Combining a tailored strength training program with transcranial direct current stimulation (tDCS) to improve upper extremity function in chronic stroke patients

Stephania Palimeris, B.Sc. (PT)

School of Physical and Occupational Therapy
McGill University
Montréal, Québec
Initial submission: January 27th, 2020

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirement of the degree of M.Sc. in Rehabilitation Science

TABLE OF CONTENTS

INDEX OF TABLES

INDEX OF FIGURES

LIST OF ABBREVIATIONS

ADL: Activities of Daily Living

ARAT: Action Research Arm Test

AROM: Active Range of Motion

AVC: Accident Vasculaire Cérébral

BBT: Box and Block Test

BDNF: Brain-Derived Neurotrophic Factor

CPM: Computational Prediction Model

CRIR: Centre de Recherche Interdisciplinaire en Réadaptation du Montréal Métropolitain

CST: Corticospinal Tract

DTI: Diffusion Tensor Imaging

ECR: Extensor Carpi Radialis

ECR (French): Essai Contrôlé Randomisé

EEG: Electroencephalography

EMG: Electromyography

FDI: First Dorsal Interosseous

FIM: Functional Independence Measure

FMA: Fugl-Meyer Assessment Scale

GEE: Generalized Estimating Equations

GRASP: Graded Repetitive Arm Supplementary Program

JRH: Jewish Rehabilitation Hospital

JTT: Jebsen-Taylor Hand Function Test

M1: Primary Motor Cortex

MAL: Motor Activity Log

MDC: Minimal Detectable Change

MEP: Motor Evoked Potential

MRI: Magnetic Resonance Imaging

MS: Membres Supérieurs

NIHSS: National Institutes of Health Stroke Scale

NMDA: N-Methyl-D-Aspartate

PEST: Parameter Estimation by Sequential Testing

PME: Potentiels Moteurs Évoqués

PROM: Passive Range of Motion

PT: Physical Therapy

RCT: Randomized Controlled Trial

REB: Research Ethics Board

REC: Research Ethics Committee

ROM: Range of Motion

S1: Sensory Cortex

SD: Standard Deviation

SMT: Stimulation Magnétique Transcrânienne

tDCS: transcranial Direct Current Stimulation

TMS: Transcranial Magnetic Stimulation

TrKB: Tropomyosin Receptor Kinase B

UL: Upper Limb

VEGF: Vascular Endothelial Growth Factor

VR: Virtual Reality

ABSTRACT

Strengthening exercises are recommended for managing persisting weakness in the extremities post-stroke. Yet, training interventions to restore upper limb (UL) function after a stroke often produce variable outcomes because of their generic nature. For this randomized controlled trial (RCT), our primary goal was to determine whether tailoring strengthening interventions using a biomarker of corticospinal integrity, as reflected in the amplitude of motor evoked potentials (MEPs) elicited by transcranial magnetic stimulation (TMS), could lead to improved function of the affected UL. A secondary aim was to determine whether adding anodal transcranial direct current stimulation could enhance response to exercise. For this multisite RCT (Montréal, Sherbrooke, Ottawa), 80 chronic stroke adults were recruited. Pre and post training, participants underwent a clinical (Fugl-Meyer Stroke Assessment; Motor Activity Log; Range of Motion) and a TMS evaluation of their affected arm. Baseline MEPs' amplitude served to estimate each participant's potential for recovery: low/moderate/high. Participants were then stratified into three groups of training intensity levels, determined by the one-repetition maximum (1RM): low:35-50% 1RM/moderate:50-65% 1RM/high:70-80% 1RM. Strength training targeted the affected arm (3 times/week for 4 weeks). In each group, participants were randomly allocated into the real or sham transcranial direct current stimulation (tDCS) group (anodal montage, 2mA, 20 minutes). Results revealed significant improvements in motor function and cortical excitability in response to tailored strength training, however, no further benefits could be attributed to tDCS. Tailored strengthening program appears to be effective in improving arm function post-stroke, even at the chronic phase, but the added value of tDCS still remains equivocal. The trial is still on-going, and a total of 105 participants are expected to be recruited.

ABRÉGÉ

Les exercices de renforcement musculaire sont importants pour la gestion de la faiblesse persistante qui se manifeste aux membres du corps, à la suite d'un accident vasculaire cérébral (AVC). Cependant, les programmes d'entraînement pour restaurer les fonctions motrices des membres supérieurs (MS) après un AVC produisent souvent des résultats variables en raison de leur nature générique. Dans le cadre de cet essai contrôlé randomisé (ECR), notre objectif principal était de déterminer si l'individualisation d'un programme d'entraînement, basée sur l'intégrité corticospinale, reflétée par l'amplitude des potentiels moteurs évoqués (PME) et provoqués par la stimulation magnétique transcrânienne (SMT), pouvait contribuer à l'amélioration des fonctions du MS affecté. Un objectif secondaire était de déterminer si l'utilisation d'une stimulation transcrânienne à courant continu durant l'entraînement pouvait améliorer la réponse à l'exercice. Pour cet ECR multisite (Montréal, Sherbrooke, Ottawa), 80 adultes présentant un AVC au stade chronique ont été recrutés. Avant et après l'entraînement, les participants ont pris part à une évaluation clinique de leur bras atteint (Fugl-Meyer Stroke Assessment; Motor Activity Log; Amplitude articulaire) et une évaluation à l'aide de la SMT. L'amplitude moyenne des PME au départ a été utilisée pour estimer le potentiel de récupération de chaque participant: faible/modéré/élevé. Les participants ont ensuite été classés en trois groupes en termes de niveaux d'intensité d'entraînement, basés sur la répétition maximale (1RM): faible: 35-50% 1RM/ modéré: 50-65% 1RM/ élevé: 70-80% 1RM. Les exercices de renforcement musculaire ciblaient le MS affecté (3 fois/semaine pendant 4 semaines). Dans chaque groupe, les participants ont été répartis au hasard dans le groupe tDCS réel ou simulé (montage anodal, 2mA, 20 minutes). Les résultats ont révélé, à la suite de ces exercices, des améliorations significatives de la fonction motrice et de l'excitabilité corticale. Cependant, aucun impact de la tDCS n'a été noté. Un programme de renforcement adapté semble donc être efficace pour améliorer la motricité du MS atteint après un AVC, et ce, même à la phase chronique, mais la valeur ajoutée de la tDCS reste équivoque. L'essai clinique est toujours en cours où le recrutement d'un total de 105 participants est attendu.

ACKNOWLEDGEMENTS

My MSc thesis could have not been accomplished without the help and support from a number of people. Firstly, I would like to convey my deepest gratitude to my supervisors and mentors Dr. Marie-Hélène Boudrias and Dr. Marie-Hélène Milot. Thank you so much for believing in me and my potentials, for being so kind and understanding, for your constant guidance and support, for the financial support throughout my degree and for giving me the opportunity to attend and present my work at different conferences. I would also like to thank Dr. Johanne Higgins, for her valuable input and advice as a member of my supervisory committee.

I would like to express my gratitude towards Dr. Gélinas for her constant cooperation, especially for her understanding throughout a difficult period towards the end of my degree. I am also very grateful for the administrative staff at the School of Physical and Occupational Therapy, Chiara Sabatino and Tina Portaro, for their assistance and support.

Furthermore, I would like to acknowledge a few people at the JRH Research Center for their professional support; thank you Jean-François Nepveu for your help and involvement with my data collection and Shaheen Ghayourmanesh for doing a great job with helping me with my statistical analysis. In addition, I would like to thank the research assistants and friends of mine Sonia Toy and Shoaib-Hasan Shaikh. It was a pleasure working with you and I could not have asked for better colleagues. I also appreciate all the patients who participated in my study. This work could not have been completed without the generous contribution of their time, kindness and patience during the entire course of the project.

I would also like to thank my dear friend and colleague Pavlos Bobos for being a great mentor, for your constant moral support and for helping me professionally and personally.

Finally, I would like to dedicate the rest of the acknowledgements to my beautiful family: my father Panagiotis, who was my hero and rock and will be dearly missed as I sadly lost him in October 2019 after a brave and heroic battle with cancer, my mother Donna, my brother Thomas and my sister Gabriella. I love you and miss you all so much, being so far away from home. Thank

you so much for your unconditional love and support and I am so grateful to have such a wonderful, loving and supportive family. I am truly blessed.

To my beloved father to whom I dedicate this work:

I will always remember you and love you from the bottom of my heart.

PREFACE

This Master's thesis was written and organized following the guidelines of McGill University's Faculty of Graduate and Postdoctoral Studies.

CHAPTER 1: Overview of stroke, recovery & rehabilitation for the upper limb: presents a review of stroke epidemiology and impact and a review of stroke recovery and rehabilitation for the affected upper limb
CHAPTER 2: Rationale & objectives: introduces the rationale and the objectives of the study
CHAPTER 3: Methods: provides a detailed description of the study methodology
CHAPTER 4: Results: presents the statistical results of the study
CHAPTER 5: Overall discussion: delivers the findings of this study, their clinical significance and provides a debate between the results of this study and the literature
REFERENCES: list of references
APPENDICES: list of appendices

This thesis complies with McGill's policy of intellectual property and all ethical standards.

CONTRIBUTION OF AUTHORS

Stephania Palimeris was responsible for participants' evaluation and data collection (Montréal site), data and statistical analyses from all three sites involved in the project, interpretation of findings, preparation of figures/tables and writing of the thesis. Dr. Marie-Hélène Milot, Dr. Marie-Hélène Boudrias, Dr. Hélène Corriveau and Dr. François Tremblay conceived the study, contributed to the design and implementation of the protocol. All researchers supervised all the aspects of the study and were responsible for obtaining funding and intellectual propriety. Sonia Toy and Shoaib-Hasan Shaikh were responsible for the recruitment and strength training of the participants at the Montréal site; Marilyn Tousignant, Antoine Guillerand, Marie-Philippe Harvey were responsible for the evaluation of the participants and Marie-Claude Girard trained the participants at the Sherbrooke site; Yekta Ansari and Francisca Avila-Ramirez were responsible for the recruitment and evaluation of the participants and Anthony Renaud trained them at the Ottawa site.

FUNDING

This study received funding from Brain Canada Foundation, Fonds de recherche du Québec Santé, Fondation Vitae, Centre de recherche interdisciplinaire en réadaptation du Montréal métropolitain (CRIR) and the Jewish Rehabilitation Hospital. In addition, it was undertaken thanks in part to funding from the Canada First Research Excellence Fund and Fonds de recherche du Québec, awarded to the Healthy Brains, Healthy Lives initiative at McGill University. Furthermore, I received the CRIR Bursary Master's Scholarship for two consecutive years in support of my research project. The funding bodies are independent of the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

ETHICS APPROVAL

This study was approved by the Research Ethics Committee (REC) of the CIUSSS de l'Estrie-CHUS (MP-22-2016-630). Institutional approval was obtained by the Centre de Recherche Interdisciplinaire en Réadaptation du Montréal Métropolitain (CRIR) Research Ethics Board (REB) to conduct the research at the Jewish Rehabilitation Hospital (CISSS de Laval).

CHAPTER 1: Overview of Stroke, Recovery & Rehabilitation for the Upper Limb

1.1 Epidemiology of Stroke

Stroke is the leading cause of severe long-term disability across the globe (Feigin, Lawes, Bennett, Barker-Collo, & Parag, 2009; Roger et al., 2011). Stroke can be defined as an acute compromise of the cerebral perfusion or vasculature or cerebrovascular accident. Although people older than 55 years are at highest risk of stroke, it can occur at any age (Feigin, Lawes, Bennett, & Anderson, 2003). The various deficits from a stroke arise from the death of brain cells caused by interrupted blood flow as a result of blockage or rupture in the supplying vessel, which is characterized as an ischemic or hemorrhagic stroke, respectively (Heart and Stroke Foundation of Canada, 2018). Ischemic strokes are the most common type, with a percentage of approximately 85% (Mozaffarian et al., 2016). Common risk factors that are generally considered for stroke are hypertension, diabetes, smoking, obesity, atrial fibrillation, and drug use, with hypertension being the leading cause, especially for ischemic strokes (Lawes, Bennett, Feigin, & Rodgers, 2004).

In Canada, stroke is the third leading cause of mortality after heart disease and cancer, with an estimate of 50,000 people being hospitalized for stroke and over 13,000 deaths each year (Statistics Canada, 2017). The majority of patients can survive after a stroke due to advances in the medical field and improved health care, which translate into a large proportion of them being left to live with multiple and different degrees of physical impairments (Heart and Stroke Foundation of Canada, 2018). According to the most recent data from 2016 Statistics Canada, approximately 741,800 Canadians are currently living with the consequences of stroke (Statistics Canada, 2017), such as alterations in functional ability, mood disorders, cognitive impairment and decreased social interaction (Carod-Artal, Egido, Gonzalez, & Varela de Seijas, 2000; Yeoh et al., 2018).

1.2 Impact of Stroke

One of the most common disabling consequences of stroke is residual muscle weakness or paresis of the affected arm (Patten, Lexell, & Brown, 2004; Prabhakaran et al., 2008), which is linked to

significant negative impacts on patients' activities of daily living (ADL) performance and can greatly diminish their quality of life (Fleming, Newham, Roberts-Lewis, & Sorinola, 2014; Rondina, Park, & Ward, 2017), as well as interpersonal relationships (Kim, Kim, & Kim, 2014). For example, many stroke survivors require assistance when performing basic daily functions, such as dressing and personal hygiene. In addition, only 50% of stroke survivors with significant initial paresis recover useful upper limb function and are able to return to work (Statistics Canada, 2017). Although the level of impairment varies across stroke patients, even a mild deterioration of motor function with a small impact on the performance of ADL can be discouraging (Ranner, Guidetti, von Koch, & Tham, 2018). This can cause major disappointment to the individual leading, ultimately, to an interruption in the use of the affected upper limb.

1.3 Mechanisms of Brain Plasticity & Motor Learning Post-Stroke

Recovery after stroke and neurorehabilitation effectiveness depend on the plasticity of neurons and circuits within the motor system (Hosp & Luft, 2011). Neuroplasticity can be defined as the ability of the brain to change its structure and/or function when exposed to internal and external constraints and goals (Kolb & Whishaw, 1998). The brain has a range of intrinsic capacities that act as a highly dynamic system, being able to change properties of its neural circuits (Nudo, 2006). These brain alterations can be described and examined in different levels such as molecular, cellular, genetics, neuronal morphology, and behavioural (Kolb & Gibb, 2014), resulting in synaptic changes, which are the primary form of plasticity related to behaviour; for example changes in neural networks organization. More specifically, once a lesion occurs, neuroplasticity takes place by means of regeneration, such as axonal and dendritic sprouting, and/or reorganization within cortical motor areas, such as modulation of synaptic plasticity (Nowak, Grefkes, Ameli, & Fink, 2009); the latter mechanism being the most prevalent past the sub-acute phase of a stroke.

Motor recovery mostly adheres to a non-linear trajectory which can reach asymptotic levels a few months post-stroke (Kwakkel, Kollen, & Lindeman, 2004). Ballester *et al.* (2019) suggested the existence of a period of enhanced plasticity, defined as the "critical window" for recovery, in which a stroke patient seems to be more responsive to treatment. However, the effect of rehabilitation on post-stroke motor recovery and its dependency on the patient's stage of stroke are less clear

(Ballester et al., 2019). The same study reported that clinical recovery scores of stroke patients with comparable baseline impairment levels but variable chronicity, showed steady decrease in sensitivity to treatment (i.e., critical window for recovery) that extended beyond 12 months post-stroke. These results suggested that there is a long-lasting critical period of enhanced neuroplasticity post-stroke that enables improvement in motor function even at later stages of recovery, which could possibly be due to the introduction of compensatory mechanisms and brain reorganization (Rabadi & Rabadi, 2006).

Most stroke rehabilitation protocols are based on motor learning, which stimulate dendrite sprouting, new synapse formation, alterations in existing synapses, and neurochemical production (Arya, Pandian, Verma, & Garg, 2011; Mulder & Hochstenbach, 2001). Motor learning is a form of relearning; it is a combination of processes correlated to practice or experience which lead to relatively permanent changes in skilled behavior (Schmidt, 1988). It is evident that, in combination with rehabilitative training and motor learning, neuronal plasticity processes may be modified or even boosted (Hara, 2015). In individuals with chronic stroke, motor learning can still occur, suggesting that the functional organization of the motor system can be modified by use and experience even at the chronic stage; by practising a task meaningfully and repetitively (Boyd et al., 2009; Cramer, 2004; Pollock et al., 2014). Taking into account, however, the fact that each individual's capacity in terms of potential for recovery and relearning varies due to the different levels of impairment, there is a clear need to identify biomarkers of recovery to help design better training interventions for the rehabilitation of stroke patients.

1.4 Predicting Motor Recovery after Stroke

Following a stroke, there have been several mechanisms proposed for motor recovery. These include activation of the motor pathway from the unaffected motor cortex to the affected limbs, peri-lesional reorganization, the contribution of secondary motor areas and recovery of a damaged lateral corticospinal tract (CST) (Calautti & Baron, 2003; Jang et al., 2010). The CST is the primary neuronal pathway for producing voluntary movement (Davidoff, 1990; Heffner & Masterton, 1983); it forms part of the descending spinal tract system with most of its axons originating from pyramidal cells that are located in the primary motor and sensory cortex (M1 and S1, respectively)

(Crossman, 2015). It has multiple functions for producing voluntary movement, which include control of motor neuron activity, afferent inputs and spinal reflexes (Davidoff, 1990; Heffner & Masterton, 1983). A lesion to the CST, can cause muscle weakness, but it can also affect synergistic movement patterns which in turn can affect dexterity, ambulation and ADL (Jang, 2009). Thus, the preservation or recovery of the CST is a key point for good potential of recovery for impaired motor function in stroke patients (Jang et al., 2010).

The possibility to predict an individual's potential for recovery of motor function after stroke may promote the use of more effective tailored rehabilitation strategies and management of patient expectations and goals (Stinear, Byblow, & Ward, 2014). Up until now, three main methods have been used to predict motor recovery and response to rehabilitation in the early days after stroke: clinical assessments, neurophysiological biomarkers and neuroimaging techniques (Stinear et al., 2014). For chronic stroke, on the other hand, neurophysiological biomarkers can be more useful when it comes to predicting response to rehabilitation (Wittenberg et al., 2016).

