THE FEASIBILITY OF FUNCTIONAL NEAR-INFRARED SPECTROSCOPY (fNIRS) TO MEASURE REHABILITATION-INDUCED CHANGES IN UPPER LIMB MOVEMENT RELATED TO MOTOR LEARNING INTERVENTIONS IN CHRONIC STROKE

By © Valiollah Mohammadi

A thesis submitted to the School of Graduate Studies

In partial fulfillment

of the requirements for the degree of Master of Science

Neuroscience, Division of Biomedical Sciences, Faculty of Medicine
Memorial University of Newfoundland

May 2025

St. John's, Newfoundland and Labrador, Canada

Abstract

Background: Functional near-infrared spectroscopy (fNIRS) offers a non-invasive approach to monitoring rehabilitation-induced brain activity changes following motor learning interventions in stroke patients. This study aimed to explore the extent of brain activity and motor performance changes resulting from such interventions.

Methods: Seven participants with chronic stroke (63.6 ± 7.5 years old; six males, one female) underwent a ten-day intervention consisting of aerobic exercise priming combined with task-specific motor practice using the Kinesiological Instrument for Normal and Altered Reaching Movements (KINARM) End-Point robotic system. Motor performance was evaluated using the Wolf Motor Function Test (WMFT), and brain activity was measured with fNIRS, focusing on key Regions of Interest (ROIs) such as the motor cortex, somatosensory cortex, and prefrontal cortex.

Results: Clinical tests such as the WMFT showed moderate improvements in upper limb recovery, but these changes were not statistically significant ($p < 0.05$). Similarly, overall fNIRS analysis revealed that changes in brain activity before and after the intervention were not statistically significant ($p < 0.05$). However, significant changes were observed in certain ROIs regarding Oxyhemoglobin (HbO) concentrations and time-to-peak values in specific cases.

Conclusion: Although motor performance improvements were modest and not statistically significant, fNIRS detected significant changes in brain activity in certain brain areas before and after the intervention. These findings highlight the potential of fNIRS as a biomarker for rehabilitation-induced neuroplasticity and offer insights for enhancing stroke recovery interventions.

Keywords: Stroke recovery, motor learning, fNIRS, KINARM, neuroplasticity

General Summary

This study investigated the feasibility of functional near-infrared spectroscopy (fNIRS) in detecting and quantifying changes in brain activity, alongside assessing upper limb motor performance, following a rehabilitation intervention. Seven participants with chronic stroke underwent a ten-day intervention combining aerobic exercise with task-specific motor practice using the Kinesiological Instrument for Normal and Altered Reaching Movements KINARM robot. The results of clinical tests, such as the Wolf Motor Function Test (WMFT), showed moderate improvements in upper limb recovery, but these changes were not statistically significant. However, fNIRS data revealed significant increases in Oxyhemoglobin (HbO) concentrations in some brain regions post-intervention.

While time-to-peak measures generally showed increases, the changes were not statistically significant in most cases. These findings suggest that while clinical improvements were modest, fNIRS successfully detected neuroplastic changes, demonstrating its sensitivity in capturing rehabilitation-induced brain activity alterations. These results highlight the potential of fNIRS as a biomarker for monitoring brain activity during stroke recovery, offering valuable insights for future research and clinical applications.

Keywords: Stroke recovery, motor learning, fNIRS, KINARM, neuroplasticity

Acknowledgments

This thesis would not have been possible without the unwavering support of many individuals. First and foremost, I would like to extend my deepest gratitude to my exceptional supervisor, Dr. Michelle Ploughman, whose constant encouragement, insightful guidance, and belief in my abilities have shaped this research. I am truly fortunate to have had the privilege of learning under her supervision.

I would also like to express my sincere thanks to my supervisory committee members, Dr. Sarah Power and Dr. Kevin Power, for their invaluable feedback and thoughtful insights, which significantly contributed to the direction and success of this project. Their expertise and guidance were critical in refining both my research and writing.

I sincerely appreciate my colleagues at the Recovery and Performance Laboratory for your camaraderie and support. I cherish the memories we've created together, from potlucks to Lab family events and Secret Santa parties. Special thanks to Alex, Hamid, and Saman for their unwavering support, friendship, and contributions throughout this journey.

I am deeply grateful to Memorial University School of Graduate Studies and the Office of Research and Graduate Studies for their financial support, which enabled this research.

To all the participants who took part in this study, thank you for your time and willingness to contribute to this research. Your participation has been instrumental in advancing this work.

I also want to express my profound gratitude to my family. To my parents, thank you for your endless sacrifices and unwavering belief in me. To my wonderful wife, whose love, patience, and understanding have been a constant source of strength, and to my 7-year-old son, who has brought me endless joy and motivation−thank you for being my foundation throughout this journey.

Finally, thank everyone who has been part of this incredible experience. Your support has been invaluable in helping me reach this milestone.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND SYMBOLS

Symbol/Abbreviation	Meaning
BDNF	Brain-Derived Neurotrophic Factor
fMRI	Functional Magnetic Resonance Imaging
fNIRS	Functional Near-Infrared Spectroscopy
FMA-UE	Fugl-Meyer Assessment for the upper extremity
HbO	Oxyhemoglobin
HbR	Deoxyhemoglobin
KINARM	the Kinesiological Instrument for Normal and Altered Reaching Movements
NIBS	Non-invasive Brain Stimulation
ROI	Region of Interest
rTMS	Repetitive Transcranial Magnetic Stimulation
TMS	Transcranial Magnetic Stimulation
tDCS	Transcranial Direct Current Stimulation
WMFT	Wolf Motor Function Test

LIST OF APPENDICES

1 CHAPTER ONE: INTRODUCTION TO STROKE REHABILITATION AND NEUROPLASTICITY

1.1 OVERVIEW

The global incidence of stroke has risen markedly, highlighting its importance as a focus for research and intervention. According to Statistics Canada, stroke ranked third among the leading causes of death in 2018, following cardiovascular diseases and cancer (Lanctôt et al., 2020). The rate of stroke mortality is gradually declining, but stroke remains a significant public health issue and stands as the world's second most common cause of death, with an annual mortality rate estimated at approximately 5.5 million individuals, alongside over 13 million new cases reported each year and about 101 million people living with the aftermath of a stroke globally (Collaborators, 2019; Feigin et al., 2022; Feigin et al., 2014; Lawlor et al., 2002; Levi et al., 2002).

Stroke is a chronic disease with acute events, and most survivors deal with significant long-term effects on their overall health. A stroke causes profound and protracted cognitive and physical impairment, resulting in recovery difficulties and consequential financial hardships. In Canadian hospitals, 62,000 stroke victims receive treatment annually, and over 400,000 individuals live with the aftereffects of their illness (Lanctôt et al., 2020), which also presents difficulties for their families. Individuals who suffer from chronic stroke symptoms might require medical attention long after their initial hospital stay; thus, developing effective strategies for assisting stroke survivors in sustaining their recovery post-hospitalization and inpatient rehabilitation is critical.

Evaluation, diagnosis, and therapy for acute stroke patients are intricate and time-sensitive processes (Mang et al., 2018). Time sensitivity emphasizes the urgency of initiating treatment to leverage neuroplasticity for functional recovery and to reduce learned non-use, ultimately improving patient outcomes.. It intricately highlights the complexity of diagnostics, treatment

decisions, and the need for a coordinated multidisciplinary approach to care. (National Clinical Guideline for Stroke) (www.stroke.org)(professional.heart.org).

Gaps in immediate stroke management protocols can cause subpar patient outcomes, which persist despite advances in medical technology. Despite best practice recommendations and technological advancements, the stroke care system needs improvement to avoid less-than-ideal patient outcomes. Mechanical thrombectomy and intravenous thrombolysis (IV-tPA) remain primary treatments for eligible patients presenting with acute ischemic stroke within specific time windows from symptom onset (Grotta, 2016). Although these treatments are effective, only 10% of patients receive them. A shortage of skilled medical professionals, failure to meet inclusion criteria, and limited access to institutions that provide tissue plasminogen activators and endovascular thrombectomy are all issues that prevent timely access to the treatment (Wang et al., 2022).

Rehabilitation, however, can play a pivotal role in the recovery process for stroke survivors. Early and intensive rehabilitation interventions aim to minimize disability and enhance functional independence (Bindawas & Vennu, 2016; Esquenazi & Packel, 2012). Multidisciplinary teams, including physiotherapists, occupational therapists, speech therapists, psychologists and social workers, collaborate to address various aspects of recovery. Rehabilitation strategies may encompass mobility training, speech and language therapy, and cognitive rehabilitation tailored to the individual's needs and impairments (Winstein et al., 2016).

Depending on the location and severity of the brain lesion, stroke-related deficits can vary widely, but they frequently involve emotional, mental, and physical challenges. Physical or motor impairments might include balance, coordination, fine motor skill difficulties, weakness, or paralysis on one side of the body. In severe instances, patients may require assistance with basic

everyday tasks, including eating, dressing, and bathing (Raghavan, 2015). One of the most prevalent disabilities following a stroke is sensory impairment, including issues perceiving objects, difficulty with spatial awareness, or loss of sensation in the face or limbs (Doyle et al., 2010). Following a stroke, cognitive deficits may include memory loss, trouble making decisions and solving problems, and issues with language and communication. (Jokinen et al., 2015). These can significantly impact a person's ability to perform daily tasks, including work, and can also result in emotional difficulties, including depression and anxiety (Hama et al., 2020; Terroni et al., 2012). After stroke, motor impairment is the most apparent deficit, which has an impact on patients' mobility, daily living activities, social involvement, and chances of returning to work, altogether contributing to a lower quality of life (Hatem et al., 2016). Neurorehabilitation focuses primarily on motor learning; people with stroke need to relearn ordinary physical tasks. Neuroplasticity and, more specifically use-dependent plasticity in rehabilitation, generated by repeated task repetition, are necessary for this learning (Nudo et al., 2001; Ward & Cohen, 2004). According to some articles, aerobic exercise can be used to "prime" the brain by increasing cerebral blood flow, promoting the release of neurotrophic factors such as brain-derived neurotrophic factor (BDNF), and enhancing cortical excitability, thereby increasing its receptiveness to use-dependent plasticity. (Wunder & Staines, 2022). Establishing an atmosphere that prepares the brain for neurorehabilitation treatments could boost the effectiveness of these interventions and increase the level of motor recovery in individuals' post-stroke (Hara, 2015).

Understanding how motor learning influences brain activity and plasticity in stroke patients is vital for developing an efficient rehabilitation program. Brain imaging techniques like Functional Near-Infrared Spectroscopy (fNIRS) provide a non-invasive way to assess brain

activity patterns and offer clinical insight in evaluating the effectiveness of different motor learning interventions (Zhang et al., 2023).

fNIRS is a relatively new brain functional imaging technique that measures variations in oxyhemoglobin (HbO) and deoxyhemoglobin (HbR) concentrations to represent the relative regional brain activity (Ghosh et al., 2012; Mihara & Miyai, 2016; Wong et al., 2021). fNIRS has advantageous spatial resolution and is low-cost, non-invasive and wearable, allowing for monitoring (Strangman et al., 2002). Moreover, fNIRS is an effective tool for brain network analysis (Hu et al., 2020) and has been utilized to analyze stroke-related brain function reorganization during rehabilitation (Sun et al., 2021).

1.2 STROKE

1.2.1 The Etiology of Stroke

Stroke, a medical emergency characterized by disrupted blood flow to the central nervous system, poses a significant threat to life and neurological function (Tadi & Lui, 2023). To comprehend the gravity of stroke and its implications, it is imperative to explore the two primary types: ischemic and hemorrhagic stroke. By delving into the causes and effects of each type, we can gain a comprehensive understanding of this critical condition (Coupland et al., 2017).

Ischemic stroke, which accounts for approximately 87% of all strokes, occurs because of occlusion of cerebral arteries, leading to reduced blood flow and oxygen supply to the brain. This chapter explores the main etiologies of ischemic stroke: large-artery atherosclerosis, cardioembolism, and small-vessel occlusion (Hankey & Blacker, 2015). Large-artery atherosclerosis is one of the primary causes of ischemic stroke. It involves the build-up of plaques in the major arteries supplying the brain, such as the carotid and vertebral arteries. These plaques

can rupture, leading to thrombus formation, which may occlude the artery or embolize the cerebral circulation (Libby et al. 2009; Goldstein et al. 2006).

Cardioembolic strokes arise when emboli originating from the heart travel to the cerebral arteries, causing occlusion. Atrial fibrillation is the most common cardiac condition associated with cardioembolic stroke, significantly increasing the risk of stroke. (Wolf et al. 1991, Hart et al. 2007). Small-vessel occlusion, also known as lacunar stroke, results from the occlusion of the small penetrating arteries that supply deep brain structures. It is often associated with chronic hypertension and diabetes (Wardlaw et al., 2019).

1.2.2 Risk Factors for Ischemic Stroke

Understanding the risk factors for ischemic stroke helps in identifying individuals at higher risk and implementing preventive strategies. Risk factors are categorized into modifiable and non-modifiable. Modifiable risk factors include hypertension, diabetes mellitus, hyperlipidemia, smoking, and atrial fibrillation, and non-modifiable risk factors include age, gender, and genetics (Meschia et al. 2014; Benjamin et al. 2019; Flossmann et al. 2004). By addressing these risk factors, individuals can significantly reduce their chances of experiencing a stroke (Boehme et al., 2017; Hussain et al., 2021; Isabel et al., 2016; Sabih, 2023).

1.2.3 Population Impact of Stroke

Stroke ranks as the second leading cause of death globally and the primary contributor to disability-adjusted life years, a metric used to gauge the impact of disease in terms of years lost (Goljar et al., 2010; Virani et al., 2020). Recent worldwide figures indicate that in 2019, approximately 101.5 million individuals suffered from a stroke, resulting in 3.3 million deaths

(Virani et al., 2021). This significantly increased from the estimated 16.9 million stroke cases in 2010 (Feigin et al., 2014). In Canada, over 800,000 new stroke cases have been documented (Canada, 2022) with Newfoundland and Labrador reporting the highest incidence rates (Government of Newfoundland and Labrador, 2022*).* These statistics underscore the pressing need for research and interventions focused on both primary and secondary stroke prevention and rehabilitation.

1.2.4 Recovery Path Following a Stroke

According to the proposed categorization by the Stroke Roundtable Consortium, the post-stroke period is typically segmented into several distinct phases. The hyperacute phase encompasses the initial 24 hours following a stroke, followed by the acute phase, lasting up to seven days. After the acute phase, the early sub-acute phase extends over the first three months; then, the late sub-acute phase spans months four to six; ultimately, the chronic phase lasts beyond six months (Bernhardt et al., 2017; Grefkes & Fink, 2020). This classification is grounded in the time-sensitive nature of recovery processes after a stroke. Shortly after cerebral ischemia occurs, a cascade of mechanisms is initiated to enhance plasticity, facilitating dendritic growth, axonal sprouting, and new synaptic connections (Carmichael et al., 2017; Carmichael et al., 2001).

The path to recovery following a stroke is influenced by factors including the individual's age, the stroke's severity, and the affected brain area (Alawieh et al., 2018). Various elements, such as neuroplasticity, rehabilitation intensity, and social support, can impact recovery (Ploughman et al., 2019). Typically, recovery unfolds in stages, with the most substantial progress seen in the initial weeks to months post-stroke. This stage is followed by a slower period of improvement that

may extend over several years. Subsequently, some individuals may reach a plateau in their recovery while others continue to improve (Horgan et al., 2009).

1.2.5 Impact of Stroke on the Individual

Stroke can impact four primary brain regions: cortical, subcortical, cerebellar, and brainstem, each associated with distinct clinical symptoms depending on the affected level and brain regions. Some symptoms and deficits can arise, including language, somatosensory, cognitive, and motor impairments (Chohan et al., 2019). Language deficits can hinder communication during daily activities (Ramos-Lima et al., 2018). Somatosensory impairment affects the processing of sensory information received by skin receptors, potentially resulting in reduced tactile sensitivity, altered temperature perception, or difficulty in identifying objects held in hand (Connell et al., 2008). Cognitive impairment and memory loss are prevalent post-stroke, with up to fifty percent of survivors estimated to develop neurocognitive disorders (Barbay et al., 2018; Lo et al., 2022). These deficits often persist into the chronic stage, affecting 40% to 60% of stroke patients, thereby complicating motor recovery efforts by impeding the relearning of lost skills (Marendic et al., 2016).

1.3 MOTOR IMPAIRMENTS IN STROKE

1.3.1 Upper Limb Motor Consequences of Stroke

Post-stroke motor impairment frequently manifests in the upper limb, complicating manual dexterity and impeding the execution of basic activities such as self-care and hygiene (Pollock et al., 2014). Studies indicate that upwards of 69% of stroke patients contend with persistent motor deficits in their upper extremities, with an individual's proficiency in arm and hand motor function

serving as a determinant factor in their capacity for independent living (Anwer et al., 2022; Byblow et al., 2015; Veerbeek et al., 2017).

Upper extremity motor dysfunction is characterized by muscular weakness or contracture, changes in muscle tone, joint laxity, and decreased motor control. These limitations impair everyday actions, including reaching, picking up, and holding onto items (Bleyenheuft & Gordon, 2014). Spasticity is identified as a significant factor contributing to motor dysfunction following a stroke (O'Dwyer et al., 1996). It involves heightened tendon reflex activity and hypertonia in specific muscles. Muscle tone regulation is influenced by inhibiting the medullary reticular formation, with modulation occurring through motor cortical areas (Mukherjee & Chakravarty, 2010; Trompetto et al., 2014).

Lost functional muscle control and movement refers to a condition that includes total loss of motor control, also known as paresis. Motor paresis, characterized by muscular weakness, emerges as a prevalent impairment in the upper extremity after a stroke, with approximately 56% of stroke survivors enduring hemiparesis persistently, even in the chronic stages of stroke recovery (Urton et al., 2007). Motor paresis of the upper extremity may be coupled with various neurological symptoms, including spasticity, sensory deficits, and impaired coordination that impede the recovery of motor function, all of which require specialized treatment interventions to address the multifaceted nature of the impairment (Page et al. 2004).

1.3.2 Motor Impairment Classification and Measurement

The classification of motor impairment in stroke patients depends on the extent, anatomical location, and specific characteristics of the motor deficit (Zhu et al., 2010). Lesions in the corona radiata, internal capsules and motor-related cortical regions (primary and secondary motor areas)

reduce the likelihood that an individual would regain upper limb function (Shelton & Reding, 2001). The National Institutes of Health Stroke Scale assesses stroke severity. This scale evaluates several domains: consciousness, language abilities, neglect, visual field loss, motor function, ataxia, sensory loss, and dysarthria. Studies by Kasner et al. (1999, 2006) have demonstrated that the National Institutes of Health Stroke Scale is reliable for assessing stroke severity and can predict long-term outcomes (Kasner, 2006; Kasner et al., 1999). Despite its utility, the National Institutes of Health Stroke Scale consolidates the ratings of all impairments into a single composite score, making it challenging to track changes in specific domains, such as motor function of the upper extremity.

Specialized assessments have been developed to gauge motor impairment in stroke patients, including the Fugl-Meyer Assessment for both the arm and leg and the Wolf Motor Function Test (WMFT) for upper limb assessment. The Fugl-Meyer Assessment entails patients attempting to move the affected limb joint by joint, with movement quality compared to the less affected side, serving as a widely used measure for assessing motor impairment post-stroke. Hernandez et al. (2019) highlighted the Fugl-Meyer Assessment's strong validity and reliability in evaluating motor function in stroke survivors (Hernández et al., 2019). The WMFT is a standardized clinical tool designed to assess upper extremity motor function in stroke and other neurological conditions. It comprises 17 tasks evaluating speed, strength, and dexterity, such as picking up small objects, turning a key, and manipulating items. The test measures task completion time and movement quality and is frequently utilized in clinical and research settings to assess treatment outcomes and formulate rehabilitation plans (Morris et al., 2001).

1.4 NEUROREHABILITATION AND STROKE

1.4.1 Plasticity and its Role in Stroke Rehabilitation

Neurological recovery following stroke follows a nonlinear, logarithmic trend (Hunter, 2002; Langhorne et al., 2011). Most recovery is reported to occur in the first three months after a stroke (Wade et al., 1983). However, there is evidence that recovery is not restricted to this period; hand and upper extremity recovery have been documented for several years following stroke (Carey et al., 1993; Yekutiel & Guttman, 1993)

Until the third month following the stroke, a varied, spontaneous neurological recovery might be regarded as a confounder of the rehabilitation intervention (Kwakkel et al., 2006). In the past, the evidence of spontaneous recovery after stroke misled some authors into believing that recovery of upper extremity function is inherent and that therapists have no impact on it (Heller et al., 1987; Wade et al., 1983). Progress in functional outcomes appearing after three months seems dependent mainly on learning adaptation strategies (Kwakkel et al., 2004). Evidence shows that neurological recovery through brain reconfiguration supporting adequate recovery or compensation may occur in the subacute and chronic periods following stroke (Krakauer, 2006).

Plasticity is the main factor in learning and is responsible for long-term alterations in the brain (Hallett, 2001) . After a stroke, the brain's capacity to adapt in response to use-dependent learning can be used to aid in brain recovery. It is thought that three physiological changes in the brain mediate spontaneous recovery: i) upregulation of proteins called neurotrophins that promote cell growth and repair, ii) modification of pre-existing neuronal pathways, and iii) creation of new synaptic connections through neuroplasticity (Wieloch & Nikolich, 2006).

A significant objective of neurorehabilitation is to assess and develop intervention techniques that generate or promote beneficial neuroplastic processes, and neuroplasticity is

essential for motor learning and recovery in stroke patients (Barsi et al., 2008). A sustained increase in the magnitude of the post-synaptic response brought on by ongoing afferent stimulation is known as long-term potentiation (Teyler & DiScenna, 1987). Repeatedly completing motor learning activities can cause long-term potentiation to reorganize the motor cortex (Rioult-Pedotti et al., 1998). Functional changes in motor-associated brain areas have been seen following motor training, and relearning movement is encoded by cortical circuitry changes brought on by synaptic alterations (Adkins et al., 2006). The modification of synapses and the growth of new dendritic connections are facilitated by growth-promoting proteins known as neurotrophins, which are believed to mediate central synaptic plasticity (Gómez-Palacio-Schjetnan & Escobar, 2013). These neurotrophins become upregulated after stroke to support plasticity and recovery (Murphy & Corbett, 2009).

1.4.2 Trajectory of Recovery

Relearning ability and the quantity of brain tissue spared determine the rehabilitation outcome and the degree of functional recovery (Knecht et al., 2011). Less than 20% of stroke patients achieve complete recovery, with most never fully regaining arm functioning (Kwakkel et al., 2003). Most spontaneous recoveries occur within the initial three months following a stroke (Cramer, 2008). Assessing cortical remodelling and modifications to existing neural networks may enable us to evaluate the extent of a patient's recovery. Recovery in the motor system varies following stroke; significant improvements in motor impairments have been shown to occur 30 days post-stroke. This critical period is marked by rapid neural reorganization and synaptic plasticity, which are crucial for motor recovery (Grefkes & Fink, 2020).

1.4.3 Importance of Rehabilitation in Stroke Recovery

The objectives of rehabilitation post-stroke aim to assist patients in relearning essential abilities such as speech, hand dexterity, and walking, which are crucial for everyday functioning (Krakauer, 2006; Schaechter, 2004). Rehabilitation consists of four main steps: determining the patient's requirements, setting realistic recovery objectives, providing treatments to help reach the goals, and evaluating the progress each person has made while receiving rehabilitation (Langhorne et al., 2011). Regaining lost physical function and movement is mainly accomplished through motor learning, which offers task- and context-specific training treatments (Langhorne et al., 2011).

Following a stroke, the brain undergoes various changes to recover and adapt. These changes are most pronounced shortly after the event and tend to decrease over time. The fundamental changes include neuroplasticity, inflammatory response, functional reorganization and glial cell activity (Cramer et al. 2008). This highlights the importance of using strategies that keep this period of opportunity open even as time goes on after the stroke (Murphy & Corbett, 2009). Both motor learning and spontaneous recovery influence patients' physical improvements during this period of opportunity (Krakauer, 2006). More research is needed to determine the ideal training duration and intensity to optimize functional recovery.

1.5 EMERGING THERAPIES TO ENHANCE PLASTICITY

Maintaining plasticity processes beyond the typical window of six months has been the focus of several emerging pieces of training, such as cardiorespiratory training, robotic-assisted therapy, constraint-induced movement therapy, task-oriented or repetitive task practice, and neuromuscular electrical stimulation (Nilsen et al., 2015; Pollock et al., 2003). These strategies are

based on repeated practice to enhance recovery and motor learning concepts. One kind of training that capitalizes on motor learning is called constraint-induced movement therapy, which involves limiting the non-paretic hand's use and promoting the affected hand's use. With intense training blocks, it seeks to produce both neuroplasticity and practice-induced changes brought on by repetition, which increases movement complexity, motivation, reward, and motor learning (Taub et al., 1993). Constraint-induced movement therapy has been demonstrated to increase the cortical representation of the afflicted hand in the ipsilesional hemisphere. Additionally, functional magnetic resonance imaging (fMRI) studies have shown changes in brain activity in both the ipsilesional and contralesional hemispheres in response to constraint-induced movement therapy, suggesting a reorganization of motor networks to support functional recovery (Schaechter et al., 2002).

Task-specific training is another intervention targeting motor impairments following stroke. It consists of 15 components (e.g., goal-directed, functional, client-centered, repetitious, context-specific, progressive, and distributed practice) and can be successfully implemented when factors such as the intensity, duration of training, and proper combination of specific components are carefully considered. (Timmermans et al., 2010). Outcomes from task-oriented training vary in dosage and intensity (i.e., dose x time). Evidence shows that increasing the amount of task-oriented practice can enhance arm function (Lin & Dionne, 2018).

Robotic-assisted therapy is another intervention for post-stroke motor deficits, showing several benefits in stroke rehabilitation (Lum et al., 2002). Additionally, it applies the principles of motor training through focused and task-oriented practice to support functional recovery (Langhorne et al., 2011; Langhorne et al., 2009). To promote neuronal plasticity, it enables synchronization of the motor and sensory systems through real-time feedback (Stefan et al., 2000).

According to studies, robotic-assisted therapy may be more successful than traditional rehabilitation techniques in enhancing motor function and minimizing impairment. For instance, a systematic review of the impact of robotic therapy on the rehabilitation of the hemiparetic arm following a stroke yielded a strong correlation between robotic therapy and increases in upper limb function, muscular strength, and daily living activities (Prange et al., 2006). According to a different study, using robots in stroke therapy enhanced motor performance and reduced upper limb muscular tone (Duret et al., 2019).

1.5.1 Cortical Priming and Motor Learning

In the context of motor learning, cortical priming refers to how prior experiences, practices, or stimuli influence the neural mechanisms involved in motor skill acquisition and performance and has been proposed as an adjuvant to motor training to regulate corticomotor excitability before training and consequently enhance motor performance, improving post-stroke neurorehabilitation results (Stoykov & Madhavan, 2015). Mechanistically, priming treatments work by altering synaptic plasticity and neuronal membrane excitability to induce long-term potentiation and depression-like effects (Ziemann & Siebner, 2008). Types of priming modalities broadly include stimulation-based priming (non-invasive brain and spinal stimulation), movement-based priming (continuous passive or active movements), and sensory-based priming (electrical stimulation) (Sivaramakrishnan & Madhavan, 2021).

