achieve 20 minutes of continuous exercise, initial intensity will be set at <40% HRR. Intensity will be increased by 5-10% HRR and/or 5 minutes per week until 30 minutes of continuous exercise at 40% HRR are achieved. The total duration for the MICT session will be 35 minutes.

HIIT Protocol (24 mins)



Ten 60-second intervals of high intensity bouts interspersed with nine 60-second low-intensity intervals. The high intensity workload will initially start at 80% of HRR and will be increased by 10% every 4 weeks.

Low intensity bouts will be performed at 30% of HRR. To reduce sudden changes in BP the workload will increase gradually over 15 seconds before the next high intensity interval. The total duration of the HIIT session, will be 24 minutes.

HR: Heart rate; HRR: Heart rate reserve; HIIT: High-intensity interval training; MICT: Moderate-intensity continuous training

Figure 2. MICT and HIIT protocol.

Adherence and Modification to Interventions

Adherence to training in both HIIT and MICT groups will monitored by exercise trainers who will track attendance in training sessions and adherence to required training intensities as described in this protocol (see below), using Borg scale and Polar HR devices. If participants miss sessions of training, they will be offered make-up sessions to complete the full 36 sessions of

training. During the period between T1 and T2, study coordinators will contact participants by telephone to encourage participant retention at T2. These calls will also serve to assess activity level post-training (see below).

If participants desire to stop training, develop health conditions or injury that preclude safe participation of exercise over the course of the intervention, we will discontinue training. Participants will be asked to not participate in another structured exercise regimen or intervention over the course of their participation in either the HIIT or MICT group, otherwise they will not be allowed to continue participation. However, during the period between T1-T2, participants will not be asked to refrain from further participation in exercise. This may influence outcomes at assessments at T2, as participants may engage in another exercise program after completing T1 assessments. In order to address this, we will use the Physical Activity Scale for Individuals with Physical Disabilities (PASIPD)[60], and administer it mid-way in between T1 and T2.

2.4 Outcomes

Assessments

Prior to the initial assessment, the assessor will obtain written consent from the participant. Baseline descriptive characteristics will be collected at T0 and include biological sex, age, weight, height, body mass index, education level, characteristics of stroke and past medical history. Additionally, degree of neurological deficit (National Institutes of Health Stroke Scale, NIHSS [61]), upper limb motor function (Chedoke McMaster Stroke Assessment, CMSA [62]) and global cognitive function (Montreal Cognitive Assessment; MoCA[63]) will be assessed at baseline. Medication use will be recorded at all time points. PASIPD[60] will be assessed at all time points and midway through the 8-week follow-up (Week 16), to account for changes in physical activity

between T1 and T2. All outcomes, apart from enjoyment, will be collected T0-T2 at both sites. To minimize participant fatigue, assessments will take place over 3 days (1.5 hours each). Data collections forms can be provided upon request to study PI's. **Figure 3** provides a timeline and collection of outcomes.

	STUDY PERIOD								
	Screening	Enrolment	Allocation	Post-allocation					
TIMEPOINT	**Pre-T0**	**T0**	**T0**	**Week 1**	**Week 6**	**Week 12**	**T1**	**Week 16**	**T2**
ENROLMENT:									
Eligibility screen	x	x							
Informed consent		x							
Baseline assessment		x							
Allocation			x						
INTERVENTIONS:									
High-intensity interval training									
Moderate-intensity interval training)									
ASSESSMENTS:									
Demographic Information		x							
NIHSS		x							
CMSA		x							
MoCA		x							
PASIPD		x					x	x	x
CSE		x					x		x
SICI		x					x		x
ICF		x					x		x
Resting BP		x					x		x
Arterial Stiffness		x					x		x
VO_2peak		x					x		x
Waist-Hip ratio		x					x		x
10mWT		x					x		x
6MWT		x					x		x
Motor Learning		x					x		x
PACES					x	x			
BREQ-3				x	x	x			x

NIHSS: National Institutes of Health Stroke Scale; CMSA: Chedoke McMaster Stroke Assessment; MoCA: Montreal Cognitive Assessment; PASIPD: Physical Activity Scale for Individuals with Physical Disabilities; CSE: Corticospinal excitability; SICI: Short intracortical inhibition; ICF: Intracortical facilitation; BP: Blood pressure; VO_2peak: Cardiorespiratory fitness; 10mWT: 10 meter walk test; 6MWT: 6 minute walk test; PACES: Physical Activity Enjoyment Scale; BREQ-3: Behavioural Regulation in Exercise Questionnaire 3.

Figure 3. Schedule of enrolment, interventions, and assessments.

Primary Outcome

Neuroplasticity

Our study will assess changes in neuroplasticity with TMS applied to the representational areas of the hand's first dorsal interosseous muscle (FDI) on M1. We selected this muscle because it can be elicited at relatively low stimulation intensities that are more comfortable for the participant [64], and because it is involved in upper limb activities of daily living such as grasping objects. We will also apply TMS on both hemispheres [22, 65], so that we can assess whether exercise will restore imbalances in interhemispheric excitability, an important marker of motor recovery after stroke [45].

General TMS Procedures:

Electromyography will be recorded from the FDI on the participants affected and unaffected side. The position of electrodes will be photographed (with permission from the participant), to ensure repeatability in all assessments (T0-T2). Using neuronavigation (Brainstorm, Rouge Research), we will co-register the heads of participants to a generic MRI template to identify and mark optimal areas for stimulation (a "hotspot") on M1 to elicit a motor evoked potential (MEP). The amplitude of the MEP will indicate the level of muscle activation in response to TMS, used to quantify excitability. Neuronavigation software will allow us to save the "hot-spot" of each person in order repeat the stimulation with better spatial accuracy [66] . Once the "hot-spot" has been identified, we will determine the resting motor threshold (RMT), the minimum intensity to obtain 10 MEPs with an amplitude of 0.05μm out of 20 stimulations [64]. Electrical stimulation over the median nerve (FDI) will be used to assess changes in muscle contractility. This is assessment has been demonstrated to be feasible for patients with stroke [67], and our

laboratory has shown that normalizing MEPs amplitude to muscle contractility is important for obtaining accurate cortico-spinal excitability data in exercise studies which utilize applied TMS at different time points [9].

Primary outcome: Cortico-spinal Excitability (CSE):

CSE will be measured using a single pulse TMS protocol. Two blocks of 25 stimulations, per hemisphere, that are elicited at an intensity of 120% of the resting RMT will be delivered over the FDI "hotspot" at rest and during an isometric contraction performed at 10% of the maximal force. This number of stimulations is sufficient to obtain a reliable measure of CSE using TMS [68]. Each stimulation will be applied 5 seconds apart to reduce the effects of repetitive TMS on excitability [69]. A total of 50 stimulations will be averaged to obtain the composite MEP amplitude [9, 70] . MEP amplitude is examined because it can predict exercise-induced improvements in procedural memory and skill retention in healthy subjects [9] and motor recovery in stroke [8].

Secondary Outcomes

Neuroplasticity

Secondary outcome: Short Intracortical Inhibition and Intracortical Facilitation (SICI and ICF):

SICI and ICF will be measured using a paired-pulse TMS protocol that will use a conditioning stimulus of 80% RMT, followed by a supra-threshold stimulus (120% RMT) delivered at rest after 2.5ms (inhibition) and 12ms (facilitation), respectively. These intervals between stimuli capture changes in excitability after motor learning[71] and are susceptible to change with exercise in people with chronic stroke[22]. The amplitude of the MEP elicited by the sent

stimulus normalized to the MEP amplitude at baseline will provide an estimate of inhibition and facilitation [46]. A total of 25 paired-pulses (separated by 2 seconds), per hemisphere, will be delivered at the FDI. Our laboratory has used these measures of excitability in previous study to investigate the effects of single bout of HIIT in individuals with chronic stroke [22]. ICF and SICI are important markers of neuroplasticity, specifically related to motor learning processes [46, 72], and has been used to predict motor recovery post-stroke [8].

Cardiovascular Health

Secondary outcome – Resting BP:

Resting BP will be taken at the brachial artery of the less affected arm using an automated BP monitor. Two readings will be taken and averaged, and if values differ by > 5 mmHg, 2 more readings will be taken, and another average will be taken for 4 readings.

Secondary outcome – Arterial Stiffness*:*

Central Pulse Wave Velocity (PWV), represents the pulse wave propagation within the arterial tree [73], and is considered the gold standard marker of arterial stiffness. PWV will measured using applanation tonometry, a noninvasive technique, to capture pulse waveforms at the carotid and femoral arteries. Central PWV will be calculated by following equation: PWV= (meters, D)/(seconds, Δt), where Δt is the travel time of the propagated wave between carotid and femoral arteries, and D is the distance between the two locations being recorded [74]. An increase in PWV is associated with an increased risk of cardiovascular morbidity and mortality, respectively [75]. Previous study has described an inverse relationship between PWV and physical fitness post-stroke [76].

***Secondary outcome – Cardiorespiratory fitness*:**

Cardiorespiratory fitness will be assessed by assessing the VO_2peak of participants. VO_2peak will be determine by a graded cardiopulmonary exercise test (CPET) on recumbent stepper which has been validated for individuals with stroke [55], and has been use by our lab in previous study[22]. Cardiovascular responses will be monitored using a 12-lead ECG and BP monitor. RPE will be recorded during the exercise test [77]. Our laboratory at the JRH will have a medical support team, including an on-call physician, in the case of any medical emergency during this assessment.

Secondary outcome – Waist-hip ratio:

Waist-hip ratio, is amongst the strongest predictors of risk for stroke, independent of other vascular risk factors [78]. It will be determined from the waist circumference measured at the level of umbilicus, and hip circumference will be taken at the level of the greater trochanters. Markers of abdominal obesity are easily measured in clinical settings and are stronger predictors of cardiovascular events [79, 80] than body mass index.

Motor Function

Secondary outcome - Gait Speed: We will assess gait speed using a self-paced 10-meter walk test (10mWT). Participants will be timed starting at the 4-meter mark, up until the 8-meter mark of the 10-meter course. Speed over 6 meters will provide the result for one trial. The average of both trials will be the outcome for gait speed. Participants will be permitted to use gait aids (e.g., walker, cane) during this assessment.

Secondary outcome -Walking Capacity:

The 6-Minute Walk Test (6MWT) will be used to measure walking capacity. Participants will walk along a 20-metre straight course as many times as possible within 6 minutes [81]. The primary outcome of this test is the distance walked (in meters) during the test. Pre and Post -test Resting BP, HR and RPE will also be assessed. During this test, participants will be permitted to use gait aids.

Secondary outcome - Motor Learning:

For this study, we will use computerized visuomotor task that will require modulating force [22] during a hand-grasping, as this skill is essential in the performance of many activities of daily living. The participant will be seated in front a computer screen, be asked to make a fist to applying force with their most affected hand on a handgrip. If the affected hand is unable to hold or modulate force on the handgrip due to disability, the unaffected side will be used.

This handgrip will control the position of cursor displayed on the screen. The goal of the motor task will be to apply appropriate force in order to move the cursor so that it touches as many targets on the screen, as accurately as possible. Participants will perform 4 blocks of 20 trials, and the score for each block will be calculated as the total time that the cursor is on the target areas, divided by the total time of each trial, multiplied by 100.

Psychosocial Responses to Exercise

***Secondary outcome - Enjoyment*:**

Enjoyment will be assessed after week 6 and T1, using the Physical Activity Enjoyment Scale (PACES), which has been validated for older adults with functional limitations [82] and people with multiple sclerosis [83]. Participants will be asked to respond to the prompt, “Please rate how

you feel at this moment about the exercise you have been doing" in relation to several domains using a 7-point scale (e.g., 1=does not make me happy, 7=makes me happy). A total score is calculated (ranging from 8 to 56). Higher scores indicate greater enjoyment.

***Secondary outcome - Motivation*:**

The Behavioral Regulation Exercise Questionnaire-3 [82, 84] will be used to assess participants' motivation for physical activity at T0, T1 and T2 and will be administered after the 1st week of training and at the end of training. Participants will respond to 24 items using a 5-point Likert scale (e.g., 0=Not true for me, 4=Very true for me), covering different types of motivations. Autonomous motivation (i.e., internally regulated motivation) scores will be calculated by averaging the score on the identified, integrated, and intrinsic regulation subscales. External motivation will consist of the mean of the external and introjected regulation scores. Earlier versions of this questionnaire (BREQ-2) have been described as reliable and have been validated questionnaire previously in individuals with coronary heart disease[85, 86]

For both questionnaires, French or English versions will be provided depending on the language preference of the participant. If a participant has a speech or language difficulty, assessors will utilize a third-party to provide clarification of the questionnaire items and participant responses.

Sample size estimation

Based on previous data[22] and using a linear mixed model, we estimated that we would require 32 participants per group (n = 64 total) to detect a 5% increase at T1 in the resting MEP amplitude and intracortical inhibition of the affected hemisphere's M1 in the HIIT group. An

increase of 5% is associated with improved motor function in stroke[71]; therefore, we will consider this difference between HIIT and MICT groups to be clinically significant. The statistical package G*Power was used to determine the sample size required to obtain a power of 80% (alpha < 0.05). We have increased the sample size to 40 per group (n=80 total) to accommodate for a 20% attrition rate.

Statistical analysis

Estimates of the effect of HIIT and MICT at the end of the intervention (T1) for all outcomes will be determined using linear mixed models. Baseline scores (at T0), age and sex will be included as covariates for sub-analysis. The primary analysis focuses on T1, but T2 will also be included in the model (except for enjoyment, which will not be measured at T2) to increase the statistical efficiency of the estimate. If group interaction effects are significant, t-tests based on the linear mixed models will be employed as planned pairwise comparisons to determine differences between HIIT and MICT. Sex-based subgroup analyses will also be performed for exploratory purposes.

Participant data will be analyzed based on intention-to-treat, therefore linear mixed models will be the preferred method of analysis as it is more flexible than analysis of variance, and allows for the correlation of repeated measures within subjects and missing data, as long as missing data are missing at random [87]. Interactions between changes between in primary, secondary outcomes will be explored with the Freedman-Schatzkin test, which allows for the identification of mediators of change in small-scale exercise studies [88].

Blinding

Participants will be blinded to group allocation until completion of T0 assessments. Due to constraints on resources, assessors will not be blinded to group allocation. However, participants will not be told that there is another training group and will not have sessions in which they train while a participant of another training group also takes place. Group allocation will be blinded in data analysis.

Data management

Data will be collected from assessments and recorded on paper case report forms. Data from these forms will be entered and stored on a secure database that is shared between both sites. Paper case reports will be stored in a secure location at each site. All information collected from participants will be recorded under a given subject identifier that will be specific to the study site (JRH site: IM201, IM202…; McMaster site: e.g., IM101 etc.).

Confidentiality

Any identifying information, outside of relevant outcome data will not be provided to the opposite site and will be stored separately from collected outcome data. Requests for data from either site will require the expressed permission of the site's PI (JRH: MR, McMaster: AT). Access to JRH and McMaster databases will be password protected with only MR and LR, and AT and KM having access to JRH and McMaster databases respectively.

Safety and adverse event monitoring

Adverse events that are related or unrelated to training, including but not limited to: injuries, falls and muscle soreness, or fatigue, that affect activities of daily living, will be asked about and documented by instructors prior to each training session.

Protocol modifications

Any changes to the current study protocol (version 1.0) will be communicated to study investigators and the research ethics boards of the Centre de Recherche de Readaptation du Montréal and Hamilton Integrated Research Board, and electronically to the trial registry (ClinicalTrials.gov).

Oversight and monitoring

The steering committee will be comprised of 4 investigators (LR, KM, MR, and AT), and will hold quarterly meetings to monitor trial activity, and be responsible for the dissemination of results (i.e., manuscripts, presentations, and knowledge translation). LR and KM will be responsible for communication among investigators, coordinating meetings or teleconferences, coordinating staffing, assisting in training workshops and day-to-day trial activities. The External Advisory Committee will include a physician in stroke rehabilitation, physical therapist, healthcare administrator and a person with stroke. They will ensure that the study design and interpretation of findings are applicable to current practice.

The Data and Safety Monitoring Committee will comprise of three individuals external and independent to the study (a statistician, a physician, a physical therapist) to audit study progress, review adverse events and advise termination of the study if the safety data are of

sufficient concern. All adverse events will be immediately reported to this committee, as well as relevant ethics boards.

Dissemination plans

Collaborators who have actively participated in the concept of the study design, protocol development and acquisition of data will be invited to co-author subsequent output from this study. Results will be disseminated through peer reviewed publications and scientific presentations as well as through the investigators' professional networks (Canadian Partnership for Stroke Recovery, Canadian Stroke Consortium, Ontario Central South Regional Stroke Program activities, Quebec Rehabilitation Research Network) and local stroke recovery groups. Exercise and rehabilitation specialists will be informed during presentations of the results of the study in our affiliated clinical sites across Canada (e.g., JRH, GF Strong Rehabilitation Centre). We will also capitalize on other initiatives led by our research team to facilitate knowledge transfer and exchange that include different stakeholders.

Datasets compiled from the acquisition of participant's data during this study, and statistical code used to analyze participant data will be made available in the repository of journals upon publication and/or available upon request.

2.5 Discussion

Cardiovascular exercise is a valuable tool in stroke rehabilitation, as it promotes mechanisms of neuroplasticity, and improves upon measures cardiovascular health, ameliorating recovery and reducing the risk of stroke recurrence. Cardiovascular exercise, in the form of MICT, is already widely employed in stroke exercise rehabilitation, but the challenge that remains is how

stroke rehabilitation professionals can implement exercise at intensities that produce the desired clinical effect (i.e., HIIT).

Following this, it is also crucial to understand how higher intensities of exercise can mediate improvement in neuroplasticity and cardiovascular health. Improvement in these domains is vital for functional recovery and reducing the burden of disability in individuals recovering from stroke. Understanding the factors which influence participation and adherence in these types of exercise can help stroke rehabilitation professionals to more effectively implement and tailor exercise prescription during treatment.

This study will be the amongst the first to comprehensively compare the effectiveness of multiple bouts of HIIT and MICT on important determinants of stroke recovery: neuroplasticity, cardiovascular health, and motor function. In addition, this study will also examine the psychosocial response to exercise, which is important for the maintenance of exercise behaviours and participation in training modalities like HIIT. The benefit of exercise for reducing recurrent stroke events and promoting functional recovery is well-known [25], however, no studies, to our knowledge, have compared the effects of HIIT vs. MICT for simultaneously improving neuroplasticity and cardiovascular health. Furthermore, few studies have examined aspects such as enjoyment and motivation, in this clinical population, which are important to evaluate exercise sustainability. Understanding the long-term effects of such interventions is also lacking in the current literature, and this study will also address outcomes in this context, by including an 8-week follow-up assessment.

This two-arm multisite study design will allow for an efficient recruitment of individuals for to meet the target sample size. Both study sites are established in settings which will provide access to a large population of individuals recovering from stroke. The prescription of exercise, by

determining HRR, will be personalized to the capacity of the participant at baseline and will also consider RPE and the use of medications such as beta-blockers, in order to accurately prescribe exercise intensities depending on the group. This will enable participant engagement and adherence to the study protocol, while also safely implementing the exercise program while progressively increasing the intensity of exercise. The apparatus for exercise, NuStep Recumbent steppers, will enable the safe participation of exercise by limiting the risk of falls and injury, in comparison to treadmill or stationary bike exercise.

In response to COVID-19-related institutional regulations and developed guidelines [89], group training will not be permitted, but this will therefore necessitate a 1:1 instructor-to-participant supervision. As part of the exercise instruction, data collection of heart rate and workload will be more readily collected and reported, and vital signs in response to exercise, such as RPE and BP will be much more easily assessed over the course of training. The collection of this data, particularly the heart rate and workload data will allow us to examine the potential efficiencies of HIIT and ability of participants to attain prescribed intensities.

The inclusion of an 8-week follow-up in this study is an important aspect that will allow us to investigate the long-term effects of HIIT and MICT, after culmination of an exercise intervention, which is understudied in the stroke population. By examining all outcomes after an 8-week period, this study will be able assess the sustainability of benefits after participation in cardiovascular exercise. By examining this in the context of comparing HIIT and MICT, we will be able to determine whether the intensity of exercise mediates the long-term effects on study outcomes.

The design of this study does have several limitations. Firstly, there are limitations in the blinding of subjects and assessors. As mentioned previously, due to a lack of resources, staffing

availability has made it not possible to blind assessors and exercise instructors from group assignment. Therefore, we are also unable to blind assessors who have conducted assessments at baseline, T0 and T2.

Secondly, the implementation of HIIT or MICT itself may influence psychosocial responses of enjoyment and motivation. Exercise instructors may require more interaction with participants in the HIIT group, because of the frequent change in intensity level and opportunity for feedback and use of encouragement. This may not occur to the same extent in the MICT group due to the continuous level of intensity. Our research group has implemented several methods, including standardized feedback across both groups to limit these potential effects of HIIT and MICT exercise instruction.

As a multicenter study, this setting may lead to potential inconsistencies between sites with respect to outcome assessments and exercise instruction. This necessitates that there is careful monitoring and standardization of assessment techniques and exercise instruction. Our research group and our Steering Committee, in particular, will coordinate training sessions, to implement proper assessment techniques and standardization in both study sites, and regular meetings to maintain adherence to standard operating procedures.

Impact of Study

As mentioned previously, there is strong evidence for the use of cardiovascular exercise, and it is a recommended component of stroke rehabilitation [90]. As it currently stands, the conventional use of MICT could be an insufficient cardiovascular stimulus to elicit improvement in neuroplasticity and cardiovascular health [91]. Attaining higher intensities of exercise using HIIT could provide stroke rehabilitation professionals, including physical therapists, an effective

method to further improve stroke recovery. This evaluation of HIIT and MICT will provide knowledge on the benefits to multiple domains pertaining the stroke recovery and adherence to exercise behaviour. Physical therapists in stroke rehabilitation will benefit from a greater understanding of the potential efficiency of HIIT as an exercise modality, and as an effective method to attain high intensities of exercise in the stroke population

This study will provide a comprehensive examination of the efficacy of a novel HIIT, in comparison to an established MICT method, for promoting neuroplasticity and cardiovascular health, while also addressing the underlying psychosocial responses to these exercise modalities. An understanding of the difference between HIIT vs. MICT exercise rehabilitation methods will provide greater understanding into intensity-related effects on mechanistic changes in neurological and cardiovascular systems during stroke recovery. This thorough appraisal of HIIT and MICT cardiovascular exercise encompasses multiple domains pertaining to stroke rehabilitation and adherence to exercise (neuroplasticity, cardiovascular health, motor function and psychosocial response to exercise).