Clinical Assessments

The initial predictors of functional independence six-months post-stroke are age, history of stroke and early neurological status (usually measured with the National Institutes of Health Stroke Scale, NIHSS) (Veerbeek, Kwakkel, van Wegen, Ket, & Heymans, 2011). It has been reported that motor recovery can also be predicted by early measures of impairment, such as the Fugl-Meyer Assessment Scale (FMA) (Buch et al., 2016; Prabhakaran et al., 2008; Stinear et al., 2017b; Winters, van Wegen, Daffertshofer, & Kwakkel, 2015), which is a performance-based index to assess sensorimotor impairment, or by assessing the presence of both finger extension and shoulder abduction in the affected UL (Nijland, van Wegen, Harmeling-van der Wel, & Kwakkel, 2010). Also, a study by Ng *et al.* (2007) revealed that higher Functional Independence Measure (FIM) score at discharge was affiliated with higher FIM score at admission, length of stay at the rehabilitation program, fewer medical complications and age. FIM is an 18-item tool of physical, psychological and social function that is used to assess a patient's level of disability and change in patient status in response to a rehabilitation intervention (Linacre, Heinemann, Wright, Granger, & Hamilton, 1994). Another study by Nijland *et al.* (2013) used the Action

Research Arm Test (ARAT) score for which experienced therapists were asked to predict future ARAT score (at 6 months) within broad categories (< 10; 10–56; and 57), based on assessment, at 72 hours after stroke and again at discharge from the acute stroke unit. The ARAT is a 19-item observational measure to assess upper limb performance, specifically coordination, dexterity and functioning (Yozbatiran, Der-Yeghiaian, & Cramer, 2008). Concurrently, clinical variables were measured to obtain a computational prediction model (CPM). Results showed that the accuracy of the therapist's predictions were lower than the CPM at 72 hours, but equally accurate at discharge, suggesting that awareness of patients' actual performance may contribute to a better appraisal of functional outcome.

In general, an absence of active movement in the upper limb on initial assessment does not necessarily translate to poor motor recovery. Clinical assessments can be useful tools for predicting motor recovery in stroke patients, however, they can be negatively affected by the lack of experience of the therapist using them or the condition of the patient, such as cognitive impairments. On the contrary, neurophysiological measures yield an objective assessment of the functional integrity of the affected limb. This supports growing interest that neuroimaging data can add to predictive models, to provide robust information for individual stroke patients.

Neurophysiological Biomarkers & Neuroimaging Techniques

The degree of damage to the corticospinal tract is linked closely with motor function recovery, but other white matter pathways may also have a role. A meta-analysis by Coupar *et al.* (2012) reported that the strongest predictors of recovery of UL motor function were initial upper limb impairment and function, assessed using the ARAT scale or similar scales, and integrity of ascending and descending white matter pathways measured using neurophysiological and neuroimaging techniques. Neuroimaging techniques that are commonly used for tracking and predicting motor recovery in stroke are: T1-weighted and diffusion weighted magnetic resonance imaging (MRI) that can assess the structural integrity of cortex and pyramidal tract (Stinear et al., 2014). In addition, electroencephalography (EEG) (Finnigan & van Putten, 2013; Wu et al., 2016) and transcranial magnetic stimulation (TMS) (Bembenek, Kurczych, Karli Nski, & Czlonkowska, 2012) are well established tools in neurological practice and in the field of research, with

applications in the prediction of motor recovery and management of stroke patients. TMS has the advantage that it is a relatively inexpensive technique, compared to MRI for example, and MEP amplitude computation is performed easily. Thus, TMS can be a valid tool for stratifying stroke patients at time of enrollment into a restorative intervention trial (Cramer, 2010).

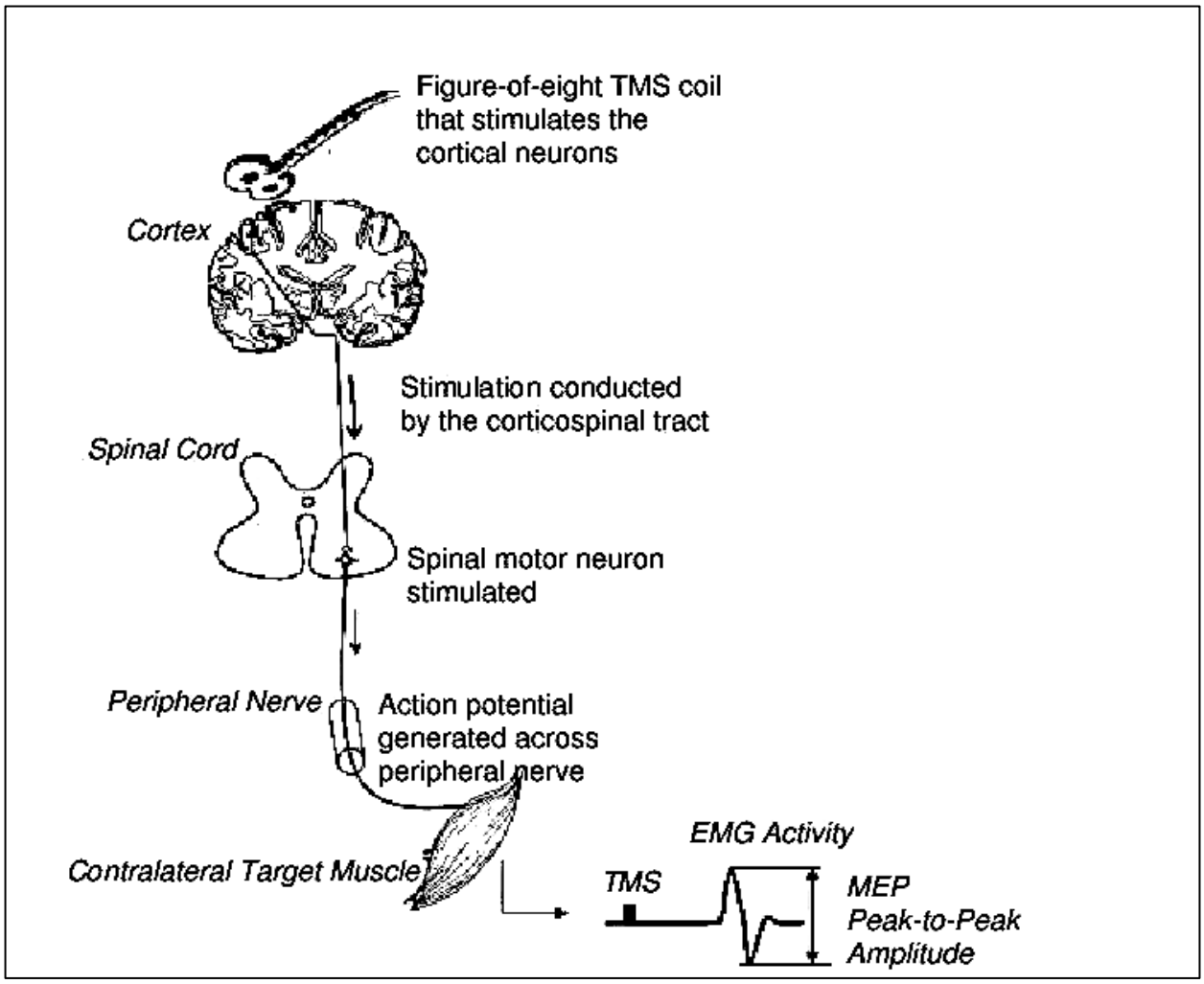
1.5 Transcranial Magnetic Stimulation (TMS) & Stroke

TMS can be used in diagnosis, prognosis, and treatment of motor deficits after stroke (Dimyan & Cohen, 2010; Hernandez-Pavon & Harvey, 2019). It is a non-invasive brain stimulation technique that allows for assessment of the integrity of the corticospinal tract post-stroke as well as cortical reorganization by the use of motor evoked potentials (MEP) (Talelli, Greenwood, & Rothwell, 2006). MEPs are action potentials elicited by a brief magnetic stimulus which is delivered, using a coil, over the M1 to depolarize underlying neural tissue, and are recorded from muscles of the affected limb, with surface electromyography (EMG) (Abbruzzese, 2010) (Figure 1). MEP recordings taken from TMS can be used in various manners to measure cortical excitability. Some of these measures include resting motor threshold (rMT), which is the lowest intensity of stimulus necessary to produce a MEP peak-to-peak amplitude ≥50 μV and provides information about a central core of neurons in the muscle representation in the motor cortex (Ziemann, Lonnecker, Steinhoff, & Paulus, 1996) and MEP amplitudes, which demonstrate the excitability of corticospinal neurons (Houde et al., 2018; Talelli et al., 2006).

The simple presence or absence of MEPs in the affected limb can offer useful prognostic information. The prognostic significance of MEPs has been demonstrated to be an important factor when it comes to the planning of post-stroke rehabilitation (Bembenek et al., 2012; Nascimbeni, Gaffuri, Granella, Colli, & Imazio, 2005). In the study of Jo *et al.* (2016), results from a TMS-induced MEP session to assess corticospinal excitability of both hand motor cortices within 3 weeks after stroke onset indicated that the quantitative parameter of TMS-induced MEP, which included MEP amplitude, rMT and latency of MEP, could be used as a parameter to predict motor function in patients with stroke. Specifically, MEP responsiveness was the strongest tool to predict motor function and the rMT ratio was a significant independent prognostic factor for motor function, at 3 months post-stroke. Jang *et al.* (2010) used TMS and tractography on 54 patients

with intracerebral hemorrhage and severe motor weakness and found that patients in whom MEPs could be elicited in the paretic upper limb, and with an intact corticospinal tract visualized with tractography, had better motor outcomes at onset and 6 months post-stroke.

Figure 1. Schematic representation of TMS-induced MEP responses



MEPs can also provide information about an individual's response to exercise (Beaulieu & Milot, 2018). For chronic stroke patients with UL disabilities, an assessment of CST integrity could play an important role in the setting of rehabilitation goals. Stinear *et al*. (2007; 2017a), for example, developed an algorithm that uses MEPs as a marker for stroke survivors' stratification for rehabilitation therapies. Based on the absence/presence of MEPs in response to TMS of the ipsilesional motor cortex, this algorithm proposes a general guideline on exercises prescription in

order to enhance functional recovery. Specifically, in the study of Stinear *et al.* (2007), clinical scores of chronic stroke patients at inception, measured using the National Institutes of Health Stroke Scale (NIHSS) and the FMA Scale, were greatly predicted by the presence or absence of MEPs in the affected UL. For patients with MEPs, UL motor function was superior but functional potential declined with increasing time since stroke. For patients without MEPs, clinical scores were strongly associated with poorer UL function, lower functional potential and less recovery of motor function, which is also consistent with previous studies (Dachy, Biltiau, Bouillot, Dan, & Deltenre, 2003; Trompetto, Assini, Buccolieri, Marchese, & Abbruzzese, 2000).

Furthermore, in another study by Bolognini *et al.* (2011), 14 chronic stroke patients participated in a double-blind sham controlled study which combined effects of bihemispheric transcranial direct current stimulation (tDCS) with constraint-induced movement therapy. TMS was used to measure corticospinal excitability and transcallosal inhibition in both motor cortices. Results showed that ipsilesional cortical excitability changes, for example increased MEP amplitude, correlated with improvement in the FMA scores and decreased time to complete the Jebsen-Taylor Hand Function Test (JTT) (Jebsen, Taylor, Trieschmann, Trotter, & Howard, 1969), a test used to evaluate fine hand motor function. These studies provide promising results that MEPs could be used to predict response to rehabilitation interventions for chronic stroke patients.

1.6 Rehabilitation Interventions for the Upper Limb after Stroke

The aim of stroke rehabilitation is to improve, among other things, muscle strength and function of the paretic limbs in order to improve quality of life after stroke. Stroke rehabilitation programs targeting the motor system should consist of meaningful, repetitive, intensive and task-specific movement training in an enhanced environment to promote neural plasticity and recovery (Takeuchi & Izumi, 2013). There are many methods and approaches that can be used in stroke rehabilitation, such as constraint-induced movement therapy and bimanual practice (Lee, Lee, Koo, & Lee, 2017; Nesin, Sabitha, Gupta, & Laxmi, 2019), robotic-assisted rehabilitation (Dehem et al., 2019), virtual reality technology (Saposnik & Levin, 2011), functional electrical stimulation (Ring & Rosenthal, 2005), mirror therapy (Yang et al., 2018), active music therapy approach (Raglio et al., 2017) and strength training programs (Patten et al., 2004). However, constraint-

induced movement therapy and bimanual practice have shown effectiveness in patients who can partially extend the wrist and fingers, meaning that it is suitable for individuals showing a fairly good recovery after their stroke (Dobkin & Dorsch, 2013). On the other hand, robotic-assisted rehabilitation and virtual reality (VR) technologies are expensive approaches, whereas functional electrical stimulation has limited implementations as it requires a one-on-one manual approach from a therapist for long periods (Wu, Huang, Chen, Lin, & Yang, 2013). Although mirror therapy and active music therapy have shown positive trends in functional and disability levels and quality of life, promising results of these therapies have not been yet confirmed (Yang et al., 2018). Finally, despite the fact that there is strong evidence that strength training alone can improve muscle strength in people with stroke, further evidence is needed to establish the carry-over effects of strength training to functional tasks (Eng, 2004; Saunders, Greig, & Mead, 2014). Yet, muscle strengthening training has been demonstrated as an essential part of rehabilitation programs offered to stroke patients (Ada, Dorsch, & Canning, 2006; Hatem et al., 2016; Patten et al., 2004).

1.6.1 Strength Training after Stroke

Muscle strengthening programs are progressive active exercises against resistance for the affected UL using machine or free weights. In a systematic review by Hatem *et al.* (2016), in which they focused on rehabilitation techniques that stimulate motor recovery of the UL after stroke, muscle strengthening exercises were recommended as a main rehabilitation intervention, amongst others, on the basis of current evidence for improving UL motor outcome in all stages of stroke (acute, subacute and chronic).

In the chronic stage of a stroke, studies have suggested that the quantity of training in terms of intensity and repetition, rather than the type of training, should be the focus of training protocols in order to maximize functional gains (Dickstein, 2008; Milot, Nadeau, Gravel, & Bourbonnais, 2013; van der Lee et al., 2001; Wallace et al., 2010). To support the rationale of this type of intervention, strength training programs aiming to improve arm function are an integral part of the Canadian Stroke Best Practice Recommendations from the Heart and Stroke Foundation (Heart and Stroke Foundation of Canada, 2015). This recommendation is based on the fact that training the affected UL post-stroke allows for improved motor function (Koski, Mernar, & Dobkin, 2004;

Patten, Condliffe, Dairaghi, & Lum, 2013), increased muscle strength (Harris & Eng, 2010; Koski et al., 2004) and greater motor cortex excitability and activity (Dong, Dobkin, Cen, Wu, & Winstein, 2006; Koski et al., 2004), all translating into clinically significant gains in daily use of the trained limb (Dong et al., 2006). However, although there is a variety of strengthening protocols that can be used in stroke rehabilitation, few studies have assessed training parameters that are critical to address each individual's needs and impairments (Pak & Patten, 2008). In parallel, recent developments in the management of post-stroke disability indicate that further gains in function can be obtained when rehabilitation interventions are combined with neurostimulation techniques designed to boost motor excitability and enhance response to exercises (Thibaut, Chatelle, Gosseries, Laureys, & Bruno, 2013).

1.7 Transcranial Direct Current Stimulation (tDCS) & Stroke

Transcranial direct current stimulation is a non-invasive brain stimulation technique that is used to modulate cortical excitability using a constant and weak current (1-2 mA) (Thair, Holloway, Newport, & Smith, 2017). This current can promote subthreshold depolarization or hyperpolarization of underlying tissue using anodal or cathodal approaches, respectively (Peters, Edwards, Wortman-Jutt, & Page, 2016). Although tDCS does not stimulate axons, it probably targets neuronal signalling by manipulating ion channels or by shifting electrical gradients. These mechanisms influence the electrical balance of ions inside and outside of the neural membrane, resulting in modulation of the resting membrane threshold (Bolognini, Pascual-Leone, & Fregni, 2009). Besides changes in membrane potential, pre or post synaptic chemical neurotransmission could also play a role in tDCS effects (Liebetanz, Nitsche, Tergau, & Paulus, 2002). For example, some studies (Liebetanz et al., 2002; Nitsche et al., 2003) tested the effects of the sodium channel blocker carbamazepine, the calcium channel blocker flunarizine and the N-Methyl-D-Aspartate receptor (NMDA-receptor) antagonist dextromethorphane on tDCS-elicited motor cortex excitability changes, in healthy human subjects. The authors determined that cortical excitability shifts, which were induced during tDCS, appeared to depend on membrane polarization, hence, modulating the conductance of sodium and calcium channels. Furthermore, the after-effects of tDCS suggested that they were NMDA-receptor dependent. In conclusion, the glutamatergic system, and in particular NMDA receptors (Paulus, 2004), seems to be essential for induction and

preservation of neuroplastic after-effect excitability enhancement induced by tDCS (Liebetanz et al., 2002).

In the context of improving motor function in stroke rehabilitation, one of the models used with tDCS is based on an imbalance of interhemispheric inhibition; the electrophysiological correlate of an evident maladaptive neural activation pattern after stroke (Nowak et al., 2009). Modulating the cortical excitability may cause synaptic plasticity, which in turn may interfere with these maladaptive processes resulting from a stroke (Nowak et al., 2009). In essence, motor cortex excitability can be modulated through three different approaches: by decreasing contralesional motor cortex excitability (cathodal tDCS), as it may interfere with the recovery of the affected hemisphere; by increasing ipsilesional motor cortex excitability (anodal tDCS); or by using bihemispheric stimulation (bilateral tDCS) (Fleming et al., 2014; Orru, Conversano, Hitchcott, & Gemignani, 2019).

Stroke survivors present considerably decreased ipsilesional corticospinal activity caused by damage to cortical tissue and descending corticospinal tract fibers, along with hyper-inhibitory signals from the contralesional hemisphere (Stinear et al., 2007; Takeuchi, Oouchida, & Izumi, 2012; Talelli et al., 2006). Anodal tDCS attends to this abnormal functioning by causing subthreshold depolarization of underlying membrane potential in the affected hemisphere, which may increase synaptic efficacy and response to neurorehabilitative therapies (Peters et al., 2016). In addition, anodal tDCS directly enhances excitability of the ipsilesional M1/corticospinal tract (Hummel et al., 2006), which, in principle, offers the potential to improve UL weakness in hemiparetic stroke patients (Zhu, Lindenberg, Alexander, & Schlaug, 2010). On the other hand, cathodal tDCS is thought to reduce inter-hemispheric inhibition from contralesional-to-ipsilesional M1 (Duque et al., 2005). This aims to suppress contralesional motor activity and could be beneficial for some patients but detrimental for others, depending on the functional significance of that contralesional activity in the affected UL use (Duque et al., 2005). Finally, comparing unilateral tDCS with bilateral M1–M1 tDCS, the study by O'Shea *et al.* (2014) reported that bilateral tDCS was less effective than unilateral anodal or cathodal tDCS bilateral tDCS, as it did not change MEPs in the healthy brain nor improved simple reaction time of the affected UL in chronic stroke patients.