Non-invasive brain stimulation (NIBS) therapies that change cortical brain excitability include transcranial direct-current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) (Wessel et al., 2015). These methods increase neuroplasticity and improve hand function using the interhemispheric model (Takeuchi & Izumi, 2012). According to the

model, motor impairments occur after stroke due to increased inhibition from the unaffected hemisphere to the affected hemisphere and lower motor output from the affected hemisphere (Murase et al., 2004). With NIBS, stroke patients can experience an improvement in their motor function by raising or reducing the excitability of the affected hemisphere relative to the non-affected hemisphere (Takeuchi et al., 2009). Pairing a motor task with NIBS has induced more plasticity and significant functional improvements in chronic stroke patients (Zimerman et al., 2012).

Exercise is a deliberate, regulated, repetitive, and purposeful action to enhance or preserve physical fitness (Dasso, 2019). Movement-based priming, such as aerobic exercise, has been shown to support the primary motor cortex's generalized excitability (Singh & Staines, 2015). Exercise leads to various outcomes, including neuromuscular adjustments, muscle function, and alterations in cardiovascular function (Cotman & Berchtold, 2002).

Aerobic and resistance training are the two primary categories into which exercise can be further divided (Pollock et al., 2000) . These kinds of training challenge different systems. Aerobic exercise increases the ability of an individual to take in and use oxygen, whereas resistance training, commonly known as strength training, encourages muscular hypertrophy and strengthening (Medicine, 2009; Pollock et al., 2000). Given our present understanding of aerobic exercise's benefits, stroke survivors may benefit more from it in terms of both their overall health and neurological state (Globas et al., 2012; Macko et al., 2005). However, there are still significant knowledge gaps regarding the optimal utilization of aerobic exercise for improving stroke recovery, particularly in generating empirical evidence that supports the ideal exercise intensity for maximizing recovery during the chronic phase of stroke (MacKay-Lyons et al., 2020; Rimmer & Wang, 2005).

In the general population, aerobic exercise has neuroprotective effects on the central nervous system and promotes plasticity (McDonnell et al., 2013). A study conducted in 1998 by Eriksson et al. revealed that new neurons could form in the human hippocampal region and that people who do aerobic exercise for more extended periods have higher hippocampal sizes (Erickson et al., 2011). According to research, acute episodes of aerobic exercise can alter the brain's intracortical networks, resulting in less inhibition and more facilitation (Singh et al., 2014). Additionally, it has been demonstrated that practicing an acute bout of aerobic exercise before learning a motor task enhances long-term memory of the motor task (Roig et al., 2012). Acute exercise can also activate important molecular and cellular mechanisms that enable brain plasticity, meaning it can act across the brain rather than just in the circuits that regulate the exercising muscles (McDonnell et al., 2013).

While the benefits of aerobic exercise in the healthy brain are becoming more and more established, further understanding of how aerobic exercise affects the brains of stroke survivors is needed. For instance, the brain experiences several changes, including neuroinflammation, neurovascular, neurochemical, and structural changes after stroke that may affect how the brain reacts to aerobic exercise (Austin et al., 2014). It has been demonstrated that after aerobic exercise, there is a rise in neurotrophin release, increased synaptogenesis, and dendritic branching in animal and clinical stroke models (Ploughman et al., 2015). Moderate-intensity aerobic exercise generates brain responses in experimental stroke models that maximize motor recovery through plasticity (Linder et al., 2019).

Increased levels of neurotrophins, specifically brain-derived neurotrophic factor (BDNF), which is directly generated in the brain by aerobic exercise, are thought to be one explanation for this. Neurotrophins are linked to neurogenesis, neuroplasticity, and neuroprotection. This could

work synergistically when combined with other forms of rehabilitation (Maejima et al., 2019; Ploughman et al., 2019). Approximately 30% of people have the BDNF genetic polymorphism (Val66Met)(Helm et al., 2017), which has been linked to impaired motor learning in those who have had strokes. Therefore, factors such as the location and severity of the stroke, genetic variations like BDNF polymorphisms, and the kinds of interventions used can all influence how the body responds to rehabilitation and possibly even change how aerobic exercise affects neuroplasticity (Mang et al., 2013).

1.6 MEASURING UPPER LIMB RECOVERY AND NEUROPLASTICITY AFTER STROKE

In discussions regarding upper limb recovery after a stroke, it is valuable to incorporate measurement frameworks like the International Classification of Functioning. Upper limb recovery can be assessed at different levels within the International Classification of Functioning framework (Stucki et al., 2002). At the functional level, patients are evaluated on how they use their limbs in everyday tasks. fMRI and fNIRS offer a deeper understanding of upper limb recovery at the mechanistic or neurobiological level. By implementing these assessments, researchers and clinicians can better understand the relationship between changes in the brain and meaningful improvements in arm and hand functionality.

In exploring the processes of plasticity and recovery in the brain post-injury, researchers utilize neuroimaging and neurophysiological techniques like fNIRS, blood-oxygen-level dependent functional magnetic resonance imaging (BOLD-fMRI), and positron emission topography (PET) as means to assess brain activity and recovery. BOLD-fMRI identifies regions of the brain associated with specific functions by monitoring changes in brain hemodynamics

during task performance, while PET identifies these regions by measuring metabolic activity. The activation of these brain regions during task execution indicates the involvement of active neurons in carrying out the task (Aguirre et al., 2002; Cramer, 2004). BOLD-fMRI and PET are beneficial because they produce high temporal and spatial resolution images (Schaechter, 2004).

These methods have constraints due to their reliance on costly equipment and specialized personnel for operation. Additionally, while they effectively gauge blood flow and neuronal activity, they do not offer insight into the inhibitory and facilitatory networks operating within the brain (Ko et al., 2013). Moreover, fNIRS has arisen as an alternative method based on hemodynamics, offering several advantages where fMRI is constrained. Notably, fNIRS excels in terms of cost, portability and demonstrates greater tolerance for motion (Scarapicchia et al., 2017).

1.7 FUNCTIONAL NEAR-INFRARED SPECTROSCOPY (fNIRS)

fNIRS is a firmly established non-invasive method for continuously assessing regional tissue oxygenation at the bedside. It was initially introduced by Jöbsis four decades ago (Jöbsis, 1977) and has since found widespread use across various clinical domains, particularly in neuroscience research (Obrig, 2014).

Like fMRI, fNIRS monitors the hemodynamic response to neural activity. However, instead of utilizing the paramagnetic properties of hemoglobin, it relies on the distinct absorption properties of biological chromophores (Ferrari & Quaresima, 2012; Hoshi, 2005). Biological chromophores are molecular groups that exhibit colour by absorbing light at various wavelengths, including those beyond the visible spectrum, such as longer (infrared) or shorter (ultraviolet) wavelengths (Semenov et al., 2020).

fNIRS offers several advantages that render it an excellent option for investigating brain function in scenarios where fMRI may not be feasible. As a research tool, fNIRS is non-invasive,

cost-effective, and boasts a temporal resolution comparable to fMRI (Hoshi, 2005; Huo et al., 2021). However, its most notable characteristic lies in its portability: recent advancements in fNIRS technology have afforded increasingly compact, wireless, and battery-powered devices (Ayaz et al., 2013; McKendrick et al., 2016). Consequently, this has facilitated research into neurocognitive processes in unrestricted environments, including outdoor and various ambulatory settings (Balardin et al., 2017; McKendrick et al., 2017).

Despite being considerably more tolerant of head motion than fMRI, motion artifacts can still affect fNIRS signals. Nonetheless, various research groups have developed real-time motion correction techniques to mitigate this issue, allowing for the exploitation of fNIRS's enhanced portability (Cui et al., 2010; Falk et al., 2011; Izzetoglu et al., 2010). Additionally, portable fNIRS devices enable investigations into paradigms impractical with fMRI, such as studying the neural correlates of walking (Perrey, 2014; Piper et al., 2014). They can also closely simulate the conditions of clinical neuropsychological assessments, such as face-to-face interactions with an examiner (Moriai-Izawa et al., 2012). Moreover, as functional neuroimaging assumes an increasingly vital role in clinical research, the insensitivity of fNIRS to standard electrical or magnetic devices, such as hearing aids, pacemakers, or cochlear implants, presents a significant advantage over fMRI limitations (Quaresima & Ferrari, 2019).

Lastly, while outside the present review's scope, another benefit of fNIRS lies in its seamless integration with other neurocognitive applications. In addition to fMRI, recent technological advancements have focused on combining fNIRS with electroencephalography (EEG) for both technological and functional purposes, aiming to advance brain-computer interface technologies (Sood et al., 2016; von Luhmann et al., 2017). Furthermore, beyond imaging modalities, fNIRS can augment and provide further insights into the mechanisms underlying

neurostimulation techniques, such as transcranial direct current stimulation (McKendrick et al., 2015).

The brain, an organ with high energy demands, exhibits increased cerebral blood flow and volume alongside neuronal activation. This phenomenon, known as "neurovascular coupling", forms the basis of several functional neuroimaging methods, including fNIRS (Chen et al., 2020; Chow et al., 2020; Csipo et al., 2019). By measuring alterations in light absorption by various hemoglobin species, fNIRS allows for calculating temporal changes in cerebral blood flow which reflect underlying neural activation (Pinti et al., 2020).

1.7.1 Mechanisms of fNIRS

Blood supply plays a crucial role in maintaining the proper functioning of the central nervous system (Mintun et al., 2001). Among the organs in our body, the brain exhibits the highest metabolic activity (Pontzer et al., 2016). Numerous factors influence brain function, with oxygen and glucose availability being the most significant. Both oxygen and glucose are essential for oxidative cellular respiration, generating energy through adenosine triphosphate molecules, the primary energy source for intracellular anabolic processes (Erecińska & Silver, 1989). The cerebral cortex comprises various functional areas delineated by Korbinian Brodmann in the 20th century (Zilles, 2018).

Each area is associated with specific functions, and the activation of these areas varies with the body's activity levels. During neural activity, the localized demand for oxygenated hemoglobin increases to the metabolic needs of individual areas. Elevated oxygen consumption in any given brain region increases local cerebral blood flow, resulting in a higher concentration of oxyhemoglobin and reduced deoxyhemoglobin levels (Chow et al., 2020; Csipo et al., 2019; Pinti

et al., 2020). Oxyhemoglobin and deoxyhemoglobin exhibit distinct absorption characteristics with near-infrared light. Consequently, the channel configuration of photon emitters and detectors in fNIRS facilitates the measurement of fluctuations in the levels of these two hemoglobin types within the blood in a specific area. These fluctuations can be quantified using the modified Beer-Lambert law (Almajidy et al., 2020; Hoshi, 2003; Naseer & Hong, 2015).

There is much to be discovered regarding fNIRS studies investigating the impact of motor learning on brain activity in stroke patients. While fNIRS offers a non-invasive and portable method for monitoring cerebral hemodynamics during motor tasks, more research is needed to examine its application in stroke populations (Zou et al., 2023). Furthermore, existing studies often focus on acute or subacute stages of stroke recovery, leaving a gap in knowledge regarding the long-term effects of motor learning interventions on brain reorganization in chronic stroke survivors (Coscia et al., 2019). Furthermore, most fNIRS studies in stroke rehabilitation tend to concentrate on motor cortex activation, overlooking potential alterations in other brain regions implicated in motor learning processes, such as the supplementary motor area and somatosensory area (Li et al., 2024). Addressing these gaps is imperative for advancing our understanding of how motor learning impacts brain function in stroke survivors and optimizing rehabilitation strategies tailored to individual patient needs.

This study aimed to explore the feasibility of using fNIRS to identify and assess biomarkers of neuroplasticity over time by measuring rehabilitation-induced changes in the brain following a motor learning intervention to improve upper limb function in people with stroke. This thesis contains three chapters. Chapter one is a literature review that introduces essential concepts related to the current understanding of stroke and the physiological impact of the event and describes imaging techniques and emerging therapies. Chapter Two examines the feasibility of using fNIRS

to measure rehabilitation-induced changes in upper limb movement related to motor learning interventions in chronic stroke patients. Lastly, Chapter Three provides an in-depth discussion of the results, expanding upon how these results answered the primary research questions and addressing potential study limitations and future research directions.

Research Questions

The two primary research questions addressed in this thesis are:

1. To what extent are there changes in brain activity, as measured by fNIRS, in the ipsilesional and contralesional hemispheres before and after the intervention? (at an individual and group level)?
2. To what extent are the observed changes in brain activity, as measured by fNIRS, aligned with the severity of upper limb impairment?

1.8 Co-Authorship Statement

This thesis reflects the original research conducted by Valiollah Mohammadi under Dr. Michelle Ploughman's supervision. While this work is the result of significant collaboration, the contributions of everyone are delineated in this statement.

Dr. Michelle Ploughman provided mentorship and guidance throughout this project. She contributed to the initial conception and refinement of the research ideas, oversaw the development of the methodology, and reviewed the data analysis and interpretation. The motor learning intervention used in this thesis was designed by Dr. Ploughman in collaboration with Dr. Lara Boyd (University of British Columbia) as part of a project funded by the Canadian Partnership for Stroke Recovery. Michael Babalola and Ayopo Onafowokan recruited participants, assessed upper limb function, applied the intervention and collected the fNIRS data. Sadman Islam assisted with fNIRS data analysis. I conducted the literature review, main fNIRS analysis, results, figures, and tables and created the discussion of results.

2 CHAPTER TWO: EXPLORING FUNCTIONAL NEAR-INFRARED SPECTROSCOPY IN STROKE REHABILITATION

2.1 INTRODUCTION

Stroke is a leading cause of long-term disability, and upper limb impairment is a common consequence, significantly affecting an individual's quality of life (Weber & Stein, 2018). Rehabilitation interventions targeting upper limb motor function and brain activity are essential for promoting recovery after stroke (Hatem et al., 2016). Recently, there has been growing interest in using technology and combined interventions to enhance stroke rehabilitation (Carbajal-Galarza et al., 2020). These interventions not only improve motor function but also have the potential to influence brain activity, which is crucial for overall recovery (Pollock et al., 2014). This study explores how ten sessions of a novel intervention (upper limb robotic motor learning preceded by a bout of brain priming (aerobic exercise) impacts brain activity measured using functional near-infrared spectroscopy (fNIRS), an area with significant knowledge gaps and high potential for novel insights (Jones & Adkins, 2015).

2.2 MOTOR LEARNING IN STROKE RECOVERY

2.2.1 Task-Oriented Practice

Motor learning in stroke recovery often involves task-oriented practice, which focuses on repetitive, goal-directed tasks to improve specific motor functions (Krakauer & Carmichael, 2017). Upper extremity rehabilitation means engaging patients in activities that require using their affected arm to perform daily tasks, such as reaching, grasping, and manipulating objects (Ward & Cohen, 2004). Task-oriented practice helps promote neuroplasticity, the brain's ability to reorganize itself by forming new neural connections (Kleim & Jones, 2008).

After stroke, the brain undergoes a process called neuroplasticity, where it attempts to reorganize itself to compensate for the damage caused by the stroke. This reorganization can involve the affected (ipsilesional) and the opposite (contralesional) hemispheres. The term "ipsilesional" refers to the hemisphere of the brain on the same side as the stroke. The ipsilesional motor cortex typically plays a crucial role in upper extremity motor recovery. After a stroke, there is often reduced activity in this region due to the damage. However, successful recovery is usually associated with restoring and increasing activity in the ipsilesional motor areas. Studies have shown that better motor outcomes are linked to the reactivation and increased recruitment of the ipsilesional sensorimotor cortex during motor tasks (Cramer et al., 1997; Ward et al., 2003) .

On the other hand, the "contralesional" hemisphere refers to the hemisphere opposite to where the stroke occurred. After a stroke, activity in the contralesional motor cortex often increases, particularly in cases where the ipsilesional hemisphere is severely damaged. However, this increased contralesional activity is typically associated with poorer motor outcomes for the affected upper extremity. This is likely because the contralesional motor cortex is not as specialized for controlling the affected limb, and its overactivation can interfere with recovery. Studies such as those by Rehme and Grefkes (2013) and Ward et al. (2007) have demonstrated that individuals who exhibit greater contralesional activation when moving the arm and hand tend to have poorer control and less functional recovery (Rehme & Grefkes, 2013; Ward & Cohen, 2004).

2.2.2 Priming Motor Learning with Neuromodulation and Aerobic Exercise.

Motor learning can be enhanced or "primed" through neuromodulation techniques and aerobic exercise (Hsieh et al., 2014). Neuromodulation methods, such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS), can facilitate motor learning

by modulating cortical excitability (Davidson et al., 2024) and can be used before or during task-oriented practice to enhance the brain's response to rehabilitation efforts.

On the other hand, aerobic exercise increases blood flow and oxygenation to the brain, which supports neural health and function (Moriarty et al., 2019). Incorporating aerobic exercise before or during motor training can prime the brain for learning by creating a more favourable environment for neuroplasticity (Page et al., 2004). Studies have shown that combining aerobic exercise with motor practice can improve motor function and cognitive performance (Duncan et al., 2005).

Several key studies have explored the impact of task-oriented practice, neuromodulation, and aerobic exercise on motor learning and recovery in stroke patients. In a study involving 32 patients with chronic stroke, 30 min per day for four weeks of hand and arm practice resulted in a significant shift in brain activation, which was measured using Functional Magnetic Resonance Imaging (fMRI) from the contralesional cortex to the stroke-affected hemisphere. This shift was associated with improved motor function and daily living activities in stroke patients (Yoo & Park, 2015).

Another study demonstrated that combining tDCS with task-oriented practice led to greater hand function improvements than task-oriented practice alone (Kaminski et al., 2022). The enhanced motor learning was attributed to the increased cortical excitability of tDCS. This study applied tDCS over the primary motor cortex on the contralesional hemisphere, which is commonly targeted because it's directly involved in controlling voluntary movements, including those of the upper limbs. Another study investigating the effects of aerobic exercise demonstrated that participants who engaged in aerobic exercise before motor practice showed more significant improvements in motor function and increased activation in motor-related brain areas, including

primary motor cortex, premotor cortex, supplementary motor area, basal ganglia, and cerebellum, compared to those who only performed motor practice (Penna et al., 2021).

2.3 ROBOTIC REACHING AND BRAIN ACTIVITY

2.3.1 Introduction to Upper Extremity Robots

Upper extremity robots are pivotal in assessing and intervening in motor function, particularly in patients with neurological impairments like stroke. These robots offer precise, repeatable, and quantifiable assessment of arm and hand movements, making them invaluable in clinical and research settings. Moreover, their ability to deliver consistent, tailored therapeutic exercises makes them practical tools for rehabilitation (Housman et al., 2009).

2.3.2 Use of Upper Extremity Robots in Assessment

Upper extremity robots are designed to assess complex arm and hand movements with high precision. For instance, the Kinesiological Instrument for Normal and Altered Reaching Movements (KINARM) Exoskeleton has been used extensively to evaluate sensorimotor deficits in stroke patients. It allows for assessing reaching and other upper limb movements in a controlled environment. The robot's ability to measure subtle changes in movement quality and speed provides a detailed understanding of the patient's motor function and guides the development of personalized rehabilitation protocols (Dukelow et al., 2010; Mehrholz et al., 2018).

2.3.3 Use of Upper Extremity Robots in Intervention

Robotic interventions have been shown to improve motor function significantly in patients with upper extremity impairments. Robots like the MIT-Manus and the ArmeoSpring have been

utilized in clinical trials to deliver repetitive, task-specific training critical for motor recovery. These robots facilitate the repetition of movements and provide real-time feedback, which is essential for motor learning (Lo et al., 2010; Timmermans et al., 2014).

Building on these advancements, the KINARM End-Point robotic system offers a unique approach to motor rehabilitation, particularly in stroke patients. The KINARM system, unlike MIT-Manus or ArmeoSpring, focuses on providing task-specific practice through its robotic handles, which allow for both unilateral and bilateral training. It consists of robotic handles (endpoints) connected to a motor system that guides the participant's arms through various tasks in a horizontal plane. These robotic handles provide haptic feedback, meaning they can apply forces to the participant's arm, aiding or resisting movement, depending on the task. This is crucial for stroke rehabilitation as it helps target specific movements and provides real-time feedback on motor performance (Babalola, 2023).

Participants interact with the system by gripping these handles, which can precisely track their movements while they perform motor tasks, such as reaching or target tracking. The system captures detailed kinematic data, such as movement trajectory, speed, and accuracy, essential for assessing motor control and function changes during the intervention. These data provide objective, quantifiable measures of motor performance, allowing for a detailed analysis of upper limb function before and after the motor learning intervention (Babalola, 2023).

The KINARM End-Point system allows for varying levels of task difficulty, which can be adjusted based on the participant's progress. This adaptability is essential in motor learning because it ensures that tasks remain challenging enough to stimulate neuroplasticity, the brain's ability to reorganize and form new neural connections, especially after an injury like a stroke. The system can impose external perturbations (unexpected forces), challenging the participant's motor

control and forcing them to adapt to changing conditions, enhancing motor learning (Dukelow et al., 2010). The KINARM End-Point system promotes recovery of upper limb function by retraining motor pathways and engaging participants in repetitive, controlled movement tasks (Coderre et al., 2010). Additionally, this robotic system is particularly useful in rehabilitation because it allows for bilateral training, where both limbs can be engaged simultaneously, or one limb can be guided while the other performs an active task (Coderre et al., 2010). This helps improve motor function on the impaired side, making it an effective tool for stroke patients with unilateral motor deficits.

2.3.4 Motor Learning in Robotic Rehabilitation

Motor learning is a critical component of robotic rehabilitation, involving integrating cognitive, sensory, and motor processes to acquire or regain motor skills. Effective motor learning requires the patient to engage cognitively with the task, which involves paying attention, understanding the movement, and adjusting based on feedback (Kumar & Michmizos, 2020). Repeated practice of movements is essential for improving coordination, strength, and the automation of motor tasks, with robots facilitating this process by providing consistent, repetitive practice (Huang & Krakauer, 2009). Visual feedback plays a crucial role in motor learning, as it helps patients correct their movements and improve spatial awareness. Sensory feedback, including proprioception, is vital for fine-tuning movements, and robots like the KINARM can provide detailed proprioceptive feedback, enabling patients to adjust their movements based on sensory input (Dukelow et al., 2010; Krakauer, 2006; Marchal-Crespo & Reinkensmeyer, 2009).

2.4 MEASURING REHABILITATION-INDUCED NEUROPLASTICITY

Neuroplasticity, the brain's remarkable ability to reorganize itself by forming new neural connections, is a crucial process underpinning recovery after stroke (Su & Xu, 2020). Following a stroke, the brain undergoes significant reorganization to compensate for lost functions, which is vital for restoring motor and cognitive abilities. Understanding the mechanisms and factors that drive neuroplasticity is essential for developing effective rehabilitation strategies.

Murphy and Corbett (2009) provide a detailed review of the plastic changes occurring during stroke recovery, highlighting the spectrum from synaptic modifications to behavioural adaptations (Murphy & Corbett, 2009). Their work underscores the complexity of neuroplasticity, illustrating that a stroke sets off a cascade of molecular and cellular events leading to the reorganization of neural networks. This reorganization is especially pronounced in the perilesional areas, where surviving neurons establish new synaptic connections to compensate for the lost function in the damaged regions. However, while neuroplasticity lays the foundation for recovery, the authors emphasize that the extent of functional recovery heavily depends on the nature and timing of rehabilitation interventions (Murphy & Corbett, 2009).

Building on this foundation, Stinear et al. (2019) discuss the application of prediction tools in stroke rehabilitation, which aim to assess recovery potential based on observed neuroplastic changes. These tools often utilize biomarkers, such as corticospinal tract integrity and motor cortex excitability, to predict motor recovery. The study highlights the pivotal role of neuroplasticity in shaping the recovery trajectory, suggesting that early assessments of neuroplastic capacity can inform the design of personalized rehabilitation programs (Stinear et al., 2019). Clinicians can optimize recovery outcomes by tailoring interventions to an individual's neuroplastic potential.

Furthering this discussion, Cirillo et al. (2020) explore neurochemical changes during the subacute stage of stroke, particularly the balance between excitation and inhibition within the motor cortex (Cirillo et al., 2020). Their findings reveal that stroke disrupts this balance, often leading to increased inhibitory processes that may hinder neuroplasticity and recovery. The authors propose that interventions to restore this balance, such as non-invasive brain stimulation or pharmacological treatments, could enhance neuroplasticity and improve functional outcomes. This research underscores the importance of understanding the post-stroke neurochemical environment and its impact on neuroplasticity (Cirillo et al., 2020).

Mooney et al. (2019) focus on the role of primary motor cortex inhibition in upper limb impairment among chronic stroke patients. Their multimodal study reveals that heightened inhibition in the primary motor cortex correlates with poorer motor outcomes, suggesting that maladaptive plasticity may contribute to persistent motor deficits (Mooney et al., 2019). They propose that reducing primary motor cortex inhibition through targeted interventions, such as TMS, could foster neuroplasticity and support better functional recovery. This study highlights the necessity for a nuanced approach to rehabilitation, considering the inhibitory-excitatory balance in the motor cortex as a crucial factor in stroke recovery (Mooney et al., 2019).

To further explore how various neuroimaging techniques contribute to understanding neuroplasticity and motor learning post-stroke, it is essential to examine the strengths and limitations of prominent methods such as fMRI, TMS, and fNIRS. Each of these tools offers unique insights into brain function and neurorehabilitation, but they also present challenges that necessitate careful consideration when applied to clinical and research settings. This section will review recent studies employing these technologies, identifying key findings and uncovering critical gaps in their current application, particularly in stroke rehabilitation.

2.4.1 Functional Magnetic Resonance Imaging (fMRI)

fMRI is widely used to measure changes in brain activation associated with rehabilitation in stroke patients. Cheng et al. (2023) investigated the alteration of brain activity using fMRI after applying repetitive TMS over the primary motor area in movement disorders patients after stroke. This study demonstrated that fMRI could observe the influence of repetitive transcranial magnetic stimulation on brain networks and reveal the neuroplasticity mechanism of post-stroke rehabilitation (Cheng et al., 2023).

Another study conducted a series of fMRI scans on seven stroke patients undergoing rehabilitation therapy to identify functional brain changes associated with upper limb improvements. This study showed that fMRI offers a promising, objective approach for specifically identifying changes in brain activity potentially responsible for rehabilitation-mediated recovery of function after stroke (Johansen-Berg et al., 2002).

In fMRI studies, one of the main limitations is the restricted use of longitudinal designs. Most studies capture brain activation patterns during or after rehabilitation but rarely follow up to track long-term changes in neuroplasticity. Furthermore, while fMRI provides rich data on brain activation, it does not capture the dynamic, moment-to-moment changes in neural activity during real-time movements, limiting its practical application in understanding stroke recovery. There is also a need for fMRI studies that consider individual variability in brain lesions and stroke severity to provide more personalized insights into recovery.

2.4.2 Transcranial Magnetic Stimulation (TMS)

TMS can assess cortical excitability and map motor function, making it valuable for evaluating CST function in stroke rehabilitation. In the study by Fan Jia et al. (2024), TMS was

used as an outcome measure to assess the effects of graded motor imagery therapy and repetitive Transcranial Magnetic Stimulation on upper extremity function in stroke patients, both individually and in combination. This study demonstrated that both graded motor imagery therapy and repetitive Transcranial Magnetic Stimulation significantly enhanced upper extremity function, with the combined approach proving even more effective. TMS assessments showed that these interventions led to increased CST excitability, indicating a neurophysiological basis for the functional improvements observe.(F. Jia et al., 2024).

A study by Auriat et al. (2015) provided a narrative review of research employing various neuroimaging and brain stimulation techniques, including Diffusion Tensor Imaging, Magnetic Resonance Spectroscopy, fMRI, and Electroencephalography with a particular focus on TMS. This review highlighted how TMS, when combined with these multimodal neuroimaging methods, is uniquely valuable in evaluating neuroplastic changes and functional recovery following a stroke (Auriat et al., 2015).