Therefore, our findings will provide significant insight into the efficacy of multiple aspects of HIIT, in comparison to conventional MICT, as a new treatment modality for clinicians to employ safely and effectively for the benefit of individuals recovering from stroke. Findings from this study will inform clinicians involved with stroke rehabilitation and inform prescription of training programs to provide long-term benefit for health and functional recovery. Information obtained from this study will help in the individualized tailoring of exercise programs following stroke, and provide integral support for future investigations into the application of HIIT in stroke populations, such as aspects of exercise dosage, and type of training

Trial Status

This trial is currently ongoing, with activity and recruitment beginning in September 2019. After a hiatus in research activities due to COVID-19 shutdowns at both sites in March 2020, recruitment resumed in August 2020 and study activities are currently underway. It is expected that recruitment will be completed by April 2023.

Abbreviations

HIIT: High-intensity interval training; MICT: Moderate-intensity continuous training; TMS: Transcranial Magnetic Stimulation; M1: Primary motor cortex; BDNF: Brain Derived Neurotrophic Factor; BP: Blood pressure; MRI/CT: Magnetic resonance imaging/computed tomography; JRH: Jewish Rehabilitation Hospital; HR: Heart rate; RPE: Rate of perceived exertion; HRR: Heart rate reserve; MoCA: Montreal Cognitive Assessment; MEP: Motor evoked potential; RMT: Resting motor threshold; FDI: First dorsal interosseus muscle; CSE: Cortico-spinal excitability; SICI: short-intracortical inhibition; ICF: Intracortical facilitation; PWV: Pulse wave velocity; CPET: cardiopulmonary exercise test; ECG: electrocardiogram; 10mWT: 10 meter walk test; 6MWT: 6-minute walk test; PACES: Physical Activity Enjoyment Scale; BREQ-3: Behavioural Regulation in Exercise Questionnaire-3;

Declarations

Funding

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Availability of data and materials

Anonymized datasets that are prepared and/or analyzed during the current study will be available from in the repository of journals upon publication. We will state in the published articles that data are available upon reasonable request to PI's MR and AT. These two investigators will have access to the final trial dataset

Authors' contributions

LR and KM were involved in study design, protocol development and manuscript preparation. BDH, KSN, and EW were involved in protocol development and manuscript editing. MR and AT are the principal investigators, and were involved conception of the study design, protocol development, grant preparation and application, manuscript preparation and editing. JJE, SNS, JF, AJN, JC and DM were involved in manuscript editing, acquisition of financial support.

Acknowledgements

Not applicable.

Ethics approval and consent to participate

Ethical approval to conduct this study has been granted by the Centre de Recherche de Readaptation du Montréal (CRIR – 1310 - 0218) and Hamilton Integrated Research Board (HIREB – 4713). Written, informed consent to participate in this study will be obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest with respect to the research and authorship, and publication of this article.

2.6 References

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2.7 Supplementary Material

- Additional File 1.

SPIRIT Checklist for *Trials*

		Reporting Item	Page and Line Number	Reason if not applicable
Administrative information				
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1: 3-4	
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 2: 48	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a	This trial is not registered with the World Health Organization, but was registered at ClinicalTrials.gov
Protocol version	#3	Date and version identifier	Page 8: 6	
Funding	#4	Sources and types of financial, material, and other support	Page 26: 29	
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	Page 27: 23-25	
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Page 26:33-35	
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Page 26:28-35	

Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Page 20-21: 47- 59, 3-15	
Introduction				
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Pages 3-6; 3-60, 3-60, 3-60, 3-35	
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	Page 4, 5, 6: 18-42, 23-52, 22-35	
Objectives	#7	Specific objectives or hypotheses	Page 6-7: 40-59, 3-47	
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	Page 8: 18-20	
Methods: Participants, interventions, and outcomes				
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 8: 42-46	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 9: 12-45	

Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 10-12: 45-60, 3-59, 3-13.	
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	Page 12 : 35-54	
Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	Page 12: 20-34	
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 12: 37-40	
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 13-18: 3-60, 3-60, 3-60, 3-60, 3-60, 3-20	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 8: 35 (Figure 1)/ Page 13: 37 (Figure 3)	
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 18: 25-42	

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 9-10: 49-57, 3-18	
Methods: Assignment of interventions (for controlled trials)				
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 10: 24-27	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page 10: 27-30	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 10: 33-35	
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 19: 25-35	
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Page 19: 25-35	
Methods: Data collection, management, and analysis				
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote	Page 13: 5-38	

		data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol		
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 12: 28-33	
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 19: 38-52	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 18-19: 47-59 ,3-20	
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 19: 3-5	
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 19: 8-12	
Methods: Monitoring				
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is	Page 21:7-15	

		independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed		
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Page 20-21: 46-60, 3-17	
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 20: 20-28	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 20: 46-60	
Ethics and dissemination				
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	Page 27: 10-18	
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	Page 20: 32-39	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 9: 42-45	

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a	Research ethics boards CRIR, and HIREB do not require additional consent provisions.
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 20: 5-16	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 27: 39-45	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 26: 49-50	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a	There are no specific provisions for post-trial care and/or compensations. However, the research activities are performed in hospitals and research centers covered by insurance policies that will cover any eventual compensation if malpractice is demonstrated.
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 21: 28-43	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	Page 21: 22-25	

Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 21: 43-50	
Appendices				
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a	No details, images or videos relating to an individual person is contained within this manuscript, which requires written informed consent.
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a	Biological specimens are not collected in this trial.

Addressing Gap #1: *How does exercise intensity affect neuroplasticity in chronic stroke?*

The randomized controlled trial (RCT) described in Chapter 2 constituted an ambitious multi-site endeavor which aimed to address several important gaps in the current existing literature on the effect of high-intensity interval training (HIIT) in stroke rehabilitation. The primary objective of this RCT, was to address the primary outcomes of change in cortico-spinal excitability (CSE), in response to a 12-week HIIT or moderate-intensity continuous protocol (MICT). From the date of publication of the manuscript in Chapter 2, and upon completion of this data collection on December 2023, this trial has remained the only and largest trial of its kind to compare HIIT vs. MICT in CSE outcomes, using transcranial magnetic stimulation (TMS).

Completion of this trial during the COVID-19 pandemic necessitated several changes to the original protocol in Chapter 2. Firstly, due to institutional restrictions at both sites recruitment of participants was either limited or prohibited for large portions of the study period from between March 2020 and August 2023. Secondly, resource constraints at the McMaster site prevented the collection of the primary CSE outcomes using TMS. Therefore, data collection of these measures relied solely on the Jewish Rehabilitation Hospital site for recruitment, data collection and training of participants eligible for assessment. Nevertheless, we were able to achieve the largest sample ($n = 56$) size of any trial to date that compares the effect HIIT vs. MICT on CSE using TMS, in a population of post-stroke individuals.

The following chapter will address the first gap in the literature identified, in Chapter 1, concerning exercise-intensity mediated effects on post-stroke neuroplasticity. In this chapter, we will discuss the potential mechanisms that underlie exercise-mediated effects on neuroplasticity, and the role of intensity, elucidated using TMS.

CHAPTER 3: Modulating Brain Excitability with High and Moderate-Intensity Cardiovascular Exercise in Chronic Stroke: A Randomized Controlled Trial.

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3.1 Abstract

Background: Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique that assesses cortico-spinal excitability (CSE), a marker of the functional integrity of the cortico-spinal tract. Acute cardiovascular exercise has shown to transiently produce changes CSE in individuals' post-stroke but the long-term neuromodulatory effects of multiple sessions of cardiovascular training and the role of exercise intensity are unknown.

Objective: To examine the effects of 12 weeks of high-intensity interval training (HIIT) vs. moderate-intensity continuous training (MICT) on CSE measures obtained with TMS applied on the ipsilesional (ILH) and contralesional (CLH) hemispheres.

Methods: Fifty-six individuals with chronic stroke were randomly assigned to a 12-week HIIT (n=28) or MICT (n=28) program. CSE measures were obtained at baseline and at the end of the intervention. Participants with cortical and/or subcortical lesions were included in linear mixed model analyses to compare exercise-induced changes in CSE measures and their respective interhemispheric ratios.

Results: HIIT and MICT increased resting motor evoked potential (MEP) amplitude ($p=0.003$), decreased resting motor threshold -rMT- ($p<0.030$), and reduced intracortical facilitation -ICF- ($p=0.049$) in the ILH. No CSE changes in the CLH were observed. HIIT and MICT rebalanced interhemispheric rMT ($p=0.020$) and ICF ratios ($p=0.040$), and increased resting MEP amplitude ratio ($p=0.020$). CSE changes were not significantly different between HIIT and MICT.

Conclusions: Cardiovascular exercise increases excitatory CSE measures in the ILH and reduces interhemispheric imbalances, but intensity does not have a moderating effect. More studies are needed to determine the functional relevance of exercise-induced changes in CSE.

Trial Registration: ClinicalTrials.gov NCT03614585

Keywords: Stroke; Cardiovascular exercise; Cortico-spinal excitability; Neuroplasticity; Transcranial Magnetic Stimulation.

Abbreviations

BDNF – brain-derived neurotrophic factor

CE - cardiovascular exercise

CI – confidence interval

CLH – contralesional hemisphere

CSE - cortico-spinal excitability

CSP – cortical silent period

CST - cortico-spinal tract

EMG – electromyography

FDI – first dorsal interosseus muscle

GABA - γ-aminobutyric acid

HIIT – high-intensity interval training

HRR – heart rate reserve

ICF – intracortical facilitation

ILH - ipsilesional hemisphere

M1 – primary motor cortex

MEP – motor evoked potential

MICT – moderate-intensity interval training

MVC – maximal voluntary contraction

NMDA - N-methyl-D-aspartate

RCT – randomized controlled trial

rMT – resting motor threshold

SICI – short-interval intracortical inhibition

T0 – baseline assessment

T1 – post-intervention assessment

T2 – follow-up assessment

TMS - Transcranial magnetic stimulation

3.2 Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique that can assess structural and functional changes in the cortico-spinal tract (CST), a structure whose integrity is key for upper limb motor recovery post-stroke[1]. Promoting neuroplasticity to optimize recovery is a primary goal of stroke rehabilitation[2]. Cortico-spinal excitability (CSE), assessed with TMS, is a surrogate measure of neuroplasticity in the CST that can be used to investigate whether interventions like cardiovascular exercise (CE) change the brain to impact motor recovery[3].

A stroke usually reduces the excitability of the ipsilesional hemisphere (ILH), disrupting interhemispheric CSE balance[4]. However, during stroke recovery, a dynamic rebalance of CSE driven by excitatory and inhibitory activity regulates processes underlying neuroprotection, neuronal repair and reorganization[5]. Excitation and inhibition are mediated by glutamate and γ-aminobutyric acid (GABA) receptors, respectively[5]. The action of these two neurotransmitters, which has shown to be important for motor learning[6, 7] and recovery[5, 8] post-stroke, can be examined with single and paired-pulse TMS protocols.

Single-pulse protocols evaluate excitation and inhibition from motor representational areas of the primary motor cortex (M1), a therapeutic target area for motor recovery post-stroke[9]. Corollaries of reduced excitability such as the absence of motor-evoked potentials (MEP)[10] and/or higher resting motor thresholds (rMT)[11] in the ILH have usually been associated with motor impairment and poor recovery[12]. Single-pulse protocols can also assess intracortical inhibition by examining the cortical silent period (CSP), a marker that has been associated with $GABA_B$ receptors activity[13].

Paired-pulse TMS protocols can measure intracortical facilitation (ICF) and short-interval intracortical inhibition (SICI). These two CSE measures provide, respectively, information on glutamate and $GABA_A$ activity in cortical circuits involved in post-stroke motor learning[6, 7] during recovery[5, 8]. Symmetry between the ILH and contralesional hemisphere (CLH) in both single and paired-pulse CSE measures has been also been identified as a marker of post-stroke recovery[14], with interhemispheric CSE balance associated with better motor outcome[1].

Regular cardiovascular exercise (CE) mitigates the risk of stroke recurrence, improves cardiorespiratory, metabolic and functional outcomes[15], and has shown promise in promoting neuroplasticity[16, 17]. In stroke animal models, CE upregulates neurotrophins such as brain-derived neurotrophic factor (BDNF)[18], a protein that affects excitatory and inhibitory mechanisms, and promotes positive adaptations such as reductions in lesion size, synaptogenesis, and dendritic growth[19]. In humans, CE has also shown to stimulate neuroplastic mechanisms[18, 20] leading to adaptations that can be captured with CSE[3, 21].

Higher CE intensities promote greater upregulation of neurotrophins[20, 22] and changes in excitation and inhibition[22-24]. In neurotypical individuals, a single bout of high-intensity CE elicits greater increases in excitability and reductions in inhibition compared to moderate-intensity exercise[22, 25]. In individuals post-stroke, acute high-intensity exercise increases MEP amplitude in the ILH[26], rebalances SICI interhemispheric ratios, and improves motor learning[27]. In contrast, acute light and moderate-intensity CE does not change CSE[28, 29]. Furthermore, a single bout of high-intensity interval training (HIIT) produces greater increases in CSE in the ILH than a bout of moderate-intensity continuous training (MICT)[21, 29].

Evaluating the long-term neuromodulation effect of CE on CSE requires multiple bouts of exercise, yet there is not enough evidence supporting the effect of chronic CE on CSE post-stroke[30,

[31]. Even less is known about the impact of exercise intensity. We conducted a 12-week randomized controlled trial (RCT) comparing HIIT and MICT on CSE in individuals in the chronic stage post-stroke (>6 months post-stroke). We hypothesized that both types of exercise would modulate CSE but that the higher intensities achieved during HIIT would produce greater increases in excitability and reductions in inhibition of the ILH, and that these changes would improve interhemispheric CSE balance.

3.3 Materials and Methods

Study Design

This registered RCT (NCT03614585) was conducted at the Jewish Rehabilitation Hospital (JRH, Laval, QC, Canada) and McMaster University (Hamilton, ON, Canada) between September 2019 to December 2024. However, due to COVID restrictions, TMS assessments were performed exclusively at the JRH. Assessments were performed at baseline (T0) and post-intervention (T1). A follow-up assessment (T2) took place 8 weeks after T1, but T2 data is reported in a separate manuscript. Age, sex, time since stroke event, stroke location and type, and medication use were collected at baseline. Measures of disability[32], degree of neurological deficit[33], upper-limb motor function[34], physical activity[35], and global cognitive function[36] were also recorded. The RCT was approved by the research ethics board (CRIR-1310-0218) and informed consent was obtained from all participants. Details of the design of the RCT can be found in the published protocol[37].

Participants

Individuals who were 40-80 years old and 6-60 months after first-ever single ischemic or hemorrhagic stroke confirmed by magnetic resonance imaging or computed tomography were

recruited. The chronic phase of stroke recovery (>6 months post-stroke)[38], was chosen to reduce the CSE variability commonly observed in earlier phases of recovery[8]. Participants were excluded if they presented with contraindications to TMS[39]. More details on inclusion/exclusion criteria are provided in the protocol[37].

Only participants with lesions located in cortical or subcortical structures were included in the analyses. Individuals with brainstem or cerebellum lesions were excluded because the spatial resolution of applying TMS on M1 limited targeting to mostly surface cortical structures and interhemispheric ratios cannot be reliably estimated when the lesion is located in brainstem or cerebellum[40]. Participants with subcortical lesions were included because subcortical structures may be reached through trans-synaptic cortico-subcortical connections[40-42].

Randomization and Blinding

A computer-generated group assignment (www.randomizer.org) using a 1:1 allocation ratio was used to randomize participants into HIIT or MICT. Investigators not involved in recruitment, consent, or data collection (MR and AT) generated the random allocation sequence. Randomization for the JRH site was conducted by the counterpart site, and allocation was concealed until after obtaining participant consent and completing baseline assessments. TMS assessors were not blinded to group allocation due to resource limitations.

Exercise Interventions

HIIT and MICT involved 12 weeks of training performed 3 days/week on recumbent steppers (NuStep T4r; NuStep LLC, Ann Arbor, MI, United States). Sessions were held on alternate days to maximize recovery and adaptations[43]. Participants were instructed to not engage

in other structured exercise programs during study participation. Prescription of exercise intensity for HIIT or MICT was determined using a cardiopulmonary exercise test[44] performed at T0. Details on the test and heart rate reserve (HRR) method[45] used for exercise prescription are provided elsewhere[37].

HIIT sessions involved 10×1 minute high intensity bouts (80-100% of HRR) interspersed with 9×1 minute of active recovery at low intensity (30% HRR). High-intensity bouts targeted 80% HRR and progressively increased 10% every four weeks. For MICT, participants initially exercised at 40% HRR for 20 minutes, and progressively increased intensity 10% HRR and duration 5 minutes every 4 weeks. Both protocols included a 3-minute warm-up and 2-minute cool-down periods at 30% HRR. Total session duration of HIIT was 24 minutes and for MICT from 25 to 35 minutes. HR was monitored using sensors (Polar Electro Oy, Kempele, Finland) and rate of perceived exertion (RPE) with the 6-20 Borg scale[46]. More training details are presented in **Supplementary Table 1**.

Transcranial Magnetic Stimulation Procedures

TMS assessments at T0 and T1 were held at a similar time of day to minimize circadian variations. Positioning of head, hands and arms including the angles of seat recline and arm placement were recorded at T0 and replicated at T1 to ensure consistency. The maximal voluntary contraction (MVC) of the muscles of the right and left hand was assessed using a custom script (LabView, National Instruments, Austin, Texas, USA)[47]. Participants were instructed to "squeeze" a response hand-grip force transducer while visual feedback on force level was provided. They performed 2 trials per hand for 3 seconds, separated by a 30-second pause. The highest MVC for each hand was recorded.

TMS was applied by using a 70-mm magnetic coil and Bistim^2 stimulator (The Magstim Company, Whitland, United Kingdom). Neuronavigation (Brainsight, Rogue Research, Montréal, Canada) was used to co-register participant head dimensions to an MRI template for the purposes of stimulation targeting and recording accurate coil position. The coil was placed at a 45° angle from the mid-line and stimulations were applied bilaterally on representational areas of the first dorsal interosseous (FDI) muscle of M1 while participants were seated. The FDI is involved in common upper limb actions such as grasping objects and its activation can be elicited with low stimulation intensities[13]. MEPs amplitude was measured bilaterally by recording electromyographic (EMG) activity using 2 Ag-Cl surface electrodes (Ambu, Copenhagen, Denmark). EMG data were acquired at 2000 Hz with a gain of 300 Hz and filtered using a high- and low-pass cut-off filter of 10 Hz and 500 Hz, respectively.

The optimal location to elicit an MEP (i.e. "hot-spot") for each hemisphere was localized at T0[27]. During hot-spot identification, and rMT, resting MEP amplitude, SICI and ICF measurements, participants were asked to keep their eyes closed but to remain awake. Once the hot-spot was identified, the rMT of the ILH and CLH was determined (see procedures below). The hot-spot was saved and used at T1 to ensure consistency. After determination of the rMT at T0 and T1, single and paired pulse TMS measures were acquired. To minimize the potential effects of repetitive TMS on MEP amplitude, single or paired pulses were applied 5 seconds apart. Twenty-five stimulations per hemisphere were delivered for each CSE measure.

Cortico-spinal Excitability Measures

Resting and Active Motor-evoked Potential Amplitude

The MEP amplitude is an estimation of the net excitability of the CST, including direct excitation of cortico-spinal neurons and indirect excitation of tangential intra-and trans-cortical neurons[6]. The average peak-to-peak MEP amplitude of each hemisphere, induced by a pulse at 120% of the rMT[48, 49], was determined during resting and active conditions. Assessing active MEP amplitude required participants to view a user interface (LabView, National Instruments, Austin, Texas, USA) to help maintain a constant muscle contraction of 10% MVC. MEP amplitude was expressed in millivolts (mV), with increases reflecting greater excitability[50].

Resting Motor Threshold

The rMT reflects cortico-cortical axonal excitability[51] and is defined as the lowest stimulation intensity that evokes an MEP of an amplitude of 0.05 mV. ILH and CLH rMTs were determined by identifying the minimum stimulator intensity to elicit 5 MEP amplitudes of a minimum of 0.05 mV from 10 consecutive stimulations[13]. The rMT was expressed as a percentage of maximum stimulator output (%MSO) intensity, with lower output indicating greater excitability.

Cortical Silent Period

The CSP provides information about the inhibition mediated by $GABA_B$ receptors[13], with an increase in CSP duration reflecting greater inhibition. The CSP was obtained from the EMG activity of 25 stimulations elicited at an intensity of 120% rMT during the active MEP amplitude protocol. First, the baseline EMG signal amplitude during the muscle contraction was measured

200 ms before stimulation. The CSP was then determined by recording the duration of time (ms) between the end of the MEP and the recovery of voluntary EMG activity (i.e., increase of 2 standard deviations above the mean baseline signal amplitude)[13, 27].

Short Intracortical Facilitation and Inhibition

Short Intracortical Facilitation (ICF) and inhibition (SICI) provide information of facilitation mediated by N-methyl-D-aspartate (NMDA) and $GABA_A$ receptors, respectively[13]. ICF and SICI were measured using a paired pulse TMS protocol, with an unconditioned pulse of 80% rMT, followed by a conditioned pulse of 120% rMT. The ICF and SICI protocols administered unconditioned and conditioned pulses 12 ms and 2.5 ms apart, respectively[9]. The mean conditioned MEP amplitude was normalized to the mean resting MEP amplitude to estimate facilitation (ICF) or inhibition (SICI)[7] using the following equation:

$$\frac{ICF\ MEP\ Amplitude\ or\ SICI\ MEP\ Amplitude}{resting\ MEP\ Amplitude} \times 100 = ICF\ (\%)\ or\ SICI\ (\%)$$

An increase in ICF and SICI values indicated an increase in intracortical facilitation and reduction in inhibition, respectively.

Interhemispheric Ratios

Interhemispheric balance between ILH and CLH CSE measures was determined by calculating their ratio. Ratio values > 1.0 indicated that interhemispheric asymmetry favoured the ILH, and values < 1.0 favoured the CLH. A ratio favouring the ILH or CLH for resting and active MEP amplitude and rMT would indicate greater excitability in the favoured hemisphere of the ratio. This also applied with respect to facilitation (ICF) and inhibition (CSP and SICI). A ratio approaching 1.0 indicates greater equilibrium between ILH and CLH.