When pairing tDCS with various neurorehabilitative applications for motor deficits, a meta-analysis by Backhaus *et al.* (2018), showed that tDCS had a statistically significant, moderate effect on motor function, when evaluated immediately after the end of the intervention period and seven days after the intervention. Other recent meta-analyses, investigating tDCS effects in combination with different rehabilitation protocols for motor deficits after stroke, presented small to moderate positive effects of tDCS on learning and functional recovery, without them always being statistically significant (Chhatbar et al., 2016; Kim, Ohn, Yang, Park, & Jung, 2009; Tedesco Triccas et al., 2016).

tDCS in Combination with Exercise

As aforementioned, tDCS is used as an adjuvant to rehabilitative therapies for stroke patients as it can be applied concurrently with physical interventions to modulate neuronal excitability (Hatem et al., 2016). In order to induce long-term clinically meaningful motor change, it has been suggested that tDCS should be paired with more challenging interventions, such as strength training, with the aim of using anodal tDCS to promote acquisition or consolidation of the training effects (O'Shea et al., 2014; Reis et al., 2009). In the study of Allman *et al.* (2016), for example, anodal tDCS was used as an adjunct to motor training in stroke patients. Participants took part in a 1-hour session of Graded Repetitive Arm Supplementary Program (GRASP), in which repetitions and weight or size of objects gradually increased over 9 days. They were also allocated into either an anodal or a sham stimulation group. The authors showed that the addition of ipsilesional anodal tDCS to a 9-day motor training program improved long-term clinical outcomes, in comparison to sham treatment, in stroke patients. Mortensen *et al.* (2016) conducted a randomized controlled trial in which participants received a 30 min training consisting of functional tasks whilst receiving tDCS (either anodal or sham) concurrently, for 5 consecutive days. They concluded that anodal tDCS combined with the training provided greater improvements in grip strength relative to sham tDCS. These studies show that tDCS is a promising add-on intervention regarding training of upper limb motor impairment.

tDCS in Chronic Stroke

Although the effects of tDCS on recovery are promising, there are multiple factors that interact to determine the motor effects to M1. Amongst others, such as type of stimulation and timing of the assessment, the stage of recovery post-stroke is one of the main factors regarding the effects of tDCS on motor recovery (Pavlova, Semenov, & Guekht, 2019). Many studies have been conducted investigating the influence of tDCS in the acute (Chang, Kim, & Park, 2015; Rossi, Sallustio, Di Legge, Stanzione, & Koch, 2013), subacute (Alber, Moser, Gall, & Sabel, 2017; Stinear & Byblow, 2014) and chronic stage of recovery (Fregni et al., 2005; Hummel et al., 2005), however, there has been no concluding as to which stage of post-stroke recovery is the preferred one for stimulation (Pavlova et al., 2019).

Concerning the chronic stage of recovery post-stroke, Hummel *et al.* (2005) found that there was a decrease in the performance time of the JTT (Jebsen et al., 1969), during and after anodal stimulation. Fregni *et al.* (2005) reported significant effects when JTT was performed after the anodal stimulation in chronic stroke patients, but not when it was performed during the stimulation. In another study by Boggio *et al.* (2007) tDCS was significantly associated with motor function improvement in chronic stroke patients evaluated using JTT, following 4 weeks of stimulation sessions. In conclusion, the beneficial effects of tDCS are still subject to controversy with studies supporting its use in the rehabilitation of stroke patients (Fregni et al., 2005; Hummel et al., 2005), while others debate its validity (Tedesco Triccas et al., 2016).

CHAPTER 2: Rationale & Objectives

The present study addresses the need to reduce the cumulative burden of stroke consequences by aiming to optimize rehabilitation of the upper limb. According to the existing literature, there is a clear need to further validate the use of MEPs as a classification tool and to explore new ways on how to refine the use of this measure, in order to optimize post-stroke training interventions. In addition, since tDCS is still relatively new in the field of stroke rehabilitation, no study to date has tried to determine whether tDCS can enhance the effects of a strength training intervention in stroke patients. Ultimately, there is an urgent need to design better training interventions for the management of post-stroke disability, notably by adapting programs to meet each individual's capacity in terms of potential for recovery. It is also necessary to determine whether non-invasive brain stimulation techniques, such as tDCS, can be used in conjunction with tailored strength training exercises to boost functional recovery after stroke.

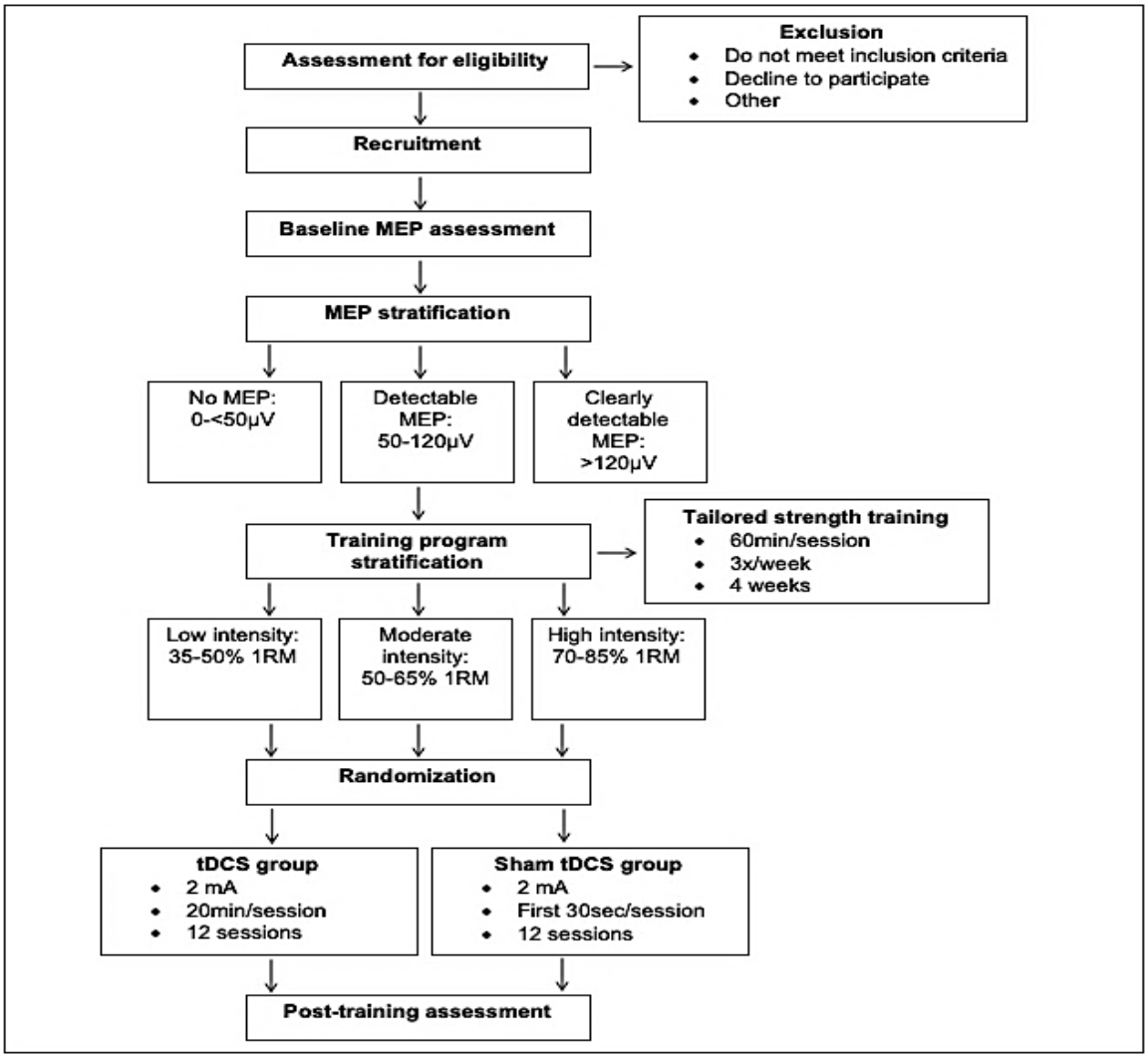
The primary objective of the study was to determine whether the use of TMS to evaluate the excitability of the brain of stroke survivors could help optimize strength training of the affected arm. More specifically, the aim was to estimate the extent to which tailored strength training interventions, based on each participant's MEPs' amplitude, are beneficial to participants in terms of improved motor function and motor cortex excitability. The secondary objective was to estimate the extent to which a 4-week tailored strength training program, in combination with anodal tDCS can further enhance motor recovery and boost the function of the affected arm, when compared to sham tDCS. As the known effects of tDCS suggest that it increases excitability of the brain, this study aimed to establish this assumption and investigate whether this change in excitability could possibly be enhanced with exercise.

CHAPTER 3: Methods

Study design

This study was a multi-centre, randomized controlled trial (RCT), which involved three different sites, throughout two provinces; Québec: Montréal and Sherbrooke, Ontario: Ottawa. This study was approved by the Research Ethics Committee (REC) of the CIUSSS de l'Estrie-CHUS (MP-22-2016-630) and was responsible for its follow-up. Figure 2 presents the study design flow diagram from recruitment and screening for eligible participants to post -training outcome assessments.

Figure 2. Study design flow diagram



Participant recruitment

The process of recruiting participants involved several recruitment procedures such as newspaper advertisements and advertisements on websites and social media, search in medical archives and former patient lists from each site. Potential participants were initially screened over the phone to determine their interest and primary eligibility of participation in the study confirmed by a script for early recruitment, after which they were invited to attend each site, for an overall screening assessment and evaluation to verify eligibility to participate (Table 1). At the beginning of the first study visit, participants were informed about the duration, procedure and possible risks or inconveniences of the study through a detailed consent form which they were then asked to sign, having fully understood the information about the project. In addition, baseline information of each participant was collected at the initial visit, such as age, sex, handedness, time since stroke, stroke type and location of stroke to help characterize the sample.

Table 1. Tests for eligibility assessment

Tests	*Evaluation Aim*	*Tasks*	*Rating Scale*
Modified Ashworth Scale	Spasticity (muscle tone) of: shoulder and elbow flexors, wrist and fingers of affected side	Evaluator placed the joint of each muscle tested in a maximally flexed position and moved to a position of maximal extension over 1s.	6-point: 0 (no increase in muscle tone) – 4 (affected part rigid in flexion or extension)
Semmes-Weinstein Monofilament Test	Sensation in different parts of the affected arm	Participants were assessed in supine position with eyes closed. A monofilament 3.84mm was placed on each site for 1s and participants indicated where they felt pressure.	12-point: 0 (no site indicated) – 12 (all sites indicated)
Pain Scale	Intensity of perceived pain at rest and movement of the affected arm	Participants were asked to indicate the level of perceived pain of the affected arm, using a scale, at rest and during a reaching movement.	10-point: 0 (no pain) – 10 (worst pain imaginable)

Vibratory Sensation Test	Sensory deficits of the affected arm	Participants were assessed in sitting position with eyes closed. Evaluator applied a graduated tuning fork on the styloid apophysis of the ulna of the affected arm and asked if they perceive the vibration and when it ends. If no sensation is perceived at that site, the same was tried on the lateral epicondyle.	8-point: 0 (no sensation of vibration) – 8 (full sensation)
Alexander Apraxia Test	Apraxia of the affected arm	Participants had to imitate 5 movements demonstrated by the evaluator.	5-point: 0 (no movement) – 5 (normal movement)
Line Cancellation Test	Visual-Spatial Neglect	A test sheet with multiple 40*25mm lines was placed in front of the participants. They were asked to cross off all the center lines using a pen and without moving the test sheet.	0 (all items identified); if not, the score was calculated by a computer-aided Score Center of Cancellation (executable cancel.exe)
Mini-Cog Test	Cognitive impairments	3 subtests: 1) Participants were instructed to repeat and remember 3 words. 2) They were asked to draw a clock and place the hands at 11:10. 3) They were asked to repeat the 3 words.	5-point: Word recall: 0 (no word recalled) – 3 points (all words recalled) Clock drawing: 0 (number or clock hands are incorrect) – 2 (number and clock hands are correct)

Inclusion/exclusion criteria

To be eligible to participate in the study, participants had to comply to the following criteria: 1) be 18 years and older; 2) have had solely one stroke; 3) be in a chronic stroke phase (> 6 months) and 4) have completed their rehabilitation treatment. Participants were excluded from the study if any of the following criteria occur: 1) a significant spasticity at the affected upper limb (a score ≥ 3 on the *Modified Ashworth Scale*) (Katz, Rovai, Brait, & Rymer, 1992); 2) a major sensory deficit (a score ≤ 8/12 using the *3.84 Semmes-Weinstein monofilament*) (Weinstein, 1993); 3) a significant pain intensity at the affected upper limb (a score ≥ 6/10 on the *Visual Analog Pain Scale*) (Boonstra, Schiphorst Preuper, Balk, & Stewart, 2014); 4) no perception of vibration either at the styloid apophysis or at the lateral epicondyle (a score ≤ 5/8 using a graduated tuning fork) (Martina, van Koningsveld, Schmitz, van der Meche, & van Doorn, 1998); 5) an apraxia (a score > 2.5 on the *Alexander Test*) (Alexander, Baker, Naeser, Kaplan, & Palumbo, 1992); 6) a presence of hemineglect (> 70% of unshaded lines on the same side as the motor deficit on the *Line Cancellation Test*) (Albert, 1973); 7) any cognitive impairments (a score ≤ 2/5 on the *Mini-Cog Test*) (Holsinger et al., 2012); 8) the presence of a neurological disorder other than a stroke; 9) adjuvant orthopaedic problems at the affected upper limb and 10) any contraindication to TMS and/or tDCS, such as epilepsy, metallic implants, a cardiac pacemaker or pregnancy.

Assessment period

Clinical and neurophysiological evaluations were used to assess motor function and motor cortex excitability, respectively, the week before (baseline) and the week after the intervention period. These evaluations were spread over 2 days and lasted approximately 1.5 h each.

- *Clinical evaluation*

- FMA (Fugl-Meyer, Jaasko, Leyman, Olsson, & Steglind, 1975): A sub-test of FMA was used to assess the affected UL functions, which include voluntary movement, reflex activity and coordination of the shoulder, elbow, forearm, wrist and hand. For the assessment, participants were asked to imitate movements of the UL that can be found in Appendix A and were initially

demonstrated on the unaffected UL for comprehension purposes. Scale items are scored on the basis of ability to complete the item using a 3-point ordinal scale where 0=cannot perform, 1=performs partially and 2=performs fully. The total possible scale score for the UL is 66.

- Motor Activity Log (MAL) (Uswatte, Taub, Morris, Light, & Thompson, 2006): This is a subjective measure of the participant's real-life functional UL performance. The MAL is administered by 30-item semi-structured interview to determine how much (amount), and how well (quality) the individual uses his affected upper limb in his own home compared to before experiencing the stroke. A 5-point ordinal scale is used where 0=never used and 5=same as pre-stroke and the overall quantitative and qualitative use of the affected UL was determined by calculating the mean for each scale (Appendix B).

- Range of motion (ROM): The range of motion of shoulder and elbow flexion and wrist extension was measured. Participants were assessed in a supine position with the relevant joint being placed align with the midline of each body part. They were asked to maximally flex or extend their joint (active range of motion-AROM) and then the assessor moved the relevant joint passively to assess the maximal joint flexion and extension (passive range of motion-PROM). A JAMAR® goniometer was used to measure the degree of full movement potential (Gajdosik & Bohannon, 1987).

This choice of variables for the clinical evaluation was made to ensure that even the most-severely impaired participants would be able to perform to some extent the required tasks, thus being equally assessed as the rest of the participants, as individuals without MEPs often have limited voluntary movement at the affected UL.

- *Neurophysiological evaluation*

The neurophysiological evaluation consisted of the assessment of the integrity of the corticospinal tract and cortical reorganization post-stroke, by the use of the peak-to-peak MEP amplitudes and the rMT. For the purposes of this evaluation, participants were seated in an armchair with both

hands resting in pronation. Surface electromyography (EMG) electrodes (Neuroline 700, Ambu, Glen Burnie, USA) were positioned over the first dorsal interosseous (FDI) muscle of both hands, after they were cleaned with alcohol. A 70-mm figure-of-eight coil attached to a TMS system (Magstim 200^2, Magstim Company, Dyfed, UK) was used to investigate the hotspot and rMT initially from the contralesional hemisphere; in the case that it is needed to help guide the identification of the hotspot for the ipsilesional hemisphere. A hotspot is defined as the position of the scalp with the lowest threshold for a specific target muscle, yielding 40% higher MEP amplitudes compared to surrounding areas (Ah Sen et al., 2017). The rMT reflected the lowest TMS intensity which was required to elicit MEP amplitudes above 50μV in 50% of the trials. It was determined using the Motor Threshold Assessment Tool software (MTAT 2.0; Clinical Researcher, Knoxville, TN, USA), which allows for fast estimation of motor threshold through the maximum-likelihood strategy based on the PEST (Parameter Estimation by Sequential Testing) algorithm. After determining the rMT, a series of suprathreshold stimuli (130% rMT, n = 10) were delivered over the hotspot of the M1 to elicit MEPs in the resting state. The intensity of TMS was set to 130% of participants' rMT in the resting state, as previous studies reported that this intensity level probes optimal changes in cortical excitability and leads to reliable MEP responses (Hernandez-Pavon & Harvey, 2019; Talelli et al., 2006). These procedures were then repeated for the ipsilesional hemisphere. In the case that no MEPs were elicited from the affected FDI, the coil was moved in order to target the representation of the affected extensor carpi radialis (ECR) muscle. If the peak-to-peak MEP amplitude of both affected FDI and ECR failed to reach a threshold above 50μV, even at the maximum intensity of 100%, then the MEP response was classified as absent (0).