Recent studies reveal a key gap in the use of TMS as an outcome measure to assess recovery due to variability in protocols across studies, including differences in stimulation frequency, intensity, and site selection. Although research has shown that repetitive Transcranial Magnetic Stimulation as an intervention can improve motor and cognitive function, more standardization is needed in using TMS to reliably measure changes in brain function and neuroplasticity. Additionally, while improvements have been observed, further studies are required to understand the long-term changes TMS can detect, the optimal timing and duration for such assessments, and how TMS-based measurements might reveal interactions with other treatments, such as conventional physical rehabilitation or cognitive training.

2.4.3 Functional Near-Infrared Spectroscopy (fNIRS)

fNIRS is a non-invasive imaging technique used to measure brain activity by detecting changes in blood oxygenation and blood volume in the brain's cortex. The use of fNIRS to assess brain activity in stroke patients has increased interest in recent years. Kim et al. (2022) conducted a study using fNIRS to analyze bilateral motor cortex activation in nine healthy subjects and five chronic stroke survivors during a pinching task performed in mirror therapy, robotic therapy, and robotic mirror therapy conditions (Kim et al., 2022). The experimental findings suggested that integrating visual feedback, somatosensory feedback, and motor intention is crucial for enhancing activity in the ipsilesional motor cortex (Kim et al., 2022).

Xie et al. (2022) conducted a study examining the effects of robot-assisted task-oriented upper limb motor training on neuroplasticity in stroke patients with varying degrees of motor dysfunction (Xie et al., 2022). The study aimed to address a critical gap: the absence of real-time neurological evaluation indicators that could help refine treatment parameters and accurately assess clinical efficacy in upper limb motor function rehabilitation. Without these indicators, adjusting robotic training to meet individual patient needs remains challenging, potentially limiting the effectiveness of robot-assisted therapy. To investigate this, 33 adult stroke patients with hemiplegic motor impairment were divided based on motor dysfunction severity: severe (n=10), moderate (n=14), and mild (n=9). fNIRS was used to measure cortical activation by analyzing HbO and HbR concentration changes across several key ROIs: the bilateral prefrontal cortex, dorsolateral prefrontal cortex, superior frontal cortex, premotor cortex, primary motor cortex, primary somatosensory cortex, and occipital cortex during both resting and motor training states.

Results showed increased cortical activation in the ipsilesional superior frontal cortex for the mild group and bilateral superior frontal cortex for the moderate group during motor training

relative to the resting state. Patients in the mild group also exhibited decreased lateralization of activation during motor training. Additionally, the values decreased significantly between contralesional dorsolateral prefrontal cortex and ipsilesional superior frontal cortex, bilateral superior frontal cortex, contralesional primary somatosensory cortex, and ipsilesional primary motor cortex, suggesting a shift towards more balanced cortical engagement. The study concluded that robot-assisted upper limb motor training could enhance neuroplasticity in specific regions, especially the superior frontal cortex, and improve motor control and learning in stroke patients (Xie et al., 2022). By utilizing fNIRS as a real-time assessment tool, this study demonstrates the potential to capture sensitive neural indicators that enable more personalized and effective robotic training prescriptions, bridging the gap in neuroplasticity monitoring during rehabilitation (Xie et al., 2022).

Liu et al. (2022) investigated the effects of brain-computer interface -robot training as a potential intervention to improve motor recovery and induce neuroplasticity in chronic stroke patients with moderate to severe upper limb paresis (Liu et al., 2022). By focusing on patients with limited response to conventional physiotherapy, the researchers aimed to address a gap in effective rehabilitation options for this population. Eighteen hospitalized stroke patients participated in 20 brain-computer interface training sessions, with assessments at multiple time points using the WMFT and FMA-UE to evaluate motor outcomes. Neuroplastic changes were monitored using fNIRS. Key ROIs included the primary motor cortex and frontal cortex, with specific focus on connectivity between ipsilesional primary motor cortex and the contralateral primary motor cortex, as well as between primary motor cortex and the frontal cortex on both sides.

The results indicated that brain-computer interface training could enhance cortical connectivity, suggesting neuroplastic adaptations that support improved motor function (Liu et al.,

2022). The study underscored the potential of fNIRS in assessing brain-computer interface -related neuroplastic changes and highlighted the need for further research to refine training protocols and explore the long-term effects and integration of brain-computer interface with conventional therapies in stroke rehabilitation. By examining real-time neuroplastic changes, this study provided a foundation for more personalized and effective interventions for patients with severe impairments (Liu et al., 2022).

Delorme et al. (2019) explored the relationship between hemodynamic patterns in sensorimotor areas and motor recovery in stroke patients over the first three months post-stroke, addressing the limited understanding of how cortical reorganization evolves during early recovery (Delorme et al., 2019). Recognizing that both hemispheres interact functionally after a stroke, the researchers aimed to clarify the timeline and patterns of brain reorganization in sensorimotor areas associated with upper limb motor recovery. Eight right-handed individuals who experienced their first ischemic or hemorrhagic stroke with mild to severe hemiparesis (mean age 60±8 years, including three women) were assessed with fNIRS and FMA-UE test over two months. Hemodynamic changes in the ipsilesional and contralesional sensorimotor regions were recorded during intermittent isometric contractions at submaximal force levels for each arm, with a lateralization index computed to monitor interhemispheric balance.

Findings revealed stable lateralization in non-paretic arm movements, like healthy controls, whereas paretic-arm movements initially engaged bilateral cortical activity that progressively shifted to ipsilesional activation with recovery. This lateralization shift over two months correlated with FMA-UE score improvements, suggesting an association between cortical reorganization and motor recovery. However, the study highlights several gaps. The mechanisms and timeline driving cortical reorganization in the sensorimotor areas remain unclear, particularly concerning variations

across different levels of impairment, stroke types, and patient ages. Additionally, the small sample size limits the generalizability of findings, and further research with larger, more diverse populations is needed to standardize neuroplasticity markers for clinical use. By identifying these gaps, the study underscores the potential of fNIRS for tracking early neuroplastic changes while emphasizing the need for further exploration in this area (Delorme et al., 2019).

Muller et al. (2024) examined motor cortical activity patterns in chronic post-stroke patients using a combined fNIRS and Electroencephalography approach to assess brain activation and its relationship to motor performance and compensatory strategies during upper limb tasks (Muller et al., 2024). This study included 21 chronic stroke patients and 21 healthy older adults who completed two functional tasks: a paced-reaching task and a circular steering task. Brain activity was recorded from the bilateral motor cortices while participants' motor performance and kinematic compensations, such as trunk use, were simultaneously tracked. Results showed that post-stroke patients exhibited poorer performance in the circular steering task and greater trunk compensation across both tasks. Notably, stroke patients over-activated their motor cortices during the paretic upper limb reaching task, and this over-activation correlated with greater trunk compensation and higher impairment scores.

The study highlights the potential of combined fNIRS, Electroencephalography and kinematic measurements for more precise spatiotemporal mapping of brain activation and functional strategies, which could enhance tracking and understanding of brain-movement interactions during stroke rehabilitation (Muller et al., 2024). These findings underscore gaps in our understanding of compensatory strategies and call for further standardization in using such multimodal techniques to track neuroplastic changes.

The study by Kim et al. (2024) explored cortical hemodynamic responses in 18 participants who had experienced chronic stroke, with a mean age of 67 years (Kim et al., 2024). The cohort was composed of patients with a mix of ischemic (eleven participants) and hemorrhagic (seven participants) stroke types, and post-stroke durations ranged widely from 14 to 206 months. The intervention focused on upper limb rehabilitation through a 12-week digital therapeutic program called MotoCog®, which aimed to improve motor function by engaging participants in upper limb tasks designed to simulate daily activities. These tasks were performed using the affected hand, and brain activity was continuously monitored using an 81-channel fNIRS system (NIRScout®, NIRx Inc.), which allowed for the observation of a wide range of cortical regions, including frontal, motor, parietal, temporal, and occipital areas. The study highlighted significant activation in the ipsilesional primary motor, primary somatosensory, and contralesional prefrontal cortices. The study reported correlations between brain activation patterns and FMA-UE score, suggesting a link between functional motor improvement and cortical reorganization (Kim et al., 2024).

While this study provides valuable insights into cortical activation during rehabilitation tasks, several limitations highlight the need for further research. Notably, the wide range of stroke chronicity (14 to 206 months) and the inclusion of both ischemic and hemorrhagic stroke types may obscure individual differences in recovery trajectories. The grouping of such diverse patient populations could potentially mask the nuanced effects of the intervention on subgroups, such as those with more severe motor impairments or differing types of stroke etiology.

Another study conducted by Ye et al. (2024) introduced an innovative approach by combining surface electromyography and fNIRS to provide a quantitative assessment of upper limb motor function in stroke patients (Ye et al., 2024). This study involved 15 stroke patients in both the subacute and chronic stages, alongside 15 healthy control participants, offering a

comparative analysis of motor function. Participants performed bilateral elbow flexion tasks, during which surface electromyography and fNIRS data were collected simultaneously. The surface electromyography data provided insights into muscle activation and synergy. At the same time, fNIRS was employed to measure cortical hemodynamics, explicitly targeting the laterality index in the posterior motor cortex and primary motor cortex. Significant differences in primary motor cortex were found between the affected and unaffected sides of stroke patients, as well as between stroke patients and healthy controls. Furthermore, the fNIRS data contributed to developing a linear regression model to predict FMA-UE scores, a clinical measure widely used to assess upper limb motor function in stroke recovery.

While the study by Ye et al. (2024) demonstrated the efficacy of combining surface electromyography with fNIRS for assessing motor cortex activity and predicting functional outcomes (Ye et al., 2024), focusing on a limited number of brain regions may restrict a more comprehensive understanding of neuroplasticity in stroke rehabilitation. Specifically, the study primarily focused on the motor cortex without extensive examination of other crucial areas, such as the somatosensory cortex and prefrontal cortex, which play integral roles in motor learning, sensory feedback, and higher-order cognitive functions during recovery.

The review conducted by Sun (2021) presents an extensive overview of the current NIRS in stroke rehabilitation, examining its utility in monitoring a wide range of brain functions, including motor, cognitive, and emotional recovery (Sun et al., 2021). The review highlights the growing use of NIRS, particularly fNIRS, in measuring cortical activation during stroke recovery, primarily focusing on motor-related regions such as the motor cortex. Sun et al. emphasize the potential of fNIRS as a prognostic tool for stroke rehabilitation, with baseline cortical activation patterns serving as predictive indicators of recovery outcomes (Sun et al., 2021). This makes

fNIRS a valuable technology for tracking neuroplasticity during rehabilitation, as evidenced by various longitudinal studies discussed in the review.

However, the review also underscores a significant limitation prevalent across many fNIRS studies: the tendency to focus solely on the motor cortex, thereby neglecting other critical brain regions such as the somatosensory cortex and prefrontal cortex, both of which are essential in understanding motor learning and recovery. By concentrating predominantly on motor cortex activity, many studies must capture the broader neural network interactions contributing to stroke recovery. Furthermore, while Sun et al. cover a broad spectrum of stroke recovery mechanisms, including cognitive and emotional recovery, the need for more attention to the interplay between different cortical regions limits the scope of these investigations, particularly in understanding how these regions collectively contribute to motor recovery (Sun et al., 2021).

The review by Huo et al. (2021) provides a detailed analysis of the application of fNIRS in stroke rehabilitation, highlighting its potential to correlate brain activation patterns with motor function improvements (Huo et al., 2021). The review synthesizes findings from various studies involving stroke patients across different recovery stages, from the acute to chronic phases, with a primary focus on ischemic stroke, given its prevalence in stroke populations. Huo et al. demonstrated that fNIRS metrics, particularly those measuring cortical hemodynamics in motor-related regions, show promise in predicting therapeutic outcomes. Yet, they also acknowledged that interpreting these metrics in clinical contexts presents significant challenges (Huo et al., 2021). The review emphasizes the need for further validation studies to link fNIRS findings more directly to functional outcomes in stroke rehabilitation.

One of the critical observations made by Huo et al. (2021) is the tendency for fNIRS studies to concentrate predominantly on cortical activity in the motor cortex, with occasional reference to

the prefrontal cortex (Huo et al., 2021). While these areas are crucial for understanding motor recovery, the review highlights a critical limitation in the literature: the need for comprehensive analysis of all brain regions involved in motor learning and recovery.

Another study by Lim (2019) determined the differences in sensorimotor cortex activation during unrestrained reaching and gripping after stroke using fNIRS (Lim & Eng, 2019). In this study, eleven individuals who had experienced chronic stroke and 11 neurologically healthy individuals participated in reaching and gripping tasks. Performance metrics and sensorimotor cortex activation were measured using fNIRS. This study aimed to understand the feasibility of using fNIRS to measure rehabilitation-induced changes in the brain following a rehabilitation intervention to improve upper limb function in people with stroke.

2.5 GAPS AND IMPORTANCE OF THE STUDY

Previous research in stroke rehabilitation has faced challenges due to diverse participant profiles, long intervention periods, limited neuroimaging scope, and inconsistent integration of functional and neural outcomes. For example, in the study by Kim et al. (2024), the wide variation in stroke types (ischemic and hemorrhagic) and chronicity (ranging from 14 to 206 months) created variability that makes it difficult to draw conclusions about the specific effects of an intervention on neuroplasticity in different patient subgroups (Kim et al., 2024). This diversity of stroke characteristics can obscure the nuanced ways different populations respond to upper limb training. In contrast, the present study narrows this variability by selecting a more homogeneous cohort—all participants are over six months post-stroke (7-33 months), focusing exclusively on the chronic phase. This consistent profile of chronic stroke survivors allows for a clearer assessment of the intervention's effect on neuroplasticity and motor learning by minimizing variability in post-stroke

duration, which was broader in Kim et al. (2024). Additionally, previous interventions, such as the 12-week MotoCog® digital rehabilitation program used by Kim et al. (2024), are lengthy and risk-capturing natural, time-related neuroplastic changes alongside intervention effects (Kim et al., 2024). This extended timeline makes it challenging to differentiate the neuroplastic changes triggered by the intervention itself from those arising from ongoing spontaneous recovery. By employing a shorter, intensive 10-day intervention centered on motor learning principles with robotic assistance (using the KINARM robot), the present study isolates intervention-specific neuroplasticity within a focused period. This approach shifts the emphasis from long-term natural recovery toward assessing the immediate, targeted effects of training on brain plasticity.

Many studies, including those by Ye et al. (2024) and Huo et al. (2021), have limited their neuroimaging focus primarily to the motor cortex (Huo et al., 2021; Ye et al., 2024). While the motor cortex is essential for movement recovery, restricting the analysis to this area overlooks the interconnected roles of other brain regions. For example, the somatosensory cortex is integral to sensory feedback and proprioception, and the prefrontal cortex contributes to attention and motor planning, both of which are vital in relearning motor tasks. By expanding the scope to include these regions, the study described in this thesis captures a more complete picture of the neural network involved in motor recovery, revealing how different brain areas contribute to functional gains.

Furthermore, previous studies often lack real-time measurements immediately before and after interventions, relying instead on periodic assessments over the course of the intervention or long-term follow-ups. This design can miss the acute neuroplastic responses that occur directly because of training. The present study addresses this by using fNIRS to capture cortical activity

immediately before and after the intervention, providing a clearer understanding of how specific brain regions in both ipsilesional and contralesional hemispheres respond to training in real time.

By integrating these insights, this work advances fNIRS as a valuable tool for personalized rehabilitation strategies. The detailed analysis of brain activity patterns can potentially tailor interventions more effectively to individual recovery profiles, ultimately contributing to improved rehabilitation outcomes for stroke patients. This comprehensive approach fills critical gaps in current stroke rehabilitation literature and provides a more complete picture of how different brain regions contribute to motor recovery. Therefore, this study aimed to explore the feasibility of using fNIRS to identify and assess biomarkers of neuroplasticity over time by measuring rehabilitation-induced changes in the brain following a motor learning intervention to improve upper limb function in people with stroke. The two primary research questions addressed in this thesis are:

1. To what extent are there changes in brain activity in the lesioned and contralesional hemispheres before and after the interventions (at an individual and group level)?
2. To what extent are observed changes in brain activity aligned with the severity of upper limb impairment?

2.6 PARTICIPANTS

Participants with chronic stroke (over six months post-stroke) were recruited from the provincial tertiary rehabilitation hospital in St. John's, Newfoundland and Labrador, Canada. They were part of an ongoing interventional study that met specific inclusion and exclusion criteria. The clinical characteristics of these participants are detailed in Table 2.1. To be included, participants had to 1) be aged between 40 and 95, 2) have upper limb movement-related deficits (either left or

right hand dominant) following a first, middle cerebral artery stroke, and 3) be in the chronic recovery phase (more than six months post-stroke). Exclusion criteria were 1) severe upper limb motor deficits preventing participation in arm rehabilitation therapy, 2) severe cognitive or aphasic deficits impeding their ability to follow instructions, 3) Contraindications to fNIRS and 4) other neurological or psychological conditions. The provincial Health Research Ethics Board (HREB # 2020.273) approved the study and its procedures in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (2014) and the Declaration of Helsinki principles. All participants gave written informed consent before participating in the study and data collection.

2.6.1 Experimental Design

This fNIRS sub-study is part of a more extensive feasibility study that examined the effects of a combined intervention of aerobic priming and skilled motor learning using the KINARM robot (Figure 2.1). The target sample size was set between 10 and 15 participants. In this main study, participants were required to visit the laboratory for two data collection sessions: one before the intervention (PRE) and another 24 hours after the last ten-day intervention (POST) session. The PRE-intervention phase involved multiple visits, one of which involved testing using fNIRS (Table 2.1). During the visit to one of the PRE testings, participants completed various forms, underwent eligibility screening, and had their Fugl-Meyer Assessment for Upper Extremity (FMA-UE) scores recorded (see section 2.6.2.1). Visit two of PRE testing was divided into two parts: part A involved a movement test using the WMFT (see section 2.6.2.2), and part B assessed brain activity before and after a 30-minute exercise intervention using fNIRS (Table 2.1). The specific motor task during fNIRS recording involved a 10-minute hand-tapping task designed to evaluate motor function (more details below). After completing the baseline assessment (Table 2.1), those who

could grasp the hand enough to hold a robotic device participated in the ten-day aerobic priming + skilled motor learning using the KINARM robot, with each session lasting 30 minutes (visits 3-12). The POST intervention phase, conducted during visit 13 (Table 2.1), included a final assessment where both movement and brain activation using fNIRS were tested. This involved a repeat of the WMFT for movement evaluation and fNIRS with hand tapping for brain activation measurement.

Table 2-1 Overview of Assessments & Sessions

Demographics	**Clinical Assessments**	**Brain Activation Test** **(fNIRS)**	**Sessions & Assessments**
1. Age **2. Sex** **3. Stroke Stage** **4. Stroke Location** **5. Affected Hand**	**1. Wolf Motor Function Test** **2. Fugl Meyer Assessment**	**1. Hand Tapping (Affected Hand)**	**1. Sessions 1 & 2 (Baseline)** **- Clinical Assessments** **- fNIRS** **2. Sessions 3-12 (Intervention)** **- Ten days of exercise with skilled motor practice on the Kinarm robot, separated by at least 48 hours** **3. Sessions 13-14 (post-24 hours)** **- Clinical Assessments** **- fNIRS**

The table provides an overview of the assessments and sessions used in the study, detailing the assessment measures, gold-standard clinical and brain imaging measures, and the demographics of the study participants.

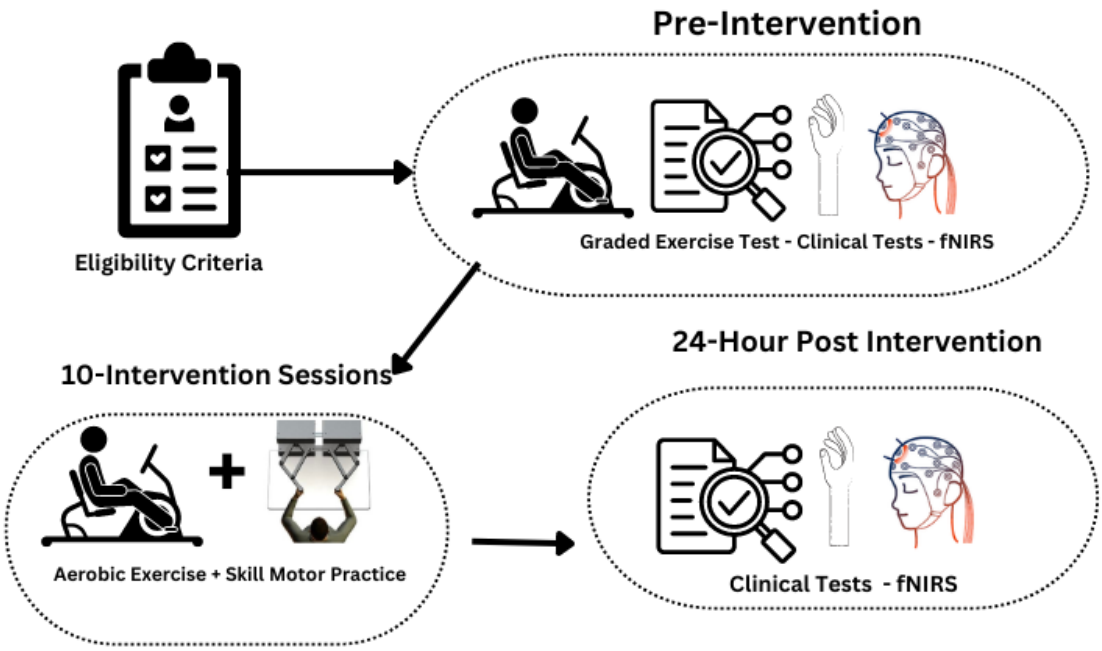

Figure 2-1 Study Schematic. This schematic representation details the research design, showing the progression of interventions and assessments throughout the study. It visually outlines the experimental timeline, emphasizing the order and interconnections of the various research components. (Original Illustration by VM)

2.6.2 Clinical Assessments

Participants in the study underwent a series of standardized clinical assessments to evaluate disease severity, performance-based impairment, and motor recovery according to the International Classification of Functioning and Disability (ICF) guidelines (Metcalf et al., 2007).

2.6.2.1 Fugl-Meyer Assessment for Upper Extremity (FMA-UE)

Hand and arm impairment was evaluated using the FMA-UE, a performance-based index developed by Fugl-Meyer et al. in 1975 to assess motor function, sensory abilities and joint functionality in patients with post-stroke hemiplegia (Fugl-Meyer et al., 1975). The FMA-UE includes 33 standardized tasks across five domains: reflex activity, flexor synergy, extensor synergy, movement coordination, and sensation. Each task is scored on a 3-point ordinal scale, with higher scores indicating better motor function, culminating in a total possible score of 66 points. The assessment typically requires 45-60 minutes to complete. Hernandez et al. (2019) assessed the inter-rater reliability of the FMA-UE, reporting high agreement among raters, which supports its reliability for both clinical and research applications (Hernández et al., 2019). Physical therapists and healthcare professionals commonly use the FMA-UE to gauge impairment and recovery levels in patients with upper limb deficits (Rech et al., 2020).

2.6.2.2 Wolf Motor Function Test (WMFT)

The WMFT assesses hand and arm function during real-world tasks post-stroke (Wolf et al., 2001). This standardized assessment tool evaluates gross and fine motor abilities related to activities of daily living through 15 timed functional tasks. Tasks include opening and closing doors, turning keys, manipulating small objects, and lifting weighted items, typically completed

within 20-30 minutes. The WMFT demonstrates high inter-rater reliability, internal consistency, and test-retest reliability (Edwards et al., 2012; Morris et al., 2001; Wolf et al., 2005). During the WMFT, a trained evaluator assesses the patient's ability to perform each task using a 6-point ordinal scale, where 0 indicates no movement and 5 represents normal movement. The evaluator also records the time taken to complete each task. If a task cannot be completed within 120 seconds, it is given a score of zero. Higher scores reflect quicker movement and better motor function. Additionally, task performance is quantified by calculating the rate (number of repetitions completed in 60 seconds). The WMFT incorporates multiple measures to comprehensively evaluate upper extremity function. These measures include overall performance scores, task completion times, the Functional Ability Scale (which rates the level of independence during task completion on a 5-point scale), strength assessments using handheld dynamometers, evaluations of grasp and release, dexterity tests involving small objects, and range of motion assessments. These measures offer a detailed assessment of upper extremity function in individuals recovering from stroke, providing crucial insights into rehabilitation progress and the effectiveness of treatments (Hodics et al., 2012).

2.6.3 Aerobic priming + Skilled Motor Practice

The combined intervention involved aerobic priming for 20 minutes and robotic upper limb skilled motor practice for two minutes and 30 seconds for a total of 22 min and 30 seconds. Aerobic priming was conducted using the NuStep recumbent bike, involving at least 20 minutes of exercise at a moderately high intensity, with a target of 60-80% of the participant's heart rate reserve. This method provides a controlled and safe approach to delivering functional aerobic training, particularly for individuals with motor impairments. Aerobic exercise enhances cardiovascular

endurance while reducing the load on weakened limbs, improving mobility and preparing participants for motor rehabilitation tasks. The skilled arm practice was conducted using a robotic device known as the KINARM. For this study, the KINARM Endpoint bimanual robotic device, equipped with software version Dexterit-E 3.8.2-8570, was utilized for the robotic assessment. The KINARM robot is a sophisticated and advanced tool designed to examine the brain's motor and sensory systems. Its validity and reliability have been confirmed in preliminary studies (Little et al., 2015; Mang et al., 2018; Semrau et al., 2013; Simmatis et al., 2017). Validity indicates how accurately a measurement tool assesses what it is intended to measure (Otaka et al., 2015).

The task conducted in this study using KINARM was an Object Hit task. The Object Hit task is a dynamic sensorimotor assessment that evaluates a participant's ability to react quickly and accurately. In this task, participants use robotic handles to hit falling virtual objects displayed on a screen. The task measure's reaction time, hand movement coordination, and motor control. It challenges participants to strike the objects while avoiding certain distractors, thus also assessing decision-making and visuospatial attention. The Object Hit task was programmed with a complex pattern that the participant learned to anticipate. Participants initially attempted to grasp the handle with their affected hand and then move the robot. Those unable to hold the handle did not proceed further. If participants could hold the robot, they completed tasks by moving their arms and holding onto the handles connected to the robot in the horizontal plane beneath a semi-transparent mirror. The handle featured a seven cm-diameter circular base to support the palm of the hand during tests. Torque sensors integrated with the handle accurately measured the users' hand position, movement, and grasp range. KINARM Standard Tasks were projected downward onto this mirror screen by a custom-built screen above, while the participants' direct view of their arms was blocked. Upon holding the robot handle, a white cursor dot appeared on the screen to indicate hand

position. Participants also experienced a force feedback mechanism, like the sensation of hitting a squash ball, while hitting target shapes with the robot handles during specific tasks (Babalola, 2023).

2.6.4 fNIRS System and Optode Array

fNIRS data were gathered using the continuous-wave NIRScoutX® 16x16 imaging system (NIRx Medical Technologies, Berlin, Germany), which comprises 16 LED sources and 16 detectors, with a sampling rate of 3.9 Hz. This study utilized 8 sources and 8 detectors, providing 16 channels covering the Prefrontal Cortex, Motor Cortex and Somatosensory Cortex of the ipsilesional and contralesional hemispheres. The probe arrangement on the cap was determined using the fNIRS Optode Location Decider (fOLD) software (Zimeo Morais et al., 2018), with sensitivity ranging from 43.1 to 87.4 (Figure 2-3). The distance between sources and detectors was maintained at 3 cm using plastic spacers. Short-distance detectors were attached to the optodes to measure superficial scalp blood flow. Before testing, individual cap sizes were determined by measuring head circumference (from the nasion to the inion). Before data recording, probes were calibrated, and each channel was checked for signal quality and noise level. A signal was considered acceptable if the gain was equal to or greater than 7 db and the noise level was less than 7.5 db during calibration. All data recordings were conducted using the NIRStar® acquisition software (NIRx Medical Technologies, Berlin, Germany).