Transcranial Magnetic Stimulation Data Processing

Frame-by-frame analysis of EMG recordings were conducted using Signal (Cambridge Electronic Design, Cambridge, UK). Recordings with abnormal EMG activity such as preceding MEPs (>0.05 mV) within 300 ms before stimulation or excessive EMG activity (>0.05 mV) on the opposite hand were removed from analysis. The average peak-to-peak MEP amplitude for single and paired-pulse TMS data from the ILH and CLH was taken at T0 and T1. Data were screened for outlier values > 3 standard deviations of the group mean. Outliers were removed if physiological factors and study procedures led assessors to conclude that removal was justified.

Statistical Analysis

Data were analyzed using intention-to-treat analyses. Estimates of the effect of HIIT or MICT at T0 and T1 on CSE measures and respective interhemispheric ratios were determined using linear mixed models (LMMs) for repeated measures, which allowed for the correlation of repeated measures within subjects and missing data, as long as data were missing at random[52].
A LMM for each measure included fixed effects of group, time, and group × time interactions. The LMM for ILH and CLH measures included the MVC of the respective hemisphere as a covariate and the LMM for interhemispheric ratios included the ILH:CLH ratio of MVC as a covariate[53]. Bayesian Information Criterion and log-likelihood ratio tests were used to determine the most appropriate covariance structure.

LMM estimates and fit parameters, 95% confidence intervals (CI), and p-values for group, time, and group × time interactions are presented in supplementary tables. Post-hoc student's t tests were performed to detect statistically significant differences in between and within-group pairwise comparisons. Details of these tests are also reported in supplementary tables. Statistical

significance was set at $p < 0.05$. All analyses were conducted using JMP®, Version 17.0. (SAS Institute Inc., Cary, North Carolina, United States).

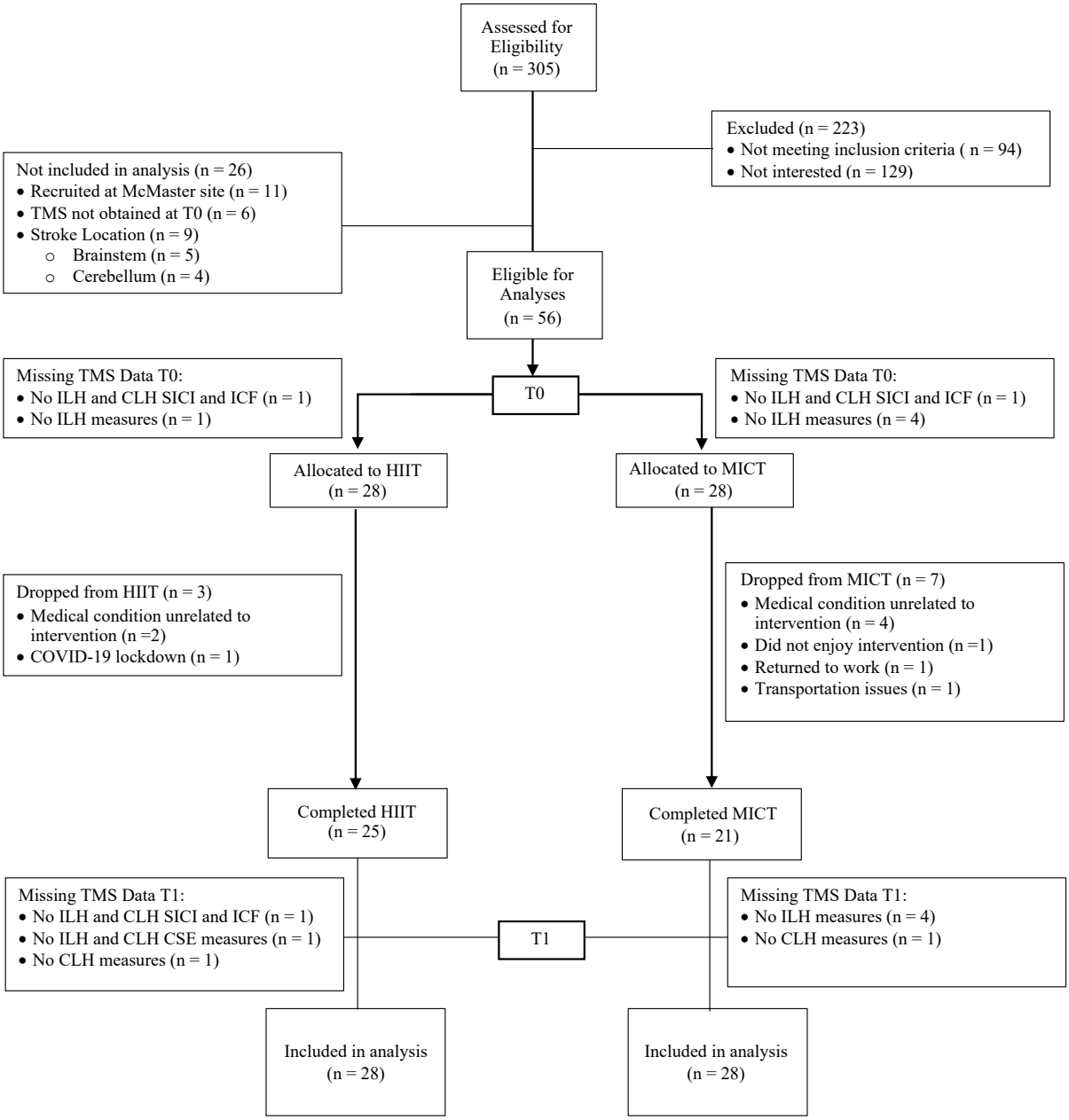

Figure 1. *CONSORT flow chart of the Randomized Controlled Trial. Abbreviations*: n: number of participants; TMS: transcranial magnetic stimulation; ILH: ipsilesional hemisphere; CLH: contralesional hemisphere; SICI: short-interval intracortical inhibition; ICF: intracortical facilitation; HIIT: high-intensity interval training; MICT: moderate-intensity continuous training; T0: baseline; T1: post-intervention.

3.4 Results

Fifty-six participants were randomized to HIIT (n=28) or MICT (n=28). Participants' characteristics were similar between groups at T0 (**Table 1**). The trial flow, including dropouts and missing TMS data, is described in **Figure 1**. No adverse events were recorded during TMS assessments or during the interventions.

Cortico-spinal Excitability Measures

Estimated means of CSE measures at T0 and T1 are presented in **Figure 2**. No group × time interactions were observed (F[1,37.1], F=1.14, p=0.29) but significant time effects for the resting MEP amplitude on the ILH were found (F[1,37.0], F=8.69, p=0.003). Pairwise comparisons revealed significant within-group increases in resting MEP amplitude in the HIIT group only (**Fig. 2A, Supplementary Table 20**). Similarly, the LMM for rMT revealed no group × time interactions (F[1,36.8], F=1.89, p=0.18) but significant time effects for ILH rMT (F[1,36.8], F=4.49, p=0.03). Pairwise comparisons revealed significant within-group decreases in this CSE measure in the MICT group only (**Fig. 2C, Supplementary Table 20**).

The LMM for ICF of the ILH did not reveal a significant group × time interaction (F[1,43.7], F=0.03, p=0.86), but a significant time effect (F[1,43.7], F=4.07, p=0.049). Pairwise comparisons, in contrast, did not reveal significant between- or within-group changes in HIIT or MICT (**Supplementary Table 20**).

No significant group effect was observed in any ILH or CLH CSE measure (**Supplementary Tables 2-13)**. Similarly, no group × time interaction or time effect was observed for ILH active MEP amplitude, CSP, and SICI (**Supplementary Tables 3, 5, 7**) or for any CLH measure (**Supplementary Tables 7-13**).

Interhemispheric Ratios

Estimated means of interhemispheric ratios are presented in **Figure 3**. No group × time interactions were observed for any CSE ratios (**Supplementary Tables 14-19**). Time effects were observed for resting MEP amplitude (F[1,40.7], F=5.94, *p*=0.02), with the ratio favouring the ILH. Pairwise comparisons revealed a significant change from T0-T1 in resting MEP amplitude ratio in HIIT participants, favouring the ILH (**Figure 3A**, **Supplementary Table 21**). Time effects suggestive of increased ILH:CLH equilibrium were observed for the rMT ratio (F[1,36.1], F=6.44, *p*=0.02).

Pairwise comparisons revealed significant within-group change in the MICT group (**Figure 3C, Supplementary Table 21**). Time effects were also observed for the ICF ratio (F[1,35.8], F=4.35, *p*=0.04), indicating a change towards ILH:CLH equilibrium (**Figure 3E**). However, despite a trend for within-group T0-T1 change in MICT (p=0.07), pairwise comparisons did not reveal significant within-group changes (**Supplementary Tables 21)**. LMMs for interhemispheric ratios did not reveal time effects for active MEP amplitude, CSP and SICI ratios (**Supplementary Tables 15, 17, 19**)

Table 1. Participant Characteristics

Variable	HIIT	MICT	*p*
N	28	28	
Sex (% of group)			0.58
Female	9 (32)	11 (39)	
Male	19 (68)	17 (61)	
Age, years (median, [IQR])	67.0 (7.9)	65.8 (8.9)	0.84
Time post-stroke, months (median, [IQR])	21.4 (15.8)	19.1 (15.0)	0.38
Type of Stroke			1.00
Ischemic	23	23	
Hemorrhagic	5	5	
Location of Stroke			0.76
Cortical	7	8	
Subcortical	21	20	
Medication			
SSRI	4	4	0.82
TCA	1	1	0.91
Atypical Antidepressant	5	2	0.33
Benzodiazepine	0	2	0.12
Muscle Relaxant	1	2	0.47
Beta Blocker	7	3	0.27
mRS (median, [IQR])	1.0 [1.8]	1.0 [1.8]	0.71
NIHSS (median, [IQR])	1.3 (1.9)	1.5 (2.0)	0.49
CMSA ILH Hand (median, [IQR])	5.3 (2.0)	5.5 (1.8)	0.88
MVC ILH Hand (median, [IQR])	0.6 (0.3)	0.8 (0.3)	0.82
MVC CLH Hand (median, [IQR])	0.8 (0.2)	0.9 (0.4)	0.58
BMI ($kg \cdot m^2$)	28.5 (5.5)	29.6 (9.4)	0.88
PASIPD (MET, median [IQR])	10 (15.5)	9.3 (21.9)	0.98
$\dot{V}O_2peak$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	16.9 (5.0)	17.0 (6.2)	0.98

Values are reported as means standard deviation (SD), unless specified otherwise. N: number of participants; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant; mRS: modified Rankin Scale; IQR: Interquartile Range; NIHSS: National Institutes of Health Stroke Scale; CMSA: Chedoke McMaster Stroke Assessment; ILH: ipsilesional hemisphere; CLH: contralesional hemisphere ; MVC: maximum voluntary contraction; BMI: body mass index $\dot{V}O_2peak$: peak oxygen uptake; PASIPD: Physical Activity Scale for Individuals with Disabilities; MET: metabolic equivalents.

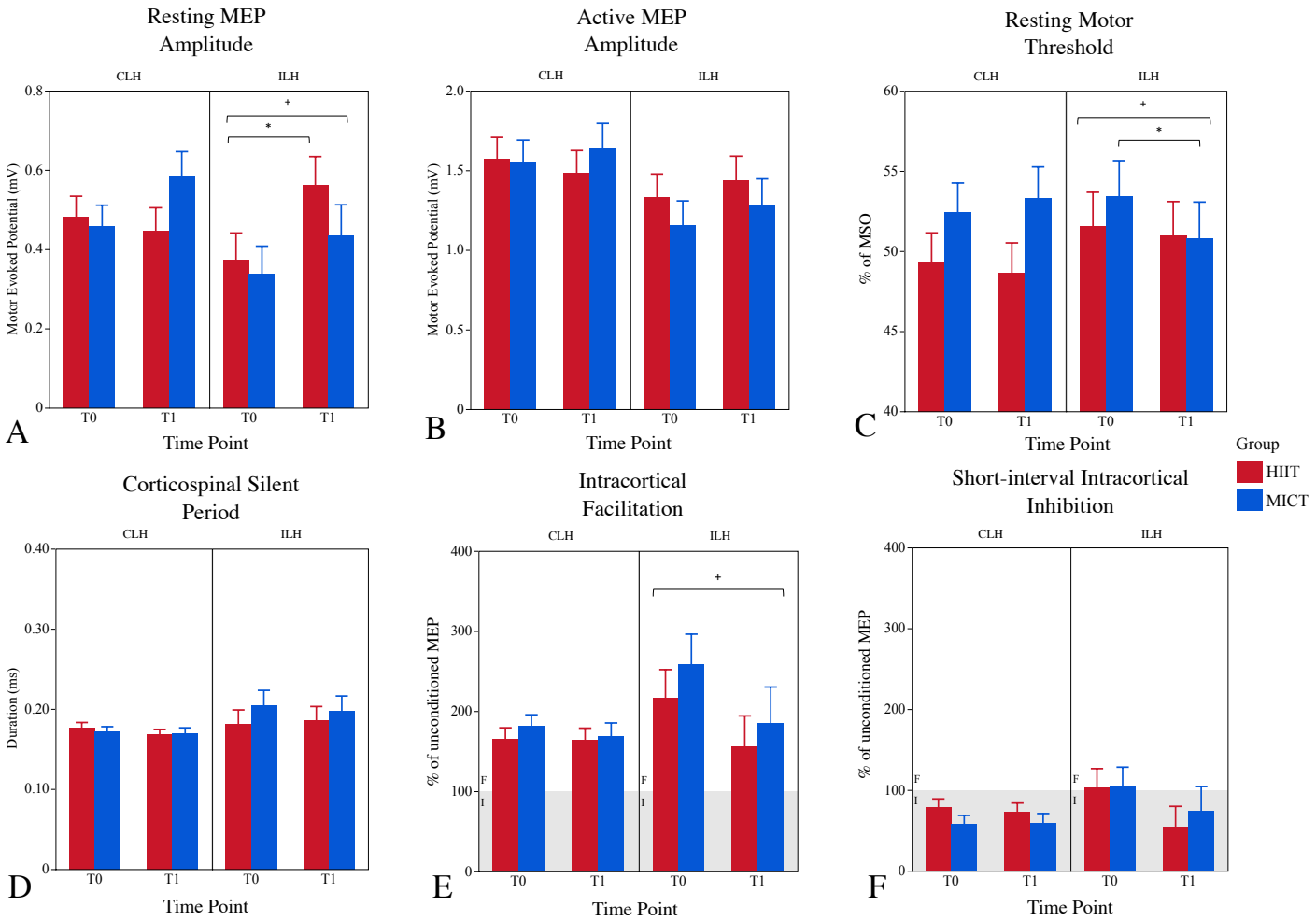

Figure 2: *Change in Cortico-spinal Excitability T0-T1.* A: Resting MEP amplitude ; B: Active MEP amplitude; C: Resting Motor Threshold; D: Cortical Silent Period; E: Intracortical Facilitation; E: Short-interval Intracortical Inhibition.
Abbreviations: MEP: motor-evoked Potential; CLH: contralesional hemisphere; ILH: ipsilesional hemisphere; HIIT: high-intensity interval training; MICT: moderate-intensity continuous training; T0: baseline; T1: post-intervention; mV: millivolts; %MSO: percentage of maximum stimulator output; F: Facilitation; I: Inhibition. $^{+}$ Indicates significant time effect ($p<0.05$) according to linear mixed model. * Indicates significant within-group differences according to pairwise comparisons. Bars are estimates of means and error bars are standard errors of the estimates. Fig 2. E & F: Values <100 indicate inhibition of conditioned MEP.

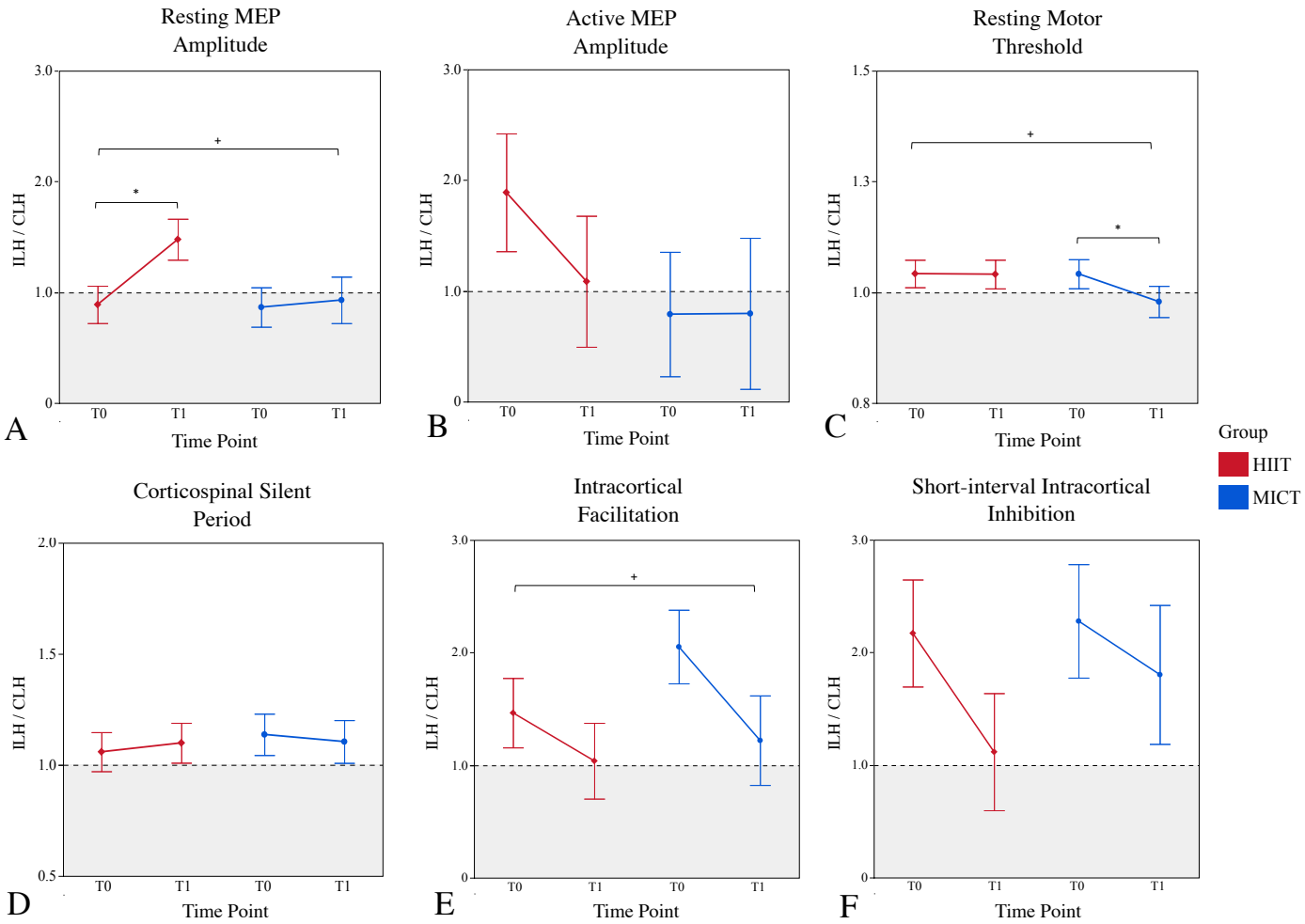

Figure 3. *Interhemispheric Ratios T0-T1.* A: Resting MEP amplitude; B: Active MEP amplitude; C: Resting Motor Threshold; D: Cortical Silent Period ; E: Intracortical Facilitation; F: Short-interval Intracortical Inhibition.
Abbreviations: ILH/CLH: Interhemispheric ratio between ipsilesional and contralesional hemisphere; MEP: motor-evoked potential; HIIT: high-intensity interval training; MICT: moderate-intensity continuous training; T0: baseline; T1: post-intervention. $^{+}$ Indicates significant time effect ($p<0.05$) according to linear mixed model.
* Indicates significant within-group differences according to pairwise comparisons. Data points are estimates of means and error bars are standard errors of the estimates. Values >1.0 indicate ILH:CLH ratios favouring IL

3.5 Discussion

This is the first study examining the potential neuromodulatory effect of HIIT and MICT on CSE in individuals with chronic stroke. Regardless of the training intensity, 12 weeks of CE modulated excitability by increasing resting MEP amplitudes and reducing rMTs in the ILH. We also observed reductions in facilitation (ICF) in the same hemisphere. Measures of inhibition, CSP and SICI, and active MEP excitability did not change significantly. Notably, changes in excitability and facilitation were exclusive to the ILH.

While group × time interactions revealed no significant differences between groups, time effects for MEP amplitudes, rMTs and ICF were significant. Furthermore, post-hoc analyses suggested that, compared to baseline values, HIIT produced more substantial increases in resting MEP amplitude and MICT more robust reductions in rMT. Analyses of interhemispheric ratios showed that ILH-specific changes in excitability and facilitation promoted a re-balancing of interhemispheric activity in rMT and ICF, in addition to a prioritization of the ILH in resting MEP amplitude ratio. Post-hoc analyses of ILH:CLH ratios mirrored group-specific within-group changes of ILH excitability and facilitation measures. Taken together, these findings show that CE has a positive effect on excitatory CSE measures in the ILH and that intensity does not have a clear moderating effect.

The increased resting MEP amplitude in ILH observed in this study aligns well with the CSE responses reported in some, but not all, previous acute-CE stroke studies[3]. Acute studies showing significant CSE responses have demonstrated that a single bout of exercise performed at moderate or high exercise intensity tends to transiently increase ILH MEP amplitude[26, 54]. For example, Forrester et al.,[54] observed an increase in resting MEP amplitude of the paretic vastus medialis following a submaximal bout of treadmill walking. Similarly,

Li et al.,[26] found a significant increase in ILH MEP amplitude in the extensor-carpi-radialis muscle of the hand after a 5-minute high-intensity bout of treadmill walking. Acute CE may transiently increase cortical concentrations of glutamate[23], which acts on neuronal and synaptic NMDA receptors[55] increasing the excitatory activity of the CST[56], potentially via upregulation of BDNF[57-59]. Our results suggest that chronic CE exposure may trigger long-term adaptations on MEP amplitude like those reported in acute studies, with HIIT providing some additional benefits.

The reductions of rMT observed in this study have not been reported in previous acute CE stroke studies[3]. However, it should be noted that, because the rMT is usually employed to establish the TMS intensity needed for assessing other CSE measures (e.g., MEP amplitude), post-exercise changes in rMT in acute studies are not always assessed[3]. Abraha et al., compared an acute bout of HIIT and MICT in 12 individuals with chronic stroke and found that neither protocol produced significant changes in ILH or CLH rMT[29]. In contrast, Boyne et al., found significant reductions in the MT of the ILH after a single bout of treadmill HIIT in 16 individuals with chronic stroke, although it should be noted that the threshold was assessed during an active contraction and not at rest[21].