Randomisation & blinding of participants

Three different levels were used to stratify participants based on the amplitude of their TMS-induced MEP responses: 1) no detectable MEPs (0-< 50 μV); 2) detectable MEPs (50-120 μV) and 3) clearly detectable MEPs (> 120 μV); adapted from Milot *et al.* (2014). Participants were then further allocated randomly into two tDCS groups using a block randomization with a block size of 2x4, within each stratum: 1) tDCS real group and 2) tDCS sham group. The participants,

the evaluators involved in the clinical and neurophysiological evaluations and the research assistants involved in the data analysis were blinded to the tDCS group assignment.

Intervention period

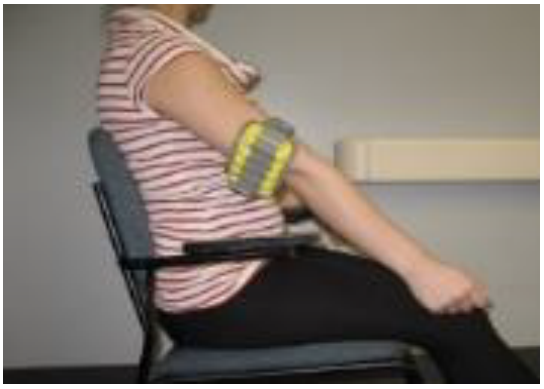
All participants took part in a supervised tailored strength training program, which followed the recommendations on exercise prescription after stroke by the American Stroke Association (ASA) (Billinger et al., 2014). According to these recommendations, the strength training program was conducted for 1 h in an outpatient rehabilitation setting, for a total of 4 weeks and was performed 3 times per week, non-consecutively. Each exercise consisted of 3 series, with 10 repetitions per exercise and a 2 min break in between exercises. The training started with a 5 min warm-up consisting of active movements of the muscles to be trained, either with light weights or no weights and ended with a 5 min cool down and stretching. All exercises were performed in a sitting position. The strength training program was supervised by an experienced trainer who monitored the participants' exercise performance and fatigue. The exercises chosen targeted muscles that are involved in the functional performance of the upper limb (Mercier & Bourbonnais, 2004). In essence, the muscles trained consisted of the wrist extensors, the elbow and shoulder flexors and the grip muscles of the affected hand, for which a JAMAR® dynamometer was used instead of free weights (Figures 3 & 4). The order of each exercise was chosen randomly, so it would differ at every session.

As intensity plays a crucial role in response to training, the intensity of the strength training program was standardized between the three MEP strata using the ASA recommendation (Billinger et al., 2014). This is a gradation of training intensity using the 1RM, which is defined as the maximum amount of weight load an individual can lift for one repetition. For participants in the MEP 0-<50μV strata (low training intensity), the training started at 35% of the 1RM for each muscle group and was then increased by 10% each week to reach 50% of the 1RM by week 4. For participants in the MEP 50-120μV strata (moderate training intensity), the training started at 50% of the 1RM to reach 65% by week 4. For the participants in the MEP≥120μV strata (high training intensity), they trained at 70% of the 1RM during week 1 and progressed to 85% of the 1RM at week 4. The 1RM was estimated by the 10RM (Brzycki, 1993) in order to avoid tendino-muscular

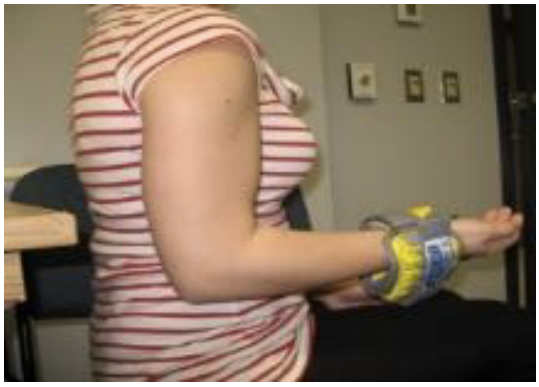
injuries and fatigue. 1RM was used as a way to progress exercises within each training group; i.e. the % of 1RM progressed differently for each group, as presented above. This was chosen as we considered that the low functioning group would respond less to training compared to the individuals in the higher training intensity group. Thus, it was not as essential for the low training group to train at a high % of their maximal strength. However, in terms of the overall effort, as assessed with the Borg Rating of Perceived Exertion (Milot, Leonard, Corriveau, & Desrosiers, 2019), the maximum effort that individuals reached throughout each session of training was equal throughout all groups and corresponded to a score of 12-13/20 to reach 15-16/20 at week 4.

Figure 3. Starting position for each muscle in the exercise training; (A) shoulder flexor, (B) elbow flexor, (C) wrist extensor, (D) grip muscle

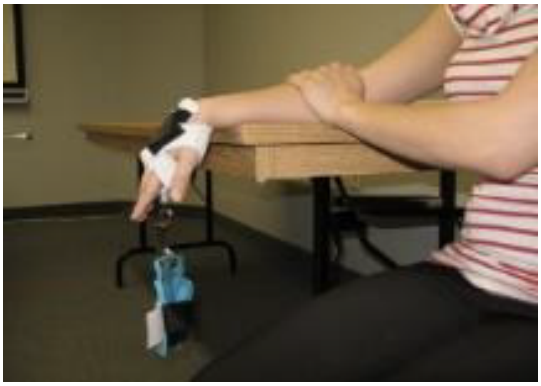
(A)



(B)



(C)



(D)

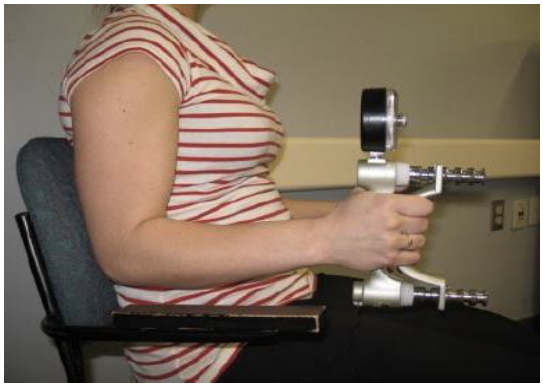
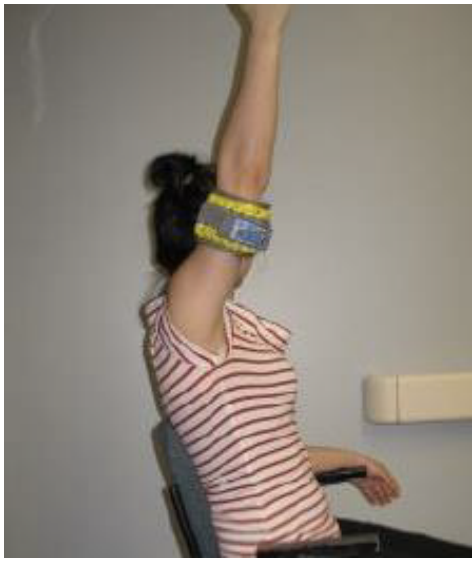
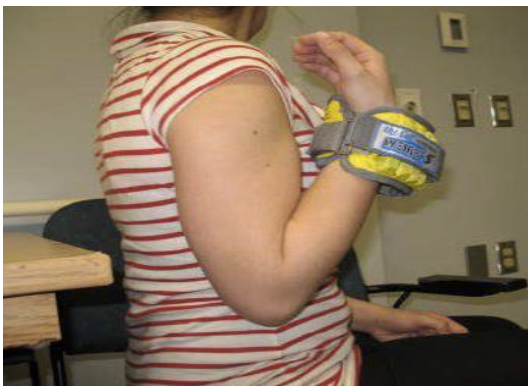


Figure 4. Ending position for each muscle in the exercise training; (A) shoulder flexor, (B) elbow flexor, (C) wrist extensor

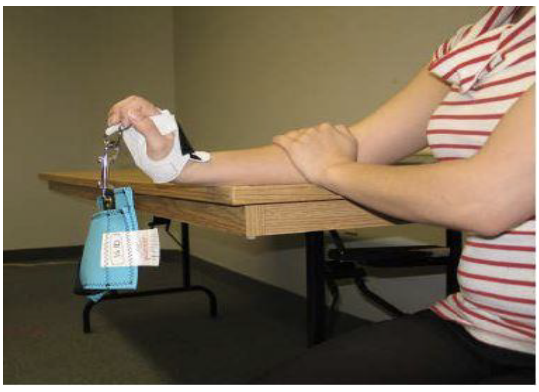
(A)



(B)



(C)



Transcranial direct current stimulation

Prior to the stimulation, the localization of the M1 hotspot of the ipsilesional hemisphere and placement of the electrodes (Neuroconn DC-Stimulator PLUS Electrodes, Neurocare Group, München, Germany) were established following the protocol of DaSilva *et al.* (2011). Specifically, the distance halfway between the nasion and inion and the distance between the right and left pre-auricular points were used to locate the vertex and then the dimensions of the hotspot were marked, as determined from the TMS evaluation. The anode electrode was placed over the M1 area, whereas the cathode was placed on the contralateral supra-orbital region. A tDCS stimulator

(Neuroconn DC-Stimulator PLUS, Neurocare Group, München, Germany) was used to generate a direct current which gradually increased in a ramp-like fashion over the first 8 s until achieving maximum intensity of 2mA. This intensity was chosen as previous studies have reported that this low intensity is sufficient to increase motor function and enhance brain activity after 5 days (Fan, Voisin, Milot, Higgins, & Boudrias, 2017; Ludemann-Podubecka, Bosl, Rothhardt, Verheyden, & Nowak, 2014). For the active tDCS group, the stimulation was applied for 20 mins during each training session for a total of 12 sessions. For the sham tDCS group, stimulation was applied for the first 30 s only, although the protocol was similar to the tDCS active group. The 30 s duration is a long enough period to induce similar perceived sensation as active tDCS, ensuring that way blindness of the participants to the tDCS type (Gandiga, Hummel, & Cohen, 2006). The parameters chosen for the application of tDCS are considered safe, according to previous studies (Bastani & Jaberzadeh, 2012; Marquez, van Vliet, McElduff, Lagopoulos, & Parsons, 2015). At the end of each training session and stimulation, participants were asked, using a home-developed questionnaire, whether they experienced any adverse symptoms related to tDCS; for example, itchiness or tingling.

Sample size & power calculations

Using a two-tailed independent samples t-test and having an alpha level of 0.05, an a priori power analysis was performed in G*Power 3.1.9.2, to calculate the sample size required in this study, with an effect size of 0.66 and a power of 85%. By allocating participants in order to provide a suitable dosage of training, based on their MEP amplitude, it was anticipated that the participants within the three MEP strata would benefit from the 4-week tailored strength training program. Thus, the sample size was calculated based on the expected difference in motor function gains between the real and sham tDCS groups. Based on the results of studies having used repetitive application of tDCS in chronic stroke survivors, we expected an 8-point gain in FMA for the tDCS real group (Bolognini et al., 2011) and at least a 6-point gain in the tDCS sham group (including participants with and without MEP), exceeding the 5-point gain minimal detectable change (MDC) of this scale (Wagner, Rhodes, & Patten, 2008). It was calculated that a total of 84 participants will be needed to detect differences between groups and taking into account an attrition rate and missing data of 20%, a total of 105 participants will be the target sample size for the purpose of

this study over the 3 sites. Due to the fact that the recruitment is on-going, a total of 80 participants were recruited so far for the purposes of this thesis; 39 at the Montréal site, 30 at the Sherbrooke site and 11 at the Ottawa site.

Outcome measures

Primary and secondary outcome measures concerned both motor function and motor cortex excitability. Specifically, they included:

- *Motor function*
- *Primary outcome measures*

  Pre and post-training changes in (1) FMA, to assess changes in motor function of the trained affected UL and in (2) MAL, both amount and quality, to assess participants' self-reported level and quality of use of the affected arm in ADL, respectively.

- *Secondary outcome measures*

  Pre and post-training changes in active and passive range of motion (AROM and PROM, respectively), comparing both affected and unaffected UL.

- *Motor cortex excitability*
- *Primary outcome measures*

  Pre and post-training changes in rMT, to assess changes in motor cortex excitability and cortical reorganization.
- *Secondary outcome measures*

  Pre and post-training changes in peak-to-peak MEP amplitude, elicited by TMS, again to assess changes in motor cortex excitability and cortical reorganization.

Data analysis

Descriptive statistics were used to identify the sociodemographic characteristics of the sample. Because the data was non-normally distributed, even after transformation, and all the residuals

were also non-normal, the Generalized Estimating Equations (GEE) was used over Repeated Measures ANOVA and Linear Mixed Model, respectively. Thus, GEE was used to analyze the effect of Training Group (three MEP strata), tDCS Group (real and sham) and Training Session (pre and post training sessions) and their interactions, with age and years since stroke being used as covariates (DV ~ Session + Training_Group + tDCS_Group + Session x Training_Group + Session x tDCS_Group + Age + Years_Since_Stroke). Full factorial model was not used, only the above terms, as based on previous research and the number of subjects, the 3-way interaction term (Session x Training_Group x tDCS_Group) and the group interaction term (Training_Group x tDCS_Group) were not essential to be included in the model. All data were analyzed with the Statistical Package of the Social Sciences (SPSS; version 26.0) with the significance level set to α=0.05. If a significant interaction was present, post-hoc analysis (simple effects) with Bonferroni correction was performed, which adjusted for Type-I error based on the number of comparisons that were used in the analysis.

.

CHAPTER 4: Results

Table 2 displays the sociodemographic characteristics of both tDCS groups. The present study consisted of 80 chronic stroke participants, from which 55 (69%) were male. The mean age of the participants was 65 years (SD = 12), with the majority being right-handed (89%). Specifically, a Fisher's exact test revealed that there was a significantly higher number of right-handed participants compared to left-handed between all participants (Fisher's Exact: $P = .029$). The mean time since stroke onset was 5 years (SD = 5), with most participants having suffered an ischemic stroke (84%). The location of the stroke was almost equally divided, as 46% of the participants experienced a left hemisphere stroke, whereas 54% experienced a right hemisphere one. None of the individuals were excluded from the data analysis.

Table 2. Sociodemographic characteristics of both tDCS groups and baseline measures for three main outcome measures FMA, MAL and rMT

Characteristics	*Sham tDCS (n=41)*	*Real tDCS (n=39)*	*Total (n=80)*
Age [mean years (SD)]	64 (13)	66 (11)	65 (12)
Years since stroke onset [mean (SD)]	5 (5)	5 (4)	5 (5)
Sex			
Male	26	29	55
Female	15	10	25
Handedness *			
Right	33	38	71
Left	8	1	9
Stroke location			
Right	22	21	43
Left	19	18	37
Stroke type			
Ischemic	35	32	67
Hemorrhagic	6	4	10
Other (Cerebellar)	0	3	3
Training group			
Low Intensity	8	8	16
Moderate Intensity	8	7	15
High Intensity	25	24	49

FMA [/66; mean (SD)]	47 (19)	48 (19)	48 (19)
MAL			
Amount [/5; mean (SD)]	2.6 (1.8)	2.6 (1.8)	2.6 (1.8)
Quality [/5; mean (SD)]	2.5 (1.7)	2.4 (1.8)	2.4 (1.7)
rMT [% of stimulator output; mean (SD)]	57 (21)	55 (19)	56 (20)

*=significance level at p<.05

Motor function

Effects of the tailored strength training program

The GEE statistical analysis revealed that there are significant main effects of training session and training group on FMA (Wald $\chi^2(1) = 47.371$, $P<.001$ and Wald $\chi^2(2) = 44.140$, $P<.001$, respectively). This indicates that time (pre and post training) and different training intensities were associated with significant higher FMA scores in all 3 groups, with the moderate training group showing the largest mean change between pre and post training. Table 3 presents the mean differences, standard error and 95% confidence interval for difference in the FMA results, considering the different training groups.

Likewise, significant main effects of training session and training group were also present for MAL (Quality) (Wald $\chi^2(1) = 51.016$, $P<.001$ and Wald $\chi^2(2) = 76.657$, $P<.001$, respectively) and MAL (Amount) values (Wald $\chi^2(2) = 28.158$, $P<.001$ and Wald $\chi^2(2) = 81.293$, $P<.001$ respectively). Furthermore, significant main effects of both training session and training group were found on AROM of the wrist (Wald $\chi^2(1) = 6.702$, $P=.010$ and Wald $\chi^2(2) = 33.598$, $P<.001$), PROM of the wrist (Wald $\chi^2(1) = 5.793$, $P=.016$, Wald $\chi^2(2) = 12.788$, $P=.002$) and PROM of the shoulder (Wald $\chi^2(1) = 5.670$, $P=.017$, Wald $\chi^2(2) = 15.708$, $P<.001$), respectively. As previously mentioned, time and training intensity of the 3 different groups were responsible for the significant changes in MAL scores, with the highest change in mean seen in the high intensity group between pre and post training, and in ROM measures for all 3 groups (Table 4). However, significant main effects on AROM of the elbow (Wald $\chi^2(2) = 11.134$, $P=.004$) were only present due to training intensity.

Table 3. Pairwise comparisons of estimated marginal means of FMA

Training Intensity Group	*Mean Difference (Post-Pre)*	*Standard Error*	*95% Wald Confidence Interval for Difference*		*Significance*
			Lower	*Upper*	
Low Intensity	4.75	1.30	2.20	7.30	<.001*
Moderate Intensity	5.35	1.21	2.97	7.72	<.001*
High Intensity	2.56	.44	1.69	3.42	<.001*

*=significance level at p<.05

Table 4. Mean and SD values for each training group for FMA, MAL amount and quality

	Training Intensity Group						
	Low		*Moderate*		*High*		*Signifi-cance*
	Pre Training	*Post Training*	*Pre Training*	*Post Training*	*Pre Training*	*Post Training*	
FMA (/66)	29 (15)	34 (16)	39 (18)	45 (17)	56 (14)	59 (12)	.038*
MAL Amount (/5)	0.6 (0.8)	0.9 (1.1)	1.8 (1.6)	1.9 (1.63)	3.5 (1.4)	3.9 (1.3)	<.001** <.001***
MAL Quality (/5)	0.6 (0.8)	0.9 (1.1)	1.7 (1.5)	2.0 (1.6)	3.3 (1.4)	3.8 (1.3)	<.001** <.001***
Shoulder (degree)							
AROM	93 (48)	103 (41)	112 (53)	123 (43)	145 (31)	147 (27)	.006*
PROM	135 (32)	137 (25)	140 (32)	148 (23)	154 (21)	157 (20)	<.017** <.001***
Elbow (degree)							
AROM	123 (14)	125 (17)	134 (14)	131 (14)	137 (10)	137 (9)	.004***
PROM	137 (10)	132 (27)	143 (14)	139 (15)	143 (10)	142 (9)	.034†

Wrist (degree)							
AROM	20	23	37	40	61	63	.010**
	(33)	(32)	(37)	(34)	(17)	(17)	<.001***
PROM	50	56	68	69	75	80	.016**
	(29)	(33)	(28)	(30)	(15)	(15)	.002***

*=significant interaction effect between training session and training group at p<.05.
= significant effect of training session at p<.05. *= significant effect of training group at p<.05.
†= significant effect of tDCS group at p<.05.