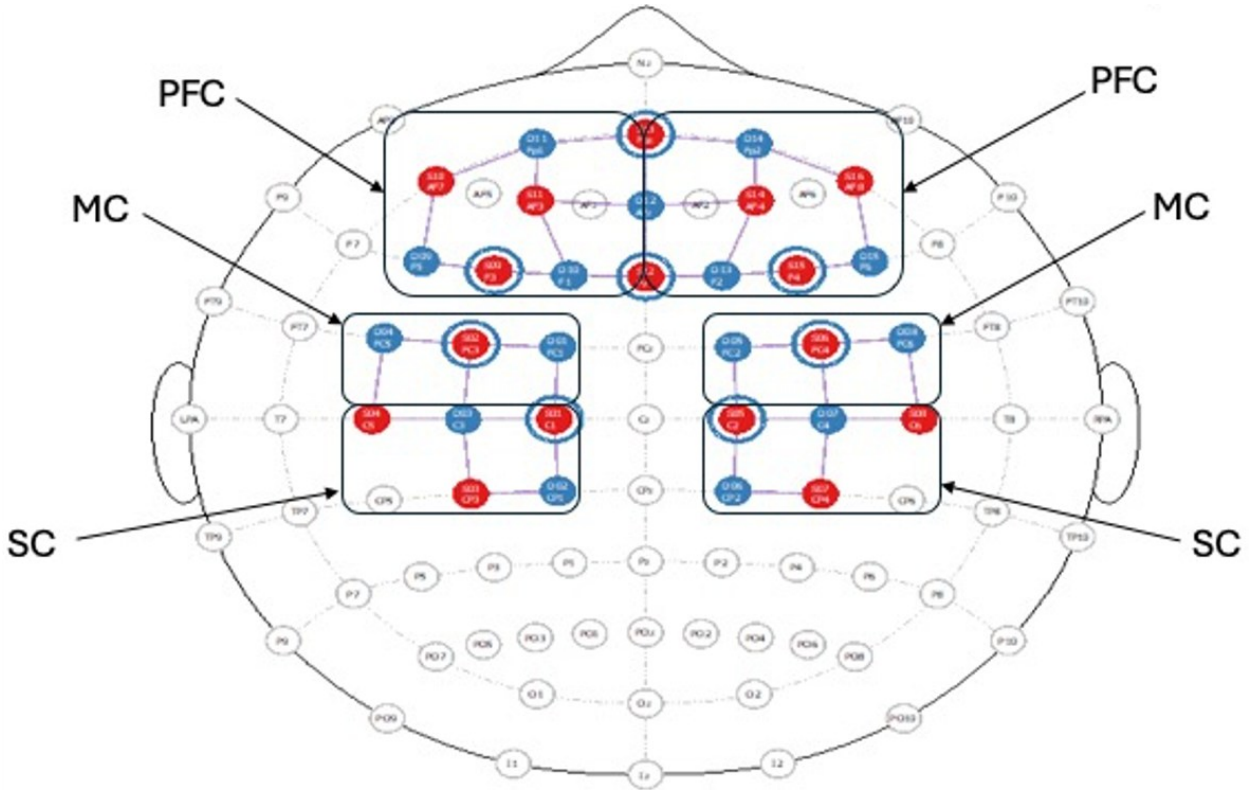

Figure 2-2 Montage Design for the fNIRS Cap This montage covers the regions of interest: the Prefrontal Cortex (PFC), Motor Cortex (MC), and Somatosensory Cortex (SC) of the Ipsilesional and Contralesional hemispheres. Red labels represent sources, and blue labels represent detectors. (Original Illustration by VM)

Participants were asked to sit comfortably in front of a screen approximately 8 feet away. Instructions and examples on completing each task were provided, followed by a practice trial without the fNIRS cap. The cap was fitted to the head, ensuring proper probe placement using the inion as a reference point. All curtains were shut to minimize excessive environmental light, and the lights were turned off. The experiment involved completing one type of motor task, as described below:

Motor Task: The motor task involved unilateral hand-tapping (affected hand) movements at a table with the paretic hand for 10 seconds, with 10 seconds of rest each. (Figure2-3)

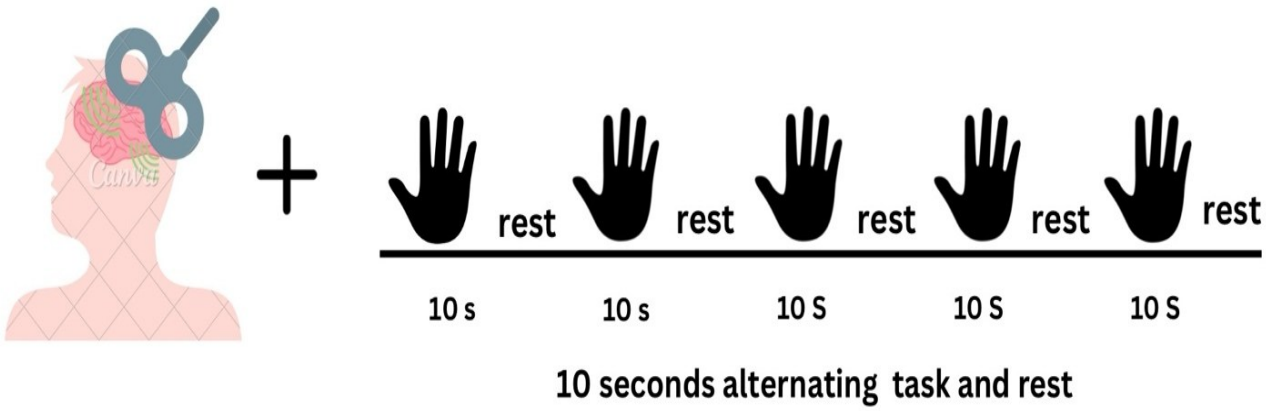

Figure 2-3 Task Sequence Arranged in a Block Design. Participants executed the task for 10 seconds, followed by 10 seconds of rest. (Original Illustration by VM)

The stimulus presentation used a block design, alternating between 10 seconds of rest and 10 seconds of task performance. Instructions for the task appeared on the screen 6 seconds before the task began. Participants were instructed to start the task upon hearing a 'beep' sound and to stop upon hearing a second sound. The task was repeated over 5 consecutive trials, 20s each. A diagram of the task sequence is provided in Figure 2-3. The NIRStim® platform (NIRx Medical Technologies, Berlin, Germany) was used to construct the stimulus presentation.

2.6.4.1 Data Analysis

2.6.4.1.1 Preprocessing

The raw fNIRS data collected during the study were initially converted into CSV format using Python and the `mne` library. This preprocessing step is essential to organize the data in a format suitable for subsequent analysis and statistical evaluation. The raw data was imported using the `mne.io.read_raw_nirx()` function, which allows the handling of continuous-wave fNIRS data. Annotations marking specific conditions, such as motor tasks, were assigned, and unwanted data segments were removed to clean the dataset.

Channels with a source-detector distance greater than 0.01 meters were selected to ensure that only the most relevant channels were included. The data were then converted from raw intensity values to optical density using the Beer-Lambert law through the `mne. preprocessing. nirs.optical_density()` and `mne.preprocessing.nirs.beer_lambert_law()` functions. Once the data had been processed, the scalp coupling index (SCI) was calculated to assess the quality of the fNIRS signals, and poorly coupled channels (SCI < 0.5) were excluded from further analysis. SCI is a widely used measure in fNIRS studies to ensure that only channels with sufficient signal quality are analyzed, helping to reduce noise and improve the reliability of the data (Lee, **2024**). After determining which channels had acceptable SCI values, the data were filtered using a bandpass filter (0.05–0.7 Hz) to isolate the physiological signals of interest while minimizing interference from noise, such as high-frequency artifacts and low-frequency drift (Huo, 2021). The use of filtering in fNIRS preprocessing is a common practice to enhance the signal-to-noise ratio and ensure that the detected signals primarily reflect hemodynamic responses.

Following this, events marking the motor tasks (tapping) were detected using event annotations embedded in the fNIRS recording. Specifically, annotations were set within the mne

framework, where event markers labeled as 'Tap' were assigned to indicate task-related activity. Unwanted annotations (e.g., 'Remove') were filtered out to ensure that only relevant task events were retained. Epochs containing significant artifacts or those not meeting predefined quality criteria were rejected to ensure the integrity of the data. This practice is widely recommended in fNIRS studies to ensure that only high-quality, task-relevant signals are included in the analysis (Jia et al., 2024). The preprocessed data were then converted into a `pandas` Data Frame, and time-locked epochs were labelled based on the experimental conditions. To facilitate further analysis, the fNIRS data were averaged across multiple trials, and the averaged dataset was saved as a CSV file for ease of access and further statistical analysis using Python's versatile data science libraries.

Following the conversion and preprocessing steps, the CSV-formatted data were analyzed to assess cortical hemodynamic responses during motor tasks before and after the interventions. The analysis involved comparing the HbO concentration across different brain regions, including the motor cortex, somatosensory cortex, and prefrontal cortex, using Python's `pandas` and `numpy` libraries. This approach allowed for efficient data manipulation, enabling the calculation of key metrics including the peak of HbO and time-to-peak values.The time-to-peak, representing the moment of maximum oxyhemoglobin concentration, was calculated using the numpy library by identifying the time point corresponding to the peak HbO value within the tapping period. This metric is essential in assessing cortical activation and was extracted for each brain region during the 0 to 10-second tapping task.

The results were visualized using the `matplotlib` library, where the time-series data were plotted to compare pre-and post-intervention responses in the ipsilesional and contralesional hemispheres. To ensure comparability across brain regions, consistent y-axis scaling was applied based on the overall minimum and maximum HbO values observed across all channels and

conditions. This approach ensured that all plots were scaled uniformly, facilitating direct visual comparison of responses across regions. This approach is consistent with previous fNIRS studies, which have employed similar methods to visualize changes in cortical activation related to motor rehabilitation (Lee et al., 2024). For statistical comparisons, paired t-tests were conducted in the group level using the scipy. stats module to evaluate significant changes in HbO concentrations and time-to-peak between the pre- and post-intervention sessions. In summary, the use of Python for both data conversion and analysis provided a robust, replicable approach for processing complex fNIRS data. The combination of data preprocessing, peak detection, statistical analysis, and visualization offered a comprehensive view of cortical activation patterns during the rehabilitation program. This method aligns with those used in recent neuroimaging research, further validating the efficacy of Python for handling large neurophysiological datasets (Gramfort et al., 2014).

2.6.4.1.2 Statistical Analysis

The statistical analysis aimed to evaluate changes in brain activity pre- and post-intervention by focusing on percentage visualizations, exploratory group-level trends, and z-score visualizations. All analyses were conducted separately for the ipsilesional and contralesional hemispheres, as these likely activate differently during the task.

For each participant, changes in brain activity were visualized using the percentage change in peak HbO concentration and time-to-peak for each region of interest (ROI). The ROIs included the prefrontal cortex, motor cortex, and somatosensory cortex in both hemispheres. The percentage change was calculated for each ROI using the formula:

$$\text{Percentage Change} = ((\text{Post} - \text{Pre}) / \text{Pre}) * 100$$

The mean values of peak HbO and time-to-peak were calculated from the five tapping intervals for each ROI. Positive percentage changes indicated increased activation or longer time-to-peak, while negative changes indicated reduced activation or shorter time-to-peak. These percentage changes were visualized using bar plots for each participant to qualitatively assess intervention effects on a case-by-case basis.

For each ROI, the average pre- and post-intervention values for peak HbO and time-to-peak were calculated using data from all valid channels within the ROI. All channels associated with a given ROI (e.g., Motor Cortex Ipsilesional) were included. The descriptive metrics (mean and standard deviation) for each ROI were used to calculate percentage changes and presented in tables.

To identify trends across all participants, an exploratory group-level analysis was conducted. This involved calculating the group-level mean and standard deviation for peak HbO and time-to-peak for each ROI across all participants. Paired t-tests were performed to assess pre- and post-intervention changes for each ROI. The data used for the exploratory group-level analysis consisted of the mean pre- and post-intervention values for each ROI from each participant (e.g., the mean peak HbO value for the Motor Cortex Ipsilesional pre- and post-intervention across all seven participants). To account for multiple comparisons, a Benjamini-Hochberg false discovery rate (FDR) correction was applied, controlling for inflated familywise error while maintaining sensitivity to meaningful effects. Given the small sample size (n=7), this analysis is underpowered, and the results are interpreted with caution as exploratory findings..

To complement the group-level exploratory analysis, z-scores were calculated for peak HbO and time-to-peak to standardize the data across participants. Z-scores were calculated for each ROI using the formula:

$$Z = (Value - Mean) / Standard\ Deviation$$

Here, the "Value" corresponds to the pre- or post-intervention mean for each ROI, while the "Mean" and "Standard Deviation" were calculated across all participants for the given ROI. Z-scores allowed for normalization of the data, making it easier to compare trends across participants while accounting for variability. The distributions of pre- and post-intervention z-scores were visualized using box plots to highlight central tendencies, variability, and potential outliers for each ROI.

Given the small sample size and exploratory nature of the group-level analysis, all statistical results are interpreted with caution. The primary focus of this analysis is to provide insights into trends in brain activity and hemodynamic response changes, rather than definitive conclusions about intervention effects.

2.7 RESULTS

2.7.1 Participants

Fifty-eight patients with chronic stroke (>6 months) were contacted to gauge their willingness to participate. Twenty-seven were excluded based on medical pathologies, spasticity, travel distance, age, or type of stroke. Seven patients could not be reached, and six declined to participate. Of the eighteen patients who agreed to participate, seven met the eligibility criteria for the main intervention study, while eleven did not and were excluded (Table 2.4). The seven participants who proceeded with the intervention (six males and one female; Table 2.3) ranged in age from 53 to 76. All seven completed the 10-day rehabilitation intervention and the assessments immediately following the sessions.

2.7.1.1 Demographics and Baseline Characteristics

These seven participants were chosen based on their ability to complete the necessary assessments, such as the FMA-UE and their capability to grasp the KINARM robot handle, which was essential for the intervention phase. Four had their right hand affected, and three had their left hand affected. The remaining participants were excluded due to severe impairments or spasticity that prevented them from engaging fully with the study protocol. The selected participants are listed in Table 2.3, ordered by FMA-UE scores from most to least impaired.

The intervention group (n=7) averaged 63.6 years of age (9.62), with six males and one female, all with over six months of stroke duration (Table 2.6). Four of the participants had a stroke affecting the left middle cerebral artery, resulting in right-hand impairment, while three of them had a stroke affecting the right middle cerebral artery, resulting in left-hand impairment (Table 2.4). Four participants attended all aerobic priming + skilled motor learning sessions, while three missed only 1-2 sessions (Table 2.4). The average FMA-UE score was 41.4(9.14). The average WMFT score was 24.57 (16.88). None of the participants required additional assistance from the physical therapist during upper-limb motor assessments. The FM-UE includes a scale from 0 to 66, with higher scores indicating better motor function. According to Duncan, Goldstein, Horner, Landsman, Samsa, & Matchar (1994), scores can be categorized into levels of severity as follows:

- Severe impairment: 0–35
- Moderately severe impairment: 36–55
- Moderate impairment: 56–66

These categories help differentiate the levels of motor impairment after stroke, with lower scores representing more significant motor deficits (Duncan et al., 1994).

The WMFT comprises 17 tasks to measure upper extremity movement and functional ability. The tasks are timed, and performance is rated on a 6-point Functional Ability Scale, with higher scores indicating better motor function (Morris et al., 2001).WMFT performance can be interpreted as follows:

Severe Impairment: Functional Ability Scale scores: 0–2. Task completion time: Over 120 seconds on average across tasks (or failure to complete most tasks). Participants require assistance or cannot complete most tasks independently, demonstrating significant motor deficits.

Moderate Impairment: Functional Ability Scale scores: 3–4. Task completion time: Between 60–120 seconds on average across tasks. Participants can complete tasks with noticeable slowness or difficulty but can finish most tasks independently.

Mild Impairment: Functional Ability Scale scores: 4–5. Task completion time: Less than 60 seconds on average across tasks. Participants complete tasks with only minor deficits in speed or precision, showing near-normal motor function.

Table 2-2 Participant Demographics

Participant	Age	Sex	Stroke side/Type	Affected hand	Time Post Stroke (day)	WMFT Score	FMA-UE Score
1	53	M	LMCA	Right	978	37	23
2	55	M	LMCA	Right	1002	19	39
3	76	M	RMCA	Left	381	14	39
4	68	M	LMCA	Right	471	15	45
5	69	F	RMCA	Left	479	14	46
6	71	M	RMCA	Left	211	15	48
7	53	M	LMCA	Right	564	58	50

Participants are in order of upper limb severity, from most severely involved to less severely involved. Abbreviations: M, Male; F, Female; FMA-UE, The Fugl-Meyer Upper Extremity; WMFT; Wolf Motor Function Test.

Table 2-3 The Attendance Rates of Participants with Chronic Stroke in the Intervention

Participant(s)	Total number of visits attended	Total number of missed appointments	Stroke Stage	Discontinued intervention (Yes/No)
1	12	2	Chronic	NO
2	14	0	Chronic	NO
3	13	1	Chronic	NO
4	14	0	Chronic	NO
5	14	0	Chronic	NO
6	14	0	Chronic	NO
7	12	2	Chronic	NO

This table displays the attendance rates of participants with chronic stroke who participated in the study. It summarizes the participant's compliance with the intervention or assessment sessions during the study.

2.7.2 Participant Analysis

2.7.2.1 Participant One (FMA-UE score=23 [severe impairment] Right arm)

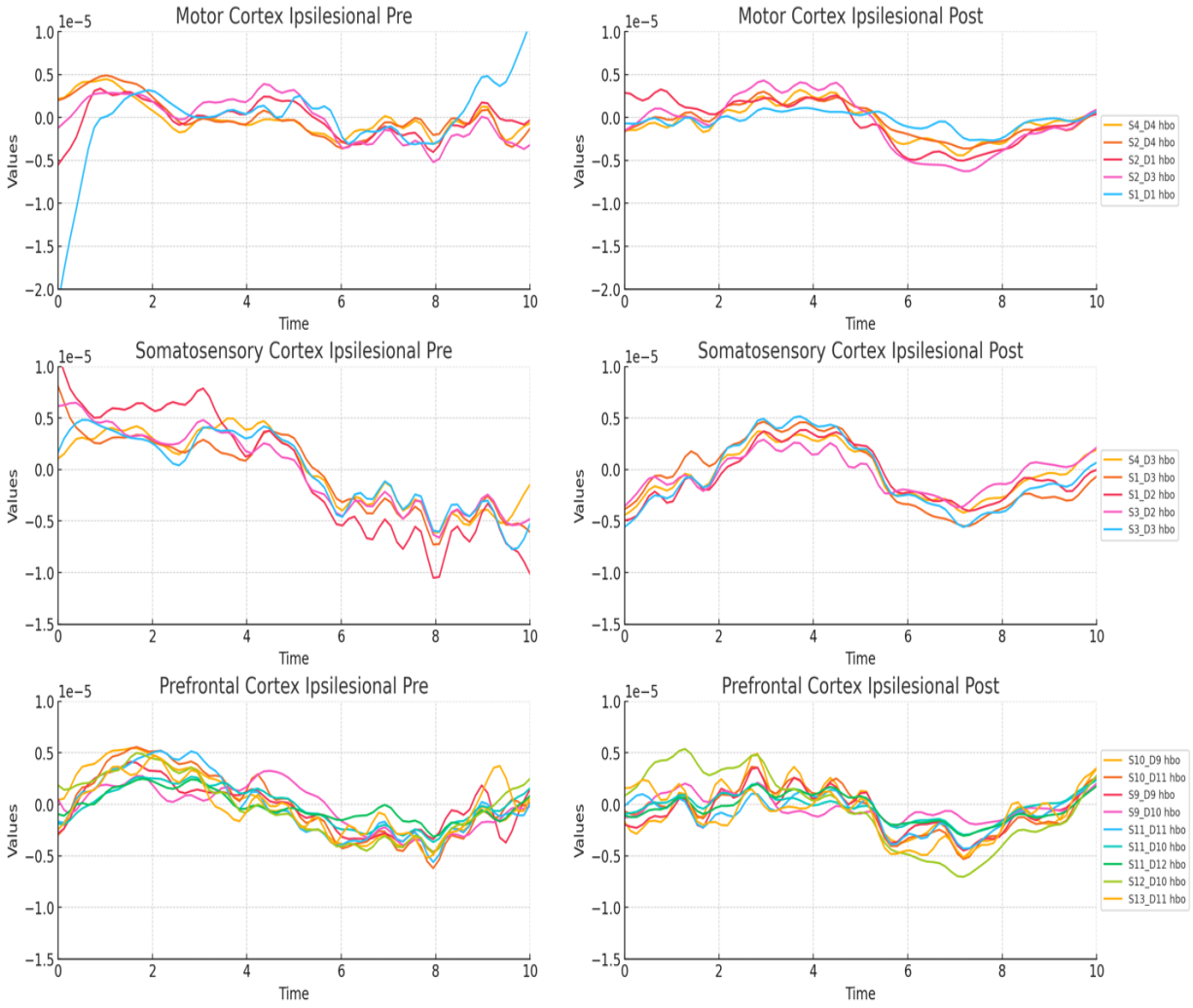

Figure 2-4 Participant One Oxyhemoglobin (HbO) levels for Ipsilesional Hemisphere. The above plots show the mean HbO levels over a 10-second period, averaged across five tapping trials, for three regions of interest in the ipsilesional hemisphere: the motor cortex, somatosensory cortex, and prefrontal cortex. Each line represents a source-detector pair (S#-D#, where S refers to the source and D refers to the detector) that corresponds to specific cortical regions within these areas. The graphs compare HbO levels before (pre) and after (post) the intervention.

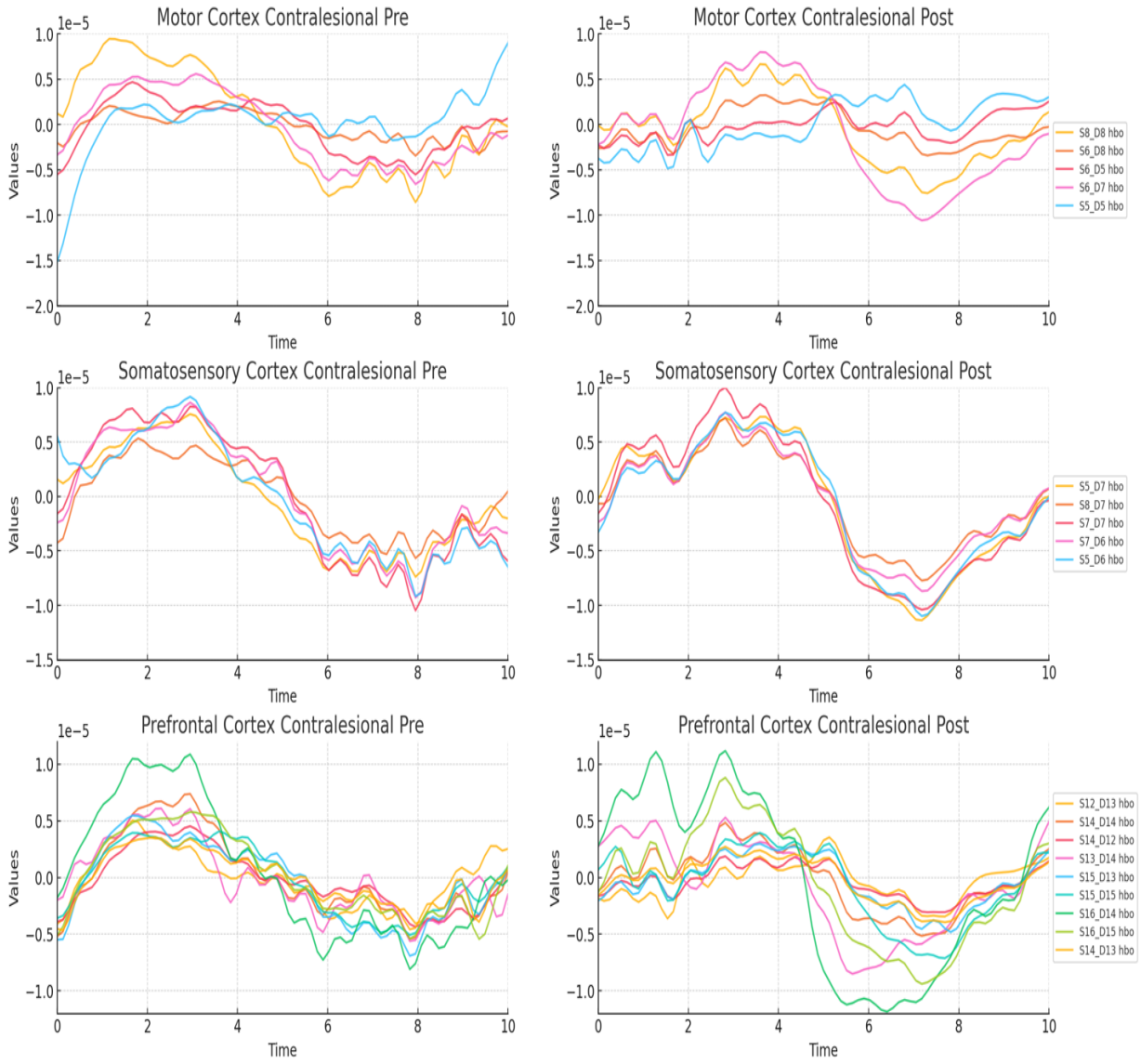

Figure 2-5 Participant One Oxyhemoglobin (HbO) levels for Contralesional Hemisphere. The above plots show the mean HbO levels over a 10-second period, averaged across five tapping trials, for three regions of interest in the contralesional hemisphere: the motor cortex, somatosensory cortex, and prefrontal cortex. Each line represents a source-detector pair (S#-D#, where S refers to the source and D refers to the detector) that corresponds to specific cortical regions within these areas. The graphs compare HbO levels before (pre) and after (post) the intervention.

Table 2-4 Participant One Peak Oxyhemoglobin (HbO) and Time-to-Peak

Effects by ROI	Peak HbO (Pre) (e-06)	Peak HbO (Post) (e-06)	Time-to-Peak (Pre) (s)	Time-to-Peak (Post) (s)
PFC Ipsilesional	**3.91**	**2.74**	**1.67**	**2.82**
PFC Contralesional	**5.38**	**4.61**	**1.79**	**2.63**
MC Ipsilesional	**3.06**	**2.62**	**1.03**	**2.95**
MC Contralesional	**4.37**	**3.42**	**1.67**	**3.59**
SC Ipsilesional	**5.67**	**3.97**	**0.13**	**2.92**
SC Contralesional	**7.63**	**7.98**	**0.13**	**2.73**

This table presents the pre-and post-intervention peak HbO concentration (in e-06) and time-to-peak (in seconds) for three regions of interest (ROI): the prefrontal cortex (PFC), the motor cortex (MC), and somatosensory cortex (SC). Data is provided for both the ipsilesional hemisphere and the contralesional hemisphere.