To date, two CE studies involving people in the chronic post-stroke period (n=14[31] and n=18[30], respectively) have found similar reductions in ILH rMT after 4 weeks of body-weight support treadmill training. Reductions in rMT and augmentation of MEP amplitude have also been observed in neurotypical individuals after 12 weeks of moderate-intensity CE[60]. Our study corroborates these findings and also shows that 12 weeks of CE reduces ILH rMT regardless of the training intensity.

We hypothesized that CE would induce increases in facilitation and reductions in inhibition in the ILH. Instead, we found a reduction in facilitation (ICF) and no significant changes in inhibition measures (CSP and SICI). The reduction of facilitation is a novel finding that has not yet been reported in acute or chronic CE stroke studies[3], and that is consistent with some, but not all, acute CE studies in neurotypical individuals[61]. It should be noted, however, that similar ICF reductions and null changes in SICI have been described in a study with neurotypical sedentary males who underwent 6 weeks of HIIT[62].

ICF represents the net facilitation of cortical circuits comprising excitatory neurons, mediated by NMDA receptors, and to a lesser extent, inhibitory interneurons mediated by GABA[51]. Our sample showed an abnormally high level of facilitation in the ILH at T0 (**Figure 2E**), a finding that is uncommon post-stroke[63]. It is possible that rather than a net facilitatory effect, chronic CE could have had a homeostatic normalization effect, reducing the abnormally high levels of facilitation in the ILH, thus maintaining CSE within a physiological range[62]. The unexpected increases in intracortical inhibition at T1 (**Figure 2D** and **2F**)[21, 27], albeit non-significant, could have also contributed to suppress the high levels of facilitation observed in this hemisphere. Future research is required to investigate the effect of chronic CE-induced reductions in facilitation and underlying mechanisms, as well as the role of inhibition post-stroke[3].

HIIT and MICT-mediated change in ILH excitability and facilitation measures led to changes in interhemispheric ratios. Specifically, we found that exercise had a rebalancing effect in the ILH:CLH ratio of rMT and ICF and that the ratio of resting MEP amplitude further prioritized ILH. Our results contrast with a previous acute-CE study by Nepveu et al.,[27] that found that a graded maximal exercise test elicited a rebalancing of ILH:CLH SICI ratio

and no significant changes in the same CSE measures. However, an important limitation of this study was the lack of standardization of the exercise bout in terms of duration and intensity,[27] both of which may have been insufficient to induce change in CSE.

When also considering the lack of change observed in the study by Abraha et al.,[29] who compared a similar battery of CSE measures after 25 minutes of HIIT and MICT, we conclude that the chronic CE paradigm used was probably the most important factor mediating our results. Since asymmetry of interhemispheric CSE is a hallmark of post-stroke motor impairment[64], these results are promising. Chronic exposure to CE, regardless of the intensity of exercise used, may have a re-balancing effect on interhemispheric CSE in people in the chronic phase of stroke recovery.

Limitations

Due to COVID-related barriers to in-person clinical research and resource limitations, the present study did not attain the estimated study sample proposed initially[37]. It is unknown if with a larger sample size, we could have detected significant differences between HIIT and MICT. The sample size, however, was enough to detect novel and significant change in CSE measures. This study also recruited a sample size that is considerably larger than any TMS chronic CSE study published in neurotypical individuals or patients' post-stroke[3].

Blinding of assessors to group allocation was not possible after baseline assessments due to restrictions in available staffing resources. However, we implemented procedures to limit confounding effects from training and data collection[37]. These included randomized group allocation to control for intergroup differences at baseline and application of strict standardized protocols to ensure consistency in TMS data collection and analysis.

Some previous studies of acute and chronic CE for people in the chronic post-stroke period describe benefits to post-stroke motor learning and function[27, 31, 65]. Similarly, the same changes in CSE observed after CE have been associated with improvements in motor function in people post-stroke[66]. The present study was not designed to measure changes in motor function. We encourage future studies to examine associations between CSE change and measures of motor function to determine the clinical relevance of these findings[3].

This RCT did not include a non-exercise control group, which could restrict comparisons on the extent of exercise-mediated effects. However, the selection of participants in the chronic stages of post-stroke recovery and the requirement that participants were not engaged in an ongoing exercise regimen or clinical services meant that participants were unlikely to experience spontaneous changes in CSE. It is unlikely that the changes in CSE observed in this study could be explained by factors unrelated to the CE interventions.

Conclusion

Relative to subacute stages of stroke recovery, the capacity to induce changes in neuroplasticity and the potential for further recovery in the chronic phase of stroke are diminished[67]. This RCT demonstrates that chronic exposure to CE has the potential to reopen a window of neuroplasticity in chronic stroke, promoting CSE changes in the ILH. Independently of exercise intensity, CE increased resting MEP amplitude and reduced rMT and ICF. Importantly, these changes resulted in optimized interhemispheric equilibrium in rMT and ICF, as well as a prioritization of the ILH in resting MEP amplitude ratio. These findings provide support for the use of CE as a neuromodulation strategy in people with chronic stroke. Whether similar changes in CSE can be observed in more impaired individuals

or in patients at earlier stages of stroke recovery, and the functional implications of these changes is yet to be elucidated.

Declaration of Interest

For all authors, the declaration of interest is none.

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3.7 Figures and Tables

Figure 1. *CONSORT flow chart of the Randomized Controlled Trial. Abbreviations*: n: number of participants; TMS: transcranial magnetic stimulation; ILH: ipsilesional hemisphere; CLH: contralesional hemisphere; SICI: short-interval intracortical inhibition; ICF: intracortical facilitation; HIIT: high-intensity interval training; MICT: moderate-intensity continuous training; T0: baseline; T1: post-intervention

Figure 2: *Change in Cortico-spinal Excitability T0-T1.* A: Resting MEP amplitude ; B: Active MEP amplitude; C: Resting Motor Threshold; D: Cortical Silent Period; E: Intracortical Facilitation; E: Short-interval Intracortical Inhibition. *Abbreviations*: MEP: Motor Evoked Potential; CLH: contralesional hemisphere; ILH: ipsilesional hemisphere; HIIT: high-intensity interval training; MICT: moderate-intensity continuous training; T0: baseline; T1: post-intervention; mV: millivolts; %MSO: percentage of maximum stimulator output; F: Facilitation; I: Inhibition. $^{+}$ Indicates significant time effect ($p<0.05$) according to linear mixed model.

* Indicates significant within-group differences according to pairwise comparisons. Bars are estimates of means and error bars are standard errors of the estimates. Fig 2. E & F: Values <100 indicate inhibition of conditioned MEP.

Figure 3. *Interhemispheric Ratios T0-T1.* A: Resting MEP amplitude; B: Active MEP amplitude; C: Resting Motor Threshold; D: Cortical Silent Period ; E: Intracortical Facilitation; F: Short-interval Intracortical Inhibition. *Abbreviations*: ILH/CLH: Interhemispheric ratio between ipsilesional and contralesional hemisphere; MEP: motor evoked potential; HIIT: high-intensity

interval training; MICT: moderate-intensity continuous training; T0: baseline; T1: post-intervention. $^{+}$ Indicates significant time effect ($p<0.05$) according to linear mixed model.

* Indicates significant within-group differences according to pairwise comparisons. Data points are estimates of means and error bars are standard errors of the estimates. Values >1.0 indicate ILH:CLH ratios favouring ILH.

Table 1. *Participant Characteristics.* Values are reported as means standard deviation (SD), unless specified otherwise. *Abbreviations*: N: number of participants; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant; mRS: modified Rankin Scale; IQR: Interquartile Range; NIHSS: National Institutes of Health Stroke Scale; CMSA: Chedoke McMaster Stroke Assessment; ILH: Ipsilesional hemisphere; CLH: Contralesional hemisphere ; MVC: Maximum voluntary contraction; BMI: Body mass index $\dot{V}O_2$peak: peak oxygen uptake; PASIPD: Physical Activity Scale for Individuals with Disabilities; MET: metabolic equivalents.

3.8 Supplementary Materials

Supplementary Table 1. *Training characteristics*

Measure	HIIT	MICT	p
Heart Rate Zone Time (%)			
<40% HRR	6.4 (4.8)	15.2 (15.4)	<0.01
40-59% HRR	17.2 (8.9)	46.7 (19.8)	<0.0001
≥ 60 % HRR	71.7 (12.6)	26.2 (23.3)	<0.0001
Median RPE (IQR)	13 (2.0)	9 (3.8)	<0.001
T0-T1 $\dot{V}O_2$peak ($mL \cdot kg^{-1} \cdot min^{-1}$)	+3.5 (2.0)	+1.7 (2.9)	0.01

Data presented as mean (SD), unless specified otherwise.
Abbreviations: HR: heart rate; HRR: heart rate reserve; RPE: rate of perceived exertion; IQR: interquartile range; T0-T1 $\dot{V}O_2$peak: Change in peak oxygen uptake from baseline to post-intervention.

Supplementary Table 2. *Model estimates and fit parameters for ILH resting MEP amplitude*

Fixed Effects Variables	***β (SE)***	***95% CI***	***p***
Group	0.04 (0.05)	-0.05, 0.13	0.37
Time			
T1	-0.07 (0.02)	-0.12, -0.03	**0.003**
Group × Time			
T1	-0.02 (0.02)	-0.07, 0.02	0.32
Covariate: IL MVC	0.13 (0.15)	-0.17, 0.44	0.39
Random Effects	***Variance (SE)***	***95% CI***	
Subject	0.08 (0.02)	0.04, 0.12	
Model Fit Statistics	***Statistic***		
Log Likelihood	34.90		
BIC	70.90		

Abbreviations: MEP: motor evoked potential; β: estimate; 95% CI: 95% confidence interval; p: statistical significance ($p<0.05$); T1: post-intervention; IL: ipsilesional hemisphere; IL MVC: affected hand maximal voluntary contraction; BIC: Bayesian information criterion.

Supplementary Table 3. *Model estimates and fit parameters for ILH active MEP amplitude*

Fixed Effects Variables	***β (SE)***	***95% CI***	***p***
Group	0.08 (0.10)	-0.12, 0.29	0.42
Time			
T1	-0.06 (0.05)	-0.15, 0.03	0.21
Group × Time			
T1	0.01 (0.05)	-0.01, 0.10	0.91
Covariate: IL MVC	1.04 (0.34)	0.37, 1.70	**0.003**
Random Effects	***Variance (SE)***	***95% CI***	
Subject	0.35 (0.11)	0.14, 0.56	
Model Fit Statistics	***Statistic***		
Log Likelihood	170.98		
BIC	206.98		

Supplementary Table 4. *Model estimates and fit parameters for ILH rMT*

Fixed Effects Variables	***β (SE)***	***95% CI***	***p***
Group	-0.41 (1.51)	-3.44, 2.61	0.78
Time			
T1	0.82 (0.37)	0.07,1.57	**0.03**
Group × Time			
T1	-0.51 (0.37)	-1.26, 0.24	0.18
Covariate: IL MVC	-4.32 (4.03)	-12.33, 3.68	0.29
Random Effects	***Variance (SE)***	***95% CI***	
Subject	86.45 (23.21)	40.96, 131.95	
Model Fit Statistics	***Statistic***		
Log Likelihood	609.04		
BIC	645.03		

Abbreviations: rMT: resting motor threshold.

Supplementary Table 5. *Model estimates and fit parameters for ILH CSP*

Fixed Effects Variables	***β (SE)***	***95% CI***	***p***
Group	-0.01 (0.02)	-0.03 , 0.02	0.48
Time			
T1	0.00 (0.00)	-0.01, 0.00	0.72
Group × Time			
T1	0.00 (0.00)	-0.01, 0.00	0.21
Covariate: IL MVC	-0.06 (0.03)	-0.12, -0.01	**0.03**
Random Effects	***Variance (SE)***	***95% CI***	
Subject	0.00 (0.00)	0.00 , 0.01	
Model Fit Statistics	***Statistic***		
Log Likelihood	-279.67		
BIC	-243.66		

Abbreviations: CSP: cortical silent period.

Supplementary Table 6. *Model estimates and fit parameters for ILH ICF*

Fixed Effects Variables	***β (SE)***	***95% CI***	***p***
Group	-17.87 (22.92)	-63.94 , 28.21	0.44
Time			
T1	33.31 (16.50)	0.04 ,66.57	**0.049**
Group × Time			
T1	-3.04 (16.50)	-36.30 , 30.23	0.85
Covariate: IL MVC	-11.71 (83.89)	-179.33 , 155.92	0.89
Random Effects	***Variance (SE)***	***95% CI***	
Subject	8946.79 (5645.32)	-2117.84 , 20011.42	
Model Fit Statistics	***Statistic***		
Log Likelihood	1141.84		
BIC	1177.57		

Abbreviations: ICF: intracortical facilitation.

Supplementary Table 7. *Model estimates and fit parameters for ILH SICI*

Fixed Effects Variables	***β (SE)***	***95% CI***	***p***
Group	-5.08 (13.06)	-31.33 , 21.18	0.70
Time			
T1	19.41 (12.93)	-6.58, 45.41	0.14
Group × Time			
T1	4.95 (12.93)	-21.05, 30.95	0.70
Covariate: IL MVC	-93.83 (50.07)	-193.97 , 6.30	0.07

Random Effects	***Variance (SE)***	***95% CI***
Subject	1201.59 (1866.25)	-2456.19, 4859.36

Model Fit Statistics	***Statistic***
Log Likelihood	1070.73
BIC	1106.46

Abbreviations: SICI: intracortical facilitation.

Supplementary Table 8. *Model estimates and fit parameters for CLH resting MEP amplitude*

Fixed Effects Variables	***β (SE)***	***95% CI***	***p***
Group	-0.03 (0.03)	-0.09, 0.04	0.38
Time			
T1	-0.02 (0.02	-0.07, 0.02	0.31
Group × Time			
T1	0.04 (0.02)	-0.01, 0.09	0.08
Covariate: IL MVC	0.52 (0.11)	0.31, 0.73	**< 0.01**

Random Effects	***Variance (SE)***	***95% CI***
Subject	0.05 (0.01)	0.03, 0.07

Model Fit Statistics	***Statistic***
Log Likelihood	14.34
BIC	51.10

Abbreviations: CL: contralesional hemisphere; CL MVC: non-affected hand maximal voluntary contraction.

Supplementary Table 9. *Model estimates and fit parameters for CLH active MEP amplitude*

Fixed Effects Variables	***β (SE)***	***95% CI***	***p***
Group	-0.04 (0.09)	-0.21, 0.14	0.68
Time			
T1	0.01 (0.05)	-0.10, 0.10	0.98
Group × Time			
T1	0.05 (0.05)	-0.06, 0.15	0.37
Covariate: IL MVC	1.38 (0.27)	0.83, 1.92	**<0.001**
Random Effects	***Variance (SE)***	***95% CI***	
Subject	0.37 (0.09)	0.19, 0.55	
Model Fit Statistics	***Statistic***		
Log Likelihood	191.50		
BIC	228.26		

Supplementary Table 10. *Model* estimates *and fit parameters for CLH rMT*

Fixed Effects Variables	***β (SE)***	***95% CI***	***p***
Group	-1.95 (1.24)	-4.44, 0.54	0.12
Time			
T1	-0.06 (0.41)	-0.89, 0.78	0.89
Group × Time			
T1	0.40 (0.42)	-0.44, 1.23	0.35
Covariate: IL MVC	-3.86 (3.04)	-9.90, 2.18	0.21
Random Effects	***Variance (SE)***	***95% CI***	
Subject	52.14 (17.96)	16.94, 87.34	
Model Fit Statistics	***Statistic***		
Log Likelihood	670.91		
BIC	707.67		

Supplementary Table 11. *Model estimates and fit parameters for CLH CSP*

Fixed Effects Variables	***β (SE)***	***95% CI***	***p***
Group	0.00 (0.00)	-0.01 , 0.01	0.82
Time			
T1	0.00 (0.00)	0.00, 0.01	0.20
Group × Time			
T1	0.00 (0.00)	0.00, 0.01	0.43
Covariate: MVC ratio	0.00 (0.01)	-0.03, 0.02	0.87
Random Effects	***Variance (SE)***	***95% CI***	
Subject	0.001 (0.00)	-0.001, 0.01	
Model Fit Statistics	***Statistic***		
Log Likelihood	-378.77		
BIC	-407.63		

Supplementary Table 12. *Model estimates and fit parameters for CLH ICF*

Fixed Effects Variables	***β (SE)***	***95% CI***	***p***
Group	-5.31 (8.31)	-22.00,11.37	0.53
Time			
T1	3.58 (6.47)	-9.44, 16.60	0.58
Group × Time			
T1	-2.81 (6.49)	-15.86, 10.25	0.67
Covariate: MVC ratio	-39.97 (29.90)	-99.42, 19.47	0.18
Random Effects	***Variance (SE)***	***95% CI***	
Subject	1068.84 (891.58)	-678.62, 2816.30	
Model Fit Statistics	***Statistic***		
Log Likelihood	1085.90		
BIC	1122.41		

Supplementary Table 13. *Model estimates and fit parameters for CLH SICI*

Fixed Effects Variables	***β (SE)***	***95% CI***	***p***
Group	8.60 (6.29)	-4.01, 21.22	0.18
Time			
T1	1.29 (4.30)	-7.35, 9.94	0.77
Group × Time			
T1	1.62 (4.32)	-7.06, 10.30	0.71
Covariate: MVC ratio	-41.75 (21.65)	-84.77, 1.28	0.06
Random Effects	***Variance (SE)***	***95% CI***	
Subject	878.65 (458.49)	-19.96, 1777.27	
Model Fit Statistics	***Statistic***		
Log Likelihood	1020.81		
BIC	1057.33		

Supplementary Table 14. *Model estimates and fit parameters for resting MEP amplitude ratio*

Fixed Effects Variables	***β (SE)***	***95% CI***	***p***
Group	0.14 (0.11)	-0.08, 0.36	0.20
Time			
T1	-0.16 (0.07)	-0.31, -0.02	**0.03**
Group × Time			
T1	-0.13 (0.07)	-0.28, 0.02	0.08
Covariate: MVC ratio	0.68 (0.37)	-0.06, 1.42	0.07
Random Effects	***Variance (SE)***	***95% CI***	
Subject	0.53 (0.12)	0.30, 0.76	
Model Fit Statistics	***Statistic***		
Log Likelihood	217.64		
BIC	253.64		

Supplementary Table 15. *Model estimates and fit parameters for active MEP amplitude ratio*

Fixed Effects Variables	***β (SE)***	***95% CI***	***p***
Group	0.35 (0.31)	-0.27, 0.96	0.26
Time			
T1	0.20 (0.29)	-0.39, 0.79	0.50
Group × Time			
T1	0.20 (0.29)	-0.39, 0.79	0.49
Covariate: MVC ratio	2.56 (1.07)	0.41, 4.71	**0.02**

Random Effects	***Variance (SE)***	***95% CI***
Subject	0.19 (1.10)	-1.97, 2.35

Model Fit Statistics	***Statistic***
Log Likelihood	432.41
BIC	468.41

Supplementary Table 16. *Model estimates and fit parameters for rMT ratio*

Fixed Effects Variables	***β (SE)***	***95% CI***	***p***
Group	0.02 (0.02)	-0.03, 0.06	0.48
Time			
T1	0.02 (0.02)	0.00, 0.03	**0.04**
Group × Time			
T1	-0.02 (0.01)	-0.03, 0.00	0.05
Covariate: MVC ratio	-1.16 (0.06)	-0.28, -0.04	**0.01**

Random Effects	***Variance (SE)***	***95% CI***
Subject	0.02 (0.01)	0.01, 0.03

Model Fit Statistics	***Statistic***
Log Likelihood	-123.27
BIC	-87.27

Supplementary Table 17. *Model estimates and fit parameters for CSP ratio*

Fixed Effects Variables	***β (SE)***	***95% CI***	***p***
Group	-0.02 (0.06)	0.15, 0.11	0.74
Time			
T1	0.00 (0.01)	-0.03, 0.03	0.89
Group × Time			
T1	-0.02 (0.01)	-0.05, 0.01	0.23
Covariate: MVC ratio	-0.14 (0.14)	-0.41, -0.13	0.31

Random Effects	***Variance (SE)***	***95% CI***
Subject	0.14 (0.05)	0.05, 0.23

Model Fit Statistics	***Statistic***
Log Likelihood	-32.91
BIC	-68.91

Supplementary Table 18. *Model estimates and fit parameters for ICF ratio*

Fixed Effects Variables	***β (SE)***	***95% CI***	***p***
Group	-0.19 (0.19)	-0.59, 0.20	0.33
Time			
T1	0.31 (0.15)	0.01, 0.61	**0.04**
Group × Time			
T1	-0.19 (0.15)	-0.40, 0.20	0.50
Covariate: MVC ratio	-0.21 (0.68)	-1.56, 1.15	0.76

Random Effects	***Variance (SE)***	***95% CI***
Subject	0.20 (0.58)	-0.92, 1.33

Model Fit Statistics	***Statistic***
Log Likelihood	316.57
BIC	352.30

Supplementary Table 19. *Model estimates and fit parameters for SICI ratio*

Fixed Effects Variables	***β (SE)***	***95% CI***	***p***
Group	-0.20 (0.29)	-0.78, 0.38	0.49
Time			
T1	0.38 (0.24)	-0.11, 0.87	0.12
Group × Time			
T1	0.14 (0.25)	-0.35, 0.64	0.56
Covariate: MVC ratio	-0.58 (1.01)	-2.60, 1.45	0.57

Random Effects	***Variance (SE)***	***95% CI***
Subject	1.16 (0.87)	-0.55, 2.86

Model Fit Statistics	***Statistic***
Log Likelihood	394.29
BIC	412.13

Supplementary Table 20. *Estimated marginal means of within and between-group (HIIT vs MICT) differences in TMS CSE measures at baseline (T0) and post-intervention (T1).*

Measure	Estimated Marginal Means at T0 and T1								HIIT vs MICT		
	H	T	HIIT	SE	p	MICT	SE	p	Value	SE	p
Resting MEP Amplitude (mV)	CLH	T0	0.48	0.05	0.59	0.46	0.05	0.06	0.02	0.10	0.76
		T1	0.44	0.06		0.59	0.06		-0.14	0.08	0.10
	ILH	T0	0.37	0.07	< 0.01	0.34	0.07	0.16	0.04	0.07	0.71
		T1	0.56	0.07		0.43	0.08		0.13	0.11	0.23
Active MEP Amplitude (mV)	CLH	T0	1.58	0.14	0.50	1.55	0.14	0.54	0.02	0.19	0.93
		T1	1.48	0.14		1.64	0.15		-0.16	0.21	0.44
	ILH	T0	1.33	0.15	0.39	1.15	0.16	0.37	0.18	0.22	0.42
		T1	1.43	0.16		1.28	0.17		0.16	0.23	0.50
Resting Motor Threshold (%MSO)	CLH	T0	49.32	1.81	0.55	52.43	1.81	0.46	-3.11	2.57	0.23
		T1	48.65	1.87		48.65	1.87		-4.69	2.67	0.08
	ILH	T0	51.59	2.08	0.53	53.43	2.21	0.02	-1.85	3.07	0.55
		T1	50.97	2.12		50.78	2.28		0.19	3.14	0.95
Cortical Silent Period (ms)	CLH	T0	0.18	0.01	0.13	0.18	0.01	0.73	-0.02	0.02	0.35
		T1	0.17	0.01		0.17	0.01		0.00	0.01	0.87
	ILH	T0	0.18	0.02	0.49	0.21	0.02	0.28	0.01	0.01	0.54
		T1	0.19	0.02		0.20	0.02		-0.01	0.01	0.64
Intracortical Facilitation (%MEP)	CLH	T0	165.27	13.94	0.93	181.51	13.96	0.50	-16.24	19.79	0.41
		T1	163.72	15.03		168.74	16.49		-5.02	22.32	0.82
	ILH	T0	215.97	35.82	0.17	257.78	38.30	0.15	-41.81	53.04	0.43
		T1	155.42	38.65		185.09	45.01		-29.67	59.73	0.62
Short-interval Intracortical Inhibition (%MEP)	CLH	T0	78.84	10.16	0.62	58.39	10.17	0.96	20.44	14.42	0.16
		T1	73.02	10.87		59.05	11.83		13.96	16.07	0.38
	ILH	T0	103.27	23.16	0.16	103.52	24.74	0.46	-0.25	34.23	0.99
		T1	54.54	25.22		74.60	29.64		-20.05	39.13	0.39

Abbreviations: H: brain hemisphere; group; T: study time point; TMS: transcranial magnetic stimulation; CSE: cortico-spinal excitability; ILH: ipsilesional hemisphere; CLH: contralesional hemisphere; MVC: maximal voluntary contraction; SE: standard error; 95% CI: 95% confidence interval; MEP: motor evoked potential; HIIT: high-intensity interval training; MICT: moderate-intensity continuous training; mv: millivolts; %MSO: percentage of maximum stimulator output; %MEP: percentage of unconditioned motor evoked potential; ms: milliseconds.