In addition, the GEE statistical analysis revealed that there is a significant interaction effect between training session and training group on the FMA values (Wald $\chi^2(2) = 6.567$, P=.038). Although, "training session" and "training group" both had significant main effects, the interaction also became significant meaning that the trend was not the same at different levels between these two factors (i.e. training session and training group). To identify why there was a significant interaction (i.e. what was the source of difference in the trend), we looked at the post-hoc analysis. The post-hoc analysis revealed that the source of interaction was lack of difference between the low and moderate intensity training groups in pre and post training sessions. Specifically, at pre training the mean difference between the FMA in the low training group (i.e. 29.89) and the moderate group (i.e. 39.00) was -9.11 and P=.212. The same was found for post training (low group=34.64, moderate group=44.35), leading to a mean difference of -9.71 and P=.138. These mean differences are the amount of difference between the average values of each group/level of that outcome measure. The pairwise table analysis revealed that these differences were not significant. The same significant interaction effect was found on the AROM for the shoulder (Wald $\chi^2(2) = 10.387$, P=.006). The post-hoc analysis revealed that the source of interaction was again lack of difference between the low and moderate intensity training groups in pre and post training sessions (mean difference of -18.83 and P=.800 and mean difference of -19.50 and P=.519, respectively). No further significant interaction effects were observed.

Effects of tDCS

The GEE statistical analysis revealed that there is a significant main effect of tDCS group on PROM of the elbow (Wald $\chi^2(1) = 4.502$, P=.034), with a decrease in both tDCS groups. This

could be attributed to the fact that there were a lot of variables in the analysis, thus a higher chance of having a Type-I error. Mean and SD values for both tDCS groups for all variables and for both tDCS groups for all variables including each training group are shown in Tables 6 and 7, respectively. Results showed no further significant effects of tDCS groups and no significant findings in motor cortex excitability.

Table 5. Mean and SD values for both tDCS groups for all variables

tDCS Group					
	Sham		*Real*		*Significance*
	Pre Training	*Post Training*	*Pre Training*	*Post Training*	
FMA (/66)	47 (19)	51 (18)	48 (19)	52 (17)	.616
MAL Amount (/5)	2.6 (1.8)	2.9 (1.8)	2.6 (1.8)	3.0 (1.8)	.691
MAL Quality (/5)	2.5 (1.7)	2.8 (1.8)	2.4 (1.8)	2.9 (1.8)	.932
Shoulder (degree)					
AROM	126 (46)	132 (39)	130 (43)	135 (37)	.479
PROM	146 (29)	150 (23)	149 (24)	152 (23)	.413
Elbow (degree)					
AROM	136 (11)	135 (9)	131 (14)	131 (15)	.095
PROM	144 (9)	143 (9)	139 (12)	136 (20)	.034*
Wrist (degree)					
AROM	47 (32)	49 (31)	50 (28)	52 (27)	.324
PROM	68 (27)	72 (29)	69 (17)	74 (19)	.514
rMT (% of stimulator output)	57 (21)	56 (20)	55 (20)	54 (21)	.352
MEP amplitudes (μV)	489 (578)	410 (501)	536 (670)	670 (757)	.163

*=significance level at p<.05

Table 6. Mean and SD values for each training group and both tDCS groups for all variables

tDCS Group	*Training Group*	*Session Group*	*FMA*	*MAL (A)*	*MAL (Q)*	*Shoulder*		*Elbow*		*Wrist*	
						(Ac)	*(P)*	*(Ac)*	*(P)*	*(Ac)*	*(P)*
Sham	Low	Pre	27	0.5	0.6	93	134	127	139	8	42
			(17)	(0.4)	(0.5)	(47)	(35)	(13)	(12)	(39)	(38)
		Post	30	0.7	0.7	100	134	128	139	11	42
			(17)	(0.6)	(0.7)	(40)	(24)	(13)	(12)	(36)	(38)
	Moderate	Pre	35	1.5	1.3	99	141	138	147	37	69
			(14)	(1.3)	(1.1)	(61)	(35)	(8)	(7)	(31)	(32)
		Post	42	1.6	1.6	113	149	134	144	40	69
			(14)	(1.4)	(1.3)	(51)	(23)	(9)	(9)	(30)	(31)
	High	Pre	58	3.6	3.5	145	152	139	145	62	76
			(12)	(1.4)	(1.3)	(28)	(25)	(9)	(8)	(16)	(16)
		Post	60	3.9	3.9	148	156	138	143	64	83
			(10)	(1.3)	(1.2)	(24)	(20)	(7)	(8)	(16)	(17)
Real	Low	Pre	32	0.7	0.7	93	135	120	135	33	59
			(14)	(1.2)	(1.0)	(52)	(31)	(16)	(7)	(23)	(17)
		Post	38	1.2	1.2	106	140	122	125	34	70
			(15)	(1.4)	(1.3)	(44)	(27)	(21)	(36)	(23)	(23)
	Moderate	Pre	44	2.2	2.2	127	138	129	137	37	68
			(23)	(1.9)	(1.9)	(41)	(31)	(18)	(18)	(46)	(26)
		Post	48	2.3	2.5	135	146	127	134	41	69
			(20)	(1.9)	(1.9)	(29)	(25)	(17)	(18)	(41)	(31)
	High	Pre	55	3.3	3.0	144	156	136	141	60	73
			(15)	(1.5)	(1.6)	(34)	(16)	(11)	(11)	(18)	(13)
		Post	58	3.8	3.6	145	157	136	141	62	77
			(14)	(1.4)	(1.5)	(31)	(19)	(11)	(11)	(18)	(12)

Note: (A)=Amount, (Q)=Quality, (Ac)=Active, (P)=Passive

Motor cortex excitability

The GEE statistical analysis revealed that there is a significant main effect of training group on the rMT of the affected UL (Wald $\chi^2(2) = 84.671$, $P<.001$), indicating lower rMT values at higher training intensities and on the MEP amplitude of the affected UL (Wald $\chi^2(2) = 28.852$, $P<.001$), indicating significantly higher MEP amplitudes at higher training intensities. Table 7 presents mean and SD values for rMT and MEP amplitude, for each training group.

Table 7. Mean and SD values for each training group for rMT and MEP amplitude

Training Intensity Group							
	Low		*Moderate*		*High*		*Signifi-cance*
	Pre Training	*Post Training*	*Pre Training*	*Post Training*	*Pre Training*	*Post Training*	
rMT (% of stimulator output)	88 (14)	85 (15)	61 (17)	59 (19)	47 (13)	45 (12)	<.001*
MEP amplitudes (μV)	32 (16)	42 (22)	212 (314)	225 (260)	668 (668)	690 (915)	<.001*

*=significant effect of training group at p<.05

CHAPTER 5: Overall Discussion

This study demonstrated significant improvements in motor function and motor cortex excitability following a 4-week tailored strength training intervention, based on each participant's MEPs' amplitude. It is the first study to demonstrate a clear effect of strength training of the affected UL in chronic stroke survivors, according to each participant's potential for recovery. However, there was no significant add-on effect of anodal tDCS to exercise on either motor function of the affected UL or motor cortex excitability, when compared to sham tDCS.

Effects of the tailored strength training program

As expected, following the 4-week tailored strength training program, improvement in UL motor function was observed in each training group. More specifically, improvements were seen in volitional movements, dexterity, range of motion, coordination and speed and in the amount and quality of the use of the affected UL, according to the FMA and MAL scale and ROM measurements. Although all three groups showed significant improvements after the strength training, greater gains in FMA scores for the low and moderate intensity training group was observed. The FMA is the main tool used to measure motor impairment after stroke and to assess the presence of isolated and/or synergistic patterns of movement (Roh, Rymer, Perreault, Yoo, & Beer, 2013). The low training group increased by 16% after the training, the moderate training group had an increase in FMA scores of 13%, whereas the high training group increased by 4%. This could be due to the fact that the participants in the higher intensity training group already had high or even maximum FMA scores before the training, thus not having much room for improvement. According to Page *et al*. (2012), scores of the FMA scale for the UL between 4.25 (6%) and 7.25 (11%) points represent clinically important differences in chronic stroke patients with minimal to moderate impairment. Although these clinical differences by these authors are applicable to the moderate and high (no clinically important differences) training groups, it is still evident that clinically meaningful differences are found in the low group, as the percentage of change is moderately high.

Active ROM is very important for motor function of the UL and is usually impaired in stroke individuals with hemiparesis due to muscle weakness in addition to abnormal and synergistic patterns of muscle recruitment (Roh et al., 2013). All training groups presented improvements in terms of AROM post-training with the highest improvement found for shoulder and wrist (both had 11% gain) in the low training group, possibly due to the increase in training intensity between the first and last sessions which made the training harder for the more severely affected participants. Enhancement of AROM of UL was also shown in the study of da Silva *et al.* (2015), where a 6-week task-oriented strength training program had positive impact in strength gain and UL function. Taking into account the results of this study and in accordance to previous studies (da Silva et al., 2015; Perez-Marcos et al., 2017; Subramanian, Lourenco, Chilingaryan, Sveistrup, & Levin, 2013), these findings suggest a link between improvements in UL function, from an intensive training program, and increase of AROM.

Our results also revealed that less TMS intensity was required to evoke motor responses (rMT) post-training in the low and high training groups, whereas for the moderate training group, its rMT slightly increased. Based on Talelli *et al.* (2006), tailored strength training was shown to enhance cortical excitability by exciting interspinal and corticospinal neurons. The authors also provided some evidence that tailored strength training can increase metabolism, thus altering synaptic connectivity within neuronal circuits and modifying the function of the corticospinal tract following a stroke (Adkins, Boychuk, Remple, & Kleim, 2006; Goodwill, Pearce, & Kidgell, 2012). It has also been suggested that rMT is correlated to motor function by integrating many elements of information about the structural and the functional integrity of the motor system (Rosso & Lamy, 2018). The findings that rMT was lower post-training in the majority of our participants indicate a progressive increase in cortical spinal excitability of the affected hemisphere, according to Prashantha *et al.* (2013). This highlights the fact that stratifying stroke patients into a tailored strength training based on their potential for recovery is effective to induce reorganization of neural circuitry within the motor cortex and ultimately improving motor function of the affected UL, even at the chronic stage.

Direct comparison of tailored strength training between studies is difficult because this is the first study that has stratified participants in three different training intensity groups, based on the level

of their impairments and CST integrity. However, we can consider that the improvement of the participants in a clinically meaningful matter could be explained by the nature of the exercises, used in this study, which complied to the principles of motor learning and neural plasticity. Firstly, exercises were intensive and repetitive, aspects that have been reported to influence motor improvement (Kwakkel et al., 2004). Secondly, exercises targeted muscle groups playing an important role in the performance of functional activities, such as reaching and grasping. This has been stated as an important factor for motor rehabilitation and is known to positively affect UL motor function, recovery and control in stroke patients (Kwakkel et al., 2004; Nielsen, Willerslev-Olsen, Christiansen, Lundbye-Jensen, & Lorentzen, 2015). Thirdly, the difficulty of the training was tailored to each participant's potential for recovery, which has been shown to be essential for motor learning and neural reorganization (Nielsen et al., 2015; Timmermans, Seelen, Willmann, & Kingma, 2009). Finally, previous studies have reported that functional improvement post-training, which has been associated with cortical reorganization (Colomer, Llorens, Noé, & Alcañiz, 2016; Levin, Weiss, & Keshner, 2015), can occur at any time after a stroke (Cameirao, Badia, Duarte, Frisoli, & Verschure, 2012; Colomer et al., 2016). This has been confirmed in previous research (Folkerts et al., 2017; Fregni & Pascual-Leone, 2006; Kwakkel et al., 2004) and in our study, as functional improvements induced by the training intervention were noted in chronic stroke patients.

Effects of tDCS

Although various studies have supported the promising significant effects of multiple and consecutive sessions of tDCS as an adjuvant treatment for interventions such as PT and strength training, VR multitask therapy, robot-assisted therapy, and for long-term recovery (Kim et al., 2009; Lee & Chun, 2014; Rocha et al., 2016; Straudi et al., 2016), we did not find that combining tDCS with tailored strength training results in further gains in terms of motor function, compared to the strength training alone, regardless of training intensity group. In fact, there is still lack of robust evidence for improvement of performance attributed to tDCS. A recent meta-analysis by Triccas *et al.* (2016), reported that the effects of tDCS combined with UL interventions only translated into a small benefit on improvement of UL function. In agreement with our finding, recent reviews and meta-analyses exploring the effects of tDCS in various rehabilitative

applications for post-stroke motor impairments, indicated that no significant gains from tDCS were observed in terms of improvement in motor function (Butler et al., 2013; Elsner, Kugler, Pohl, & Mehrholz, 2016; Marquez et al., 2015).

Regarding brain excitability, although the tDCS group post-training required lower TMS intensity to evoke motor responses (rMT) and had larger overall muscle response (MEP amplitude) compared to pre training, there was no significant difference observed between the two tDCS groups. This is in agreement with the study of Hummel *et al.* (2005) in which tDCS did not affect motor thresholds in their participants, eliciting only a trend for increase in intracortical facilitation. This measure has not been investigated in our study. Association between increases in motor cortical excitability and performance improvements in motor function have been reported in patients with brain lesions, but cause-effect links are still not clear (Liepert et al., 1998). Although application of tDCS during different phases post-stroke (acute/subacute/chronic) could possibly represent a relevant factor for significant effects, Backhaus *et al.* (2018) reported that time passed after stroke onset has no major impact regarding neuroplastic changes in the course of functional recovery.

Effects on motor function regarding the type of tDCS (anodal on ipsilesional M1; cathodal on contralesional M1; bihemispheric) have been found to have equivalent results in terms of efficacy on the intervention (Backhaus et al., 2018). The intensity and duration of the application (i.e. over time vs. single application) are also factors that could influence tDCS and its long-term effects. It has been reported that duration of aftereffects and excitability changes due to tDCS can last for more than 60 mins after a single session of tDCS, at an intensity of 1mA (Kim et al., 2009). Hummel *et al.* (2005) applied tDCS in a sham-controlled study for 3 different sessions, whilst chronic stroke patients performed the JTT, and found that hand function improvements in the tDCS condition persisted for more than 25 mins after the end of the stimulation, but had returned to baseline levels when measured 10 days after the stimulation. In our study, there were no significant effects of tDCS, even after 12 sessions and 20 mins of stimulation at 2mA. This could be due to the fact that strength exercise has been found to have more compelling and longer lasting effects (Ada et al., 2006), which may have outweighed the effects of tDCS.

Exercise has widespread positive effects on multiple levels of brain function, such as the cellular and molecular levels of brain organization (Taubert, Villringer, & Lehmann, 2015). In healthy individuals, high-intensity exercise has been shown to enhance neuroplastic changes in the brain and increase blood lactate, which has been associated with increased motor cortical excitability (Coco et al., 2010). This could explain why the high-intensity exercise used in our study may be effective in inducing motor cortical excitability changes. A neurochemical model has also been suggested to explain the effects of exercise on motor cortical excitability by enhancing the levels of memory-related trophic factors like brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) or neuromodulatory transmitters like dopamine, epinephrine or norepinephrine in peripheral blood circulation (Li, Charalambous, Reisman, & Morton, 2019; Taubert et al., 2015). BDNF and its receptor tropomyosin receptor kinase B (TrKB), are important molecular intersections for increasing motor cortical excitability after exercise (Klintsova, Dickson, Yoshida, & Greenough, 2004). It has been shown that tDCS also enhances secretion of brain-derived neurotrophic factor (BDNF) with strong effects on neuronal survival and plasticity (Gomez Palacio Schjetnan, Faraji, Metz, Tatsuno, & Luczak, 2013) and may also be associated with increases in angiogenic markers, such as VEGF (Zhang, Liu, He, Liu, & Feng, 2011). Although both interventions have been shown to interfere with brain organization and cortical excitability, the results of our study indicate that the effects of tailored strength exercise on brain function might be too potent to discriminate the add-on effects of tDCS. In addition, effects of tDCS alone have been found in previous studies to be short lived compared to exercise, which could also be a factor of not finding significant add-on effects after the training (Nitsche et al., 2007; Young & Forster, 2007).

Effect of the training program on participants' perception of use of their trained arm and overall appreciation

Subjective measure of arm performance in everyday life situations, represented by MAL scores, was also improved after strength training. The greatest gain from the training program was found in the low training group, in both MAL amount and quality of use scores, with an increase of 45% and 54%, respectively. The other two groups also had improvements that reached 8% and 18% in the moderate training group and 11% and 15% in the high training group for MAL amount and

quality, respectively. According to Lang *et al.* (2008), a change of 0.5 points (10%) on the MAL scale has been determined as clinically meaningful in a population of people with chronic hemiparesis from a stroke. Thus, we can say that the objective changes in arm function, reported by the participants, translate into a marked subjective improvement of the trained UL.

Furthermore, at the end of each participant's training program, they were asked questions regarding their overall appreciation of the training, how it has amended and/or what differences they noticed when performing simple ADLs. The majority of the participants noticed or kept track of small changes in their everyday activities, such as: "I can carry the garbage bags easier with my affected arm", "I can hold the steering wheel better with my affected hand", "I can drink my coffee without feeling my arm weak or trembling". One participant brought us a paper copy of her handwriting before the training and how it had improved after training. Another participant chose to write a small memoir with notes from each day of his training; about his feelings, thoughts and improvement throughout his participation. This suggests that improvements in ADLs could have been underestimated, as they cannot be assessed with standardized measurements quantitatively, however they are still clinically meaningful to this population.