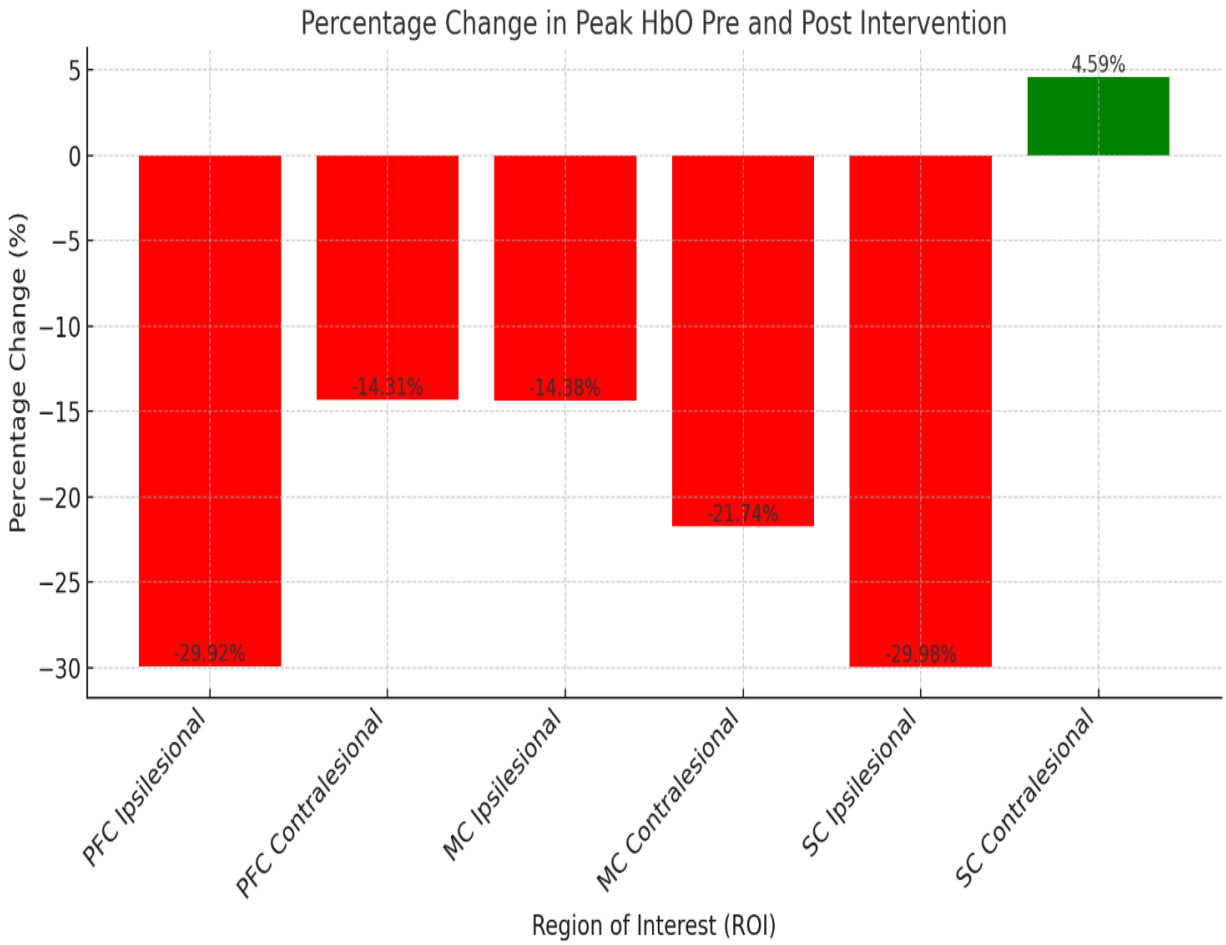

Figure 2-6 Participant One Percentage Change in Peak Oxyhemoglobin (HbO). The bar chart depicts the percentage change in the peak of HbO across several regions of interest (ROIs) between the pre-and post-intervention. The regions evaluated include the prefrontal cortex (PFC), motor cortex (MC), and somatosensory cortex (SC) for both the ipsilesional and contralesional hemispheres.

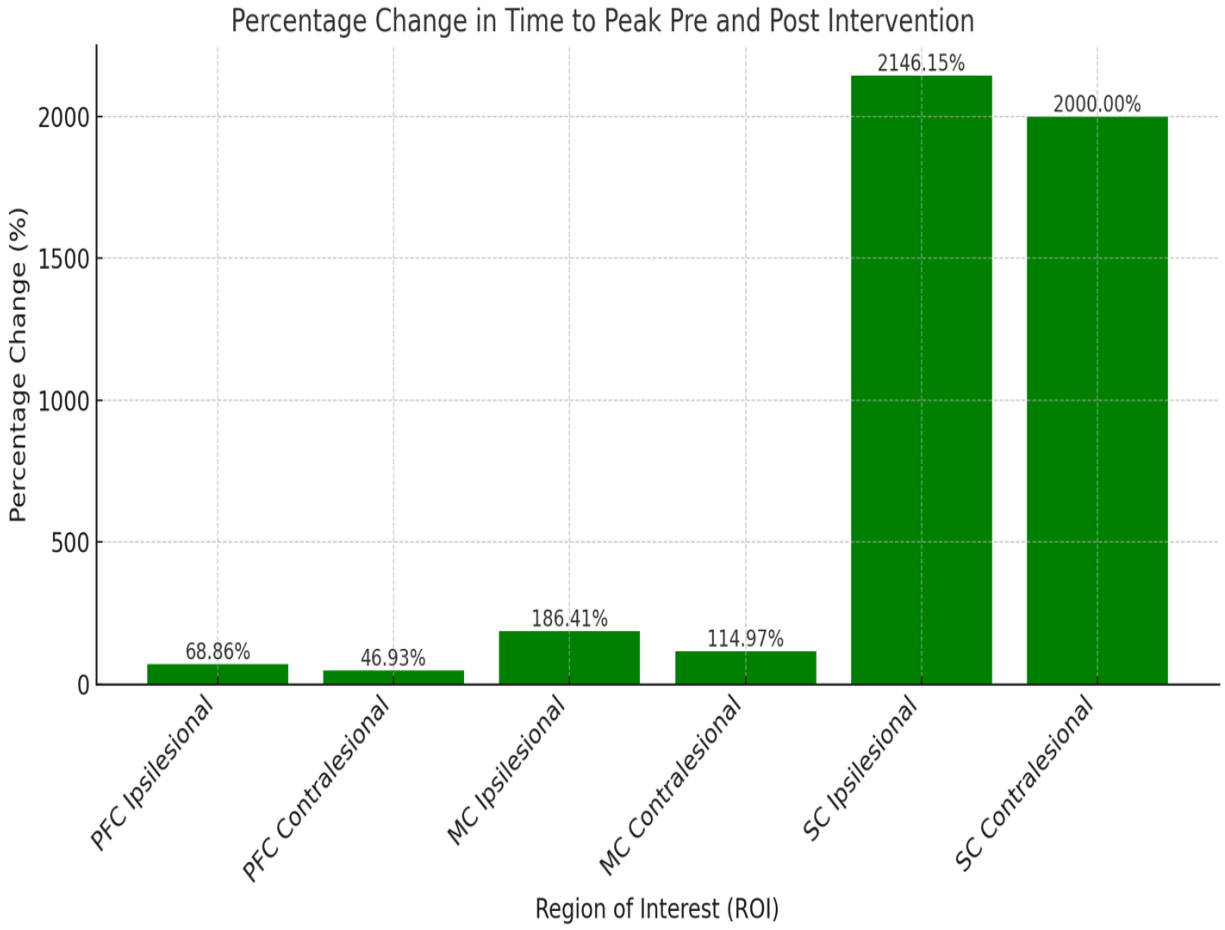

Figure 2-7 Participant One Percentage Change in Time-to-Peak. The bar chart depicts the percentage change in time-to-peak across several regions of interest (ROIs) between the pre-and post-intervention. The regions evaluated include the prefrontal cortex (PFC), motor cortex (MC), and somatosensory cortex (SC) for both the ipsilesional and contralesional hemispheres.

Participant One presented with a Left-Sided Middle Cerebral Artery (LMCA) stroke, with an FMA-UE score of 23, indicating extremely severe motor impairment. The analysis revealed a general trend of decreased peak HbO across most ROIs. The largest reductions were observed in the ipsilesional prefrontal cortex (-29.03%) and ipsilesional somatosensory cortex (-30.56%). These reductions may reflect challenges in cortical oxygenation post-intervention, potentially associated with the participant's severe motor impairment. In contrast, a slight increase was observed in the contralesional somatosensory cortex (+4.59%), which may suggest some compensatory activation in the contralesional hemisphere.

The time-to-peak analysis showed substantial delays in most ROIs. The ipsilesional somatosensory cortex exhibited a large increase (+2146.15%), and the contralesional somatosensory cortex showed a similar increase (+2000.00%). These delays may suggest inefficiencies in neural processing within somatosensory regions, which are critical for integrating sensory feedback for motor control. Similarly, the motor cortex regions demonstrated increased time-to-peak, with the ipsilesional motor cortex showing an increase of +186.41%, potentially reflecting slower activation in response to motor tasks post-intervention.

These trends suggest that the intervention may not have enhanced neural activation in this participant, as indicated by the decreased peak HbO in most ROIs. The observed delays in time-to-peak could reflect challenges in neural processing and execution of motor tasks, potentially linked to the participant's extensive neural damage and severe motor dysfunction. However, given the exploratory nature of this analysis and the underpowered sample size, these findings should be interpreted with caution and require further investigation in larger cohorts.

2.7.2.2 Participant Two (FMA-UE score=39 [moderately severe impairment] Right arm)

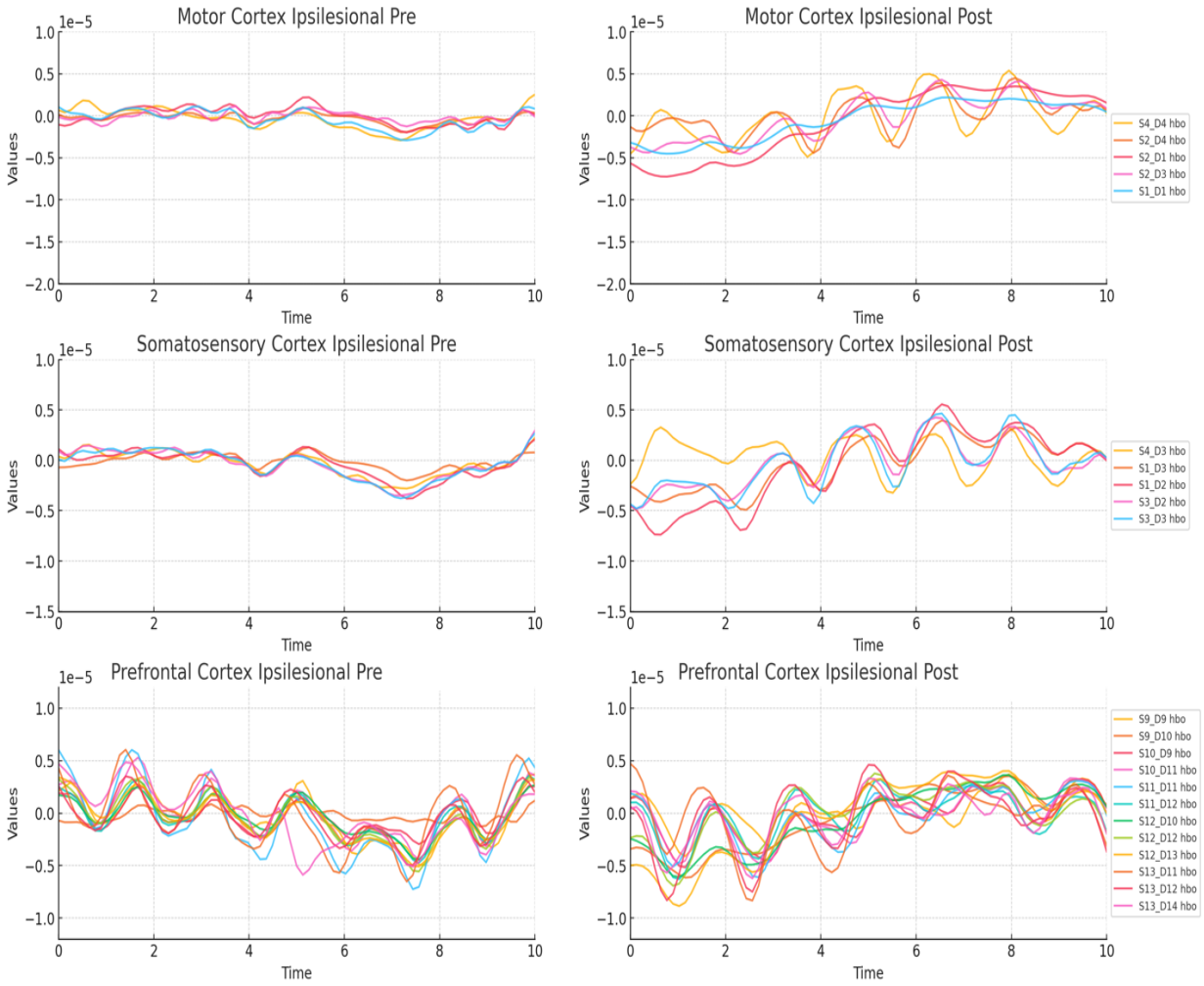

Figure 2-8 Participant Two Oxyhemoglobin (HbO) levels for Ipsilesional Hemisphere. The above plots show the mean HbO levels over a 10-second period, averaged across five tapping trials, for three regions of interest in the ipsilesional hemisphere: the motor cortex, somatosensory cortex, and prefrontal cortex. Each line represents a source-detector pair (S#-D#, where S refers to the source and D refers to the detector). The graphs compare HbO levels before (pre) and after (post) the intervention.

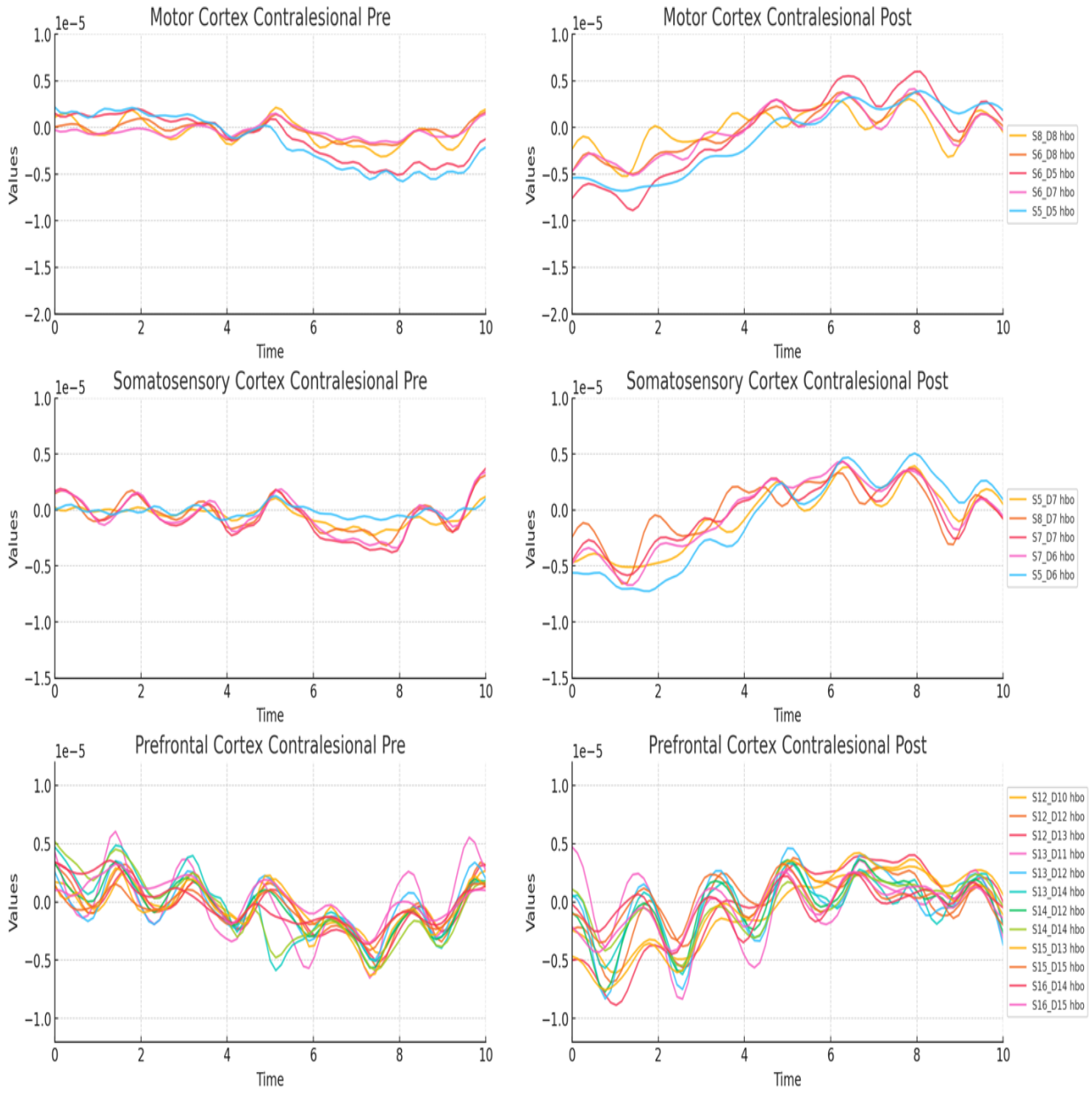

Figure 2-9 Participant Two Oxyhemoglobin (HbO) levels for Contralesional Hemisphere. The above plots show the mean HbO levels over a 10-second period, averaged across five tapping trials, for three regions of interest in the contralesional hemisphere: the motor cortex, somatosensory cortex, and prefrontal cortex. Each line represents a source-detector pair (S#-D#, where S refers to the source and D refers to the detector). The graphs compare HbO levels before (pre) and after (post) the intervention

Table 2-5 Participant Two Peak Oxyhemoglobin (HbO) and Time-to-Peak

Effects by ROI	Peak HbO (Pre) (e-06)	Peak HbO (Post) (e-06)	Time-to-Peak (Pre) (s)	Time-to-Peak (Post) (s)
PFC Ipsilesional	**3.28**	**2.65**	**1.67**	**7.82**
PFC Contralesional	**3.21**	**3.05**	**1.41**	**6.67**
MC Ipsilesional	**1.08**	**3.76**	**5.13**	**8.08**
MC Contralesional	**1.30**	**4.09**	**1.79**	**7.95**
SC Ipsilesional	**2.15**	**4.11**	**9.87**	**6.54**
SC Contralesional	**2.48**	**4.07**	**9.87**	**6.28**

This table presents the pre-and post-intervention peak HbO concentration (in e-06) and time-to-peak (in seconds) for three regions of interest (ROI) based on pre-and post-intervention.: the prefrontal cortex (PFC), the motor cortex (MC), and somatosensory cortex (SC). Data is provided for both the ipsilesional hemisphere and the contralesional hemisphere.

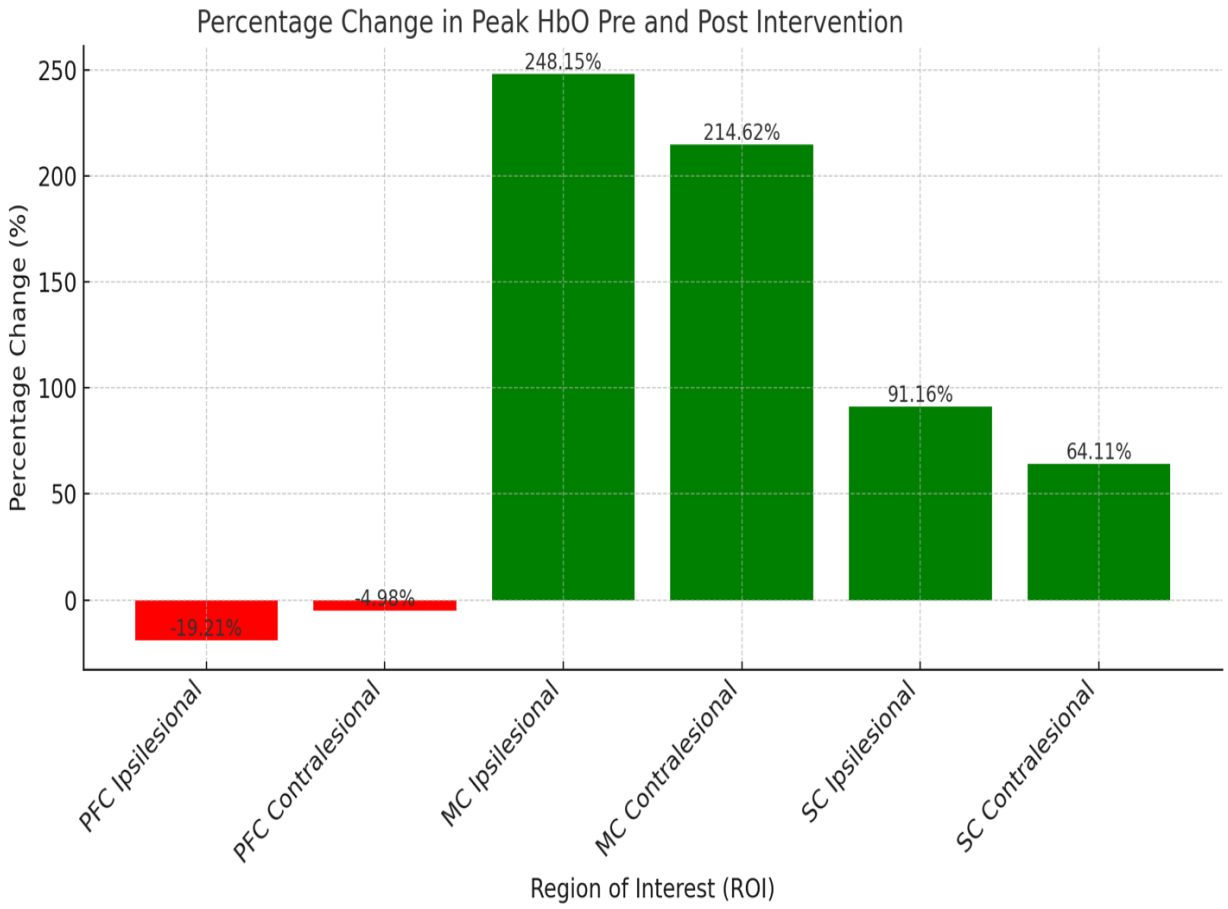

Figure 2-10 Participant Two Percentage Change in Peak Oxyhemoglobin (HbO). The bar chart depicts the percentage change in the peak of HbO across several regions of interest (ROIs) between the pre-and post-intervention. The regions evaluated include the prefrontal cortex (PFC), motor cortex (MC), and somatosensory cortex (SC) for both the ipsilesional and contralesional hemispheres.

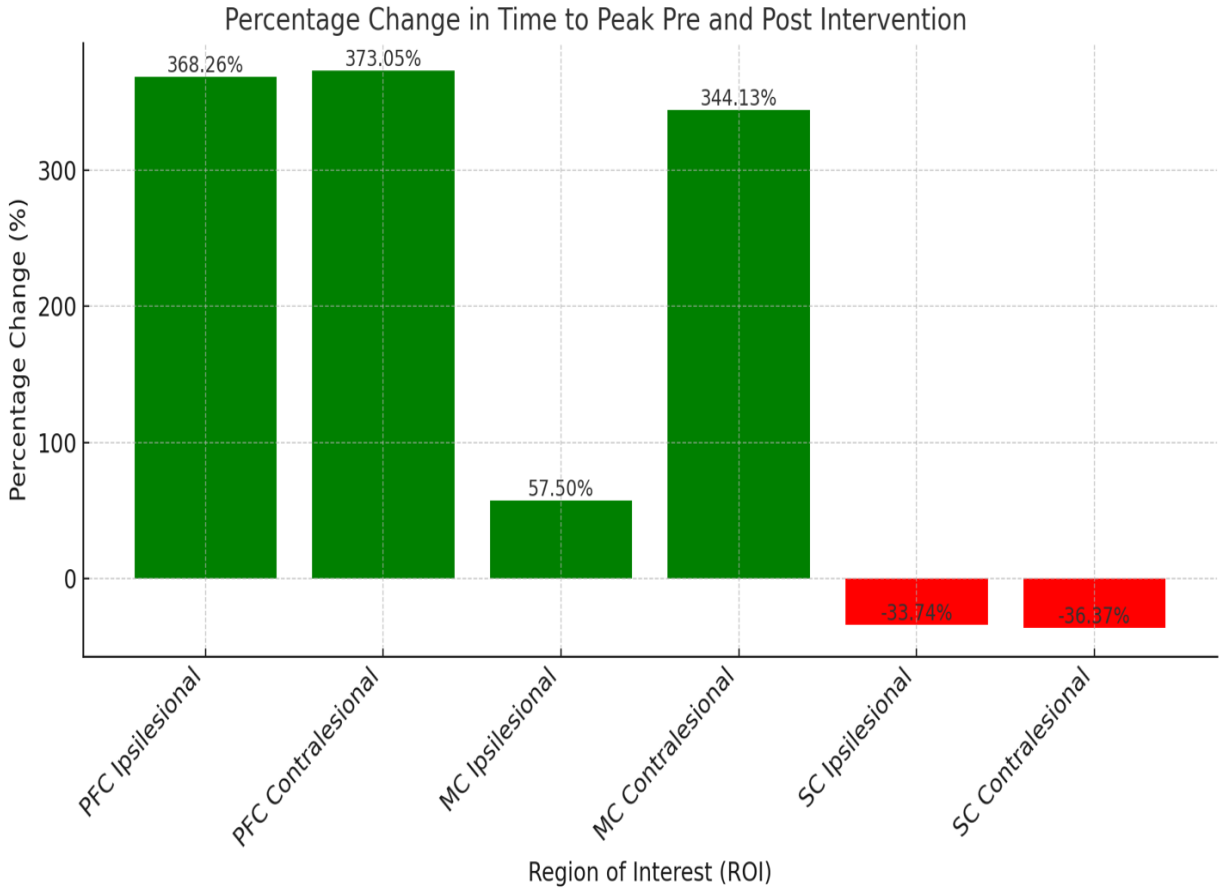

Figure 2-11 Participant Two Percentage Change in Time-to-Peak. The bar chart depicts the percentage change in time-to-peak across several regions of interest (ROIs) between the pre-and post-intervention. The regions evaluated include the prefrontal cortex (PFC), motor cortex (MC), and somatosensory cortex (SC) for both the ipsilesional and contralesional hemispheres.

This participant presented with a Left-Sided Middle Cerebral Artery (LMCA) stroke and an FMA-UE score of 39, indicating moderately severe impairment. The analysis showed increases in both peak HbO and time-to-peak across most ROIs. These trends may reflect enhanced neural activity in motor and sensory regions, particularly in the ipsilesional motor cortex, which could be associated with improved motor function.

In contrast, decreases in prefrontal activity and increases in time-to-peak suggest possible shifts in neural processing dynamics. The observed patterns may indicate a compensatory reorganization, where the participant's brain potentially relied more on motor and sensory regions for task performance while exhibiting reduced activation in cognitive control areas such as the prefrontal cortex. The delayed time-to-peak across regions may reflect inefficiencies in neural processing, consistent with the participant's moderately severe impairment.

Overall, the participant's mixed patterns of activation and timing highlight the complexity of neural reorganization in response to the intervention.