*Values in bold indicate significant difference ($p<0.05$) according to post-hoc student's t-test.

Supplementary Table 21. *Estimated mean within-group differences in TMS ILH:CLH CSE ratios from baseline (T0) to post-intervention (T1) controlling for MVC ratio*

Ratio	Group	Baseline Mean			Change Score T0-T1		
		Value	SE	95% CI	Value	95% CI	p
Resting MEP Amplitude	HIIT	0.89	0.03	0.55, 1.22	-0.59	-0.98, -0.20	<0.01
	MICT	0.87	-0.13	0.51, 1.22	-0.06	-0.51, 0.38	0.77
Active MEP Amplitude	HIIT	1.89	0.09	0.83, 2.95	0.80	-0.77, 2.39	0.31
	MICT	0.79	-0.09	-0.33, 1.91	-0.01	-1.75, 1.74	0.99
Resting Motor Threshold	HIIT	1.04	0.68	0.98, 1.10	0.00	-0.04, 0.05	0.95
	MICT	1.04	-0.91	0.98, 1.11	0.06	0.02, 0.11	0.01
Cortical Silent Period	HIIT	1.06	0.01	0.88, 1.24	-0.04	-0.12, 0.04	0.29
	MICT	1.14	0.00	0.95, 1.32	0.03	-0.06, 0.12	0.46
Intracortical Facilitation	HIIT	1.47	1.54	0.85, 2.08	0.43	-0.36, 1.22	0.28
	MICT	2.05	12.77	1.40, 2.70	0.83	-0.08, 1.74	0.07
Short-interval Intracortical Inhibition	HIIT	2.17	5.83	1.23, 3.12	1.05	-0.25 2.35	0.11
	MICT	2.28	-0.66	1.28, 3.28	0.48	-1.01, 1.96	0.52

Abbreviations: TMS: transcranial magnetic stimulation; CSE: cortico-spinal excitability; ILH: ipsilesional hemisphere; CL: contralesional hemisphere; MVC: maximal voluntary contraction; SE: standard error; 95% CI: 95% confidence interval; MEP: motor evoked potential; HIIT: high-intensity interval training; MICT: moderate-intensity continuous training.
*Values in bold indicate significant difference ($p<0.05$) according to post-hoc student's t-test.

Addressing Gap #2: *How does exercise intensity affect motivation and enjoyment in post-stroke individuals?*

The promising findings of Chapter 3 reveal that HIIT and MICT equivalently promote benefit in key measures of CSE that are potentially associated with functional improvement in stroke recovery. In addition to benefits to neuroplasticity, this RCT also revealed that HIIT and MICT produced improved cardiorespiratory fitness ($\dot{V}O_2$peak) in recently published findings[110]. Indeed, HIIT elicited significantly greater ($p = 0.015$) improvements in $\dot{V}O_2$peak (+3.52 mL/kg/min vs. 1.71 mL/kg/min) than MICT[110], despite less time dedicated to exercise sessions, an important consideration for stroke clinicians[111]. This RCT has therefore demonstrated that HIIT is a viable and efficacious method to ameliorate two key therapeutic targets in stroke recovery, neuroplasticity, and cardiovascular health. However, there remains an important question regarding the acceptability of using high-intensity exercise in post-stroke individuals.

In Chapter 1, the importance of psychosocial intrapersonal factors, motivation and enjoyment and their influence on exercise engagement in clinical populations, were highlighted as an important consideration for HIIT implementation. Yet, no study has addressed this gap in the literature concerning post-stroke individuals' motivation and enjoyment responses to a HIIT vs. MICT cardiovascular exercise program. In the following chapter, this important question will be addressed, alongside contributing factors to motivation and enjoyment responses, and their relevance for the implementation of HIIT in stroke rehabilitation.

CHAPTER 4: Psychosocial Responses to a Cardiovascular Exercise Randomized Controlled Trial: Does Intensity Matter for Individuals Post-Stroke?

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4.1 Abstract

Objective: This study compared the effect of cardiovascular high-intensity interval training (HIIT) vs. moderate-intensity continuous training (MICT) on psychosocial responses associated with exercise engagement, motivation, and enjoyment, in individuals with chronic stroke.

Design: A secondary analysis of motivation and enjoyment outcomes collected from a randomized controlled trial (NCT03614585) comparing 12-weeks of HIIT vs MICT in participants with chronic stroke (6-60 months post-stroke) was conducted.

Setting: General community.

Participants: Seventy-one individuals with chronic stroke (mean ± SD, age: 65.5 ± 8.4 years, 19.4 ± 13.4 months post-stroke, 38% female).

Interventions: Twelve-week, 3x/per week progressive cardiovascular HIIT or MICT program conducted on NuStep recumbent steppers.

Main Outcome Measures: Motivation (Behavioral Regulation in Exercise Questionnaire-3) was measured at week 1, 6 and 12. Enjoyment outcomes comprised of affective response (Feeling Scale) assessed at each training session, and post-exercise enjoyment (Physical Activity Enjoyment Scale) assessed at week 6 and 12. Linear mixed models of motivation constructs and composite scores, mean affective response per session, and post-exercise enjoyment were used to compare the effect of HIIT vs. MICT.

Results: HIIT elicited lower affective response during training sessions ($F\ [2,63.5] = 3.99$, $p = 0.02$). However, HIIT and MICT did not differ in post-exercise enjoyment ($F\ [2,56.1] = 0.07$, $p = 0.79$) or any motivation constructs ($p>0.05$).

Conclusions: Despite lower affective response during exercise, HIIT and MICT elicit equivalent motivation and post-exercise enjoyment. This study provides further support for the

implementation of HIIT in stroke rehabilitation by demonstrating sustained responses of motivation and post-enjoyment. Future studies should consider potential strategies that positively reinforce these important psychosocial responses to implement HIIT in post-stroke rehabilitation.

Key Words: Exercise; Enjoyment; High-Intensity Interval Training; Motivation; Stroke

Abbreviations

BREQ-3 – Behavioral Regulation in Exercise Questionnaire version 3

CE – Cardiovascular exercise

FS – Feeling Scale

HIIT – High intensity Interval Training

HR – Heart Rate

HRR – Heart Rate Reserve

IQR – Interquartile Range

LMM – Linear Mixed Model

MICT – Moderate Intensity Continuous Exercise

PACES – Physical Activity Enjoyment Scale

RCT – Randomized Controlled Trial

RPE – Rate of Perceived Exertion

SDT – Self Determination Theory

$\dot{V}O_2$peak – Peak Oxygen Uptake

VT – Ventilatory Threshold

4.2 Introduction

Moderate-intensity continuous training (MICT) is currently the recommended format of cardiovascular exercise (CE) in stroke rehabilitation[1]. Recently, we have shown that high-intensity interval training (HIIT) is a superior intervention to MICT for improving cardiovascular health and mobility outcomes after stroke[2, 3]. The novelty of HIIT, is that it combines short bouts of high and low intensity of CE to facilitate the attainment of high exercise intensities while requiring less time commitment and exercise volume[4].

However, enthusiasm for HIIT in clinical populations has been tempered by reports that suggest high levels of exertion may be challenging for typically sedentary individuals[5], including people post-stroke[6], resulting in negative psychosocial responses[7]. Though post-stroke individuals express a willingness to engage in CE[8], and HIIT in particular[9], its tolerability may be influenced by an interaction between exercise intensity and psychosocial responses to exercise such as lack of motivation[9-12] and enjoyment[13-15].

Motivation, or a lack thereof, may influence exercise participation in individuals' post-stroke[10, 16]. According to Self-Determination Theory, motivation to exercise spans a continuum of lesser to more self-determined behaviors that are also dichotomized as self-determined "autonomous" motivation and externally sourced "controlled" motivation[17]. Autonomous motivation has been associated with greater likelihood of participating in moderate-to-vigorous exercise than controlled motivation in individuals with chronic stroke[11].

Autonomous motivation is also associated with enjoyment[18,19] which has been shown to mediate the relationship between motivation and exercise engagement in cardiac rehabilitation[20]. High-intensity exercise requires increased work of breathing and perceived exertion that may elicit negative enjoyment responses during exercise performance (i.e. affective response)[21] which could

influence the maintenance of exercise behaviours[22]. Interestingly, acute CE studies with neurotypical subjects demonstrate that, despite more positive affective responses during MICT[23, 24], enjoyment assessed after completion of a HIIT session (i.e. post-exercise enjoyment) is equivalent or greater than MICT[23, 24].

Considering the anticipated clinical benefits of HIIT, studies are needed to examine the effect of exercise intensity on psychosocial responses to determine its suitability in stroke rehabilitation. However, there is a lack of information on the comparative effects of HIIT vs MICT programs on motivation and enjoyment in stroke populations. To address this gap, we conducted a secondary analysis of a RCT to compare motivation and enjoyment responses during a 12-week HIIT vs MICT in individuals with chronic stroke[25]. We hypothesized that HIIT would elicit more negative affective responses than MICT during training sessions[26], but similar responses in motivation and post-exercise enjoyment[27, 28].

4.3 Methods

Study Design

This RCT was conducted at the Jewish Rehabilitation Hospital (Laval, Québec, Canada) and McMaster University (Hamilton, Ontario, Canada) from September 2019 to December 2023. Ethics approval was obtained from the research ethics boards of each study site (Jewish Rehabilitation Hospital: CRIR - 1310-0218; McMaster University: HIREB - 4713) and informed written consent was provided prior to participation. The full protocol has been published[25] and a CONSORT flow chart is provided in **Figure 1.**

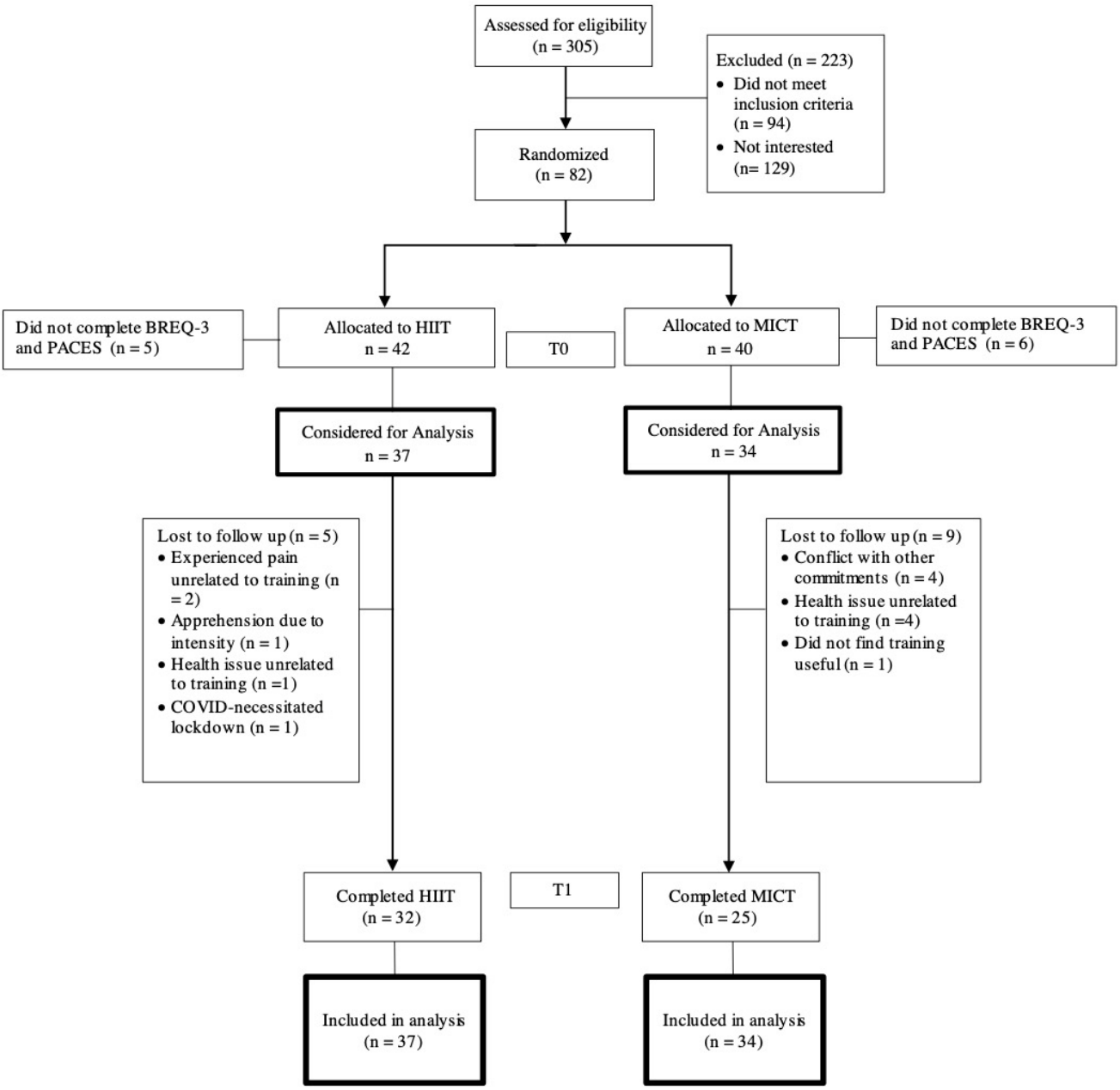

Figure 1. CONSORT Flow Chart. *Abbreviations*: HIIT: High-Intensity Interval Training; MICT: Moderate-Intensity Continuous Training; n: number of participants; T0: baseline; T1: post-intervention; BREQ-3: Behavioral Regulation in Exercise Questionnaire, version 3; PACES: Physical Activity Enjoyment Scale.

Participants

Participants were included if they were between 40-80 years old, 6-60 months following first-ever stroke event (ischemic or hemorrhagic), living in the community, and able to follow instructions. Participants were excluded if they had significant disability (modified Rankin Scale score > 2)[29], were engaged in stroke rehabilitation services or a structured exercise program, and had any neurological or musculoskeletal comorbidities that prevented safe participation. To be included in this secondary analysis, participants needed to complete a minimum of one week of training.

Randomization

Participants were randomly assigned into HIIT or MICT after baseline assessments. Randomization was conducted by blinded investigators (MR, Jewish Rehabilitation Hospital; AT, McMaster University) for the counterpart site using a computer-generated sequence (www.randomizer.org) with a 1:1 allocation ratio, stratified by each site, with variable block sizes. Prior to completion of baseline assessments, assessors were blinded to group allocation but could not remain blinded after baseline due to resource constraints.

Intervention

Participants allocated to HIIT or MICT trained 3 days per week over 12 weeks, with sessions held on alternate days in gym facilities at both sites. Participants exercised on recumbent steppers (NuStep T4r, NuStep LLC, Ann Arbor MI, United States). Details on exercise prescription and protocols are provided in **Supplementary Materials**. In response to institutional

COVID-19 guidelines, training sessions were conducted with a 1:1 trainer-to-participant ratio. Participants exercised at different times to limit contamination bias.

Outcomes

Motivation

The 24-item Behavioral Regulation in Exercise Questionnaire version 3 (BREQ-3) was administered after the last session (within 5-10 minutes post-session) of week 1, 6 and 12 to assess motivation to exercise. Administering the BREQ-3 at week 1 provided participants with sufficient experience of the intervention to meaningfully respond to the questionnaire. Motivation constructs of the BREQ-3[30] are provided in **Table 1**.

The questionnaire was scored using a 5-point Likert scale ranging from 0 "not true for me" to 4 "very true for me". Mean scores were calculated for each construct, and for composite measures of autonomous and controlled motivation[31]. Autonomous motivation was calculated as: [(mean intrinsic regulation + mean integrated regulation + mean identified regulation) / 3]. Controlled regulation was calculated as: [(mean introjected regulation + mean external regulation) / 2]. For each time point, mean scores (out of a maximum of 4.0) from each BREQ-3 construct and composite measures were included in analyses.

Table 1. *Motivation constructs of the Behavioral Regulation in Exercise Questionnaire-3*

Motivation Constructs		
External Regulation	C	Performance of activity in response to external reward or punishment
Introjected Regulation	C	Performance of activity to receive positive, or avoid negative, feelings
Identified Regulation	A	Performance of activity is associated with perceived benefits
Integrated Regulation	A	Performance of activity is amalgamated into sense of self
Intrinsic Regulation	A	Inherent satisfaction derived from performance of activity

Motivation constructs are ordered from least to most self-determined.

Abbreviations: C: controlled motivation composite measure ; A: autonomous motivation composite measure.

Enjoyment: Affective Response

Affective response during exercise sessions was measured using the Feeling Scale (FS)[32]. The FS is a single-item 11-point scale ranging from -5 ("Very Bad") to +5 ("Very Good"), where participants respond to 'How are you feeling?". For HIIT sessions, FS was administered at the 45th second of the first high-intensity interval (12.5% of training, FS1), during the 5th high intensity interval (41.7%, FS2), and during the last high-intensity interval (91.7%, FS3). For MICT, the FS was administered 5 minutes after the warmup (14-20%, FS1), at the mid-point of training (~50%, FS2), and before the cool-down (88-91.4%, FS3)[28]. A composite mean score at each time point (FS1, FS2, FS3) per session was calculated. Positive and negative FS scores indicated positive and negative affective responses, respectively.

Enjoyment: Post-exercise Enjoyment

The 8-item Physical Activity Enjoyment Scale (PACES) was used to measure post-exercise enjoyment[33]. Participant completed the PACES within 5-10 minutes after the last exercise session of week 6 and 12. Starting at week 6 allowed participants to have sufficient experience with the intervention to respond meaningfully to the questionnaire. Participants were asked to rate "How you feel at the moment about the exercise you have been doing?" using a 7-point bipolar rating scale (e.g., 1 = I find it pleasurable … 7 = I do not find it pleasurable). Scores ranged from 8-56 and higher scores indicated greater enjoyment[33].

Statistical Analysis

For baseline participant and training characteristic data, significant differences ($p < 0.05$) between groups were determined using t-tests and Wilcoxon rank sums tests for normal and non-normally distributed data, respectively, and chi-square tests for categorical data. Linear mixed models (LMM) were conducted to examine change in motivation (BREQ-3 constructs and composite scores) and enjoyment (affective response, FS; post-exercise enjoyment, PACES) between HIIT and MICT groups. Analysis of BREQ-3 constructs, and composite scores were examined at week 1, 6 and 12. The LMM for FS compared mean responses at FS1, FS2 and FS3 of all training sessions. PACES was analysed at week 6 and 12.

Each model included subjects as random slopes, fixed effects for group × time point interaction, and covariates of age and sex[34]. Bayesian Information Criterion and log-likelihood ratio were determined to select the best-fitting mixed model. If significant group × time point interactions were found, post-hoc pairwise comparisons using Tukey's Honest Significant Difference (HSD) test were conducted to detect significant between and within-group differences.

All analyses were conducted using JMP®, Version 17.0. (SAS Institute Inc., Cary, NC, United States). Statistical significance level was set at $p < 0.05$.

4.4 Results

From September 2019 to December 2023, 82 participants were randomized to HIIT or MICT. Eleven participants (HIIT = 5; MICT = 6) did not complete the BREQ-3 or PACES at any time point and were excluded from analyses. Seventy-one participants (65.5 ± 8.4 years old, 19.4 ± 13.4 months post-stroke) were included in this secondary analysis.

Participant flow and reasons for attrition are described in **Figure 1**. Thirty-seven participants randomized into HIIT and 34 randomized into MICT were included in the analysis (**Figure 1**). From this sample, 10 participants (HIIT = 4; MICT = 6) completed week 1, but did not complete training before week 6, and 4 participants (HIIT = 1; MICT = 3) did not complete training before week 12.

Participant characteristics are reported in **Table 2** and training characteristics are reported in **Table 3.** No significant differences were observed between groups at baseline (**Table 2**). HIIT participants spent significantly more time at high exercise intensities ($p < 0.001$, mean percentage [SE]: 70.2% [2.6], **Table 3**), and reported a significantly higher median RPE ($p < 0.001$, median RPE [IQR]: 13 [2], **Table 3**) compared to the MICT group. For participants that were included in this secondary analysis, 99% training session attendance was achieved (HIIT: 1139/1152; MICT: 893/900).