Limitations

As the project was conducted throughout three different sites in Canada, with multiple researchers involved, a limitation of the study could be attributed to lack of consistency of the data collection. Although the research team made sure to train all the personnel involved at three sites, not all sites benefited from the same material. For example, only one site used a stereotaxic neuronavigation system for the placement of the TMS coil at each evaluation. It is suggested that future studies should optimize localization of M1 for the application of tDCS. Furthermore, a selection bias could be present in our study, as patients with major impairments who were not able to perform the exercises using weights were excluded. There was a smaller sample size of participants in the low and moderate training group compared to the high training group, without this influencing the precision of the data analysis. This, in addition to the multiple exclusion criteria, may also limit generalizability of the results in the overall chronic stroke population. Additionally, FMA scores

were high in many patients pre-training, meaning that subtle changes in motor impairment could be not be quantified using this scale.

Conclusion

This study presented positive results of tailored strength training, regardless of tDCS group, as an effective intervention for the promotion of UL motor function and cortical excitability in chronic stroke patients. Despite recruiting participants with a wide range of impairment, the results are a strong indicator that it is feasible to train stroke patients to improve UL motor performance, even at the chronic phase. This is the first RCT study that integrated strength training program of the affected UL, with a state-of-the-art brain evaluation protocol (TMS) to allow tailoring of the intensity of training based on each stroke patient's potential for recovery. We did not find that tDCS had a significant add-on effect in terms of motor function. More studies are needed to clarify the long-term effects of tailored strength training for chronic patients and potential add-on benefits that tDCS may have in addition to exercise.

REFERENCES

Abbruzzese, G. (2010). Motor Evoked Potential. In K. Kompoliti & L. V. Metman (Eds.), *Encyclopedia of Movement Disorders* (pp. 194-195). Oxford: Academic Press.

Ada, L., Dorsch, S., & Canning, C. G. (2006). Strengthening interventions increase strength and improve activity after stroke: a systematic review. *Aust J Physiother, 52*(4), 241-248. doi:10.1016/s0004-9514(06)70003-4

Adkins, D. L., Boychuk, J., Remple, M. S., & Kleim, J. A. (2006). Motor training induces experience-specific patterns of plasticity across motor cortex and spinal cord. *J Appl Physiol (1985), 101*(6), 1776-1782. doi:10.1152/japplphysiol.00515.2006

Ah Sen, C. B., Fassett, H. J., El-Sayes, J., Turco, C. V., Hameer, M. M., & Nelson, A. J. (2017). Active and resting motor threshold are efficiently obtained with adaptive threshold hunting. *PLoS One, 12*(10), e0186007. doi:10.1371/journal.pone.0186007

Alber, R., Moser, H., Gall, C., & Sabel, B. A. (2017). Combined Transcranial Direct Current Stimulation and Vision Restoration Training in Subacute Stroke Rehabilitation: A Pilot Study. *Pm r, 9*(8), 787-794. doi:10.1016/j.pmrj.2016.12.003

Albert, M. L. (1973). A simple test of visual neglect. *Neurology, 23*(6), 658-664. doi:10.1212/wnl.23.6.658

Alexander, M. P., Baker, E., Naeser, M. A., Kaplan, E., & Palumbo, C. (1992). Neuropsychological and neuroanatomical dimensions of ideomotor apraxia. *Brain, 115 Pt 1*, 87-107. doi:10.1093/brain/115.1.87

Allman, C., Amadi, U., Winkler, A. M., Wilkins, L., Filippini, N., Kischka, U., . . . Johansen-Berg, H. (2016). Ipsilesional anodal tDCS enhances the functional benefits of rehabilitation in patients after stroke. *Sci Transl Med, 8*(330), 330re331. doi:10.1126/scitranslmed.aad5651

Arya, K. N., Pandian, S., Verma, R., & Garg, R. K. (2011). Movement therapy induced neural reorganization and motor recovery in stroke: a review. *J Bodyw Mov Ther, 15*(4), 528-537. doi:10.1016/j.jbmt.2011.01.023

Backhaus, W., Anziano, M., & Hummel, F. (2018). Transcranial direct current stimulation and its effects on upper extremity neurorehabilitative training in stroke: A meta-analysis. *Neurological Disorders and Stroke International, 1*(1).

Ballester, B. R., Maier, M., Duff, A., Cameirão, M., Bermúdez, S., Duarte, E., . . . Verschure, P. F. M. J. (2019). A critical time window for recovery extends beyond one-year post-stroke. *Journal of Neurophysiology, 122*(1), 350-357. doi:10.1152/jn.00762.2018

Bastani, A., & Jaberzadeh, S. (2012). Does anodal transcranial direct current stimulation enhance excitability of the motor cortex and motor function in healthy individuals and subjects with stroke: a systematic review and meta-analysis. *Clin Neurophysiol, 123*(4), 644-657. doi:10.1016/j.clinph.2011.08.029

Beaulieu, L. D., & Milot, M. H. (2018). Changes in transcranial magnetic stimulation outcome measures in response to upper-limb physical training in stroke: A systematic review of randomized controlled trials. *Ann Phys Rehabil Med, 61*(4), 224-234. doi:10.1016/j.rehab.2017.04.003

Bembenek, J. P., Kurczych, K., Karli Nski, M., & Czlonkowska, A. (2012). The prognostic value of motor-evoked potentials in motor recovery and functional outcome after stroke - a systematic review of the literature. *Funct Neurol, 27*(2), 79-84. 3812773

Billinger, S. A., Arena, R., Bernhardt, J., Eng, J. J., Franklin, B. A., Johnson, C. M., . . . Tang, A. (2014). Physical activity and exercise recommendations for stroke survivors: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke, 45*(8), 2532-2553. doi:10.1161/STR.0000000000000022

Boggio, P., Nunes, A., Rigonatti, S., Nitsche, M., Pascual-Leone, A., & Fregni, F. (2007). Repeated sessions of noninvasive brain DC stimulation is associated with motor function improvement in stroke patients. *Restorative neurology and neuroscience, 25*(2), 123-129. 17726271

Bolognini, N., Pascual-Leone, A., & Fregni, F. (2009). Using non-invasive brain stimulation to augment motor training-induced plasticity. *Journal of neuroengineering and rehabilitation, 6*, 8. doi:10.1186/1743-0003-6-8

Bolognini, N., Vallar, G., Casati, C., Latif, L. A., El-Nazer, R., Williams, J., . . . Fregni, F. (2011). Neurophysiological and behavioral effects of tDCS combined with constraint-induced movement therapy in poststroke patients. *Neurorehabil Neural Repair, 25*(9), 819-829. doi:10.1177/1545968311411056

Boonstra, A. M., Schiphorst Preuper, H. R., Balk, G. A., & Stewart, R. E. (2014). Cut-off points for mild, moderate, and severe pain on the visual analogue scale for pain in patients with chronic musculoskeletal pain. *PAIN®, 155*(12), 2545-2550. doi:10.1016/j.pain.2014.09.014

Boyd, L. A., Edwards, J. D., Siengsukon, C. S., Vidoni, E. D., Wessel, B. D., & Linsdell, M. A. (2009). Motor sequence chunking is impaired by basal ganglia stroke. *Neurobiol Learn Mem, 92*(1), 35-44. doi:10.1016/j.nlm.2009.02.009

Brzycki, M. (1993). Strength Testing—Predicting a One-Rep Max from Reps-to-Fatigue. *Journal of Physical Education, Recreation & Dance, 64*(1), 88-90. doi:10.1080/07303084.1993.10606684

Buch, E. R., Rizk, S., Nicolo, P., Cohen, L. G., Schnider, A., & Guggisberg, A. G. (2016). Predicting motor improvement after stroke with clinical assessment and diffusion tensor imaging. *Neurology, 86*(20), 1924-1925. doi:10.1212/wnl.0000000000002675

Butler, A. J., Shuster, M., O'Hara, E., Hurley, K., Middlebrooks, D., & Guilkey, K. (2013). A meta-analysis of the efficacy of anodal transcranial direct current stimulation for upper limb motor recovery in stroke survivors. *J Hand Ther, 26*(2), 162-170; quiz 171. doi:10.1016/j.jht.2012.07.002

Calautti, C., & Baron, J. C. (2003). Functional neuroimaging studies of motor recovery after stroke in adults: a review. *Stroke, 34*(6), 1553-1566. doi:10.1161/01.Str.0000071761.36075.A6

Cameirao, M. S., Badia, S. B., Duarte, E., Frisoli, A., & Verschure, P. F. (2012). The combined impact of virtual reality neurorehabilitation and its interfaces on upper extremity functional recovery in patients with chronic stroke. *Stroke, 43*(10), 2720-2728. doi:10.1161/strokeaha.112.653196

Carod-Artal, J., Egido, J. A., Gonzalez, J. L., & Varela de Seijas, E. (2000). Quality of life among stroke survivors evaluated 1 year after stroke: experience of a stroke unit. *Stroke, 31*(12), 2995-3000. doi:10.1161/01.str.31.12.2995

Chang, M. C., Kim, D. Y., & Park, D. H. (2015). Enhancement of Cortical Excitability and Lower Limb Motor Function in Patients With Stroke by Transcranial Direct Current Stimulation. *Brain Stimul, 8*(3), 561-566. doi:10.1016/j.brs.2015.01.411

Chhatbar, P. Y., Ramakrishnan, V., Kautz, S., George, M. S., Adams, R. J., & Feng, W. (2016). Transcranial Direct Current Stimulation Post-Stroke Upper Extremity Motor Recovery

Studies Exhibit a Dose-Response Relationship. *Brain Stimul, 9*(1), 16-26. doi:10.1016/j.brs.2015.09.002

Coco, M., Alagona, G., Rapisarda, G., Costanzo, E., Calogero, R. A., Perciavalle, V., & Perciavalle, V. (2010). Elevated blood lactate is associated with increased motor cortex excitability. *Somatosens Mot Res, 27*(1), 1-8. doi:10.3109/08990220903471765

Colomer, C., Llorens, R., Noé, E., & Alcañiz, M. (2016). Effect of a mixed reality-based intervention on arm, hand, and finger function on chronic stroke. *Journal of neuroengineering and rehabilitation, 13*(1), 45. doi:10.1186/s12984-016-0153-6

Coupar, F., Pollock, A., Rowe, P., Weir, C., & Langhorne, P. (2012). Predictors of upper limb recovery after stroke: a systematic review and meta-analysis. *Clin Rehabil, 26*(4), 291-313. doi:10.1177/0269215511420305

Cramer, S. C. (2004). Changes in motor system function and recovery after stroke. *Restorative neurology and neuroscience, 22*(3-5), 231-238.

Cramer, S. C. (2010). Stratifying patients with stroke in trials that target brain repair. *Stroke, 41*(10 Suppl), S114-116. doi:10.1161/strokeaha.110.595165

Crossman, A. R. a. N., D. (2015). *Neuroanatomy. An illustrated Colour Text*(5th Edition ed.).

da Silva, P. B., Antunes, F. N., Graef, P., Cechetti, F., & Pagnussat Ade, S. (2015). Strength training associated with task-oriented training to enhance upper-limb motor function in elderly patients with mild impairment after stroke: a randomized controlled trial. *Am J Phys Med Rehabil, 94*(1), 11-19. doi:10.1097/phm.0000000000000135

Dachy, B., Biltiau, E., Bouillot, E., Dan, B., & Deltenre, P. (2003). Facilitation of motor evoked potentials in ischemic stroke patients: prognostic value and neurophysiologic correlations. *Clin Neurophysiol, 114*(12), 2370-2375. doi:10.1016/s1388-2457(03)00252-9

DaSilva, A. F., Volz, M. S., Bikson, M., & Fregni, F. (2011). Electrode positioning and montage in transcranial direct current stimulation. *J Vis Exp*(51). doi:10.3791/2744

Davidoff, R. A. (1990). The pyramidal tract. *Neurology, 40*(2), 332-339. doi:10.1212/wnl.40.2.332

Dehem, S., Gilliaux, M., Stoquart, G., Detrembleur, C., Jacquemin, G., Palumbo, S., . . . Lejeune, T. (2019). Effectiveness of upper-limb robotic-assisted therapy in the early rehabilitation phase after stroke: A single-blind, randomised, controlled trial. *Ann Phys Rehabil Med*. doi:10.1016/j.rehab.2019.04.002

Dickstein, R. (2008). Rehabilitation of gait speed after stroke: a critical review of intervention approaches. *Neurorehabil Neural Repair, 22*(6), 649-660. doi:10.1177/1545968308220060201

Dimyan, M. A., & Cohen, L. G. (2010). Contribution of transcranial magnetic stimulation to the understanding of functional recovery mechanisms after stroke. *Neurorehabil Neural Repair, 24*(2), 125-135. doi:10.1177/1545968309345270

Dobkin, B. H., & Dorsch, A. (2013). New evidence for therapies in stroke rehabilitation. *Current atherosclerosis reports, 15*(6), 331-331. doi:10.1007/s11883-013-0331-y

Dong, Y., Dobkin, B. H., Cen, S. Y., Wu, A. D., & Winstein, C. J. (2006). Motor cortex activation during treatment may predict therapeutic gains in paretic hand function after stroke. *Stroke, 37*(6), 1552-1555. doi:10.1161/01.STR.0000221281.69373.4e

Duque, J., Hummel, F., Celnik, P., Murase, N., Mazzocchio, R., & Cohen, L. G. (2005). Transcallosal inhibition in chronic subcortical stroke. *Neuroimage, 28*(4), 940-946. doi:10.1016/j.neuroimage.2005.06.033

Elsner, B., Kugler, J., Pohl, M., & Mehrholz, J. (2016). Transcranial direct current stimulation (tDCS) for improving activities of daily living, and physical and cognitive functioning, in

people after stroke. *Cochrane Database Syst Rev, 3*, Cd009645. doi:10.1002/14651858.CD009645.pub3

Eng, J. J. (2004). Strength Training in Individuals with Stroke. *Physiotherapy Canada. Physiotherapie Canada, 56*(4), 189-201. doi:10.2310/6640.2004.00025

Fan, J., Voisin, J., Milot, M. H., Higgins, J., & Boudrias, M. H. (2017). Transcranial direct current stimulation over multiple days enhances motor performance of a grip task. *Ann Phys Rehabil Med, 60*(5), 329-333. doi:10.1016/j.rehab.2017.07.001

Feigin, V. L., Lawes, C. M., Bennett, D. A., & Anderson, C. S. (2003). Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. *Lancet Neurol, 2*(1), 43-53. doi:10.1016/s1474-4422(03)00266-7

Feigin, V. L., Lawes, C. M., Bennett, D. A., Barker-Collo, S. L., & Parag, V. (2009). Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol, 8*(4), 355-369. doi:10.1016/s1474-4422(09)70025-0

Finnigan, S., & van Putten, M. J. (2013). EEG in ischaemic stroke: quantitative EEG can uniquely inform (sub-)acute prognoses and clinical management. *Clin Neurophysiol, 124*(1), 10-19. doi:10.1016/j.clinph.2012.07.003

Fleming, M. K., Newham, D. J., Roberts-Lewis, S. F., & Sorinola, I. O. (2014). Self-perceived utilization of the paretic arm in chronic stroke requires high upper limb functional ability. *Arch Phys Med Rehabil, 95*(5), 918-924. doi:10.1016/j.apmr.2014.01.009

Folkerts, M. A., Hijmans, J. M., Elsinghorst, A. L., Mulderij, Y., Murgia, A., & Dekker, R. (2017). Effectiveness and feasibility of eccentric and task-oriented strength training in individuals with stroke. *NeuroRehabilitation, 40*(4), 459-471. doi:10.3233/nre-171433

Fregni, F., Boggio, P. S., Mansur, C. G., Wagner, T., Ferreira, M. J., Lima, M. C., . . . Pascual-Leone, A. (2005). Transcranial direct current stimulation of the unaffected hemisphere in stroke patients. *Neuroreport, 16*(14), 1551-1555. doi:10.1097/01.wnr.0000177010.44602.5e

Fregni, F., & Pascual-Leone, A. (2006). Hand motor recovery after stroke: tuning the orchestra to improve hand motor function. *Cogn Behav Neurol, 19*(1), 21-33. doi:10.1097/00146965-200603000-00003

Fugl-Meyer, A. R., Jaasko, L., Leyman, I., Olsson, S., & Steglind, S. (1975). The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. *Scand J Rehabil Med, 7*(1), 13-31. 1135616

Gajdosik, R. L., & Bohannon, R. W. (1987). Clinical measurement of range of motion. Review of goniometry emphasizing reliability and validity. *Phys Ther, 67*(12), 1867-1872. doi:10.1093/ptj/67.12.1867

Gandiga, P. C., Hummel, F. C., & Cohen, L. G. (2006). Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. *Clin Neurophysiol, 117*(4), 845-850. doi:10.1016/j.clinph.2005.12.003

Gomez Palacio Schjetnan, A., Faraji, J., Metz, G. A., Tatsuno, M., & Luczak, A. (2013). Transcranial Direct Current Stimulation in Stroke Rehabilitation: A Review of Recent Advancements. *Stroke Research and Treatment, 2013*, 14. doi:10.1155/2013/170256

Goodwill, A. M., Pearce, A. J., & Kidgell, D. J. (2012). Corticomotor plasticity following unilateral strength training. *Muscle Nerve, 46*(3), 384-393. doi:10.1002/mus.23316

Hara, Y. (2015). Brain plasticity and rehabilitation in stroke patients. *J Nippon Med Sch, 82*(1), 4-13. doi:10.1272/jnms.82.4

Harris, J. E., & Eng, J. J. (2010). Strength training improves upper-limb function in individuals with stroke: a meta-analysis. *Stroke, 41*(1), 136-140. doi:10.1161/STROKEAHA.109.567438

Hatem, S. M., Saussez, G., Della Faille, M., Prist, V., Zhang, X., Dispa, D., & Bleyenheuft, Y. (2016). Rehabilitation of Motor Function after Stroke: A Multiple Systematic Review Focused on Techniques to Stimulate Upper Extremity Recovery. *Frontiers in human neuroscience, 10*, 442-442. doi:10.3389/fnhum.2016.00442

Heart and Stroke Foundation of Canada. (2015). Management of the Arm and Hand Following Stroke. Retrieved from http://www.strokebestpractices.ca/index.php/stroke-rehabilitation/part-two-providingstroke-rehabilitation-to-maximize-participation-in-usual-life-roles/management-of-the-armand-hand-following-stroke/

Heart and Stroke Foundation of Canada. (2018). Statistics on stroke. Retrieved from https://www.heartandstroke.ca/stroke/what-is-stroke

Heffner, R. S., & Masterton, R. B. (1983). The role of the corticospinal tract in the evolution of human digital dexterity. *Brain Behav Evol, 23*(3-4), 165-183. doi:10.1159/000121494