2.7.2.3 Participant Three (FMA-UE score=39 [moderately severe impairment] Left arm)

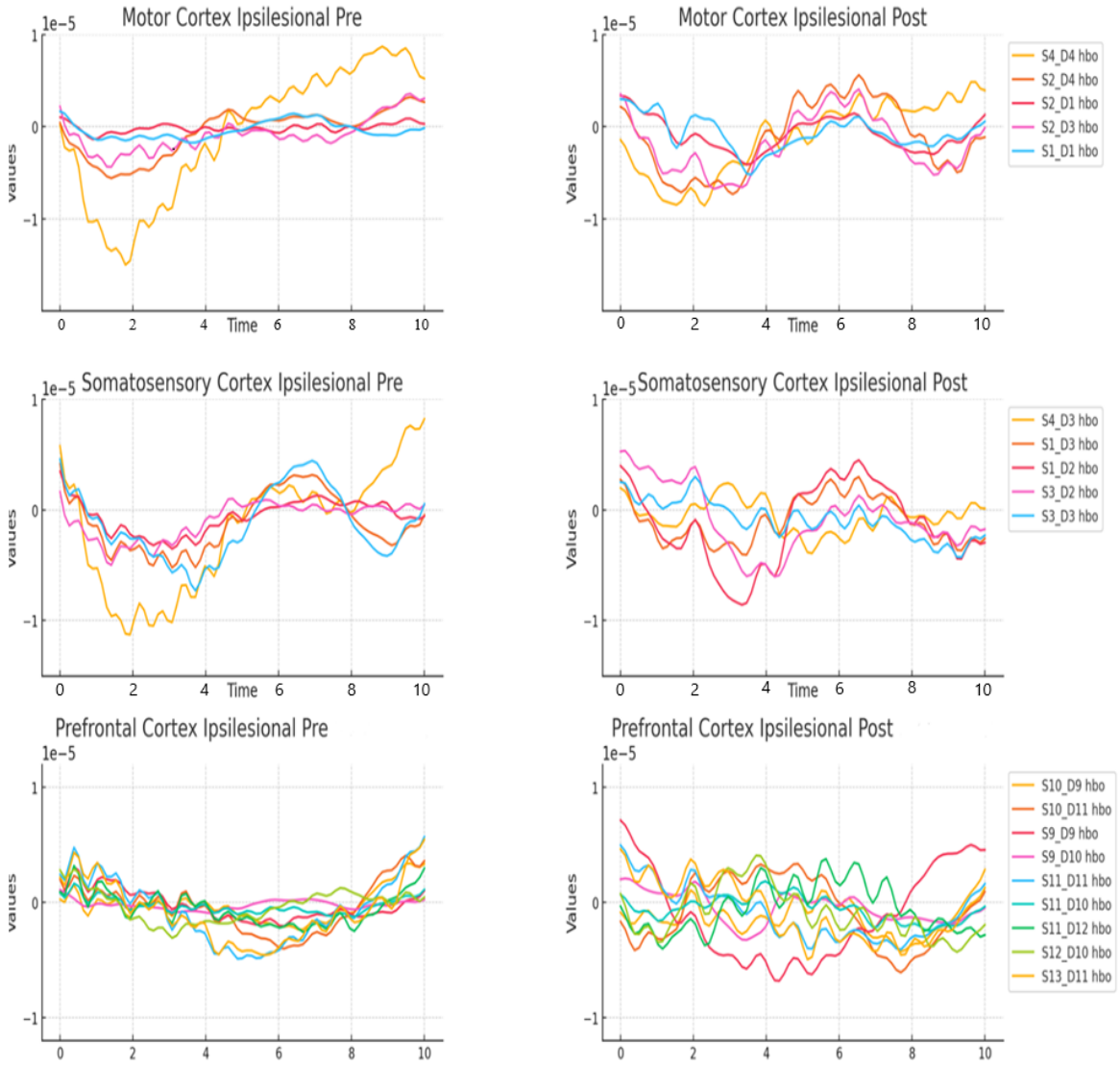

Figure 2-12 Participant Three Oxyhemoglobin (HbO) levels for Ipsilesional Hemisphere. The above plots show the mean HbO levels over a 10-second period, averaged across five tapping trials, for three regions of interest in the ipsilesional hemisphere: the motor cortex, somatosensory cortex, and prefrontal cortex. Each line represents a source-detector pair (S#-D#, where S refers to the source and D refers to the detector) that corresponds to specific cortical regions within these areas. The graphs compare HbO levels before (pre) and after (post) the intervention.

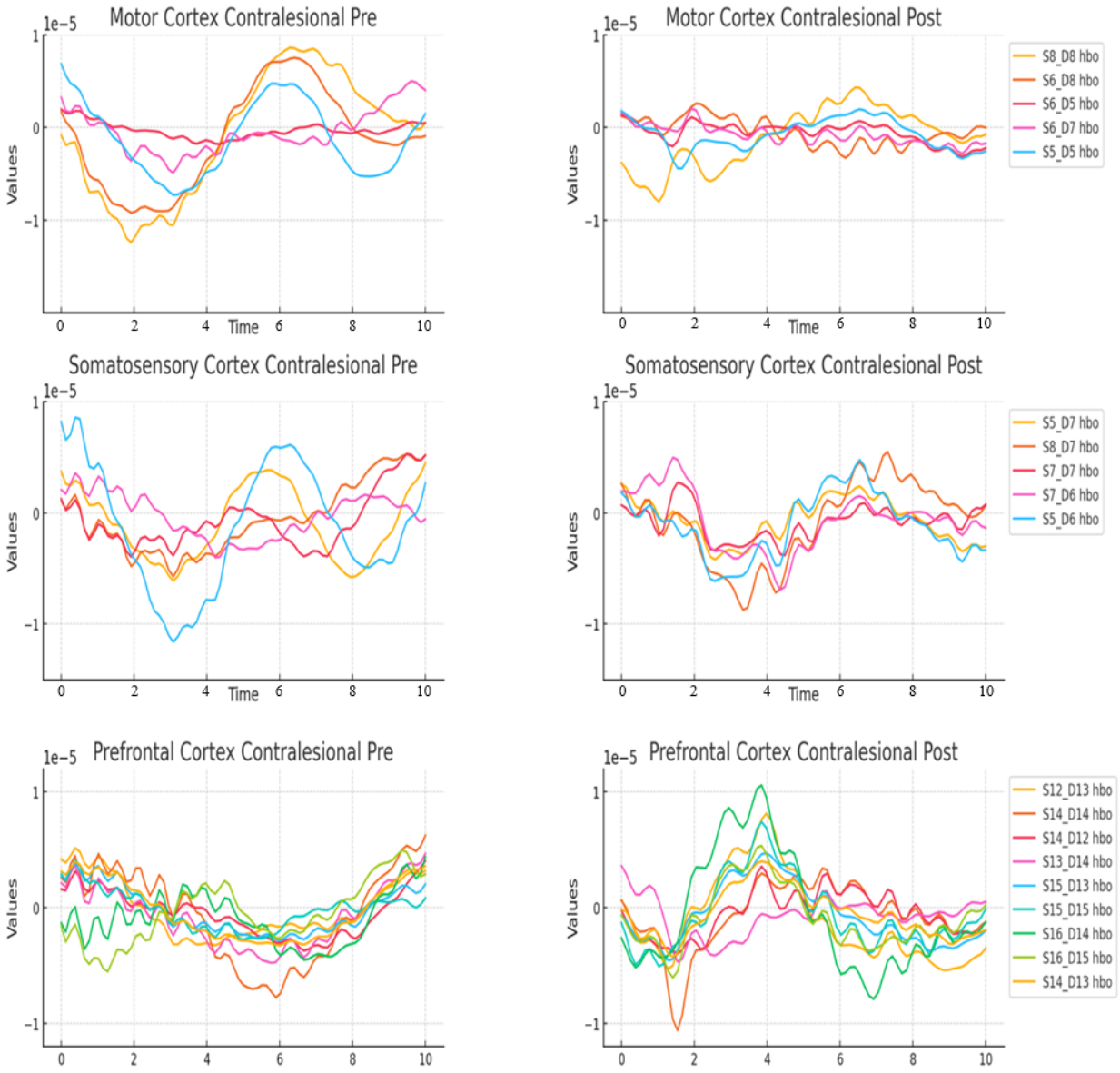

Figure 2-13 Participant Three Oxyhemoglobin (HbO) levels for Contralesional Hemisphere. The above plots show the mean HbO levels over a 10-second period, averaged across five tapping trials, for three regions of interest in the contralesional hemisphere: the motor cortex, somatosensory cortex, and prefrontal cortex. Each line represents a source-detector pair (S#-D#, where S refers to the source and D refers to the detector) that corresponds to specific cortical regions within these areas. The graphs compare HbO levels before (pre) and after (post) the intervention.

Table 2-6 Participant Three Peak Oxyhemoglobin (HbO) and Time-to-Peak

Effects by ROI	Peak HbO (Pre) (e-06)	Peak HbO (Post) (e-06)	Time-to-Peak (Pre) (s)	Time-to-Peak (Post) (s)
PFC Ipsilesional	**2.65**	**5.18**	**9.78**	**3.85**
PFC Contralesional	**2.85**	**2.07**	**9.78**	**0.15**
MC Ipsilesional	**3.77**	**1.18**	**6.41**	**6.54**
MC Contralesional	**3.08**	**3.10**	**9.49**	**6.54**
SC Ipsilesional	**3.57**	**2.79**	**0.38**	**6.51**
SC Contralesional	**7.37**	**2.30**	**0.27**	**0.27**

This table presents the pre-and post-intervention peak HbO concentration (in e-06) and time-to-peak (in seconds) for three regions of interest (ROI) based on pre-and post-intervention.: the prefrontal cortex (PFC), the motor cortex (MC), and somatosensory cortex (SC). Data is provided for both the ipsilesional hemisphere and contralesional hemisphere.

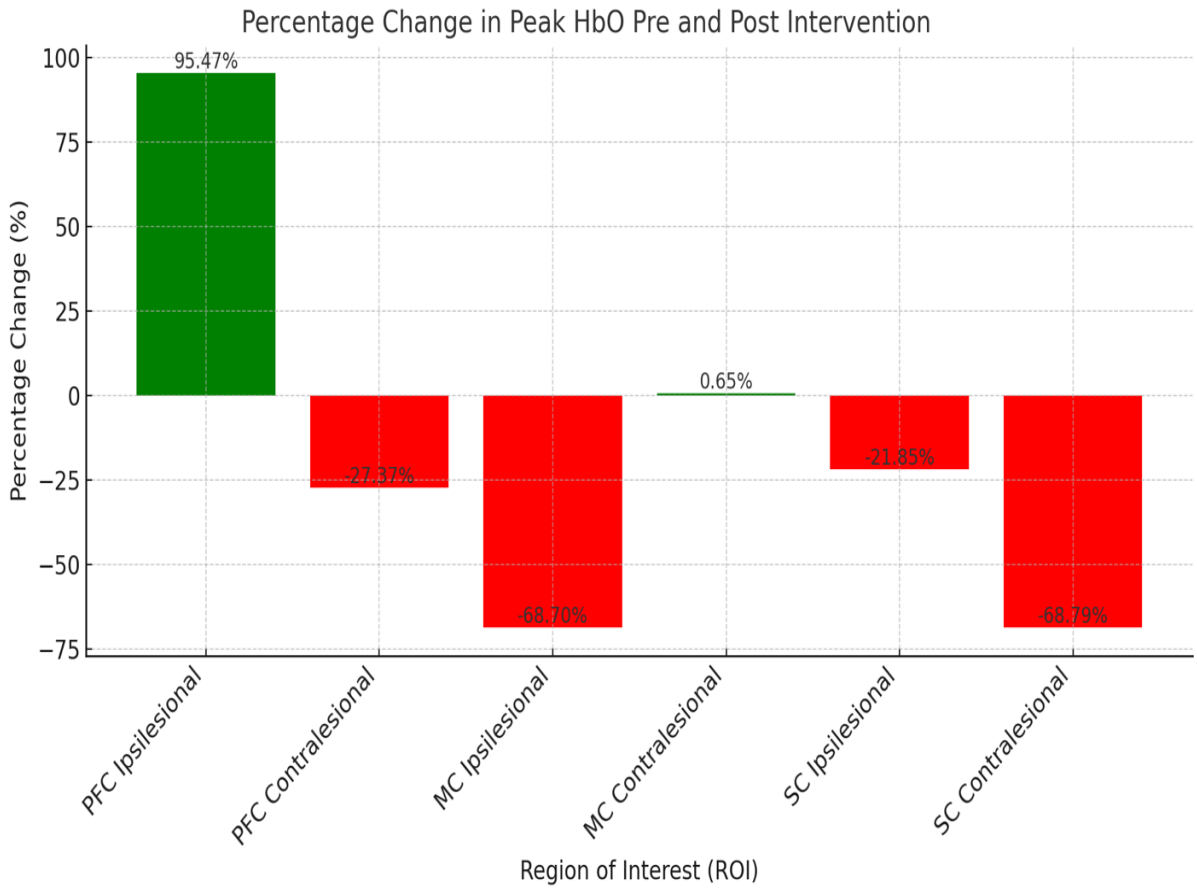

Figure 2-14 Participant Three Percentage Change in Peak Oxyhemoglobin (HbO). The bar chart depicts the percentage change in peak HbO across several regions of interest (ROIs) between the pre-and post-intervention. The regions evaluated include the prefrontal cortex (PFC), motor cortex (MC), and somatosensory cortex (SC) for both the ipsilesional and contralesional hemispheres.

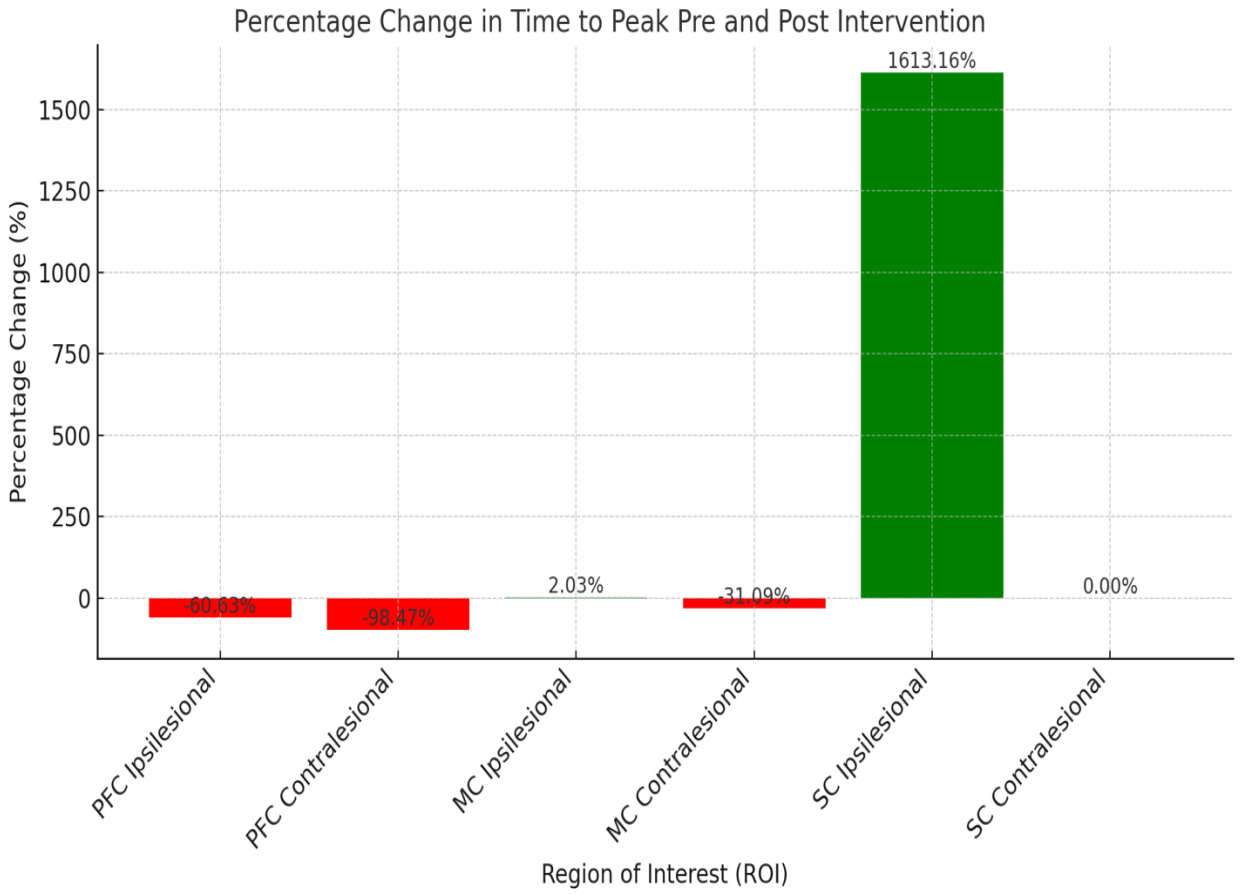

Figure 2-15 Participant Three Percentage Change in Time-to-Peak. The bar chart depicts the percentage change in time-to-peak across several regions of interest (ROIs) between the pre-and post-intervention. The regions evaluated include the prefrontal cortex (PFC), motor cortex (MC), and somatosensory cortex (SC) for both the ipsilesional and contralesional hemispheres.

This participant presented with a Right-Sided Middle Cerebral Artery (RMCA) stroke, with an FMA-UE score of 39, indicating moderately severe impairment. The analysis revealed noticeable regional differences between peak HbO and time-to-peak. The intervention appeared to enhance neural activity in the ipsilesional prefrontal cortex, with a +95.47% rise in peak HbO, while leading to delayed neural activation in the ipsilesional somatosensory cortex, with a +1613.16% increase in time-to-peak.

The increased efficiency in the prefrontal regions contrasts with the delayed response in sensory areas, potentially reflecting compensatory mechanisms or differing effects of the intervention on motor versus cognitive regions. These patterns may align with the participant's moderately severe impairment, suggesting significant but region-specific neural reorganization following the intervention.

2.7.2.4 Participant Four (Fugl-Meyer score= 45 [moderately severe impairment] Right arm)

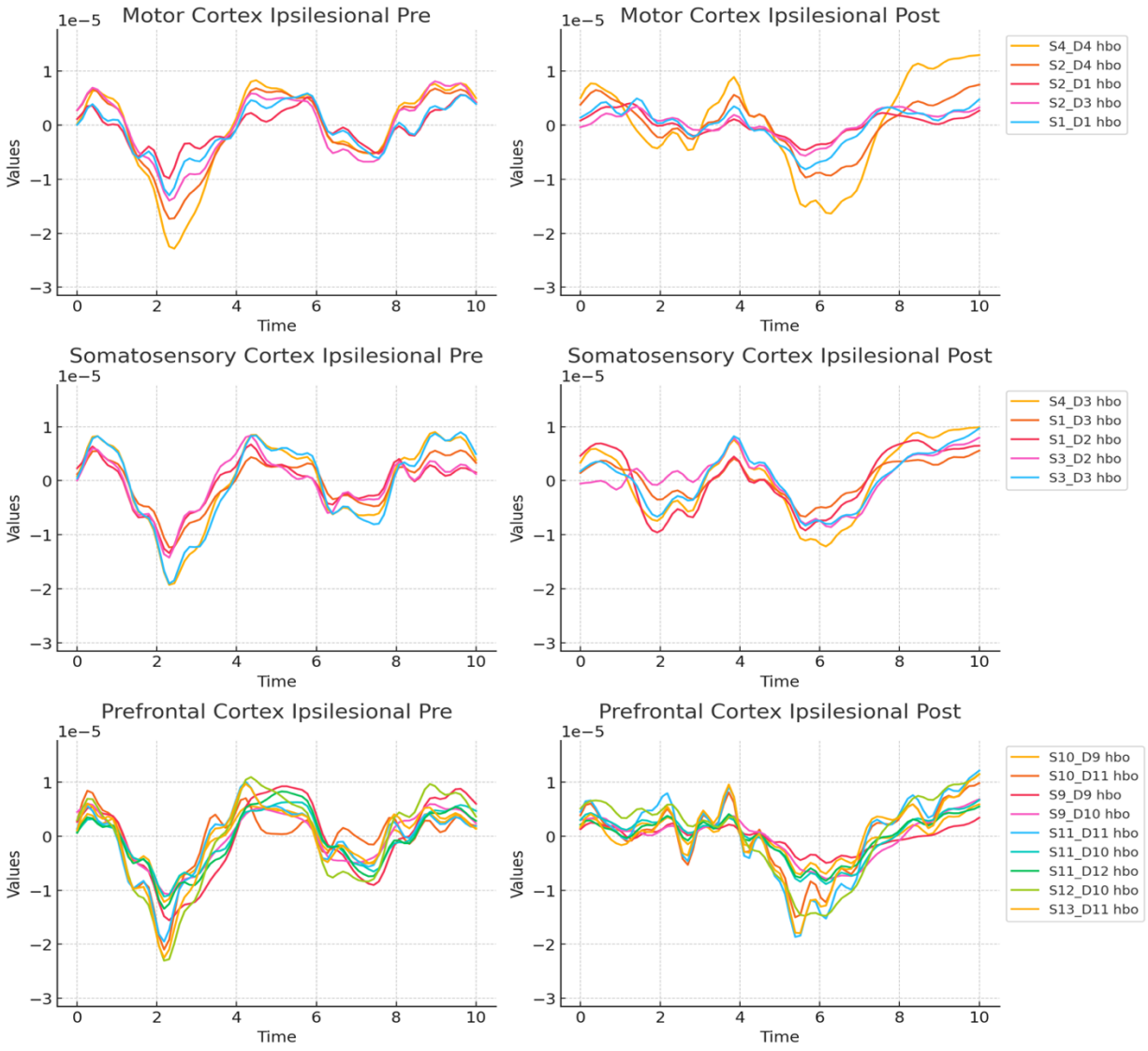

Figure 2-16 Participant Four Oxyhemoglobin (HbO) levels for Ipsilesional Hemisphere. The above plots show the mean HbO levels over a 10-second period, averaged across five tapping trials, for three regions of interest in the ipsilesional hemisphere: the motor cortex, somatosensory cortex, and prefrontal cortex. Each line represents a source-detector pair (S#-D#, where S refers to the source and D refers to the detector) that corresponds to specific cortical regions within these areas. The graphs compare HbO levels before (pre) and after (post) the intervention.

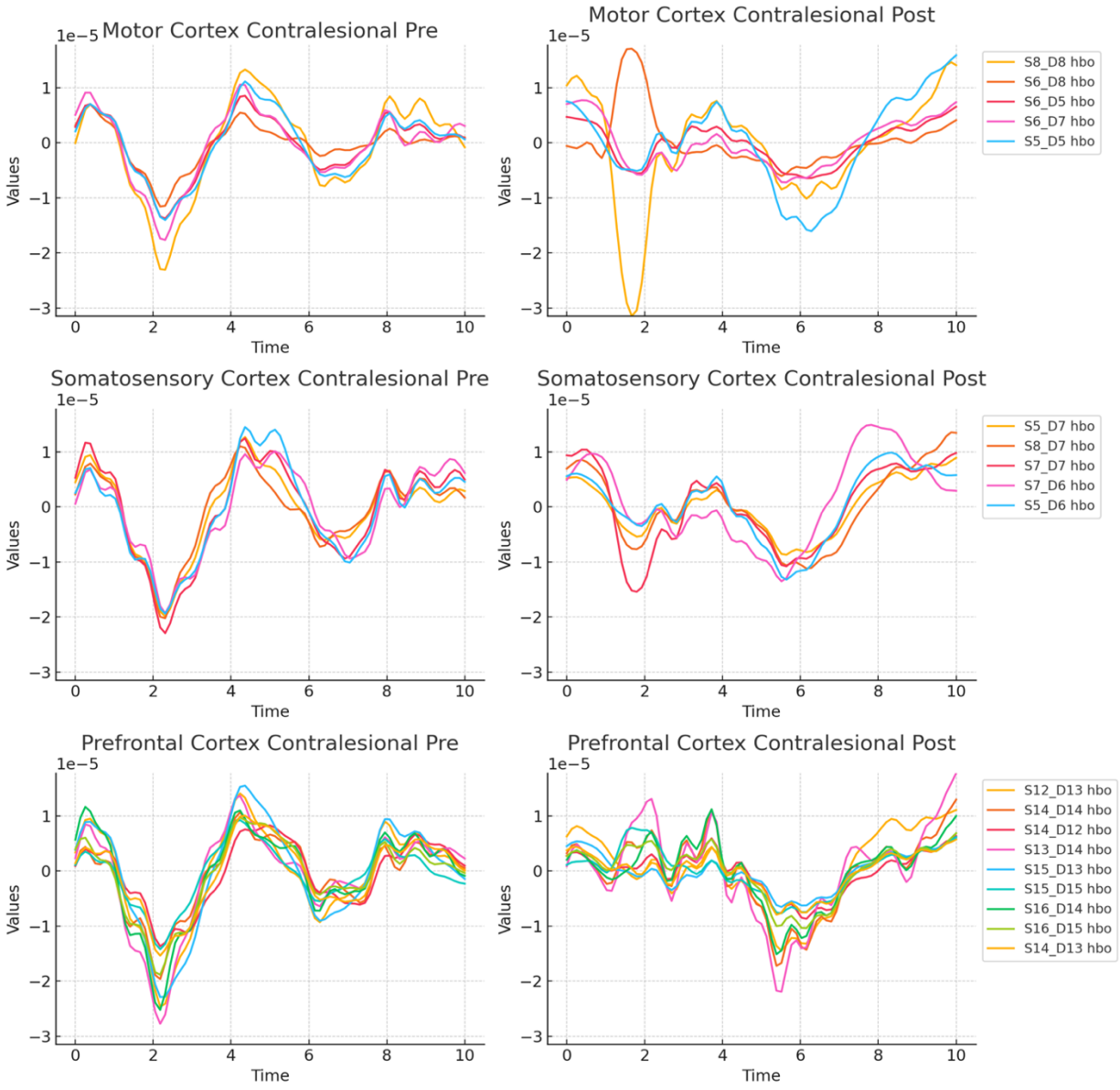

Figure 2-17 Participant Four Oxyhemoglobin (HbO) levels for Contralesional Hemisphere. The above plots show the mean HbO levels over a 10-second period, averaged across five tapping trials, for three regions of interest in the contralesional hemisphere: the motor cortex, somatosensory cortex, and prefrontal cortex. Each line represents a source-detector pair (S#-D#, where S refers to the source and D refers to the detector) that corresponds to specific cortical regions within these areas. The graphs compare HbO levels before (pre) and after (post) the intervention.

Table 2-7 Participant Four Peak Oxyhemoglobin (HbO) and Time-to-Peak

Effects by ROI	Peak HbO (Pre) (e-06)	Peak HbO (Post) (e-06)	Time-to-Peak (Pre) (s)	Time-to-Peak (Post) (s)
PFC Ipsilesional	**7.26**	**7.70**	**4.23**	**9.86**
PFC Contralesional	**1.12**	**8.33**	**4.23**	**9.86**
MC Ipsilesional	**6.66**	**5.13**	**9.62**	**9.65**
MC Contralesional	**8.68**	**7.59**	**4.54**	**9.65**
SC Ipsilesional	**7.23**	**7.21**	**4.36**	**9.76**
SC Contralesional	**1.20**	**8.88**	**4.36**	**8.46**

This table presents the pre-and post-intervention peak HbO values (in e-06) and time-to-peak (in seconds) for three regions of interest (ROI) based on pre-and post-intervention.: the prefrontal cortex (PFC), the motor cortex (MC), and somatosensory cortex (SC). Data is provided for both the ipsilesional hemisphere and contralesional hemisphere.