Table 2. *Baseline participant characteristics*

Measure	**HIIT**	**MICT**	***p***
n	37	34	
Sex (n)			0.97
Female (n, % of group)	14 (38)	13 (38)	
Male (n, % of group)	23 (62)	21 (62)	
Age (Years) (mean, SD)	66.3 (7.3)	64.7 (9.6)	0.43
Months Post-Stroke [median, IQR]	12.9 [22.5]	11.5 [16.5]	0.30
Stroke Type (n)			0.63
Ischemic	31	27	
Hemorrhagic	6	7	
NIHSS [median, IQR]	1 [2.0]	1 [2.3]	0.30
mRS [median, IQR]	1 [1.5]	1 [1.0]	1.00
MoCA [median, IQR]	26 [6.0]	25 [7.5]	0.18
$\dot{V}O_2$peak ($mL \cdot min^{-1} \cdot kg^{-1}$) (mean, SD)	17.3 (5.9)	17.4 (6.0)	0.91
BMI (kg/m^2) [median, IQR]	27.3 [5.9]	27.7 [7.7]	0.98
PASIPD (MET/day) [median, IQR]	9.9 [16.0]	7.4 [18.2]	0.65

Abbreviations: HIIT: High-Intensity Interval Training; MICT: Moderate-Intensit Continuous Training; n: number of samples; NIHSS: National Institutes of Health Strok Scale; mRS: modified Rankin Scale; MoCA: Montreal Cognitive Assessment; $\dot{V}O_2$peak Peak oxygen uptake; BMI: Body Mass Index; PASIPD: Physical Activity Scale fc Individuals with Disabilities; MET: Metabolic Equivalents. * $p < 0.05$, significar difference between groups.

Table 3. *Training characteristics*

Measure	HIIT	MICT	*p*
Average HR	101.5 (17.1)	94.2 (14.1)	0.03
Heart Rate Zone Time (%)			
Very Light, Light (<40% HRR)	11.7 (1.2)	23.1 (3.2)	<0.044
Moderate (40-59% HRR)	18.1 (1.6)	46.7 (3.5)	<0.001
High (≥ 60 % HRR)	70.2 (2.6)	30.4 (4.1)	<0.001
Median RPE (IQR)	13 (2)	9 (3)	<0.001

Data presented as mean (± SE), unless specified otherwise.

Abbreviations: HIIT: High-Intensity Interval Training; MICT: Moderate-intensity Continuous Training; HR: Heart Rate; HRR; Heart Rate Reserve; RPE: Rate of Perceived Exertion; IQR: Interquartile Range; T0: Baseline; T1: Post-intervention; $\dot{V}O_2$peak: peak oxygen uptake.

Motivation

No significant group × time point interaction occurred for any BREQ-3 measure (external regulation, F [2,60.4] = 1.08, $p = 0.35$; introjected regulation, F [2,72.5] = 0.46, $p = 0.64$; identified regulation, F [2,67.8] = 0.01, $p = 0.99$; integrated regulation, F [2, 63.8] = 0.90, $p = 0.41$; intrinsic regulation, F[2,62.6] =0.62, $p = 0.54$). No group × time point interactions were observed for autonomous (F [2,62.0] = 0.42, $p = 0.66$) and controlled scores (F [2,66.8] = 0.47, $p = 0.63$). Details of LMMs including estimates, SE, 95% confidence intervals and significance for the group × time point interaction term are presented in **Table 4**.

Enjoyment

The LMM for affective response revealed a group × time point interaction (F [2,63.6] = 3.99, $p = 0.02$). Tukey's HSD comparisons revealed no between-group differences at FS1 (mean difference [95% CI, significance]; p-value: -0.91 [-2.03,0.16]; $p = 0.14$) but HIIT was lower at FS2

(-1.35 [-2.38, -0.33]; p = 0.003) and FS3 (-1.33, -[2.38, -0.28]; p = 0.01). **Figure 2** illustrates within-group change in affective response only occurred in HIIT, decreasing from FS1-FS2 (0.36 [0.06,0.66]; p = 0.01). Affective response in HIIT remained lower at FS3 relative to FS1 (0.35 [0.02, 0.69]; p = 0.03).

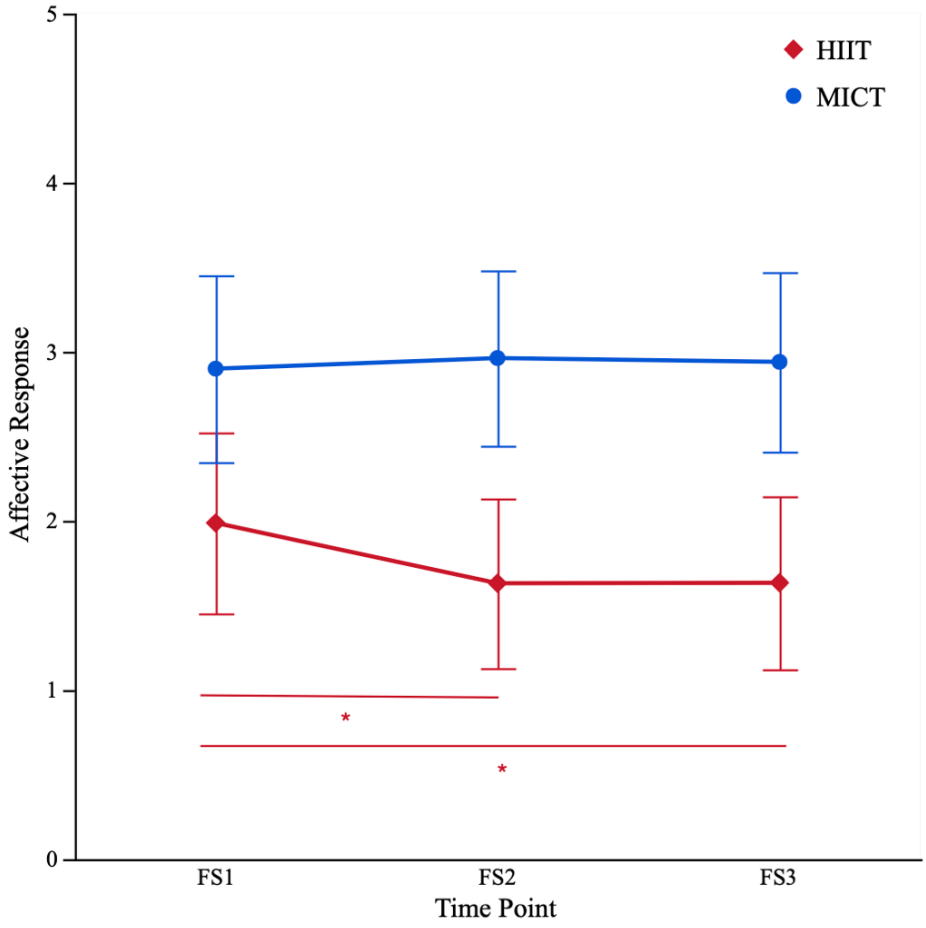

Figure 2. Estimated marginal means (95% CI) of affective response (Feeling Scale, FS) in HIIT vs. MICT sessions. *Abbreviations*: HIIT: High-Intensity Interval Training; MICT: Moderate-Intensity Continuous Training; FS1: start of training session; FS2: mid-way through training session; FS3: end of session before cool-down. *Significant (p < 0.05) within-group difference

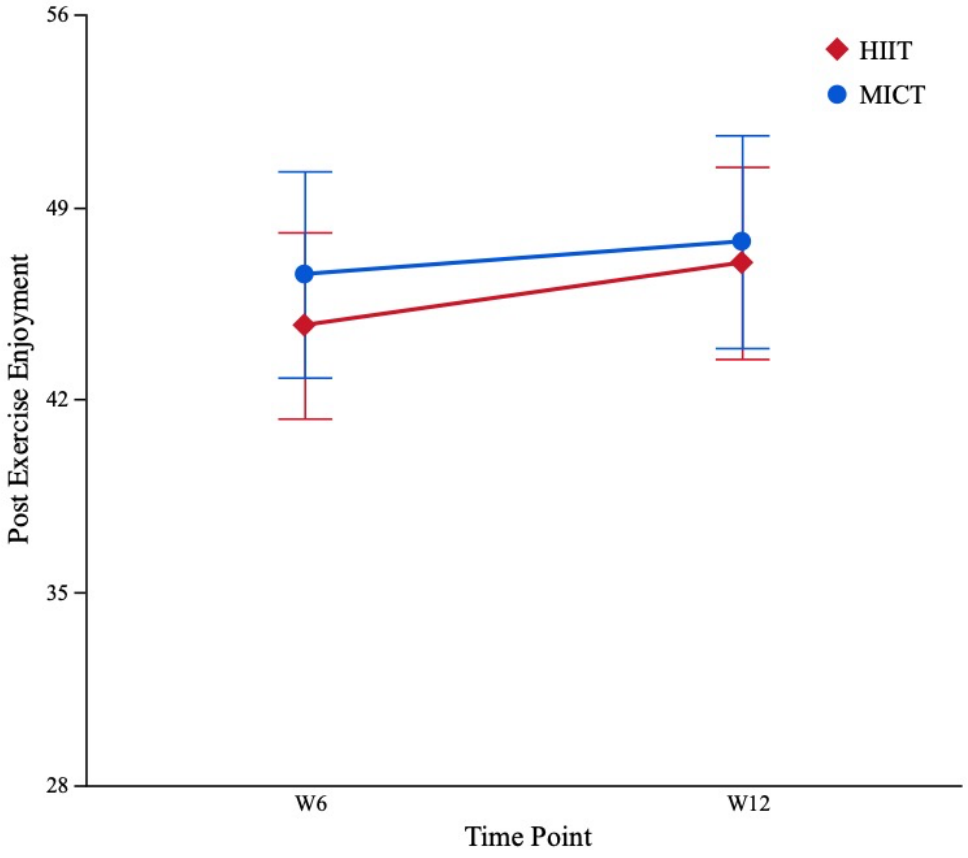

Figure 3. Estimated marginal mean (95% CI) post-exercise enjoyment (Physical Activity Enjoyment Scale, PACES) in HIIT vs. MICT. *Abbreviations*: HIIT: High-Intensity Interval Training; MICT: Moderate-Intensity Continuous Training; W6: Week 6; W12: Week 12.

There were no group × time point interaction between HIIT and MICT for post-exercise enjoyment (PACES) between W6-W12 (F [2,56.1] = 0.07, p = 0.79). **Figure 3** illustrates that post-exercise enjoyment similar for both groups at week 6 and did not significantly change over time (**Table 4**).

Table 4. *Baseline means (± SE) and Linear mixed models (group × time point interaction) for BREQ-3 constructs, Autonomous and Controlled composite scores and PACES.*

Measure	T0 HIIT (± SE)	T0 MICT (± SE)	Δ Time Point	β	± SE	CI (95%)	*p*
External Regulation	0.75 (0.16)	0.63 (0.17)	W1-W6	0.06	0.05	-0.04, 0.15	0.25
			W6-W12	-0.07	0.05	-0.16, 0.03	0.16
Introjected Regulation	2.27 (0.19)	2.26 (0.20)	W1-W6	0.04	0.08	-0.13, 0.20	0.64
			W6-W12	0.02	0.08	-0.13, 0.17	0.74
Identified Regulation	3.11 (0.11)	3.19 (0.11)	W1-W6	0.00	0.05	-0.10, 0.09	0.92
			W6-W12	0.00	0.04	-0.08, 0.08	0.98
Integrated Regulation	2.99 (0.18)	3.03 (0.18)	W1-W6	0.07	0.07	-0.06, 0.20	0.28
			W6-W12	-0.06	0.05	-0.17, 0.04	0.22
Intrinsic Regulation	3.02 (0.12)	3.15 (0.13)	W1-W6	0.04	0.05	-0.05, 0.13	0.37
			W6-W12	0.01	0.04	-0.07, 0.10	0.79
Autonomous Motivation	3.04 (0.11)	3.09 (0.12)	W1-W6	0.04	0.04	-0.04, 0.11	0.36
			W6-W12	-0.02	0.04	-0.09, 0.05	0.60
Controlled Motivation	1.51 (0.14)	1.45 (0.15)	W1-W6	0.05	0.05	-0.05, 0.15	0.36
			W6-W12	-0.02	0.05	-0.11, 0.08	0.68
PACES	44.8 (1.9)	46.5 (2.1)	W6-W12	-0.19	0.73	-1.65, 1.26	0.79

Abbreviations: T0: Baseline; T1: Post-intervention; HIIT: High-Intensity Interval Training; MICT: Moderate-intensity Continuous Training Δ Time Point: Change in between time points; β: estimate; SE: standard error; BREQ-3:behavioral regulation in exercise questionnaire, version 3; PACES: Physical Activity Enjoyment Scale; W1: Week 1; W6: Week 6; W12: Week 12; CI: Confidence Interval. *$p < 0.05$.

4.5 Discussion

This is the first study examining motivation and enjoyment responses to HIIT vs. MICT CE in post-stroke individuals. In agreement with our hypotheses, motivation was similar between HIIT and MICT, and while affective response was lower during HIIT sessions, post-exercise enjoyment was equivalent between groups. These findings provide important insight for the implementation of HIIT, relative to MICT, in stroke survivors.

Motivation was equivalent between groups and did not significantly change over time. The lack of group × time point interaction in motivation could be due to a ceiling effect stemming from a predisposition in this sample to be motivated to participate in an exercise-based program[8]. This is evidenced by our sample's relatively high baseline autonomous motivation scores such as identified (group, mean, SE; HIIT, 3.11 ± 0.11 and MICT, 3.19 ± 0.11; **Table 4**) and intrinsic regulation (HIIT, 3.02 ± 0.12 and MICT, 3.15 ± 0.13; **Table 4**). In contrast, HIIT protocols in individuals with obesity and diabetes[35, 36] have been shown to increase identified[35] and intrinsic motivation[35, 36]. For example, Batrakoulis et al.[35] reported that HIIT significantly increased identified and intrinsic motivation in obese women, however, these values were relatively low at baseline (mean, SD; 1.71 ± 0.47 and, 2.71 ± 0.61 respectively)[35]. Nevertheless, our study demonstrated that HIIT and MICT elicited equivalent high autonomous motivations that were maintained from week 1-12 (**Table 4**). This is a promising finding and suggests that despite higher workload demands of HIIT compared to MICT, motivation is not negatively affected, which is a reported concern for stroke survivors[10].

Affective response during HIIT sessions was lower than MICT, and progressively declined over the duration of the session, while remaining consistent during MICT sessions (**Figure 2**). Our findings align with Dual Mode Theory[21], which posits that high intensity exercise may produce

negative experiences as workload demands surpass physiological markers like ventilatory threshold (VT)[37]. Our findings also correspond with prior work conducted in neurotypical participants by Thum et al.,[24] which found that one bout of HIIT elicited a low affective response, compared to MICT, which was associated with greater blood lactate concentration during the HIIT.

In the present trial, our HIIT participants reported greater levels of exertion (RPE) and exercised at significantly higher exercise intensities (according to % of HRR) than MICT participants (**Table 3**). Therefore, HIIT participants likely spent a greater amount of time in a period of physiological expenditure that may have conferred a progressively diminishing affective response. Future research in post-stroke individuals is warranted to examine the association between physiological measures and psychosocial responses in response to HIIT.

As hypothesized, though affective response was lower in HIIT, post-exercise enjoyment did not differ between groups and did not change significantly over the study period (**Figure 3**). Indeed, post-exercise enjoyment was relatively high throughout training (week 6-12) for both groups (**Table 4**). This differs from a meta-analysis of acute CE studies by Niven et al., which showed that HIIT elicits a lower affective response than MICT, but greater post-exercise enjoyment[26].

The contrast between affective response and post-exercise enjoyment could be attributed to the timing of assessments. For example, a study by Olney et al.,[23] comparing acute high and low volume HIIT, MICT and sprint interval training in neurotypical subjects revealed a similar dichotomy between affective response and post-exercise enjoyment in the present study. The authors attributed their results to administration of PACES 10 minutes post-exercise, which could have provided sufficient time for psychological feelings of affect to "rebound" as participants returned to a pre-exercise physiological state[23, 28]. We administered the PACES in a similar

window which may explain why HIIT participants experienced lesser affective response than MICT during exercise, but they responded similarly to the PACES after their sessions.

However, similar post-exercise enjoyment between groups in the present study conflicts with most chronic exercise interventions which show that HIIT elicits greater post-exercise enjoyment than MICT[38]. Considering the relationship between autonomous motivations and enjoyment[18,19] in other clinical populations[20], we speculate that the lack of group × time point interactions in post-exercise enjoyment in the present study may be also related to potential ceiling effects of autonomous motivation constructs. Participants that were motivated to engage in exercise[8] prior to participation may have also found it enjoyable[20], regardless of protocol and intensity of exercise.

Relevance for HIIT implementation in Clinical Practice

To take advantage of the benefits of HIIT[3], also demonstrated by this RCT[2], clinicians should consider aspects of this study's design that facilitated meeting participant's needs of autonomy, competence and relatedness[39] thereby sustaining autonomous motivation and enjoyment[40] in both groups. For instance, a strength of our intervention was personalized exercise prescription that facilitated attainable exercise intensities (**Table 3**), contributing to feelings of competency[41]. Achieving target intensities and perceiving beneficial adaptations from exercise may contribute to further engaging in HIIT, which has been described in post-stroke individuals[9].

Standardized encouragement and feedback, a critical factor in encouraging exercise adherence[41], may have also reinforced feelings of autonomy and competency[41] in both groups. Prior studies have not described procedures to standardize feedback between HIIT and MICT even though it may influence responses[42] because of the potential for different levels of interaction due

to exercise intensity and structure. This is particularly relevant for HIIT, as it is likely to produce negative affective responses due to the difficulty of high intensity exercise.

Though COVID-related restrictions prohibited group training formats in the present study, implementation of HIIT in groups should be considered to increase adherence[43]. For HIIT in particular, group training and interactions with trainers have been described as a positive factor by stroke survivors[9]. Positive interactions and support between trainers and trainees could reinforce relatedness in participating post-stroke individuals[40]. Future research should account for interpersonal interactions between trainers and trainees[10] and also examine strategies that build competency, autonomy and relatedness for long-term adherence high-intensity exercise.

Study Limitations

Given that psychosocial responses were secondary outcomes in this RCT, this study was not powered specifically to detect differences in motivation or enjoyment outcomes. However, to our knowledge, this is the only study to examine these outcomes in post-stroke individuals, and possesses the largest sample size, irrespective of study design and population.

As participants presented relatively with low levels of neurological and motor disability (**Table 2**), results may not be generalizable to individuals with more severe physical disability. The phase of stroke (chronic) of participants, may also reduce the generalizability of our findings to earlier acute or subacute phases that may present with greater impairment. These characteristics may impact self-perceptions of capacity to exercise[8], however HIIT is feasible in sub-acute stroke populations[44] and the strategies employed in this study (personalized exercise prescription and encouragement) could also be applied in these populations.

The administration of assessments could also introduce potential limitations. Due to their subjective nature, responses may be influenced by individual biases, mood fluctuations, and varying interpretations of items. Likewise, the lack of blinding between assessors and participants may have introduced bias, however assessors were trained to administer questionnaires in a standardized manner to avoid differing assessor-influenced responses. Nonetheless, we acknowledge that these limitations should give caution for the generalizability of results.

Conclusions

Post-stroke individuals in HIIT programs appear to experience and maintain similar motivation and post-exercise enjoyment to MICT, despite lower affective response. This may be explained by a predisposition to engage in exercise in post-stroke individuals, and strategies that facilitate exercise engagement. These findings suggest that HIIT is tolerable with respect to two key indicators of maintenance of exercise, in addition to being clinically beneficial. Future study and clinical practice should consider the effect of strategies that promote motivation and enjoyment in high-intensity exercise interventions for stroke survivors.

4.6 References

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Suppliers

a. NuStep T4r; NuStep LLC

b. Polar H10; Polar Electro Oy

c. JMP® Version 17.0; SAS Institute Inc.

4.7 Figures and Tables

Figure 1. CONSORT Flow Chart. *Abbreviations*: HIIT: High-Intensity Interval Training; MICT: Moderate-Intensity Continuous Training; n: number of participants; T0: Baseline; T1: Post-intervention; BREQ-3: Behavioral Regulation in Exercise Questionnaire, version 3; PACES: Physical Activity Enjoyment Scale.

Figure 2. Estimated marginal means (95% CI) of affective response (Feeling Scale, FS) in HIIT vs. MICT sessions. *Abbreviations*: HIIT: High-Intensity Interval Training; MICT: Moderate-Intensity Continuous Training; FS1: start of training session; FS2: mid-way through training session; FS3: end of session before cool-down. *Significant ($p < 0.05$) within-group difference

Figure 3. Estimated marginal mean (95% CI) post-exercise enjoyment (Physical Activity Enjoyment Scale, PACES) in HIIT vs. MICT. *Abbreviations*: HIIT: High-Intensity Interval Training; MICT: Moderate-Intensity Continuous Training; W6: Week 6; W12: Week 12.

Table 1. *Motivation constructs of the Behavioral Regulation in Exercise Questionnaire-3*

Table 2. *Baseline participant characteristics*

Table 3. *Training characteristics*

Table 4. *Baseline means (± SE) and Linear mixed models (group × time point interaction) for BREQ-3 constructs, Autonomous and Controlled composite scores and PACES.*

4.8 Supplementary Materials

Exercise Prescription

At baseline, participants underwent a graded cardiopulmonary exercise test (CPET) on a NuStep recumbent stepper[1, 2] to determine their peak oxygen uptake ($\dot{V}O_2$peak) and maximal heart rate (max HR). Additionally resting HR was obtained after lying down for 10 minutes in a supine position. Exercise intensity for either group was determined using the heart rate reserve (HRR) method[2, 3] calculated as HRR = (max HR at $\dot{V}O_2$peak – resting HR) x (% exercise intensity) + (resting HR), in combination with RPE[4]. For participants taking HR limiting medication (e.g., beta-blockers), a modified HRR equation was used (HRR = 0.8 x [max HR at $\dot{V}O_2$peak – resting HR] + [resting HR])[3].

Exercise Intervention

High-intensity interval training (HIIT)

A short-interval HIIT protocol[5] was employed involving ten 60-second intervals of high intensity bouts interspersed with nine 60-second low-intensity intervals[6]. The high intensity workload initially started at 80% of HRR and increased by 10% every 4 weeks. Low intensity bouts were performed at 30% of HRR. To reduce sudden changes in BP and ensure that target intensity is achieved[7], the workload at the low intensity interval increased gradually over 15 seconds prior to the next high intensity interval. A warm-up and cool down at 30% HRR bookended each training session. The total duration of the HIIT session was 24 minutes.