Hernandez-Pavon, J. C., & Harvey, R. L. (2019). Noninvasive Transcranial Magnetic Brain Stimulation in Stroke. *Physical Medicine and Rehabilitation Clinics of North America, 30*(2), 319-335. doi:10.1016/j.pmr.2018.12.010

Holsinger, T., Plassman, B. L., Stechuchak, K. M., Burke, J. R., Coffman, C. J., & Williams, J. W., Jr. (2012). Screening for cognitive impairment: comparing the performance of four instruments in primary care. *J Am Geriatr Soc, 60*(6), 1027-1036. doi:10.1111/j.1532-5415.2012.03967.x

Hosp, J. A., & Luft, A. R. (2011). Cortical Plasticity during Motor Learning and Recovery after Ischemic Stroke. *Neural Plasticity, 2011*, 9. doi:10.1155/2011/871296

Houde, F., Laroche, S., Thivierge, V., Martel, M., Harvey, M. P., Daigle, F., . . . Leonard, G. (2018). Transcranial Magnetic Stimulation Measures in the Elderly: Reliability, Smallest Detectable Change and the Potential Influence of Lifestyle Habits. *Front Aging Neurosci, 10*, 379. doi:10.3389/fnagi.2018.00379

Hummel, F., Celnik, P., Giraux, P., Floel, A., Wu, W. H., Gerloff, C., & Cohen, L. G. (2005). Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. *Brain, 128*(Pt 3), 490-499. doi:10.1093/brain/awh369

Hummel, F. C., Voller, B., Celnik, P., Floel, A., Giraux, P., Gerloff, C., & Cohen, L. G. (2006). Effects of brain polarization on reaction times and pinch force in chronic stroke. *BMC Neuroscience, 7*(1), 73. doi:10.1186/1471-2202-7-73

Jang, S. H. (2009). The role of the corticospinal tract in motor recovery in patients with a stroke: a review. *NeuroRehabilitation, 24*(3), 285-290. doi:10.3233/nre-2009-0480

Jang, S. H., Ahn, S. H., Sakong, J., Byun, W. M., Choi, B. Y., Chang, C. H., . . . Son, S. M. (2010). Comparison of TMS and DTT for predicting motor outcome in intracerebral hemorrhage. *J Neurol Sci, 290*(1-2), 107-111. doi:10.1016/j.jns.2009.10.019

Jebsen, R. H., Taylor, N., Trieschmann, R. B., Trotter, M. J., & Howard, L. A. (1969). An objective and standardized test of hand function. *Arch Phys Med Rehabil, 50*(6), 311-319. 5788487

Jo, J. Y., Lee, A., Kim, M. S., Park, E., Chang, W. H., Shin, Y. I., & Kim, Y. H. (2016). Prediction of Motor Recovery Using Quantitative Parameters of Motor Evoked Potential in Patients With Stroke. *Ann Rehabil Med, 40*(5), 806-815. doi:10.5535/arm.2016.40.5.806

Katz, R. T., Rovai, G. P., Brait, C., & Rymer, W. Z. (1992). Objective quantification of spastic hypertonia: correlation with clinical findings. *Arch Phys Med Rehabil, 73*(4), 339-347. doi:10.1016/0003-9993(92)90007-j

Kim, D. Y., Ohn, S. H., Yang, E. J., Park, C. I., & Jung, K. J. (2009). Enhancing motor performance by anodal transcranial direct current stimulation in subacute stroke patients. *Am J Phys Med Rehabil, 88*(10), 829-836. doi:10.1097/PHM.0b013e3181b811e3

Kim, K., Kim, Y., & Kim, E. (2014). Correlation between the Activities of Daily Living of Stroke Patients in a Community Setting and Their Quality of Life. *J Phys Ther Sci, 26*(3), 417-419. doi:10.1589/jpts.26.417

Klintsova, A. Y., Dickson, E., Yoshida, R., & Greenough, W. T. (2004). Altered expression of BDNF and its high-affinity receptor TrkB in response to complex motor learning and moderate exercise. *Brain Res, 1028*(1), 92-104. doi:10.1016/j.brainres.2004.09.003

Kolb, B., & Gibb, R. (2014). Searching for the principles of brain plasticity and behavior. *Cortex, 58*, 251-260. doi:10.1016/j.cortex.2013.11.012

Kolb, B., & Whishaw, I. Q. (1998). Brain plasticity and behavior. *Annu Rev Psychol, 49*, 43-64. doi:10.1146/annurev.psych.49.1.43

Koski, L., Mernar, T. J., & Dobkin, B. H. (2004). Immediate and long-term changes in corticomotor output in response to rehabilitation: correlation with functional improvements in chronic stroke. *Neurorehabil Neural Repair, 18*(4), 230-249. doi:10.1177/1545968304269210

Kwakkel, G., Kollen, B., & Lindeman, E. (2004). Understanding the pattern of functional recovery after stroke: facts and theories. *Restor Neurol Neurosci, 22*(3-5), 281-299. 15502272

Lang, C. E., Edwards, D. F., Birkenmeier, R. L., & Dromerick, A. W. (2008). Estimating minimal clinically important differences of upper-extremity measures early after stroke. *Arch Phys Med Rehabil, 89*(9), 1693-1700. doi:10.1016/j.apmr.2008.02.022

Lawes, C. M., Bennett, D. A., Feigin, V. L., & Rodgers, A. (2004). Blood pressure and stroke: an overview of published reviews. *Stroke, 35*(4), 1024. 15053002

Lee, M. J., Lee, J. H., Koo, H. M., & Lee, S. M. (2017). Effectiveness of Bilateral Arm Training for Improving Extremity Function and Activities of Daily Living Performance in Hemiplegic Patients. *J Stroke Cerebrovasc Dis, 26*(5), 1020-1025. doi:10.1016/j.jstrokecerebrovasdis.2016.12.008

Lee, S. J., & Chun, M. H. (2014). Combination transcranial direct current stimulation and virtual reality therapy for upper extremity training in patients with subacute stroke. *Arch Phys Med Rehabil, 95*(3), 431-438. doi:10.1016/j.apmr.2013.10.027

Levin, M. F., Weiss, P. L., & Keshner, E. A. (2015). Emergence of virtual reality as a tool for upper limb rehabilitation: incorporation of motor control and motor learning principles. *Phys Ther, 95*(3), 415-425. doi:10.2522/ptj.20130579

Li, X., Charalambous, C. C., Reisman, D. S., & Morton, S. M. (2019). A short bout of high-intensity exercise alters ipsilesional motor cortical excitability post-stroke. *Top Stroke Rehabil, 26*(6), 405-411. doi:10.1080/10749357.2019.1623458

Liebetanz, D., Nitsche, M. A., Tergau, F., & Paulus, W. (2002). Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. *Brain, 125*(Pt 10), 2238-2247. doi:10.1093/brain/awf238

Liepert, J., Miltner, W. H., Bauder, H., Sommer, M., Dettmers, C., Taub, E., & Weiller, C. (1998). Motor cortex plasticity during constraint-induced movement therapy in stroke patients. *Neurosci Lett, 250*(1), 5-8. doi:10.1016/s0304-3940(98)00386-3

Linacre, J. M., Heinemann, A. W., Wright, B. D., Granger, C. V., & Hamilton, B. B. (1994). The structure and stability of the Functional Independence Measure. *Arch Phys Med Rehabil, 75*(2), 127-132.

Ludemann-Podubecka, J., Bosl, K., Rothhardt, S., Verheyden, G., & Nowak, D. A. (2014). Transcranial direct current stimulation for motor recovery of upper limb function after stroke. *Neurosci Biobehav Rev, 47*, 245-259. doi:10.1016/j.neubiorev.2014.07.022

Marquez, J., van Vliet, P., McElduff, P., Lagopoulos, J., & Parsons, M. (2015). Transcranial direct current stimulation (tDCS): does it have merit in stroke rehabilitation? A systematic review. *Int J Stroke, 10*(3), 306-316. doi:10.1111/ijs.12169

Martina, I. S., van Koningsveld, R., Schmitz, P. I., van der Meche, F. G., & van Doorn, P. A. (1998). Measuring vibration threshold with a graduated tuning fork in normal aging and in patients with polyneuropathy. European Inflammatory Neuropathy Cause and Treatment (INCAT) group. *J Neurol Neurosurg Psychiatry, 65*(5), 743-747. doi:10.1136/jnnp.65.5.743

Mercier, C., & Bourbonnais, D. (2004). Relative shoulder flexor and handgrip strength is related to upper limb function after stroke. *Clin Rehabil, 18*(2), 215-221. doi:10.1191/0269215504cr724oa

Milot, M. H., Leonard, G., Corriveau, H., & Desrosiers, J. (2019). Using the Borg rating of perceived exertion scale to grade the intensity of a functional training program of the affected upper limb after a stroke: a feasibility study. *Clin Interv Aging, 14*, 9-16. doi:10.2147/cia.S179691

Milot, M. H., Nadeau, S., Gravel, D., & Bourbonnais, D. (2013). Gait Performance and Lower-Limb Muscle Strength Improved in Both Upper-Limb and Lower-Limb Isokinetic Training Programs in Individuals with Chronic Stroke. *ISRN Rehabilitation, 2013*, 10. doi:10.1155/2013/929758

Milot, M. H., Spencer, S. J., Chan, V., Allington, J. P., Klein, J., Chou, C., . . . Cramer, S. C. (2014). Corticospinal excitability as a predictor of functional gains at the affected upper limb following robotic training in chronic stroke survivors. *Neurorehabil Neural Repair, 28*(9), 819-827. doi:10.1177/1545968314527351

Mortensen, J., Figlewski, K., & Andersen, H. (2016). Combined transcranial direct current stimulation and home-based occupational therapy for upper limb motor impairment following intracerebral hemorrhage: a double-blind randomized controlled trial. *Disabil Rehabil, 38*(7), 637-643. doi:10.3109/09638288.2015.1055379

Mozaffarian, D., Benjamin, E. J., Go, A. S., Arnett, D. K., Blaha, M. J., Cushman, M., . . . Turner, M. B. (2016). Executive Summary: Heart Disease and Stroke Statistics--2016 Update: A Report From the American Heart Association. *Circulation, 133*(4), 447-454. doi:10.1161/cir.0000000000000366

Mulder, T., & Hochstenbach, J. (2001). Adaptability and Flexibility of the Human Motor System: Implications for Neurological Rehabilitation. *Neural Plasticity, 8*(1-2), 131-140. doi:10.1155/np.2001.131

Nascimbeni, A., Gaffuri, A., Granella, L., Colli, M., & Imazio, P. (2005). Prognostic value of motor evoked potentials in stroke motor outcome. *Eura Medicophys, 41*(2), 125-130. 16200027

Nesin, S. M., Sabitha, K. R., Gupta, A., & Laxmi, T. R. (2019). Constraint Induced Movement Therapy as a Rehabilitative Strategy for Ischemic Stroke-Linking Neural Plasticity with

Restoration of Skilled Movements. *J Stroke Cerebrovasc Dis, 28*(6), 1640-1653. doi:10.1016/j.jstrokecerebrovasdis.2019.02.028

Ng, Y. S., Stein, J., Ning, M., & Black-Schaffer, R. M. (2007). Comparison of clinical characteristics and functional outcomes of ischemic stroke in different vascular territories. *Stroke, 38*(8), 2309-2314. doi:10.1161/strokeaha.106.475483

Nielsen, J. B., Willerslev-Olsen, M., Christiansen, L., Lundbye-Jensen, J., & Lorentzen, J. (2015). Science-based neurorehabilitation: recommendations for neurorehabilitation from basic science. *J Mot Behav, 47*(1), 7-17. doi:10.1080/00222895.2014.931273

Nijland, R. H., van Wegen, E. E., Harmeling-van der Wel, B. C., & Kwakkel, G. (2010). Presence of finger extension and shoulder abduction within 72 hours after stroke predicts functional recovery: early prediction of functional outcome after stroke: the EPOS cohort study. *Stroke, 41*(4), 745-750. doi:10.1161/strokeaha.109.572065

Nijland, R. H. M., van Wegen, E. E. H., Harmeling-van der Wel, B. C., Kwakkel, G., & Investigators, f. t. E. P. o. F. O. A. S. (2013). Accuracy of Physical Therapists' Early Predictions of Upper-Limb Function in Hospital Stroke Units: The EPOS Study. *Physical Therapy, 93*(4), 460-469. doi:10.2522/ptj.20120112

Nitsche, M. A., Fricke, K., Henschke, U., Schlitterlau, A., Liebetanz, D., Lang, N., . . . Paulus, W. (2003). Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. *J Physiol, 553*(Pt 1), 293-301. doi:10.1113/jphysiol.2003.049916

Nitsche, M. A., Roth, A., Kuo, M. F., Fischer, A. K., Liebetanz, D., Lang, N., . . . Paulus, W. (2007). Timing-dependent modulation of associative plasticity by general network excitability in the human motor cortex. *J Neurosci, 27*(14), 3807-3812. doi:10.1523/jneurosci.5348-06.2007

Nowak, D. A., Grefkes, C., Ameli, M., & Fink, G. R. (2009). Interhemispheric competition after stroke: brain stimulation to enhance recovery of function of the affected hand. *Neurorehabil Neural Repair, 23*(7), 641-656. doi:10.1177/1545968309336661

Nudo, R. J. (2006). Mechanisms for recovery of motor function following cortical damage. *Curr Opin Neurobiol, 16*(6), 638-644. doi:10.1016/j.conb.2006.10.004

O'Shea, J., Boudrias, M. H., Stagg, C. J., Bachtiar, V., Kischka, U., Blicher, J. U., & Johansen-Berg, H. (2014). Predicting behavioural response to TDCS in chronic motor stroke. *Neuroimage, 85 Pt 3*, 924-933. doi:10.1016/j.neuroimage.2013.05.096

Orru, G., Conversano, C., Hitchcott, P. K., & Gemignani, A. (2019). Motor stroke recovery after tDCS: a systematic review. *Rev Neurosci*. doi:10.1515/revneuro-2019-0047

Page, S. J., Fulk, G. D., & Boyne, P. (2012). Clinically important differences for the upper-extremity Fugl-Meyer Scale in people with minimal to moderate impairment due to chronic stroke. *Phys Ther, 92*(6), 791-798. doi:10.2522/ptj.20110009

Pak, S., & Patten, C. (2008). Strengthening to promote functional recovery poststroke: an evidence-based review. *Top Stroke Rehabil, 15*(3), 177-199. doi:10.1310/tsr1503-177

Patten, C., Condliffe, E. G., Dairaghi, C. A., & Lum, P. S. (2013). Concurrent neuromechanical and functional gains following upper-extremity power training post-stroke. *Journal of neuroengineering and rehabilitation, 10*, 1-1. doi:10.1186/1743-0003-10-1

Patten, C., Lexell, J., & Brown, H. E. (2004). Weakness and strength training in persons with poststroke hemiplegia: rationale, method, and efficacy. *J Rehabil Res Dev, 41*(3a), 293-312. doi:10.1682/jrrd.2004.03.0293

Paulus, W. (2004). Outlasting excitability shifts induced by direct current stimulation of the human brain. *Suppl Clin Neurophysiol, 57*, 708-714. doi:10.1016/s1567-424x(09)70411-8

Pavlova, E. L., Semenov, R. V., & Guekht, A. B. (2019). Effect of tDCS on Fine Motor Control of Patients in Subacute and Chronic Post-Stroke Stages. *J Mot Behav*, 1-13. doi:10.1080/00222895.2019.1639608

Perez-Marcos, D., Chevalley, O., Schmidlin, T., Garipelli, G., Serino, A., Vuadens, P., . . . Millán, J. d. R. (2017). Increasing upper limb training intensity in chronic stroke using embodied virtual reality: a pilot study. *Journal of neuroengineering and rehabilitation, 14*(1), 119. doi:10.1186/s12984-017-0328-9

Peters, H. T., Edwards, D. J., Wortman-Jutt, S., & Page, S. J. (2016). Moving Forward by Stimulating the Brain: Transcranial Direct Current Stimulation in Post-Stroke Hemiparesis. *Frontiers in human neuroscience, 10*, 394. doi:10.3389/fnhum.2016.00394

Pollock, A., Baer, G., Campbell, P., Choo, P. L., Forster, A., Morris, J., . . . Langhorne, P. (2014). Physical rehabilitation approaches for the recovery of function and mobility following stroke. *Cochrane Database Syst Rev*(4), Cd001920. doi:10.1002/14651858.CD001920.pub3

Prabhakaran, S., Zarahn, E., Riley, C., Speizer, A., Chong, J. Y., Lazar, R. M., . . . Krakauer, J. W. (2008). Inter-individual variability in the capacity for motor recovery after ischemic stroke. *Neurorehabil Neural Repair, 22*(1), 64-71. doi:10.1177/1545968307305302

Prashantha, D. K., Sriranjini, S. J., Sathyaprabha, T. N., Nagaraja, D., & Pal, P. K. (2013). Evaluation of the motor cortical excitability changes after ischemic stroke. *Ann Indian Acad Neurol, 16*(3), 394-397. doi:10.4103/0972-2327.116955

Rabadi, M. H., & Rabadi, F. M. (2006). Comparison of the action research arm test and the Fugl-Meyer assessment as measures of upper-extremity motor weakness after stroke. *Arch Phys Med Rehabil, 87*(7), 962-966. doi:10.1016/j.apmr.2006.02.036

Raglio, A., Zaliani, A., Baiardi, P., Bossi, D., Sguazzin, C., Capodaglio, E., . . . Imbriani, M. (2017). Active music therapy approach for stroke patients in the post-acute rehabilitation. *Neurol Sci, 38*(5), 893-897. doi:10.1007/s10072-017-2827-7

Ranner, M., Guidetti, S., von Koch, L., & Tham, K. (2018). Experiences of participating in a client-centred ADL intervention after stroke. *Disabil Rehabil*, 1-9. doi:10.1080/09638288.2018.1483434

Reis, J., Schambra, H. M., Cohen, L. G., Buch, E. R., Fritsch, B., Zarahn, E., . . . Krakauer, J. W. (2009). Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. *Proc Natl Acad Sci U S A, 106*(5), 1590-1595. doi:10.1073/pnas.0805413106

Ring, H., & Rosenthal, N. (2005). Controlled study of neuroprosthetic functional electrical stimulation in sub-acute post-stroke rehabilitation. *J Rehabil Med, 37*(1), 32-36. doi:10.1080/16501970410035387

Rocha, S., Silva, E., Foerster, A., Wiesiolek, C., Chagas, A. P., Machado, G., . . . Monte-Silva, K. (2016). The impact of transcranial direct current stimulation (tDCS) combined with modified constraint-induced movement therapy (mCIMT) on upper limb function in chronic stroke: a double-blind randomized controlled trial. *Disabil Rehabil, 38*(7), 653-660. doi:10.3109/09638288.2015.1055382

Roger, V. L., Go, A. S., Lloyd-Jones, D. M., Adams, R. J., Berry, J. D., Brown, T. M., . . . Wylie-Rosett, J. (2011). Heart disease and stroke statistics--2011 update: a report from the

American Heart Association. *Circulation, 123*(4), e18-e209. doi:10.1161/CIR.0b013e3182009701

Roh, J., Rymer, W. Z., Perreault, E. J., Yoo, S. B., & Beer, R. F. (2013). Alterations in upper limb muscle synergy structure in chronic stroke survivors. *J Neurophysiol, 109*(3), 768-781. doi:10.1152/jn.00670.2012

Rondina, J. M., Park, C. H., & Ward, N. S. (2017). Brain regions important for recovery after severe post-stroke upper limb paresis. *J Neurol Neurosurg Psychiatry, 88*(9), 737-743. doi:10.1136/jnnp-2016-315030

Rossi, C., Sallustio, F., Di Legge, S., Stanzione, P., & Koch, G. (2013). Transcranial direct current stimulation of the affected hemisphere does not accelerate recovery of acute stroke patients. *Eur J Neurol, 20*(1), 202-204. doi:10.1111/j.1468-1331.2012.03703.x

Rosso, C., & Lamy, J.-C. (2018). Does Resting Motor Threshold Predict Motor Hand Recovery After Stroke? *Frontiers in neurology, 9*, 1020-1020. doi:10.3389/fneur.2018.01020

Saposnik, G., & Levin, M. (2011). Virtual reality in stroke rehabilitation: a meta-analysis and implications for clinicians. *Stroke, 42*(5), 1380-1386. doi:10.1161/strokeaha.110.605451

Saunders, D. H., Greig, C. A., & Mead, G. E. (2014). Physical activity and exercise after stroke: review of multiple meaningful benefits. *Stroke, 45*(12), 3742-3747. doi:10.1161/strokeaha.114.004311

Schmidt, R. A. (1988). *Motor control and learning: A behavioral emphasis, 2nd ed*. Champaign, IL, England: Human Kinetics Publishers.