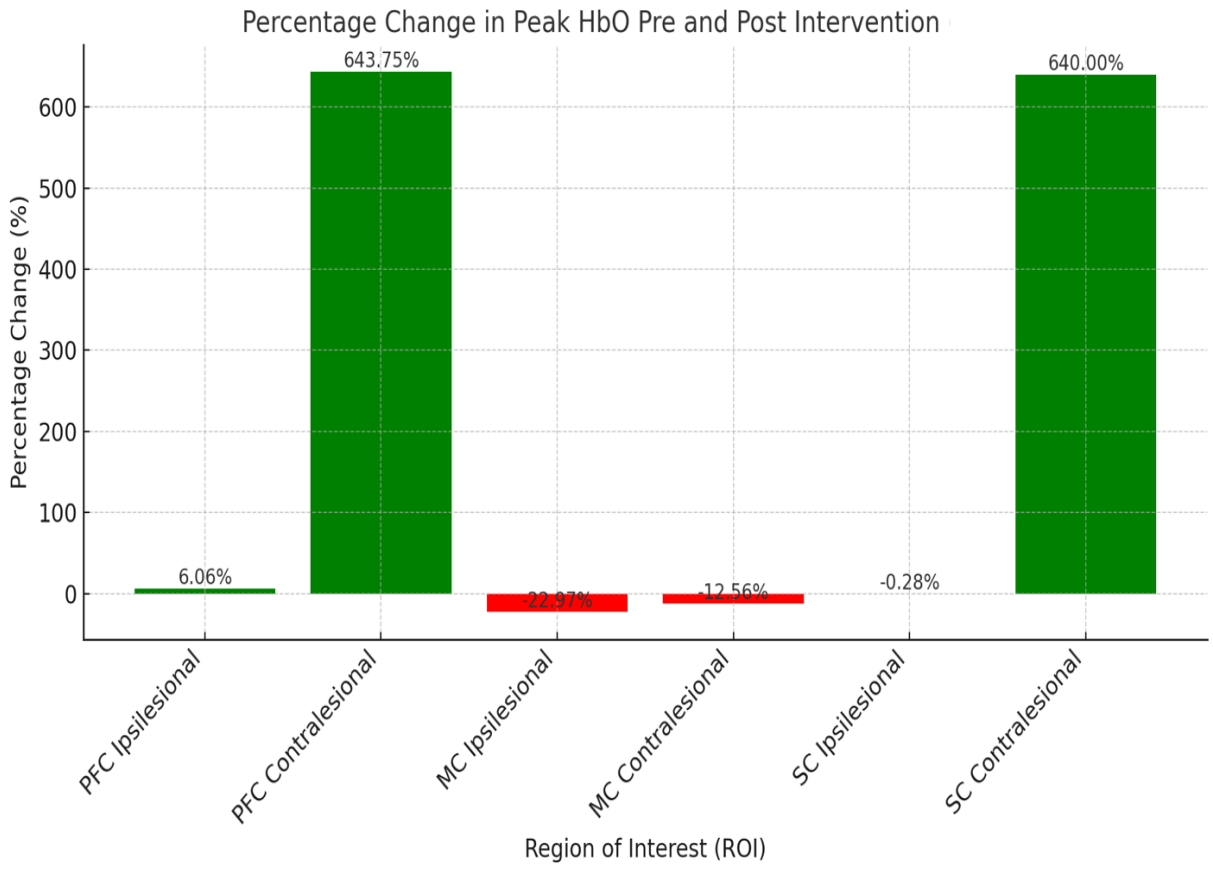

Figure 2-18 Participant Four Percentage Change in Peak Oxyhemoglobin (HbO). The bar chart depicts the percentage change in peak HbO across several regions of interest (ROIs) between the pre-and post-intervention. The regions evaluated include the prefrontal cortex (PFC), motor cortex (MC), and somatosensory cortex (SC) for both the ipsilesional and contralesional hemispheres.

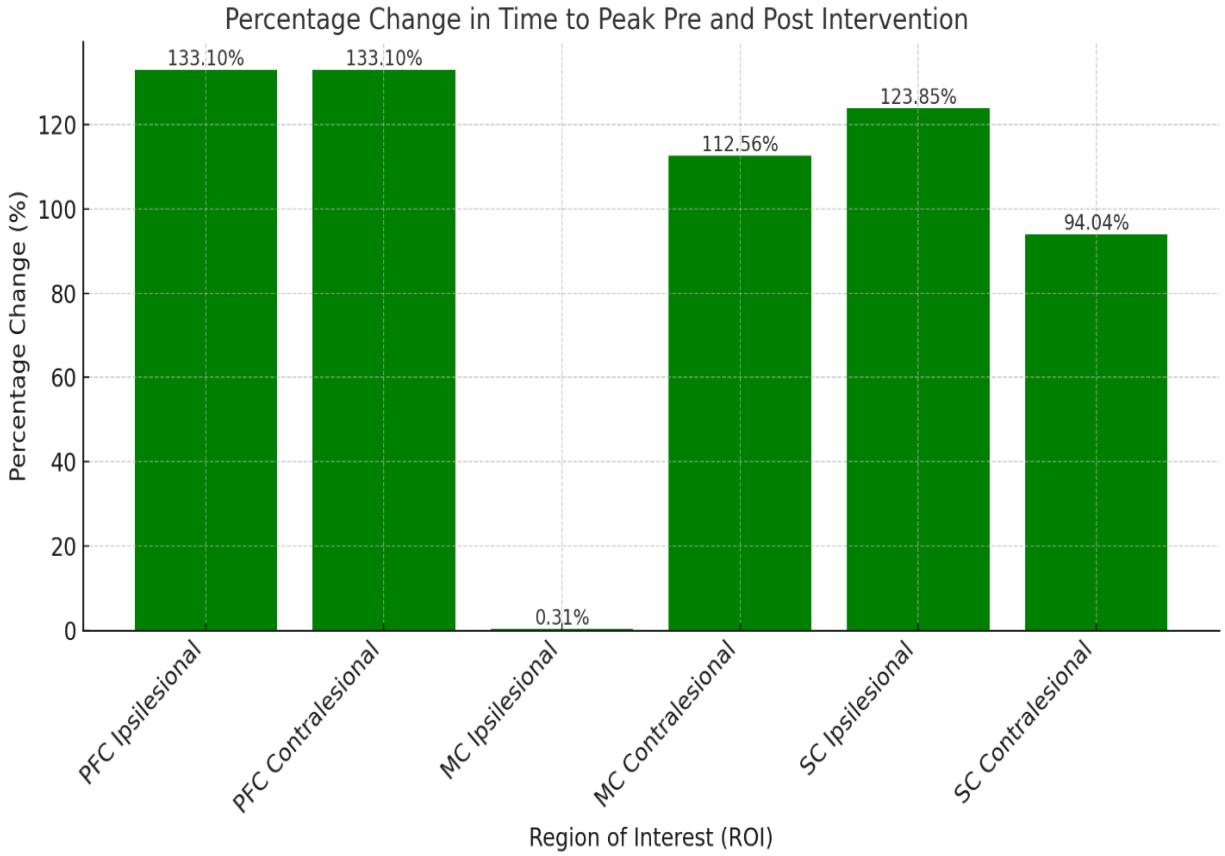

Figure 2-19 Participant Four Percentage Change in Time-to-Peak. The bar chart depicts the percentage change in time-to-peak across several regions of interest (ROIs) between the pre- and post-intervention. The regions evaluated include the prefrontal cortex (PFC), motor cortex (MC), and somatosensory cortex (SC) for both the ipsilesional and contralesional hemispheres.

This participant presented with a Left-Sided Middle Cerebral Artery (LMCA) stroke, with an FMA-UE score of 45, indicating moderately severe impairment. The results showed substantial increases in peak HbO in some regions, particularly in the contralesional prefrontal cortex (+643.75%) and contralesional somatosensory cortex (+640.00%). Conversely, the ipsilesional motor cortex exhibited a decrease of -22.97% in peak HbO. Time-to-peak changes showed increases across all regions, including the ipsilesional prefrontal cortex (+133.10%), the ipsilesional somatosensory cortex (+123.85%), and the contralesional motor cortex (+112.56%). Additionally, the time-to-peak for the ipsilesional motor cortex increased by +133.10%, indicating a delayed neural response post-intervention.

These trends suggest that the intervention may have elicited heightened neural activity in the contralesional hemisphere, particularly in the prefrontal and somatosensory cortices, while the ipsilesional motor cortex showed reduced activation. The increases in time-to-peak across regions may reflect delayed neural responses, potentially indicative of compensatory mechanisms in brain activation. This pattern aligns with the participant's moderately severe impairment and suggests differential neural reorganization across hemispheres and regions following the intervention.

2.7.2.5 Participant Five (FMA-UE score= 46 [moderately severe impairment] Left arm)

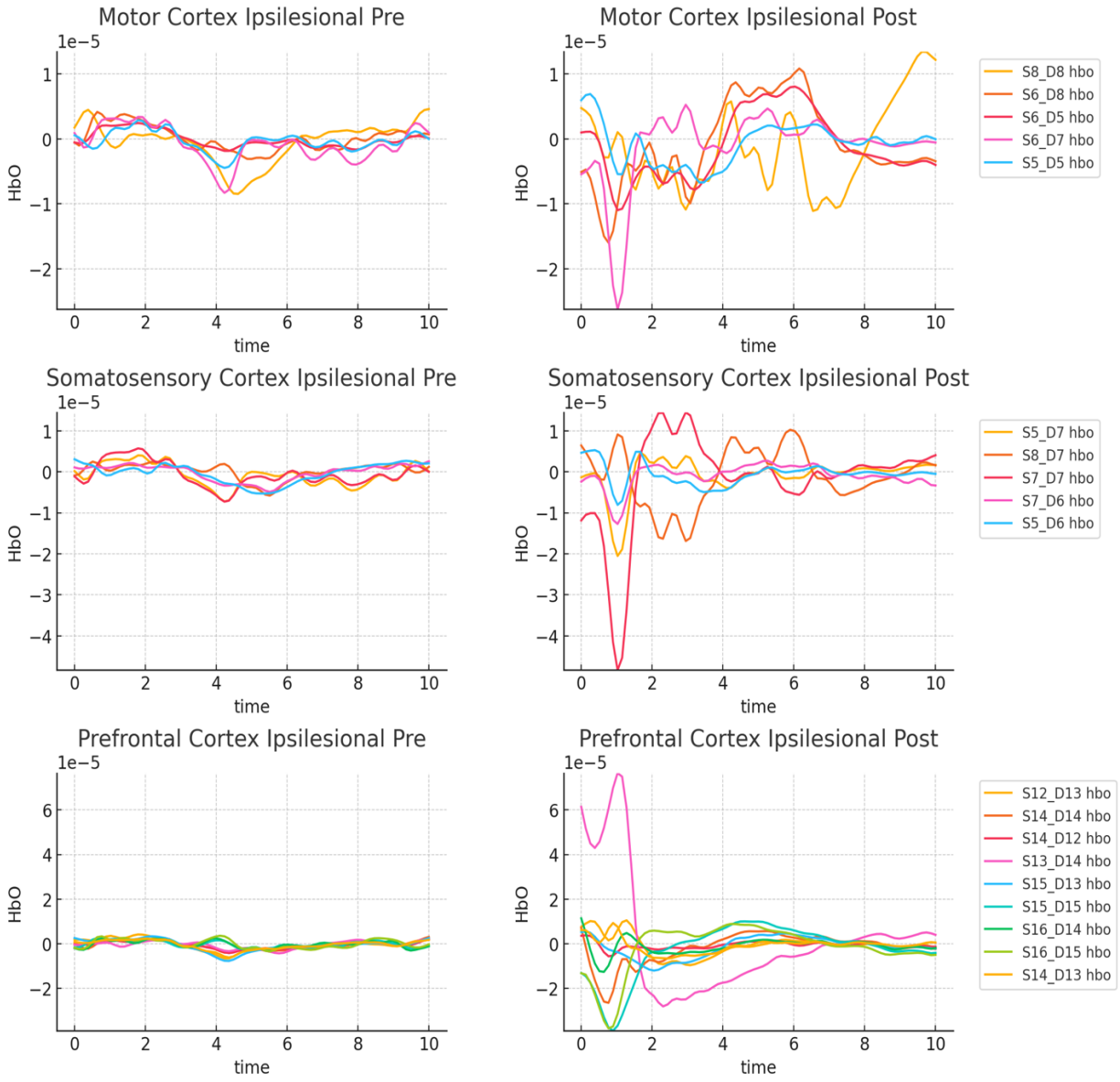

Figure 2-20 Participant Five Oxyhemoglobin (HbO) levels for Ipsilesional Hemisphere. The above plots show the mean HbO levels over a 10-second period, averaged across five tapping trials, for three regions of interest in the ipsilesional hemisphere: the motor cortex, somatosensory cortex, and prefrontal cortex. Each line represents a source-detector pair (S#-D#, where S refers to the source and D refers to the detector) that corresponds to specific cortical regions within these areas. The graphs compare HbO levels before (pre) and after (post) the intervention.

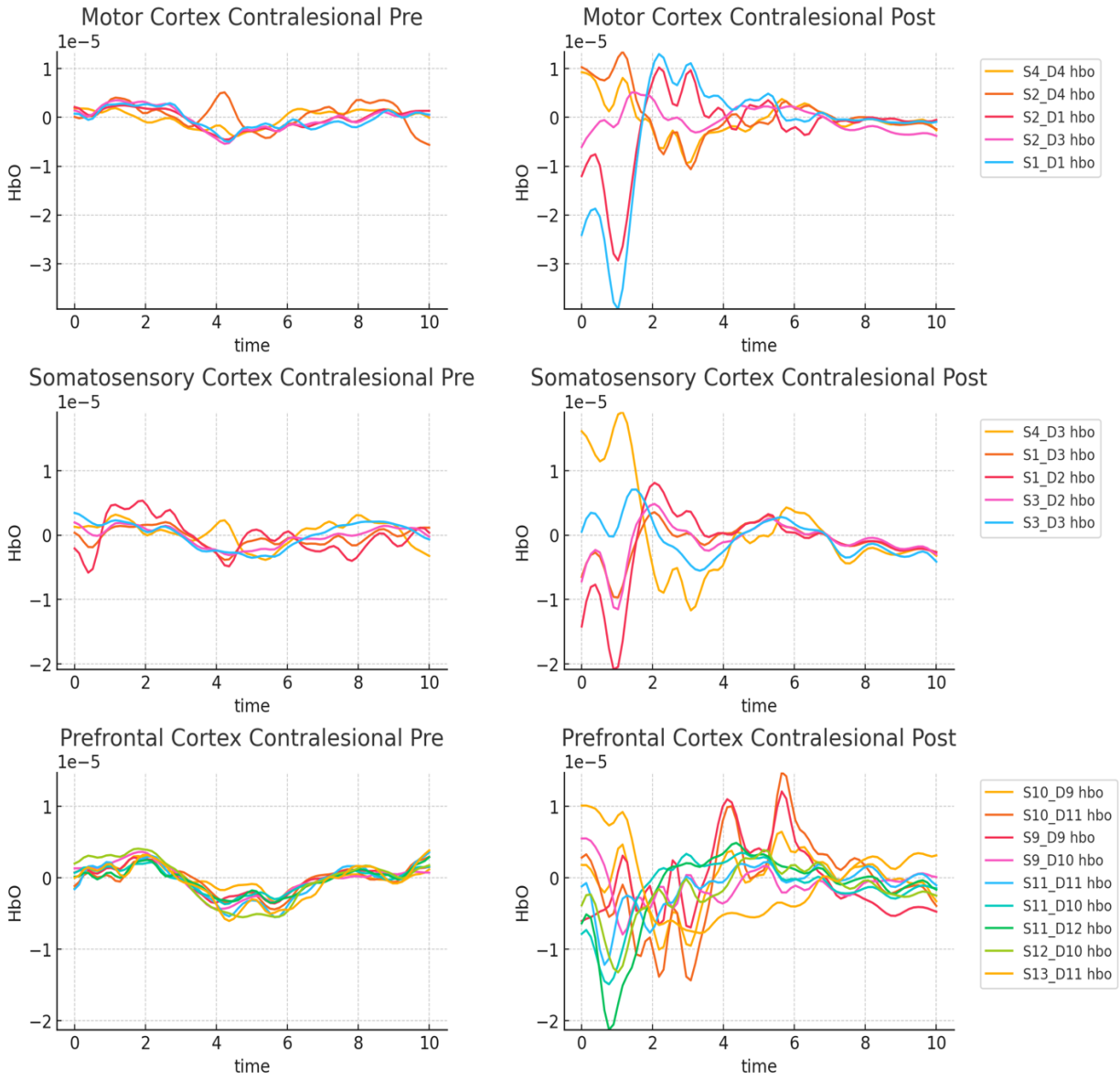

Figure 2-21 Participant Five Oxyhemoglobin (HbO) levels for Contralesional Hemisphere. The above plots show the mean HbO levels over a 10-second period, averaged across five tapping trials, for three regions of interest in the contralesional hemisphere: the motor cortex, somatosensory cortex, and prefrontal cortex. Each line represents a source-detector pair (S#-D#, where S refers to the source and D refers to the detector) that corresponds to specific cortical regions within these areas. The graphs compare HbO levels before (pre) and after (post) the intervention.

Table 2-8 Participant Five Peak Oxyhemoglobin (HbO) and Time-to-Peak

Effects by ROI	Peak HbO (Pre) (e-06)	Peak HbO (Post) (e-06)	Time-to-Peak (Pre) (s)	Time-to-Peak (Post) (s)
PFC Ipsilesional	**2.39**	**-5.65**	**2.05**	**0.75**
PFC Contralesional	**3.00**	**3.69**	**2.05**	**5.64**
MC Ipsilesional	**2.36**	**4.72**	**1.86**	**5.90**
MC Contralesional	**2.89**	**3.35**	**1.15**	**1.92**
SC Ipsilesional	**2.75**	**1.65**	**1.79**	**5.13**
SC Contralesional	**2.67**	**3.49**	**1.15**	**1.79**

This table presents the pre-and post-intervention peak HbO concentration (in e-06) and the time-to-peak (in seconds) for three regions of interest (ROI) based on pre-and post-intervention.: the prefrontal cortex (PFC), motor cortex (MC), and somatosensory cortex (SC). Data is provided for both the ipsilesional hemisphere and the contralesional hemisphere.

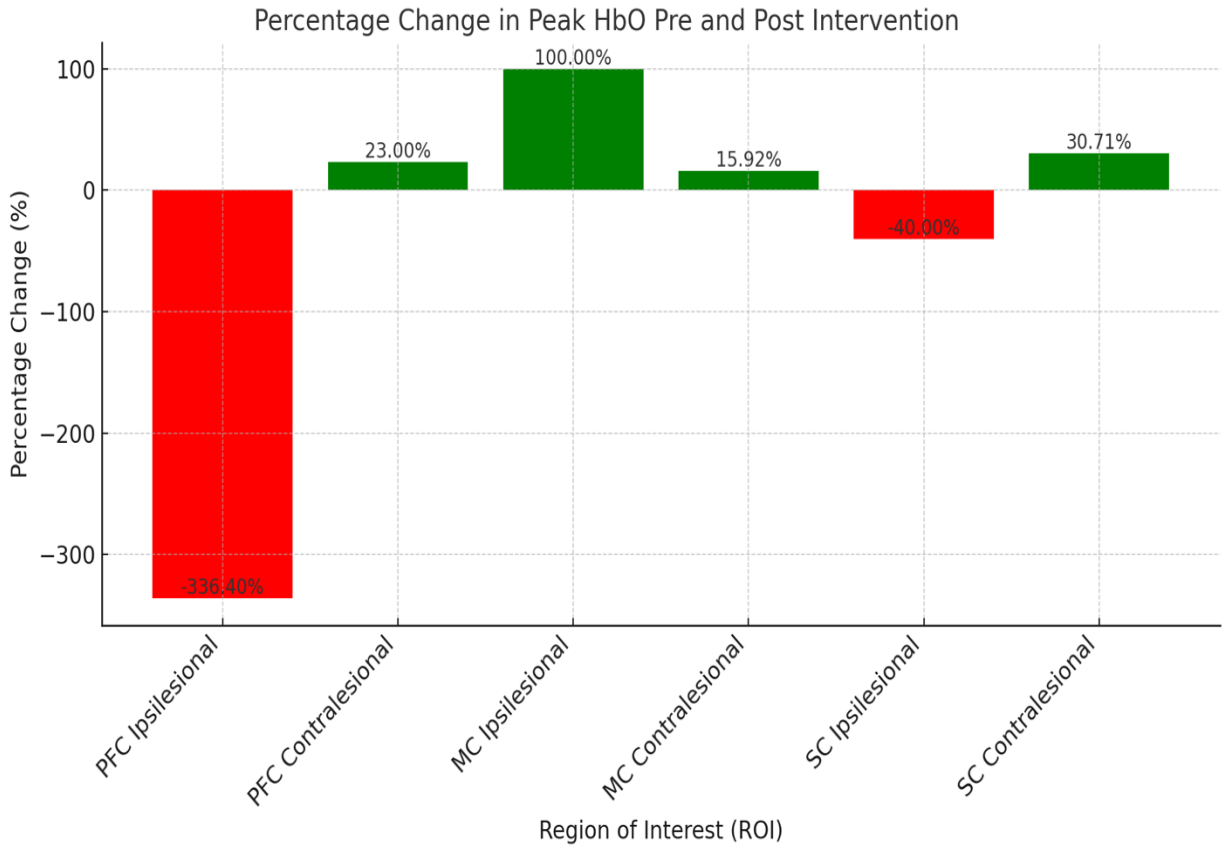

Figure 2-22 Participant Five Percentage Change in Peak Oxyhemoglobin (HbO). The bar chart depicts the percentage change in the peak HbO across several regions of interest (ROIs) between the pre-and post-intervention. The regions evaluated include the prefrontal cortex (PFC), motor cortex (MC), and somatosensory cortex (SC) for both the ipsilesional and contralesional hemispheres.

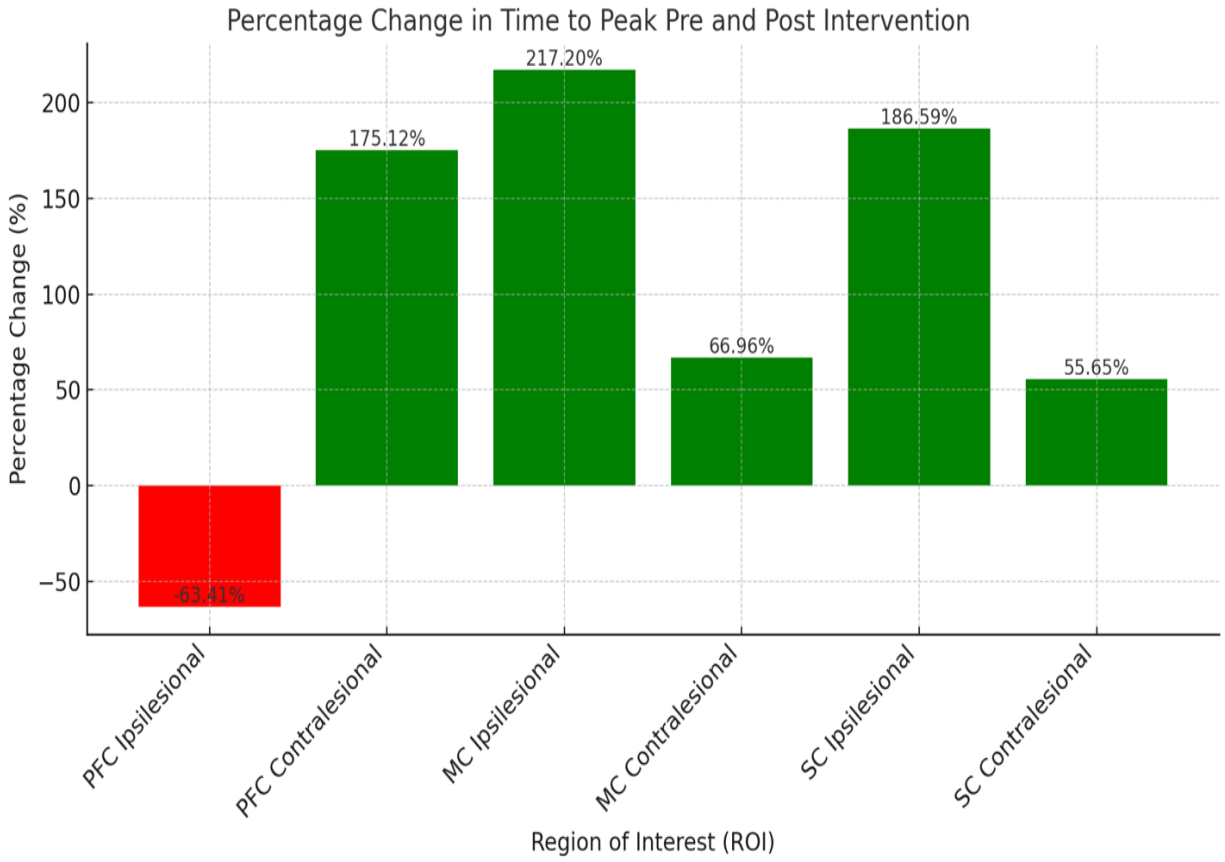

Figure 2-23 Participant Five Percentage Change in Time-to-Peak. The bar chart depicts the percentage change in time-to-peak across several regions of interest (ROIs) between the pre- and post-intervention. The regions evaluated include the prefrontal cortex (PFC), motor cortex (MC), and somatosensory cortex (SC) for both the ipsilesional and contralesional hemispheres.

This participant presented with a Right-Sided Middle Cerebral Artery (RMCA) stroke, with the ipsilesional hemisphere being the right side. The participant had an FMA-UE score of 46, indicating moderately severe impairment.

The results demonstrated a mixed pattern of peak HbO changes. The ipsilesional motor cortex showed a notable increase (+100.00%), while the contralesional motor cortex exhibited a smaller increase (+15.92%). The ipsilesional prefrontal cortex showed a marked decrease in peak HbO (-336.40%), suggesting a reduction in oxygenation post-intervention. In contrast, the contralesional prefrontal cortex showed a small positive change (+23.00%). Within the somatosensory cortex, the ipsilesional side decreased (-40.00%), while the contralesional side increased by +30.71%.

The time-to-peak results revealed substantial increases across most regions. The ipsilesional motor cortex increased by +217.20%, and the contralesional motor cortex increased by +66.96%. Similarly, the ipsilesional somatosensory cortex exhibited a large increase (+186.59%), while the contralesional somatosensory cortex showed a smaller increase (+55.65%). Interestingly, the ipsilesional prefrontal cortex showed a marked decrease in time-to-peak (-63.41%), while the contralesional prefrontal cortex exhibited a substantial increase (+175.12%).

These trends suggest a complex response to the intervention, with notable neural activation in motor and somatosensory regions, particularly on the ipsilesional side, which may align with improved motor function. The observed reduction in time-to-peak in the ipsilesional prefrontal cortex could indicate faster hemodynamic responses post-intervention, while the increases in time-to-peak in motor and somatosensory areas might reflect more sustained neural processing.