Moderate-intensity continuous training (MICT)

A conventional MICT protocol typically employed in stroke rehabilitation programs[8] was used. Initial intensity started at 40% HRR and progressively increased by 10% HRR every 4 weeks

up to 60% HRR. Duration of sessions at target intensity also increased by 5 minutes, every 4 weeks until the end of the intervention. If initial tolerance was low, to achieve 20 minutes of continuous exercise, initial intensity was set at <40% HRR. Intensity then increased by 5-10% HRR and/or 5 minutes per week until 30 minutes of continuous exercise at 40% HRR are achieved. A warm-up and cool down at 30% HRR bookended each training session. The total duration for the MICT session was 25 minutes from week 1-4, 30 minutes from week 5-8 and 35 minutes from weeks 9-12.

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CHAPTER 5: DISCUSSION

5.1 Overview

The studies within this thesis demonstrate that chronic HIIT and MICT promote long-term adaptations in neuroplasticity, measured by TMS, and, despite lesser affective response during HIIT, elicit similar motivation and post-exercise enjoyment in individuals with chronic stroke. These novel studies conducted within the framework of an RCT, described in Chapter 2, are the first to examine the effects of chronic CE on neuroplasticity and psychosocial responses to exercise and to compare the effects of exercise intensity in the chronic stroke population.

Firstly, the study presented in Chapter 3, was particularly novel because previous studies in stroke populations have mostly utilized acute-CE paradigms which may not have been an effective study design for eliciting adaptations in TMS CSE measures[21, 73]. Additionally, the current state of chronic-CE+TMS research lacks a robust comparison of exercise intensity in stroke, to determine long-term adaptations. This thesis demonstrated that chronic HIIT and MICT can equivalently promote mechanisms of CSE in the ILH of subjects with chronic stroke with cortical and subcortical lesions. This novel study also demonstrated that chronic CE-induced changes, exclusive to the ILH, promotes an interhemispheric rebalancing in CSE, which could be associated with better motor function prognosis in recovery. Cumulatively, these findings suggest that chronic CE, at a minimum of moderate intensity, can elicit beneficial long-term adaptations in chronic stroke recoverees were previously considered unlikely to exhibit substantial changes in this phase of recovery[3, 12].

The exciting promise of potentiating neuroplasticity in chronic stroke with HIIT and MICT, also coincides with a growing body of evidence, from this RCT[110] and others[40], that HIIT produces greater benefits in cardiorespiratory risk factors and functional outcomes. Considering the

potentially time-efficient benefits of HIIT, compared to MICT in stroke rehabilitation, it may therefore appear to be more palatable for clinicians and patients alike. However, the sustainability of high-intensity exercise in stroke necessitates an examination of intrapersonal factors that influence exercise engagement.

Therefore, the study presented in Chapter 4 of this thesis examined the effects of chronic HIIT and MICT on widely studied factors in exercise behaviors: psychosocial responses of motivation and enjoyment. This study was also a novel examination of the effects of chronic CE, and intensity of exercise on these psychosocial outcomes in the stroke population. Previous research has only examined this in a qualitative or observational context, without comparing different exercise intensities[79, 89, 112, 113]. Findings of this study indicated that HIIT and MICT elicited similar motivational and post-exercise exercise enjoyment, despite a lower affective response experienced by HIIT-participants during exercise.

These findings suggest that higher self-determined behaviours, indicative of greater "autonomous motivation", and enjoyment, were elicited and maintained by chronic CE, irrespective of exercise intensities endured during HIIT or MICT sessions. These findings could also bode well for patient engagement and the sustainability of HIIT in clinical practice, in comparison to the commonly applied MICT method. Coupled with the benefits to neuroplasticity and potential motor recovery, the established benefits for cardiovascular and functional outcomes, the case for HIIT in stroke recovery is further strengthened.

In the next section of the discussion, findings from Chapter 3 will be discussed, focusing on the potential mechanisms of HIIT and MICT-induced adaptations in CSE in chronic stroke. Additionally, the potential implications of such findings for future research and clinical applications will be addressed. Secondly, an examination of the results from Chapter 4, including

factors that may explain the psychosocial response to HIIT and MICT, will be provided. Likewise, how the findings of this thesis may be applied in future practice and the directions of future research will be explored. Lastly, the weaknesses and limitations of the RCT, the methodology, which was described in Chapter 1, and studies (Chapters 3 and 4) within this thesis will be addressed, and directions suggested for future research.

5.2 Summary of findings

In Chapter 3, it was determined that chronic HIIT and MICT elicited an increase in resting MEP amplitude and reduced rMT exclusively in the ILH for individuals with cortical and subcortical lesions (ischemic and hemorrhagic) in the chronic phase of recovery. These changes in TMS measures, indicative of increased ILH excitability, were elicited by HIIT and MICT protocols. Additionally, HIIT and MICT elicited similar reductions in ICF that also occurred exclusively in the ILH. This reduction of ILH ICF was proposed to be the result of a homeostatic return to "normative" levels of facilitation. It was also proposed that HIIT and MICT-mediated increases in inhibition (SICI), though non-significant, could have influenced a net reduction in the excitability of cortical circuits measured by ICF.

These cumulative ILH-exclusive change in TMS measures of excitability and facilitation was reflected in significant change in ILH:CLH ratio measures of excitability and facilitation. In contrast, no such change occurred in the CLH. Both ILH adaptations, and a lack thereof in the CLH, elicited by HIIT and MICT produced a "re-balancing" of rMT and ICF between the ILH and CLH. Additionally, a greater shift towards ILH resting excitability also occurred. These findings indicated that chronic HIIT and MICT demonstrated similar efficacy in shifting the interhemispheric balance between excitability and facilitation measures, promoting greater equilibrium or prioritization between both hemispheres or the ILH exclusively.

These findings are the first, in an exercise-based stroke trial, to demonstrate that chronic CE can promote long-term adaptations, and that moderate and high-intensity CE are sufficient to elicit them. This study also demonstrates that a chronic exercise component may be necessary to elicit long-term durable adaptations in neuroplasticity measures, as was previously suggested by Abraha et al.,[73] and others[21]. In the following section, potential mechanisms of chronic-CE induced increase in ILH excitability and facilitation TMS measures, alongside shifts in the respective ILH:CLH balance of these TMS measures will discussed.

5.3 Potential mechanisms of HIIT and MICT-induced neuroplasticity in chronic stroke

Increased excitability, and diminished facilitation despite a lack of change in markers of inhibition indicate that chronic HIIT and MICT induces mechanisms of excitatory glutamatergic activity in the brain and, more specifically, the CST. Potentiating excitatory glutamatergic activity and blocking GABAergic action has been previously described as a therapeutic target for post-stroke motor recovery[11, 16]. As mentioned in Chapter 1, chronic CE, depending on exercise intensity, may mediate these adaptations through a myriad of neurotrophic molecular factors such as BDNF, IGF-1 and VEGF, metabolic by-products of exercise such as lactate. These factors could produce structural adaptations of the brain and CST[7, 43, 114] that may lead to increased excitability and reduced inhibition[50] in stroke-affected regions of the brain and CST.

CE-induced molecular and metabolic factors promote excitability in chronic stroke

In this section, we will discuss potential molecular and metabolic mediators, IGF-1, VEGF and BDNF, that may underlie the exercise-induced adaptations in CSE described in Chapter 3. These mediators are frequently discussed in the current literature on exercise-induced

neuroplasticity in stroke[20, 21, 115, 116]. However, these molecular and metabolite factors do not preclude other potential mechanisms that could mediate exercise-induced neuroplasticity. Multiple different mechanisms and pathways should be considered when examining exercise-induced neuroplasticity in stroke recovery as described in several reports and reviews on the subject[7, 9, 39, 69, 116-118].

Insulin Growth Factor-1 and Vascular Endothelial Growth Factor

Insulin growth factor 1 and vascular endothelial growth factor are proteins that have been implicated in the regulation of cellular mechanisms of neuroplasticity, such as neurogenesis, and potentially related to improved functional recovery post-stroke[119, 120]. Animal models show that IGF-1 may work in concert with BDNF to facilitate neural growth and synaptogenesis[21]. VEGF primarily acts via angiogenic mechanisms, but it also is involved in the regulation of neural growth and synaptic plasticity[21], in addition to promoting the production of BDNF and IGF-1[20].

Both proteins have been demonstrated be responsive to CE in neurotypical populations, with both IGF-1 and VEGF demonstrated to increase post-acute CE[121], however chronic CE interventions have been reported to increase basal VEGF, but diminish IGF-1[122]. In trials with post-stroke individuals, studies comparing the effect of acute[50] and chronic CE interventions, at different intensities on IGF-1 and VEGF, are currently limited and report mixed findings[20].

For instance, Boyne et al., reported that acute HIIT interventions (treadmill or recumbent stepper) significantly increased circulating IGF-1 blood concentrations, in comparison to a MICT treadmill bout of exercise (25 minutes for both interventions)[50]. Boyne et al., also reported that VEGF only significantly increased after HIIT treadmill exercise[50]. Chronic CE interventions with stroke populations, to date, have not demonstrated efficacy in inducing change in either IGF-1[123]

and VEGF[124] levels. Ploughman et al.,[123] used a 10-week, 3x/week vigorous-intensity exercise training paired with cognitive training, for individuals in the chronic phase of stroke, that did not elicit a significant change in basal IGF-1 levels, compared to standard care control. Likewise, Krawczyk et al.,[124] used a 12-week, 5x/week cycle ergometer-based HIIT for individuals in the acute phase of recovery, reported no significant change in VEGF levels compared to a standard care control.

Currently, studies that examine the relationships between exercise-induced change in IGF-1 and VEGF, and TMS measures of neuroplasticity have not been conducted in stroke subjects. In neurotypical subjects, associations between these molecular factors and TMS measures is also limited. VEGF has not been examined in any TMS trials and only one study by Nicolini et al., [70], using a 3-day x 6-week cycle-ergometer-based HIIT with neurotypical sedentary males, has examined IGF-1. They reported no change in IGF-1 and no associations with resting excitability, although their intervention did not elicit any change in this TMS measure[70].

Brain-derived Neurotrophic Factor and Lactate

In contrast to IGF-1 and VEGF, BDNF has been examined more frequently in stroke CE trials[49, 125, 126]. Both acute and chronic CE interventions have reported greater efficacy in intensity-dependent augmenting BDNF levels. BDNF is of particular interest because it has been directly associated with increased excitability through mechanisms such as the encouraging presynaptic release of glutamate[127] and postsynaptic regulation of NMDA receptors[128]. In-vitro and in-vivo animal models have also shown that BDNF can disrupt GABA receptor functioning[129], and GABA-mediated inhibitory action[130].

BDNF is widely found throughout the brain, but it is also found in other peripheral sources such as the lungs, heart, and spleen, and expressed in cells such as fibroblasts and vascular smooth muscle cells. These peripheral sources contribute to serum BDNF concentrations which serve as a feasible method to estimate the central BDNF response to exercise, in stroke and neurotypical trials. Using peripheral sources of BDNF in humans to infer its direct impact in the brain and projections in the CST is problematic because peripheral BDNF cannot cross the blood-brain-barrier[131]. Studies in animal and human models suggest that a metabolite, lactate, may act as a link between exercise and BDNF-mediated mechanisms of neuroplasticity in the brain[132-134]

Lactate is a by-product of glycolysis during moderate-to-high intensity CE[135], that is also an important energy substrate for neurons. In-vitro and animal studies, administration of lactate have also been demonstrated to induce BDNF production through neuronal signalling cascades. Intravenous administration of lactate in humans, which removes the potential influence of other molecules triggered by exercise, has been described to increase peripheral BDNF concentrations[133]. In animal models, lactate is thought to induce central BDNF production by crossing the blood-brain-barrier via monocarboxylate transporters (MCT), promoting glutamatergic NMDA receptor activity[136] and stimulating a signalling cascade that upregulates BDNF gene expression[132].

BDNF and lactate-mediated mechanisms and subsequent neuronal and synaptic adaptations could manifest in increased excitability[137]. Coco et al., demonstrated this by using a maximal exercise bout in neurotypical human subjects increased blood lactate, which was also correlated with reduced rMT, thereby indicating greater excitability[137]. In chronic stroke individuals, Boyne et al.,[49] also reported a significant reduction in ILH active motor threshold of the quadriceps femoris muscle post- acute HIIT treadmill exercise, compared to the MICT-

treadmill, that coincided with a significant increase in BDNF. BDNF concentrations were not associated with the change in excitatory TMS measures (lowered active motor threshold) but were negatively associated with the reduction of CSP (indicative of lowered inhibition)[49].

With respect to the study in Chapter 3, the cumulative effects of BDNF and lactate-mediated adaptations, elicited by repeated "doses" of HIIT and MICT may have promoted a more excitatory environment in the ILH, resulting in increased resting excitability and lowered rMT. Previous stroke trials with chronic CE paradigms, and chronic stroke subjects, have demonstrated a CE-mediated increase in blood serum concentrations of BDNF, however the extent of increases and correlation to structural adaptations is intensity dependent[126, 138]. A recent meta-analyses conducted by Ashcroft et al.,[138] reported that chronic CE interventions, using high-intensity paradigms such as HIIT, elicit large significant increases in BDNF concentrations of stroke survivors (mean difference: 3.42 ng/mL; 95% CI: 1.92-4.92, $p < 0.01$). In contrast, moderate-intensity interventions, utilized in only three studies[126, 139, 140], were reported to non-significantly decrease BDNF concentrations (mean difference: -0.22 ng/mL; 95% CI: -3.31 – 2.88)[138].

To date, only one study, by Hsu et al.,[126] has compared the effect of a chronic HIIT vs MICT CE intervention (12-weeks, 3x/week on cycle ergometers) on BDNF concentrations in chronic stroke individuals. They reported that only basal BDNF levels post-HIIT were significantly increased and also found that in-vitro treatment of neuroblastic cells with post-exercise serum BDNF from HIIT participants produced greater structural adaptations of dendritic growth[126]. These findings suggest that chronic CE, particularly HIIT, could elicit structural adaptations that could potentially induce functional changes in neuroplasticity that were observed in the present study. Regarding lactate, no studies in stroke populations have been conducted using chronic CE paradigms, to examine its response to the effect of exercise intensity. However, Boyne

et al.,[50] also reported a positive association between exercise intensity, blood lactate and BDNF response during acute-CE HIIT and MICT paradigms (treadmill or recumbent stepper).

It is important to note that the inference that only HIIT is sufficient to elicit augmented excitatory effects, conflicting with the original hypotheses stated in in Chapter 2. We reported that both HIIT and MICT have elicited long-term adaptations of augmented ILH excitability. Several explanations could explain this discrepancy, such as the intensities of intervention or the characteristics of participants themselves.

The intensity of exercise during the MICT intervention in Chapter 3 may have also reached sufficient levels to release BDNF and lactate. Participants in the MICT group spent most of the time at a moderate intensity (46.7%; **Supplementary Table 1**, **Chapter 3**), yet a considerable amount time was also spent at a high intensity level (26.2%; **Supplementary Table 1**, **Chapter 3**). Inducing a response of circulating BDNF is reported to require an intensity level above ~70% of HR_{max}[141], also falling within a classification of moderate-intensity[42] (**Table 2**, **Chapter 1**). The intensity level also falls within the threshold or upward inflection point of blood lactate production[49, 135], and this may be another mediator through which HIIT and MICT elicited similar augmentation in TMS excitability measures.

It therefore plausible that both groups had repeated exposure at sufficient intensities to induce greater BDNF and lactate responses and ultimately produce adaptations that manifested in increased ILH excitability. However, it is difficult to infer our results with studies by Hsu et al.,[126] and others[139] that compared HIIT and MICT on BDNF serum levels, as they do not report time spent at prescribed moderate or high-intensities.

Characteristics of subjects within this study could also affect BDNF responses. Stroke severity[142], age[143], sex[144] and genetic profile are reported to influence the basal levels of BDNF,

and could influence exercise-induced BDNF responses to HIIT and MICT. However, participants were not significantly different in this study with respect to group composition of sex, age, and stroke severity (**Table 1**; **Chapter 3**), nor other previous studies[126]. Genetic factors, such as the presence of the Val66Met polymorphism[45] could influence the presence of basal and exercise-induced BDNF response to HIIT or MICT but this characteristic was not collected in the present study.

Irrespective of HIIT vs. MICT effects on VEGF, IGF-1, BDNF and lactate responses, the association of these adaptations with TMS measures in stroke is also limited in the current literature[34]. Currently, no studies exist concerning chronic-CE induced adaptations in circulating molecular factors with individuals with stroke, and their relationship to TMS CSE measures. Considering the importance of BDNF, as a potential contributor to post-stroke motor recovery, and the role it plays in excitability and inhibitory mechanisms, future studies that utilize TMS should consider incorporating methods that include an analysis of CSE marker associations with peripheral BDNF. Study designs should also account for participant characteristics, mentioned above, that could influence the variability of BDNF response to chronic CE, and to different exercise intensities.

As mentioned earlier, it must be acknowledged that the proposed BDNF+lactate relationship is certainly not the only mediating factor in the effect of exercise, and intensity, on post-stroke neuroplasticity, and cortical excitability[118] in particular. Singh et al.,[118] provides an excellent summary of the potential effects of other neurotransmitter and neurochemical mediators such dopamine, serotonin, norepinephrine and cortisol, in response to acute CE[118]. These mediators may be associated with post-stroke motor functioning[145], and have also been demonstrated to influence cortical excitatory:inhibitory function[146-148]. However, our

understanding of their effects and relationship with exercise intensity is limited in post-stroke individuals, and currently no studies have examined their relationship to CSE measures. Future studies will be needed to help elucidate the complex relationship between exercise and the potential myriad of neurotransmitter and neurochemical mediators in post-stroke neuroplasticity.

HIIT and MICT reduce intracortical facilitation: A negative-feedback mechanism?

Unexpectedly, a reduction in ILH ICF was also observed, a novel finding not yet described in acute nor chronic stroke trials[20, 34]. A similar simultaneous ICF reduction and null change in SICI in response to chronic CE was also described by Nicolini et al., [70]. Similar to Nicolini et al.,[70] and others[53], we proposed that chronic HIIT and MICT CE produced a homeostatic normalization of ILH ICF. Currently, a specific mechanism that could explain this effect of chronic CE has not been elucidated.

To hypothesize a mechanism, reductions in ILH ICF may have been caused by a negative-feedback mechanism mediated by increased ambient glutamate binding to extrasynaptic NMDA receptors of GABAergic neurons (**Figure 1**). Studies in animal models demonstrate that in vivo (mice model) enhancement of extrasynaptic NMDA receptors on GABAergic interneurons potentiate their excitability, thus augmenting inhibitory activity[149]. This bidirectional modulation of excitability and inhibition of cortical circuits, assessed by ICF, is mediated by extrasynaptic NMDA receptors that contain a GluN2C/2D subunit[149].

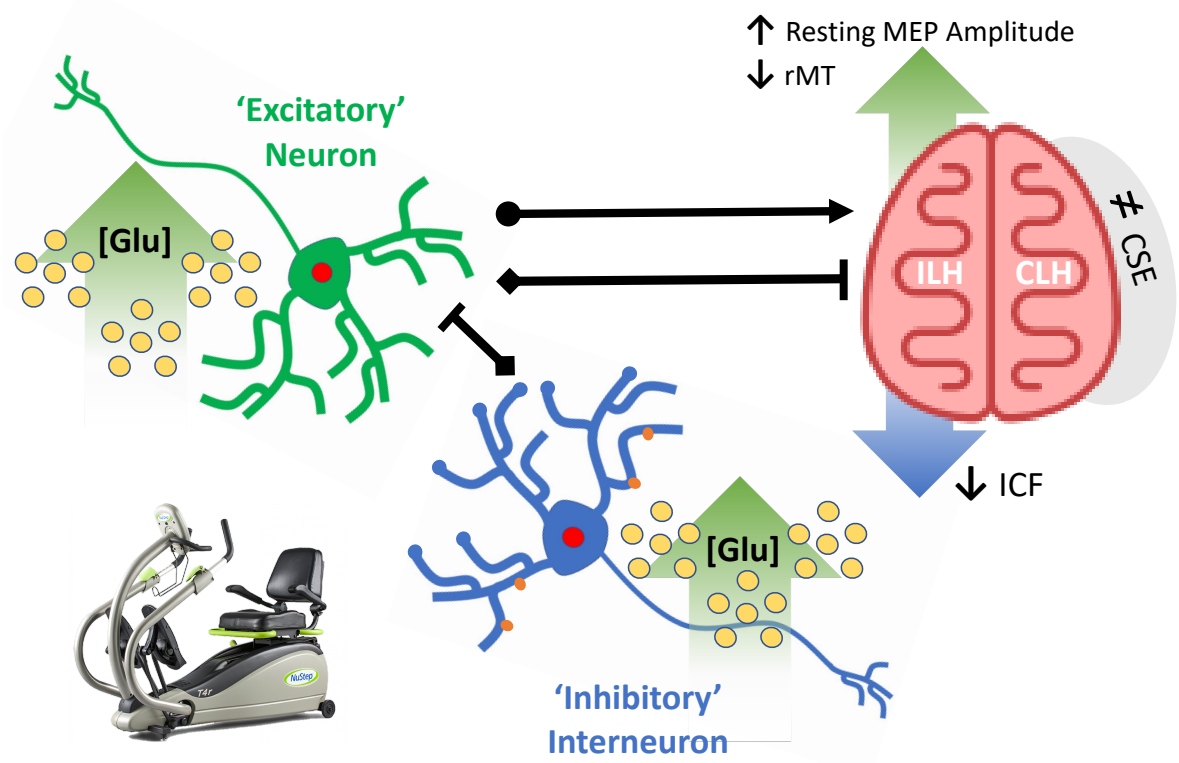

Figure 1: Proposed Model for Exercise-Induced Excitatory-Inhibitory Negative Feedback Loop. Increased ambient glutamate concentration, activates excitatory neurons and GABAergic inhibitory interneurons which act in concert to increase resting excitability (increased Resting MEP Amplitude and lowered rMT), while also reducing intracortical facilitation. These changes occurred exclusively in the ILH. *Abbreviations:* [Glu]: ambient glutamate concentration; MEP: motor-evoked potential; rMT: resting motor threshold; ILH: ipsilesional hemisphere; CLH: contralesional hemisphere; CSE: cortico-spinal excitability; ICF: intracortical facilitation.

Chronic HIIT and MICT CE may have increased ambient glutamate, induced by several mechanisms including molecular and metabolic factors mentioned above, potentiating excitatory neurons, leading to increased resting MEP amplitude, and lowered rMT. A by-product of this increased glutamatergic activity could also regulate inhibitory GABAergic neurons, therefore keeping ICF in a homeostatic balance. This model of bidirectional glutamatergic feedback could also explain the lack of GABAergic inhibitory change in CSP ($GABA_B$ receptor-mediated inhibition), and a non-significant increase in SICI ($GABA_A$ receptor-mediated inhibition). HIIT and MICT CE shifted the ILH to a more glutamatergic excitatory state, away from GABAergic

inhibition. This resulted in glutamate serving two tasks and maintaining homeostasis in cortical circuitry: potentiation of intracortical excitability and ensuring its regulation through activation of inhibitory neurons within intracortical network.