Statistics Canada. (2017). Leading causes of death, total population, by age group and sex, Canada. (Table 102-0561). *CANSIM (death database). Ottawa (Ontario): Statistics Canada.* Retrieved from http://www5.statcan.gc.ca/cansim/a05?lang=eng&id=1020561

Stinear, C. M., Barber, P. A., Smale, P. R., Coxon, J. P., Fleming, M. K., & Byblow, W. D. (2007). Functional potential in chronic stroke patients depends on corticospinal tract integrity. *Brain, 130*(Pt 1), 170-180. doi:10.1093/brain/awl333

Stinear, C. M., & Byblow, W. D. (2014). Predicting and accelerating motor recovery after stroke. *Curr Opin Neurol, 27*(6), 624-630. doi:10.1097/wco.0000000000000153

Stinear, C. M., Byblow, W. D., Ackerley, S. J., Smith, M. C., Borges, V. M., & Barber, P. A. (2017a). PREP2: A biomarker-based algorithm for predicting upper limb function after stroke. *Ann Clin Transl Neurol, 4*(11), 811-820. doi:10.1002/acn3.488

Stinear, C. M., Byblow, W. D., Ackerley, S. J., Smith, M. C., Borges, V. M., & Barber, P. A. (2017b). Proportional Motor Recovery After Stroke: Implications for Trial Design. *Stroke, 48*(3), 795-798. doi:10.1161/strokeaha.116.016020

Stinear, C. M., Byblow, W. D., & Ward, S. H. (2014). An update on predicting motor recovery after stroke. *Ann Phys Rehabil Med, 57*(8), 489-498. doi:10.1016/j.rehab.2014.08.006

Straudi, S., Fregni, F., Martinuzzi, C., Pavarelli, C., Salvioli, S., & Basaglia, N. (2016). tDCS and Robotics on Upper Limb Stroke Rehabilitation: Effect Modification by Stroke Duration and Type of Stroke. *Biomed Res Int, 2016*, 5068127. doi:10.1155/2016/5068127

Subramanian, S. K., Lourenco, C. B., Chilingaryan, G., Sveistrup, H., & Levin, M. F. (2013). Arm motor recovery using a virtual reality intervention in chronic stroke: randomized control trial. *Neurorehabil Neural Repair, 27*(1), 13-23. doi:10.1177/1545968312449695

Takeuchi, N., & Izumi, S.-I. (2013). Rehabilitation with Poststroke Motor Recovery: A Review with a Focus on Neural Plasticity. *Stroke Research and Treatment, 2013*, 13. doi:10.1155/2013/128641

Takeuchi, N., Oouchida, Y., & Izumi, S. (2012). Motor control and neural plasticity through interhemispheric interactions. *Neural Plast, 2012*, 823285. doi:10.1155/2012/823285

Talelli, P., Greenwood, R. J., & Rothwell, J. C. (2006). Arm function after stroke: neurophysiological correlates and recovery mechanisms assessed by transcranial magnetic stimulation. *Clin Neurophysiol, 117*(8), 1641-1659. doi:10.1016/j.clinph.2006.01.016

Taubert, M., Villringer, A., & Lehmann, N. (2015). Endurance Exercise as an "Endogenous" Neuro-enhancement Strategy to Facilitate Motor Learning. *Frontiers in human neuroscience, 9*, 692. doi:10.3389/fnhum.2015.00692

Tedesco Triccas, L., Burridge, J. H., Hughes, A. M., Pickering, R. M., Desikan, M., Rothwell, J. C., & Verheyden, G. (2016). Multiple sessions of transcranial direct current stimulation and upper extremity rehabilitation in stroke: A review and meta-analysis. *Clin Neurophysiol, 127*(1), 946-955. doi:10.1016/j.clinph.2015.04.067

Thair, H., Holloway, A. L., Newport, R., & Smith, A. D. (2017). Transcranial Direct Current Stimulation (tDCS): A Beginner's Guide for Design and Implementation. *Frontiers in neuroscience, 11*, 641-641. doi:10.3389/fnins.2017.00641

Thibaut, A., Chatelle, C., Gosseries, O., Laureys, S., & Bruno, M. A. (2013). La stimulation transcrânienne à courant continu : un nouvel outil de neurostimulation. *Revue Neurologique, 169*(2), 108-120. doi:10.1016/j.neurol.2012.05.008

Timmermans, A. A., Seelen, H. A., Willmann, R. D., & Kingma, H. (2009). Technology-assisted training of arm-hand skills in stroke: concepts on reacquisition of motor control and therapist guidelines for rehabilitation technology design. *Journal of neuroengineering and rehabilitation, 6*, 1. doi:10.1186/1743-0003-6-1

Trompetto, C., Assini, A., Buccolieri, A., Marchese, R., & Abbruzzese, G. (2000). Motor recovery following stroke: a transcranial magnetic stimulation study. *Clin Neurophysiol, 111*(10), 1860-1867. doi:10.1016/s1388-2457(00)00419-3

Uswatte, G., Taub, E., Morris, D., Light, K., & Thompson, P. A. (2006). The Motor Activity Log-28: assessing daily use of the hemiparetic arm after stroke. *Neurology, 67*(7), 1189-1194. doi:10.1212/01.wnl.0000238164.90657.c2

van der Lee, J. H., Snels, I. A., Beckerman, H., Lankhorst, G. J., Wagenaar, R. C., & Bouter, L. M. (2001). Exercise therapy for arm function in stroke patients: a systematic review of randomized controlled trials. *Clin Rehabil, 15*(1), 20-31. doi:10.1191/026921501677557755

Veerbeek, J. M., Kwakkel, G., van Wegen, E. E., Ket, J. C., & Heymans, M. W. (2011). Early prediction of outcome of activities of daily living after stroke: a systematic review. *Stroke, 42*(5), 1482-1488. doi:10.1161/strokeaha.110.604090

Wagner, J. M., Rhodes, J. A., & Patten, C. (2008). Reproducibility and minimal detectable change of three-dimensional kinematic analysis of reaching tasks in people with hemiparesis after stroke. *Phys Ther, 88*(5), 652-663. doi:10.2522/ptj.20070255

Wallace, A. C., Talelli, P., Dileone, M., Oliver, R., Ward, N., Cloud, G., . . . Marsden, J. F. (2010). Standardizing the intensity of upper limb treatment in rehabilitation medicine. *Clinical rehabilitation, 24*(5), 471-478. doi:10.1177/0269215509358944

Weinstein, S. (1993). Fifty years of somatosensory research: from the Semmes-Weinstein monofilaments to the Weinstein Enhanced Sensory Test. *J Hand Ther, 6*(1), 11-22; discussion 50. 8343870

Winters, C., van Wegen, E. E., Daffertshofer, A., & Kwakkel, G. (2015). Generalizability of the Proportional Recovery Model for the Upper Extremity After an Ischemic Stroke. *Neurorehabil Neural Repair, 29*(7), 614-622. doi:10.1177/1545968314562115

Wittenberg, G. F., Richards, L. G., Jones-Lush, L. M., Roys, S. R., Gullapalli, R. P., Yang, S., . . . Lo, A. C. (2016). Predictors and brain connectivity changes associated with arm motor function improvement from intensive practice in chronic stroke. *F1000Research, 5*, 2119-2119. doi:10.12688/f1000research.8603.2

Wu, C. Y., Huang, P. C., Chen, Y. T., Lin, K. C., & Yang, H. W. (2013). Effects of mirror therapy on motor and sensory recovery in chronic stroke: a randomized controlled trial. *Arch Phys Med Rehabil, 94*(6), 1023-1030. doi:10.1016/j.apmr.2013.02.007

Wu, J., Srinivasan, R., Burke Quinlan, E., Solodkin, A., Small, S. L., & Cramer, S. C. (2016). Utility of EEG measures of brain function in patients with acute stroke. *J Neurophysiol, 115*(5), 2399-2405. doi:10.1152/jn.00978.2015

Yang, Y., Zhao, Q., Zhang, Y., Wu, Q., Jiang, X., & Cheng, G. (2018). Effect of Mirror Therapy on Recovery of Stroke Survivors: A Systematic Review and Network Meta-analysis. *Neuroscience, 390*, 318-336. doi:10.1016/j.neuroscience.2018.06.044

Yeoh, Y. S., Koh, G. C.-H., Tan, C. S., Lee, K. E., Tu, T. M., Singh, R., . . . Luo, N. (2018). Can acute clinical outcomes predict health-related quality of life after stroke: a one-year prospective study of stroke survivors. *Health and quality of life outcomes, 16*(1), 221-221. doi:10.1186/s12955-018-1043-3

Young, J., & Forster, A. (2007). Review of stroke rehabilitation. *Bmj, 334*(7584), 86-90. doi:10.1136/bmj.39059.456794.68

Yozbatiran, N., Der-Yeghiaian, L., & Cramer, S. C. (2008). A standardized approach to performing the action research arm test. *Neurorehabil Neural Repair, 22*(1), 78-90. doi:10.1177/1545968307305353

Zhang, P., Liu, Z. T., He, G. X., Liu, J. P., & Feng, J. (2011). Low-voltage direct-current stimulation is safe and promotes angiogenesis in rabbits with myocardial infarction. *Cell Biochem Biophys, 59*(1), 19-27. doi:10.1007/s12013-010-9107-y

Zhu, L. L., Lindenberg, R., Alexander, M. P., & Schlaug, G. (2010). Lesion load of the corticospinal tract predicts motor impairment in chronic stroke. *Stroke, 41*(5), 910-915. doi:10.1161/strokeaha.109.577023

Ziemann, U., Lonnecker, S., Steinhoff, B. J., & Paulus, W. (1996). Effects of antiepileptic drugs on motor cortex excitability in humans: a transcranial magnetic stimulation study. *Ann Neurol, 40*(3), 367-378. doi:10.1002/ana.410400306

APPENDICES

Appendix A. Fugl-Meyer Assessment scale for the upper limb (/66)

Fugl-Meyer Stroke Assessment Scale (Part1 – Upper limb)

Material :

- Percussion hammer
- Stop watch
- Ball, card, pot, pen, …
- Chair, table, bag

Subject position :

- Sitting comfortably on a chair
- Head is straight and feet are flat on the floor
- The trunk is as symmetrical as possible
- The trunk and arms are bare

General instructions :

All the sub-tests must be demonstrated on the unaffected side first to ensure understanding of the subject.

Procedure :

1- **Reflex activity**

Reflex activity of the biceps is tested with the percussion hammer according to the method described in Hoppenfled (1972). The flexion reflex of the fingers is obtained by stimulating Hoffman's reflex. It is obtained by a sudden relaxation of a forced flexion of the forefinger and the middle finger. The response obtained is the flexion of fingers and thumb.

2- **Volitional movement within synergies**

Starting position: hands flat on the thighs

*"Fully supinate your forearm, flex your elbow and bring your hand to your ear of the unaffected side (*little finger touching the ear lobe). *Now try to do the same movement with your affected hand."*

Starting position: upper limb in complete flexion synergy. If the subject cannot take position, passively place the limb.

"Place your hand on the lateral side of the opposite knee, like this. Now try to make the same movement with your affected hand."

3- Volitional movement combining synergies

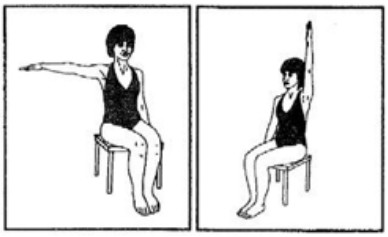
"Place your hand behind your back, like this. Do the same thing with your affected side."

"Now raise your arm in front of you at the shoulder level, without bending your elbow (the forearm is in semi-pronation/supination). *Repeat this movement with*

To avoid pain at the shoulder joint, I ask the subject to place his forearm in supination with his thumb up

With your elbow bent, turn your hand face up, and then down, like this. Repeat this movement with your affected side."

4- Volitional movement out of synergy



"Raise your arm to your side. Make the same movement with your affected side without bending the elbow, and without moving your hand."

The forearm must remain in pronation, with the elbow extended.

"Raise your arm in front of you, over your head. Make the same movement with your affected arm, without bending the

To avoid pain at the shoulder joint, I ask the subject to put his forearm in supination with his thumb up

"Now let your arm hang alongside your body, with your elbow extended. Turn your hand face up and then down, like this."

N

The shoulder should remain at 30°-90° of flexion for the pronation/supination.

5- Normal reflex activity

Reflex activity is assessed as for test 1.

The subject attains a maximum of 2, only if a score of 6 was obtained in test 4.

6- Wrist

Starting position: elbow in 90° flexion, shoulder in neutral position.

"Extend your wrist, while keeping your elbow bent. Make the same movement with your affected side."

If needed, the arm can be passively supported.

"Bend and extend your wrist a few times, while keeping your elbow bent. Make the same movement with your affected side."

Starting position: elbow in extension, shoulder slightly elevated and forearm in pronation.

"Extend your wrist while keeping your elbow extended. Make the same movement with your affected side."

"Bend and extend your elbow a few times while keeping your elbow extended. Repeat with your affected side."

"Make circles with your wrist, while keeping your elbow extended. Repeat with your affected side."

7- Hand

Starting position: elbow in 90° flexion, forearm in pronation.

"Close your hand to make a fist. Repeat with your affected hand."
If needed, the arm can be passively supported.

"With your hand closed at first, open it completely by extending your fingers. Repeat with your affected hand."

Starting position: elbow in 90° flexion, forearm in pronation or semi-pronation.

"Place your fingers like this (pretend you are holding a purse). Make the same movement with your affected hand." The elbow must remain extended.

"Hold this card between your thumb and index finger. Do the same thing with your affected hand." The subject must perform a genuine adduction of the thumb.

"Hold this pen, as for writing (opposing the thumb pad against the pad of the index finger). Do the same thing with your affected hand."

"Take this pot by holding it like this. Do the same thing with your affected hand."

"Hold this ball like this. Do the same thing with your affected hand."

8- Coordination/speed

Starting position: sitting with hands on lap.

"With your eyes closed, bring your finger from your knee to your nose, as fast as possible. Repeat the same movement with your affected side"

- Use a stopwatch to time how long it takes the subject to do 5 repetitions.
- Record the time for both the unaffected and affected sides.
- Observe for evidence of tremor or dysmetria during the movement.

Appendix B. Motor Activity Log

Activity	Quantitative Scale (0---5)	Qualitative Scale (0---5)	If no, why? (code)	Comments :
1. Turn on a light with a light switch				
2. Open drawer.				
3. Remove an item of clothing from a drawer				
4. Pick up the phone				
5 Wipe off a kitchen counter or other surface				
6. Get out of a car *(includes only the movement needed to get body from sitting to standing outside of the car, once the door is open)*				
7. Open refrigerator.				
8. Open a door by turning a door knob/handle				
9. Use a TV remote control.				
10. Wash your hands *(includes lathering and rinsing hands; does not include turning water on and off with a faucet handle).*				
11. Turning water on/off with knob/lever on faucet				
12. Dry your hands.				
13. Put on your socks				
14. Take off your socks.				

Activity	Quantitative Scale (0---5)	Qualitative Scale (0---5)	If no, why? (code)	Comments :
15. Put on your shoes *(includes tying shoestrings and fastening straps)*				
16. Take off your shoes *(includes untying shoestrings and unfastening straps)*				
17. Get up from a chair with armrests.				
18. Pull chair away from the table before sitting down				
19. Pull chair toward table after sitting down				
20. Pick up a glass, bottle, drinking cup, or can *(does not need to include drinking)*				
21. Brush your teeth *(does not include preparation of toothbrush or brushing dentures unless the dentures are brushed while left in the mouth)*				
22. Put on makeup base, lotion, or shaving cream on the face.				
23. Use a key to unlock a door				
24. Write on paper *(If hand used to write pre-stroke is more affected, score item; if non-writing hand pre-stroke is more affected, drop item and assign N/A)*				
25. Carry an object your hand *(draping an item over the arm is not acceptable)*				
26. Use a fork or spoon for eating *(refers to the action of bringing food to the mouth with a fork or spoon)).*				
27. Comb your hair				
28. Pick up a cup by a handle				
29. Button a shirt				
30. Eat half a sandwich or finger foods				
Total (mean)	_____ /5	_____ /5		