This mechanism is highly speculative, however, and has not been explicitly examined in either animal or human models of stroke. Currently, there is a paucity of studies with chronic CE paradigms, using TMS or other techniques, that can confirm this finding and further research is required to determine the validity of this mechanism. Future studies, using chronic CE, are necessary to confirm the present study's findings and methodology of TMS protocols need to be designed to elaborate ICF and SICI mechanisms.

Chronic HIIT and MICT modulate interhemispheric excitability

The cumulative adaptations in resting MEP amplitude, rMT and ICF were exclusively found in the ILH (**Figure 2**, **Chapter 3**). This resulted in changes in ILH:CLH ratios that were driven solely by ILH measures, as no changes were observed in the CLH (**Supplementary Table 20**, **Chapter 3**). Corresponding increases in ILH excitability measures did not coincide with reductions in the CLH. This was also the case with ILH and CLH ICF, but in the reverse direction.

These findings have not yet been reported in individuals with stroke, with only one study by Nepveu et al.,[44] measuring TMS CSE measures of chronic stroke subjects in response to acute maximal graded exercise test[150], reporting a shift toward equilibrium in ILH:CLH SICI. The authors of this study did not observe any direct changes in other CSE measures or ratios[44]. Aside from the influence of varying intensity and duration of the acute CE bout[44], the effect of acute CE would be insufficient for inducing long-term adaptations[21, 73] that would manifest in interhemispheric re-balancing.

The lack of corresponding decrease in CLH excitability also further builds upon evidence[31] against the proposed interhemispheric inhibition model, which supposes that increased CLH excitability enforces excess inhibition in the ILH, impairing motor function[151]. It is proposed that excessive excitability and inhibition of the CLH and ILH, respectively, work together via interhemispheric connective tracts of white matter (corpus callosum) to impair movement on the affected side[152].

Neuromodulation techniques, such as repetitive TMS and transcranial direct current stimulation, have been previously applied to suppress CLH excitability to promote equilibrium between hemispheres[32], thereby theoretically improving motor function[153]. A meta-analyses by McDonnell and Stinear[31], has called this model into question by demonstrating that the CLH M1 excitability of acute/subacute and chronic stroke individuals is not significantly different between neurotypical counterparts[31], indicating that it is relatively static after stroke recovery. This is in-contrast to the ILH, in which the excitability-inhibition balance is dynamic[11, 154].

The study, in Chapter 3, further demonstrates that the behaviour of CLH CSE in post-stroke is similar to neurotypical individuals, and that it is not responsive to chronic CE. The implications of these findings support the potential for using chronic CE to modulate the excitability-inhibition balance of the brain exclusively in the ILH, which apparently remains dynamic despite being in the chronic phase of recovery. These findings may also have important implications for motor recovery in individuals with stroke, as interhemispheric imbalances between CSE are associated with poorer motor functioning[154].

HIIT and MICT privileges the ILH in chronic stroke: re-opening a window of plasticity?

Findings of increased ILH excitability, and diminished facilitation, despite a lack of change in markers of inhibition indicate that chronic HIIT and MICT induces mechanisms of excitatory glutamatergic activity in the brain and CST, in lieu of GABAergic inhibition in chronic stroke. Potentiating excitatory glutamatergic activity and blocking GABAergic action has been previously described as a therapeutic target for post-stroke motor recovery[11, 16].

Chapter 3 provides exciting new knowledge that neuroplasticity mechanisms in the lesioned hemisphere are not static as previously assumed[3, 12], and that exercise, in either HIIT or MICT modalities can still potentiate mechanisms of plasticity. This "re-opening" of neuroplasticity also introduces new possibilities of improving motor function in the chronic phase of stroke, which was previously thought to plateau during this phase of recovery[12].

5.4 Psychosocial responses of motivation and enjoyment to high-intensity CE in post-stroke individuals: building the case for HIIT in stroke rehabilitation

As the evidence for HIIT in stroke rehabilitation builds regarding improving neuroplasticity, as demonstrated in Chapter 3, and cardiovascular outcomes, greater consideration is needed for factors which affect implementation of HIIT. Psychosocial responses, such as motivation and enjoyment, may play an important role in post-stroke exercise rehabilitation. Previous reports describe that motivation is influences functional outcomes in post-stroke rehabilitation[155] and engagement in exercise behaviours[79, 89]. It is also important to consider that an assumption of SDT is that greater autonomous or self-determined behaviours (such as intrinsic motivation) coincide with greater enjoyment derived from exercise. Until the current study described in Chapter 4, enjoyment had not yet been studied in the context of post-stroke exercise

rehabilitation. However, the relationship between motivation, enjoyment and engagement in exercise has been examined in other clinical populations[88]. For example, Klompstra et al.,[88] reported that heart failure patients' motivation to engage in physical activity, such as exercise, was mediated by the enjoyment of the activity.

Debate on the efficacy of HIIT for clinical populations, such as stroke, stems from the issue that it is high-intensity exercise will elicit negative responses due to heightened physiological demands[77]. Considering the potential ramifications of motivation and enjoyment on the sustainability of HIIT in stroke rehabilitation, there remains a critical a gap in literature, regarding these intrapersonal psychosocial responses to high-intensity exercise, that may impact the suitability of HIIT for stroke populations. Therefore, in Chapter 4, we explored this question by conducting a secondary analysis of psychosocial responses, motivation, and enjoyment, to chronic CE HIIT and MICT.

HIIT (and MICT) sustains motivation and enjoyment for individuals with chronic stroke

In Chapter 4, we determined that though HIIT elicited lesser affective responses than MICT during exercise sessions, participants in both groups responded equivalently in high autonomous motivation (and respective regulations) and post-exercise enjoyment (**Table 4**, **Chapter 4**). This secondary analysis is the first, to our knowledge, to examine the effect of HIIT vs. MICT on motivation and enjoyment, in individuals with stroke and it is among very few studies that compare the effects of intensity while using a chronic CE paradigm.

High self-determined motivation and enjoyment that was sustained in HIIT, in comparison to MICT, illustrates that HIIT does not have a negative effect on psychosocial responses to exercise which might render high-intensity exercise unpalatable and therefore not tolerable in

stroke rehabilitation. Greater self-determined behavioral regulations (identified, integrated, and intrinsic) which also comprise the composite autonomous motivation score were relatively high in both groups and did not change throughout participation. Participation in HIIT did not elicit a significant effect on these key measures associated with adherence to physical activity in chronic stroke populations[79], which remained high throughout the 12 weeks of training. Likewise, though HIIT elicited less positive affective responses during exercise than MICT, while progressively declining over the duration of sessions, participants did not report that post-exercise enjoyment (according to the PACES questionnaire) after HIIT was less enjoyable than MICT.

These findings correspond with other studies of neurotypical and clinical populations in both acute and chronic paradigms. Additionally, they also appear to be in accordance with qualitative studies of stroke survivors and their perspectives on participating in CE programs, and in HIIT in particular[113]. Findings from the present study in Chapter 4, may provide important lessons for HIIT's future use in research and clinical practice.

Could addressing psychological "needs" facilitate HIIT in stroke recovery?

In Chapter 4, similar high autonomous motivation and post-exercise enjoyment in both groups were explained by potential ceiling effects stemming from a predisposition of participants who desired to engage in exercise (protocol and intensity). However, both groups, also maintained these responses over the duration of the training, which poses important questions as to the factors that contributed to participants' responses. Understanding how the HIIT intervention, as implemented, was able to sustain high motivation and enjoyment may have important clinical implications for its future use in stroke rehabilitation. Chapter 4 briefly touched upon the concept of basic psychological "needs" that have been described as necessary to build autonomous

motivations[156], thereby also encouraging enjoyment[157,158], that were also may have been met by both HIIT and MICT interventions (**Figure 2**).

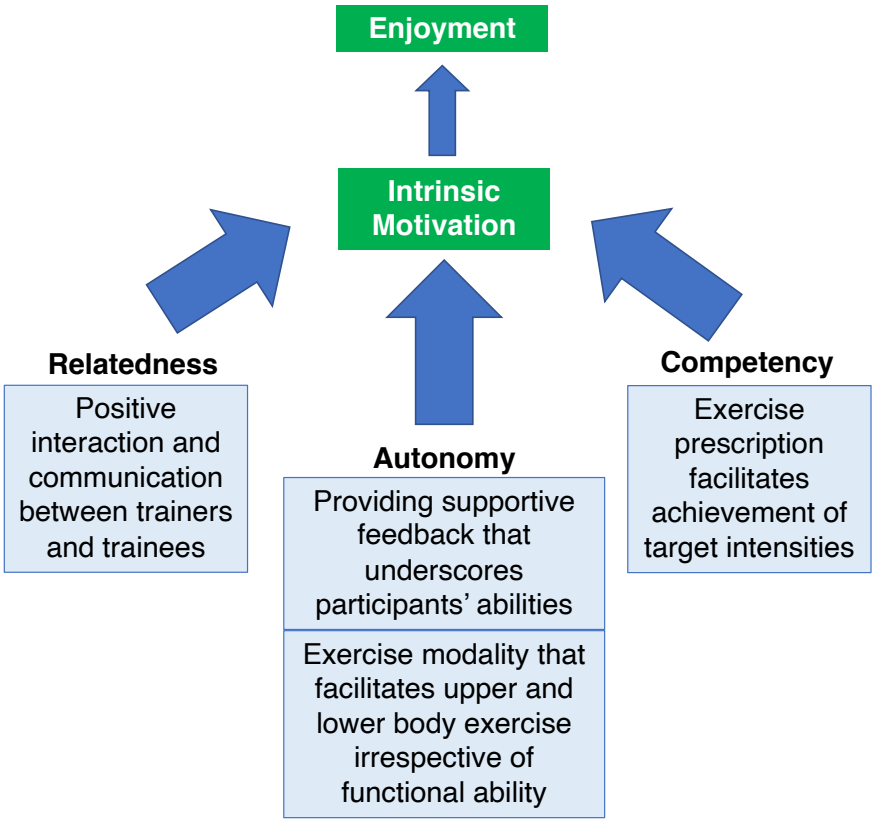

Figure 2. Psychosocial needs of relatedness, autonomy and competency and their contribution to motivation and enjoyment.

We proposed that equivalent and sustained motivation and post-exercise enjoyment responses could suggest that both HIIT and MICT participants met their needs of autonomy, competency, and relatedness[159]. For participants in our sample, engagement in exercise offered by this RCT aided the perception of meeting these needs and connotate perceptions of obtaining benefits to physical function and well-being[112]. Several aspects of this study's implementation (**Figure 2**) including standardized trainer-participant interactions, choice of exercise modality

(i.e., NuStep recumbent stepper), and exercise prescription and progression may have facilitated meeting these needs (See Chapter 4).

Meeting these psychological needs of post-stroke individuals and their relation to engagement in exercise are potentially important factors to consider for the implementation of HIIT. Recently, an observational study by Lau et al., (2023) examined associations between psychological needs, motivation, and physical activity participation in post-stroke individuals[89] in the general community. They reported that, autonomy, competency and relatedness were associated with higher autonomous motivation[89] and proposed several strategies that we will discuss, which could reinforce these needs, some of which map onto study methodology that we have implemented. Additionally, other proposed strategies also align with themes reported by qualitative studies[113], including one recently by Moncion et al., (2024),[160] currently under review, which drew upon responses from participants in the present RCT.

Firstly, with respect to autonomy, Lau et al., discussed that using strategies, previously examined by Kayser et al.,[161] to promote an "autonomy-supportive environment", through providing choice, a rationale for why the activity is important, empathy with the participant, a sense of collaborative effort and acknowledging participants' strengths. This randomized controlled trial, encompassing recruitment, assessments, and training, may have addressed these components (**Figure 2**). For example, enrollment in the study necessitated the use of informative consent forms which outlined the advantages of exercise in stroke recovery, underscoring why participation in the study was important. Interactions between trainers and participants through feedback will have also created situations in which participants received acknowledgements of capabilities during exercise and fostered a sense of empathy and collaboration with training staff.

Standardized feedback and encouragement, from trainers, may have also provided constructive information that promoted feelings of competence by enabling participants to know how their performance related to their overall progression. The progression of exercise prescription would have also allowed for a gradual increase in capabilities that would not dissuade participants, whereas immediately commencing with high-intensities could provide have resulted in feelings of incompetence and a restricted sense of autonomy performing exercise.

Standardized feedback and encouragement may also have enhanced relatedness. Lau et al., also suggest that meaningful relationships between trainers and trainees are important as an avenue for social support, and creation of a trustworthy environment[89]. The implementation of 1:1 trainer:participant exercise sessions could have fostered these connections, promoting a sense of relatedness within participants.

As mentioned in Chapter 4, the concept of feedback is an important aspect that has not been well addressed in the methodologies of previous studies comparing psychosocial responses to HIIT. Studies comparing HIIT and MICT paradigms lack standardization in terms of feedback and encouragement from trainer to trainee. Interactions between trainers and trainees during a HIIT session, may be more frequent due to the increased difficulty of exercise, in comparison to MICT due to frequent changing of intervals that increase the frequency of interactions between trainer and trainee. This increased interaction could have evolved into a "coaching" experience, which reinforced psychological needs, thereby sustaining motivation and enjoyment more effectively than with MICT protocols.

In Chapter 4 we accounted for this dynamic by standardization of participant:trainee feedback and interactions at consistent intervals and conducting training sessions in a "neutral" environment without salient sources of stimulation or motivation like music. Future exercise

intervention trials should aim to control such potential confounders during participation of exercise trials comparing interval and continuous protocols. Implementation of HIIT in clinical settings should also consider strategies to enhance and sustain motivation and enjoyment, by addressing psychological needs in HIIT programs.

5.5 Limitations and implications for future research: High-intensity exercise opens a window of opportunity

This thesis has addressed important gaps in the current literature on the effect cardiovascular exercise intensity and the effect of HIIT in post-stroke recovery. Previous reports have extolled the potential benefits that a time-efficient, high-intensity exercise format like HIIT could provide in stroke rehabilitation[39], especially considering concerns among clinicians regarding a lack of time to implement CE in rehabilitation practice[111]. Yet, inconsistent results regarding the neuroplastic benefit that HIIT may impart in post-stroke individuals, are based on literature that mostly consists of acute-CE paradigms. In addition, concerns regarding the palatability of HIIT in clinical populations because of adverse psychosocial responses[77] may affect its sustainability in stroke survivors.

We have shown that HIIT can promote potentially positive functional change in neuroplasticity in a chronic stroke population, while also eliciting a sustained motivation and enjoyment response. These two findings, though consequential in seemingly separate domains, are also very relevant for one common purpose: using high-intensity exercise to ameliorate stroke recovery.

Utilizing high-intensity exercise in a HIIT format may work to synergistically improve or "restart" neuroplasticity mechanisms in chronic stroke individuals, previously thought to plateau

in this phase of stroke recovery[12], and also improve upon important cardiovascular risk factors for future stroke and morbidity[40]. Participating in HIIT may also be experienced as a desirable activity[113], which reinforces motivation and enjoyment in exercise, helping with future adherence to high-intensity exercise to continue to reap the potential benefits that result in its participation. HIIT should therefore be seen as a viable and effective format of cardiovascular exercise that could be a viable tool to augment recovery and sustain these attained benefits.

However, there are important limitations of this thesis to consider, which have been addressed in the manuscripts presented in Chapter 3 and 4. In the following section, we will also consider these aspects in relation to future research and implementation of HIIT, and the relationship of our results to motor and functional recovery.

Long-term appraisal of HIIT vs. MICT in post-stroke rehabilitation is needed

Firstly, to fully examine whether HIIT is successful in mediating and sustaining benefits long-term, future study designs need to incorporate a longitudinal view of HIIT that addresses change in outcomes pre-to-post intervention and determines whether changes are sustained long-term. To date, however, there are no studies that examine the long-term effects of a HIIT by examining neuroplasticity outcomes after a follow-up period following the intervention.

Though this RCT demonstrated that benefits in cardiorespiratory fitness were sustained 8-weeks post-cessation of HIIT to a greater extent than MICT[110], we were not able to evaluate CSE measures at this time point due to an insufficient sample size at this time point. Future studies should incorporate follow-up assessments at multiple time points after the end of the training period to examine the long-term adaptations in neuroplasticity mechanisms resulting from HIIT.

In addition, we were not able to evaluate whether motivation and enjoyment responses during study participation would translate into the further continuance of exercise behaviours and engagement high-intensity exercise for HIIT participants. Although this thesis demonstrates that HIIT elicits high motivation and positive enjoyment responses that bode well for continued engagement in exercise[79, 88], we are not able to ascertain whether participation in HIIT, as part of this study, will translate to future exercise behaviours. Future studies could address this through follow-up assessments and continued monitoring of exercise behaviours.

Studies are needed to examine HIIT vs. MICT effects on motor function

The desire to potentiate neuroplasticity with high-intensity exercise, is pursued with the aim of improving functional recovery in aspects such as motor function[12]. Although this study was designed to address upper-limb motor learning and function in response to HIIT and MICT (see Chapter 2), we were unsuccessful in collecting and analyzing this outcome for Chapter 3.

Considering the promising findings concerning CE-induced excitability and interhemispheric re-balancing, a behavioural motor function outcome may have provided greater understanding of the relationship between neuroplasticity markers and the functional relevance of the CSE adaptations to motor recovery[162]. Presently, studies that examine the relationship between these markers and behavioural functional outcomes in stroke recovery are not consistently explored in the current literature[20]. Few studies of both acute and chronic CE paradigm studies have explored associations between exercise-induced change in CSE and motor function[20, 44, 67]. Those that have, have not examined the effects of exercise intensity, in addition to inconsistencies with study design.

For example, Yen et al.,[67] using a 4-week body-weight supported treadmill walking intervention, revealed reductions in CLH rMT and increased cortical map size that were associated with improved balance and gait (step-length) parameters. However, comparisons on the effect of intensity could not be made as characteristics of the exercise intervention such as the specific intensities of exercise prescription and the level of intensity that subjects worked at were not made available. The sample size (n=14) was also very small and limited the relevance of statistical analyses. The task-specificity of the exercise intervention is also an important consideration that may have influenced performance of motor functioning outcomes and impacted the ability of a study to determine a causal relationship between chronic CE and improved motor functioning in stroke.

Irrespective of the lack of behavioural motor outcome in Chapter 3, it is also important to note that subjects' performance of upper-limb functional ability, measured by the Chedoke-McMaster Stroke Assessment (arm and hand scale)[163], suggested that participants were relatively high-functioning at baseline (**Table 1**, **Chapter 3**). Post-stroke individuals who exhibit milder levels of functional impairment could produce potential ceiling effects in behavioral measures of motor function[164]. High levels of upper-limb functional ability could therefore obscure the relationship between potential motor function adaptations and exercise-induced modulation of the intra- and inter-hemispheric excitability and inhibition, diminishing the relevance of a motor function outcome.

Future studies should therefore also consider the degree of impairment exhibited by the sample population, to limit this potential source of ceiling effects, which may influence the interpretation of exercise-induced changes in neuroplasticity and motor function. The inclusion of post-stroke subjects that present with significant upper-limb impairments will provide a greater

opportunity to measure tangible benefits of exercise-induced neuroplasticity that would otherwise be unexplored in high-functioning participants.

Despite the lack of behavioural motor function data in the present study, and the lack of consistency in the present state of literature, future trials will be able incorporate novel findings from Chapter 3 to support an examination of chronic CE effects on motor function in stroke populations. Significant thought should be given to aspects of study design, such as the inclusion of lower-functioning subjects, to enhance the relevance of future trials. Ultimately, determining the extent of functional improvement associated with chronic exercise-induced improvement in markers of neuroplasticity, a novel finding from this thesis, will provide greater understanding of the clinical efficacy of CE interventions, like HIIT, for stroke rehabilitation.

CHAPTER 6: CONCLUSION

This thesis, and the studies that comprise it, have met the objective of examining the effect of exercise intensity on neuroplasticity and psychosocial responses to exercise in post-stroke individuals in the chronic stroke phase. We have demonstrated that chronic cardiovascular HIIT and MICT can provide significant benefit to mechanisms of neuroplasticity in individuals in the chronic phase of stroke, while also maintaining high motivation and enjoyment in participants.

Based on the first and largest RCT of its kind in this stroke population, described in Chapter 2, novel findings in Chapter 3 reveal, that, relative to MICT, HIIT is a time-efficient method to promote neuroplasticity in chronic stroke survivors. By eliciting shifts in the excitability-inhibition balance in favour of increased excitability and a re-balancing of interhemispheric excitatory CSE measures, HIIT (and MICT) has been demonstrated to promote functional brain change previously thought to be unlikely in the chronic phase of stroke. Likewise, previous assumptions that HIIT may be unsuitable for post-stroke individuals, due to potential negative effects on psychosocial responses to exercise, have also been challenged in Chapter 4. We have demonstrated that HIIT, though it may be perceived as more intense due to its strenuous workload demands, and elicit less positive affective response during sessions, remains just as motivating and enjoyable as MICT.

The next steps of these promising findings are to develop study designs which further explore the complex mechanisms which underlie neuroplastic change induced by exercise and its effect on motor functioning. Furthermore, a greater understanding of how to sustain HIIT in research and clinical settings, from the perspective of factors which support motivation and enjoyment, will need to be addressed to determine its long-term sustainability. Taken together, findings from this thesis have contributed to the current state of literature which is currently expanding the applicability of HIIT to clinical populations, like stroke. Findings from this should

encourage researchers, clinicians, and stroke survivors alike, to view high-intensity cardiovascular exercise as an opportunity to improve health, physical function, and continued exercise engagement in individuals' post-stroke.

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APPENDIX

1. Letter of attestation from Dr. Kevin Moncion.

2024-07-29

To whom it may concern,

I am writing to confirm that I, Kevin Moncion, have given approval and permission for Lynden Rodrigues to use the following protocol paper as part of his thesis submission:

Rodrigues, L., Moncion, K., Eng, J.J. et al. Intensity matters: protocol for a randomized controlled trial exercise intervention for individuals with chronic stroke. Trials 23, 442 (2022). https://doi.org/10.1186/s13063-022-06359-w

This manuscript will be not used or published in another manuscript-based thesis.

Should you require any further information or clarification, please do not hesitate to contact me.

Sincerely,

Kevin Moncion