2.7.2.6 Participant Six (Fugl-Meyer score= 48 [moderately severe impairment] Left arm)

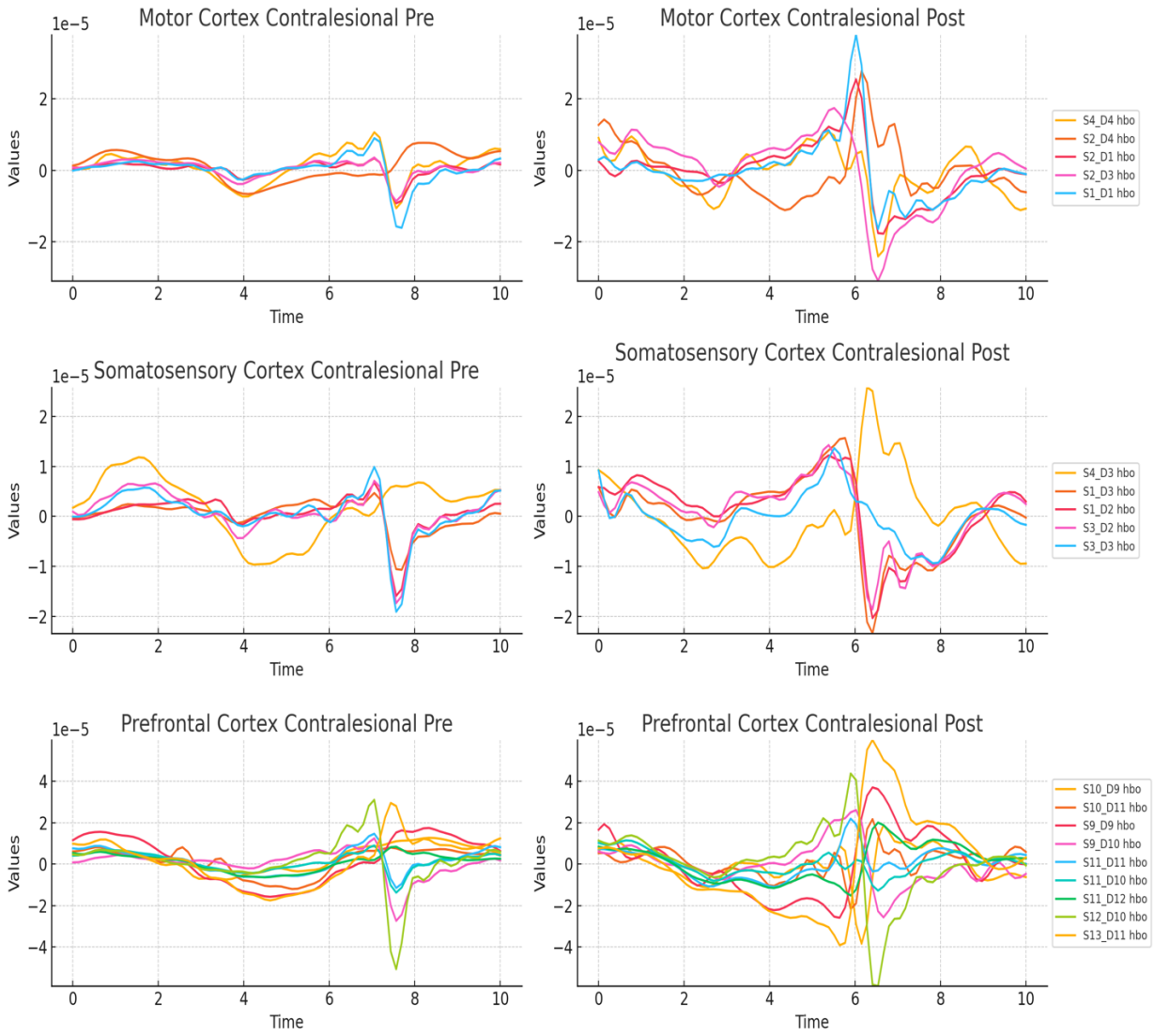

Figure 2-24 Participant Six Oxyhemoglobin (HbO) levels for Ipsilesional Hemisphere. The above plots show the mean HbO levels over a 10-second period, averaged across five tapping trials, for three regions of interest in the ipsilesional hemisphere: the motor cortex, somatosensory cortex, and prefrontal cortex. Each line represents a source-detector pair (S#-D#, where S refers to the source and D refers to the detector) that corresponds to specific cortical regions within these areas. The graphs compare HbO levels before (pre) and after (post) the intervention.

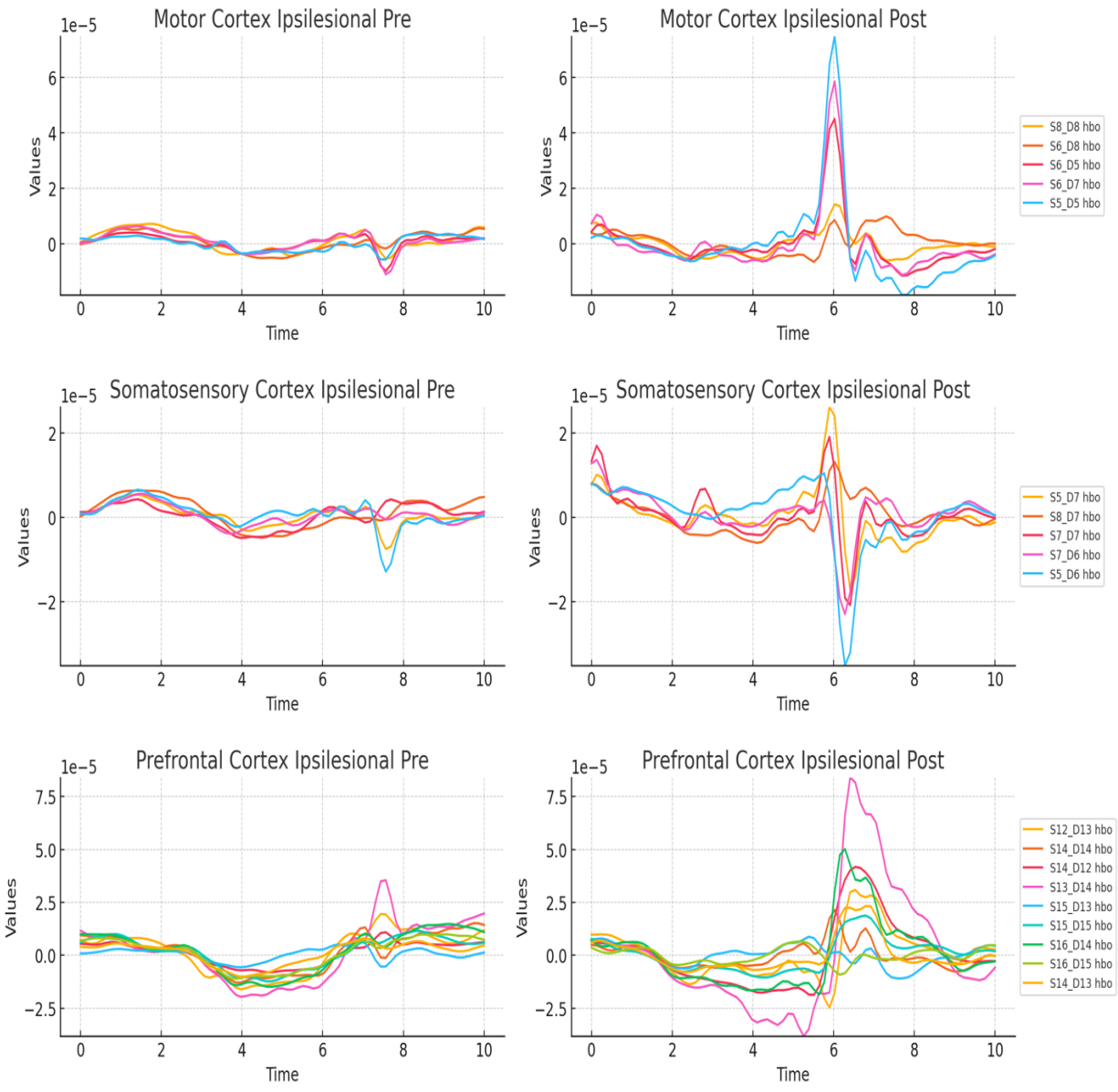

Figure 2-25 Participant Six Oxyhemoglobin (HbO) levels for Contralesional Hemisphere. The above plots show the mean HbO levels over a 10-second period, averaged across five tapping trials, for three regions of interest in the contralesional hemisphere: the motor cortex, somatosensory cortex, and prefrontal cortex. Each line represents a source-detector pair (S#-D#, where S refers to the source and D refers to the detector) that corresponds to specific cortical regions within these areas. The graphs compare HbO levels before (pre) and after (post) the intervention.

Table 2-9 Participant Six Peak Oxyhemoglobin (HbO) and Time-to-Peak

Effects by ROI	Peak HbO (Pre)	Peak HbO (Post)	Time-to-Peak (Pre) (s)	Time-to-Peak (Post) (s)
PFC Ipsilesional	**9.62 e-06**	**2.55 e-05**	**8.33**	**6.41**
PFC Contralesional	**3.58 e-06**	**8.99 e-06**	**6.25**	**0.13**
MC Ipsilesional	**5.11 e-06**	**4.03 e-05**	**1.41**	**6.03**
MC Contralesional	**3.06 e-06**	**1.87 e-05**	**6.55**	**6.03**
SC Ipsilesional	**5.56 e-06**	**1.22 e-05**	**1.41**	**5.90**
SC Contralesional	**1.96 e-07**	**1.07 e-05**	**7.35**	**5.51**

This table presents the pre-and post-intervention peak HbO concentration (in e-06) and time-to-peak (in seconds) for three regions of interest (ROI) based on pre- and post-intervention.: the prefrontal cortex (PFC), the motor cortex (MC), and somatosensory cortex (SC). Data is provided for both the ipsilesional hemisphere and the contralesional hemisphere.

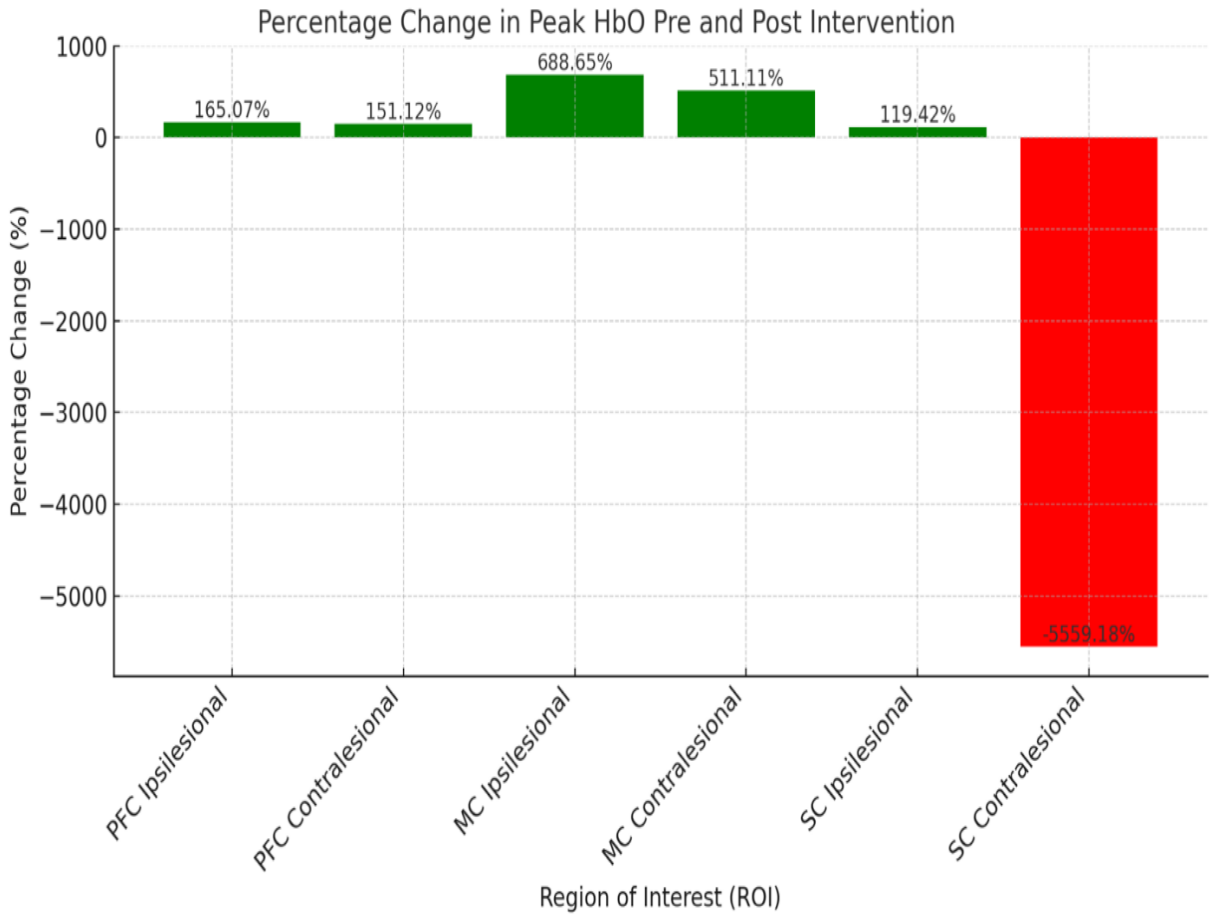

Figure 2-26 Participant Six Percentage Change in Peak Oxyhemoglobin (HbO). The bar chart depicts the percentage change in peak HbO across several regions of interest (ROIs) between the pre- and post-intervention. The regions evaluated include the prefrontal cortex (PFC), motor cortex (MC), and somatosensory cortex (SC) for both the ipsilesional and contralesional hemispheres.

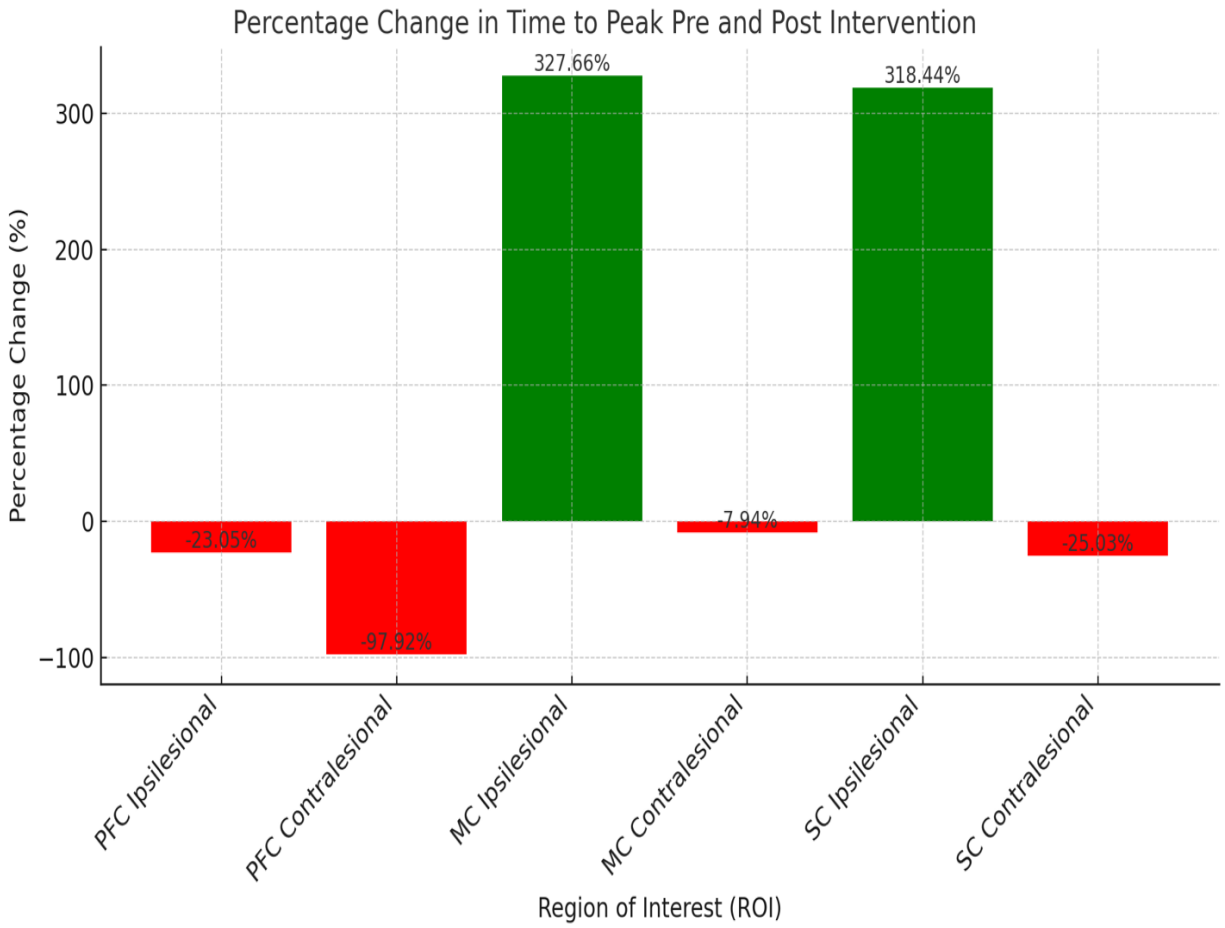

Figure 2-27 Participant Six Percentage Change in Time-to-Peak. The bar chart depicts the percentage change in time-to-peak across several regions of interest (ROIs) between the pre-and post-intervention. The regions evaluated include the prefrontal cortex (PFC), motor cortex (MC), and somatosensory cortex (SC) for both the ipsilesional and contralesional hemispheres.

This participant presented with a Right-Sided Middle Cerebral Artery (RMCA) stroke, with the ipsilesional hemisphere being the right side. The participant had an FMA-UE score of 48, indicating moderately severe impairment.

The results showed substantial increases in peak HbO in most regions, particularly in the ipsilesional motor cortex (+688.65%) and ipsilesional somatosensory cortex (+511.11%). In contrast, the contralesional somatosensory cortex exhibited a large decrease (-5559.18%). Time-to-peak changes reflected large positive increases, most notably in the ipsilesional motor cortex (+327.66%) and ipsilesional somatosensory cortex (+318.44%). Interestingly, the contralesional prefrontal cortex showed a marked reduction in time-to-peak (-97.92%).

These trends suggest that the intervention may have enhanced neural activity in the ipsilesional hemisphere, particularly in the motor and somatosensory cortices, which could align with improved motor function in stroke recovery. The extreme decrease in peak HbO in the contralesional somatosensory cortex might reflect a compensatory shift in brain activation, where the unaffected hemisphere reduces activation as the ipsilesional hemisphere regains function. This pattern may align with the participant's moderately severe impairment, suggesting significant but region-specific neural reorganization following the intervention.

2.7.2.7 Participant Seven (Fugl-Meyer score= 50 [moderately severe Right arm impairment])

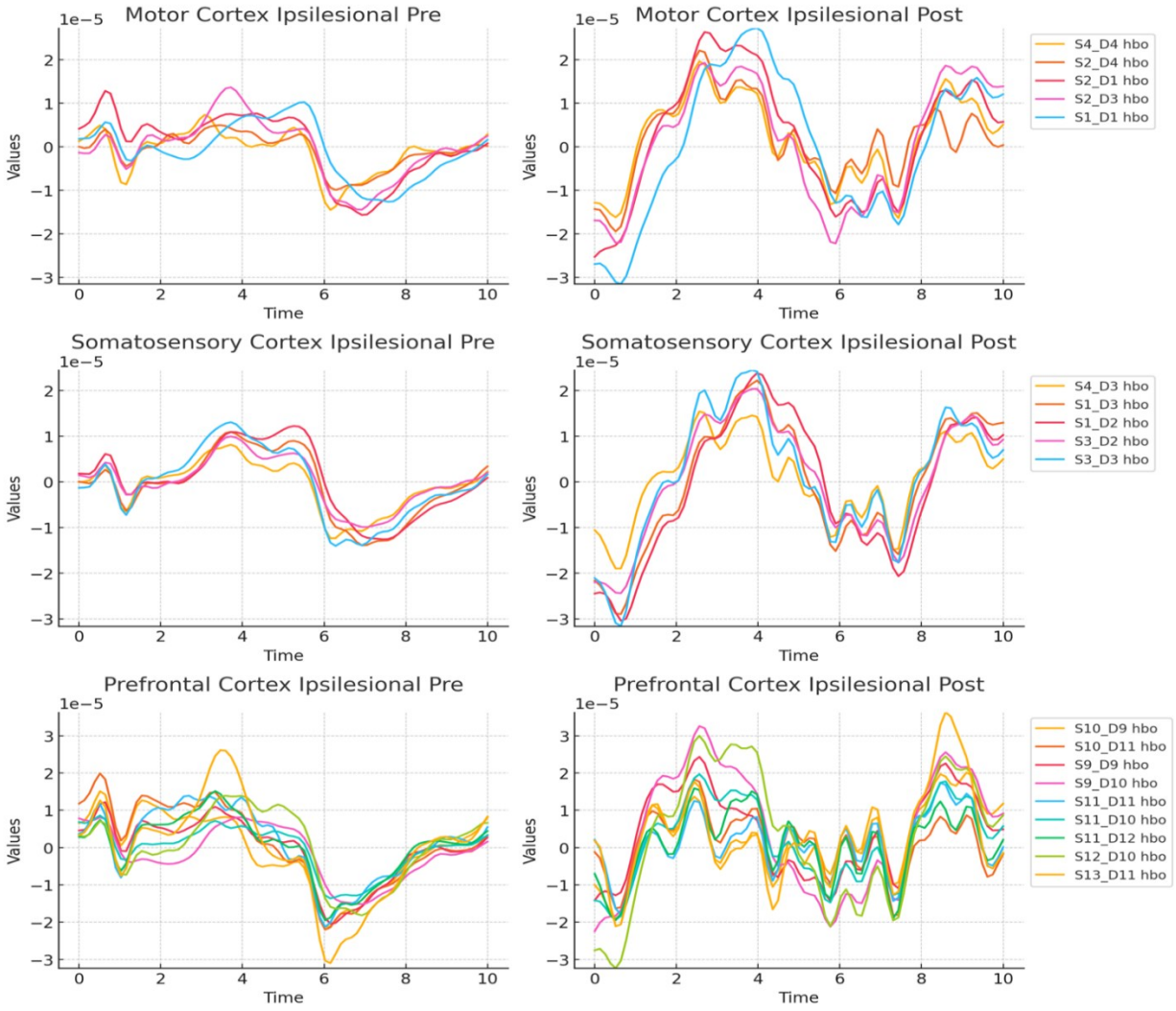

Figure 2-28 Participant Seven Oxyhemoglobin (HbO) levels for Ipsilesional Hemisphere.

The above plots show the mean HbO levels over a 10-second period, averaged across five tapping trials, for three regions of interest in the ipsilesional hemisphere: the motor cortex, somatosensory cortex, and prefrontal cortex. Each line represents a source-detector pair (S#-D#, where S refers to the source and D refers to the detector) that corresponds to specific cortical regions within these areas. The graphs compare HbO levels before (pre) and after (post) the intervention.

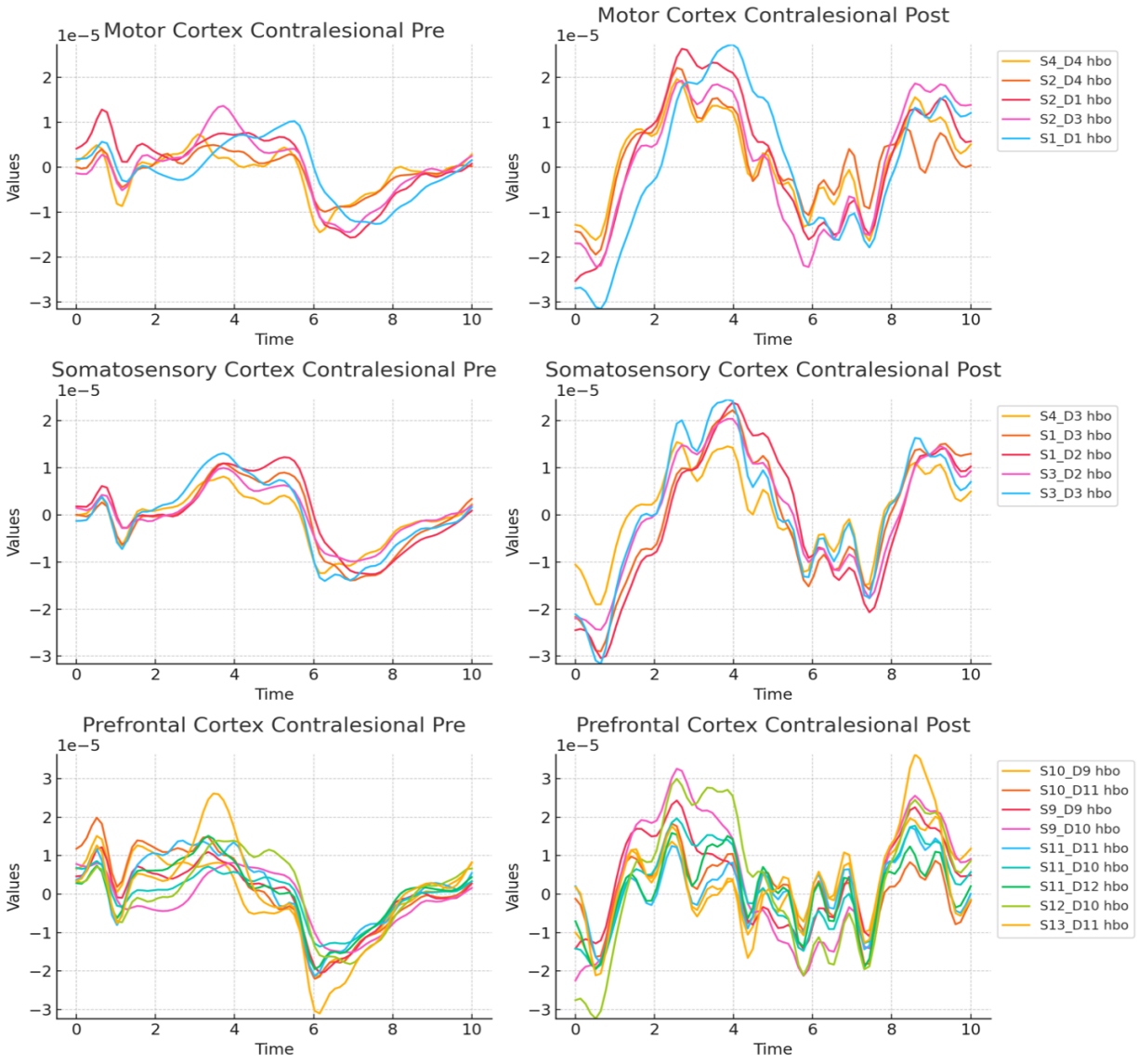

Figure 2-29 Participant Seven Oxyhemoglobin (HbO) levels for Contralesional Hemisphere. The above plots show the mean HbO levels over a 10-second period, averaged across five tapping trials, for three regions of interest in the contralesional hemisphere: the motor cortex, somatosensory cortex, and prefrontal cortex. Each line represents a source-detector pair (S#-D#, where S refers to the source and D refers to the detector) that corresponds to specific cortical regions within these areas. The graphs compare HbO levels before (pre) and after (post) the intervention.

Table 2-10 Participant Seven Peak Oxyhemoglobin (HbO) and Time-to-Peak

Effects by ROI	Peak HbO (Pre) (e-05)	Peak HbO (Post) (e-05)	Time-to-Peak (Pre) (s)	Time-to-Peak (Post) (s)
PFC Ipsilesional	**1.33**	**1.98**	**0.51**	**2.37**
PFC Contralesional	**1.89**	**2.98**	**3.46**	**2.44**
MC Ipsilesional	**6.51**	**2.08**	**3.72**	**2.69**
MC Contralesional	**1.07**	**2.65**	**3.85**	**2.56**
SC Ipsilesional	**1.06**	**2.10**	**3.72**	**3.97**
SC Contralesional	**1.08**	**2.49**	**5.26**	**2.56**

This table presents the pre-and post-intervention peak HbO values (in e-06) and time-to-peak (in seconds) for three regions of interest (ROI) based on pre-and post-intervention.: the prefrontal cortex (PFC), the motor cortex (MC), and the somatosensory cortex (SC). Data is provided for both the ipsilesional hemisphere and the contralesional hemisphere.

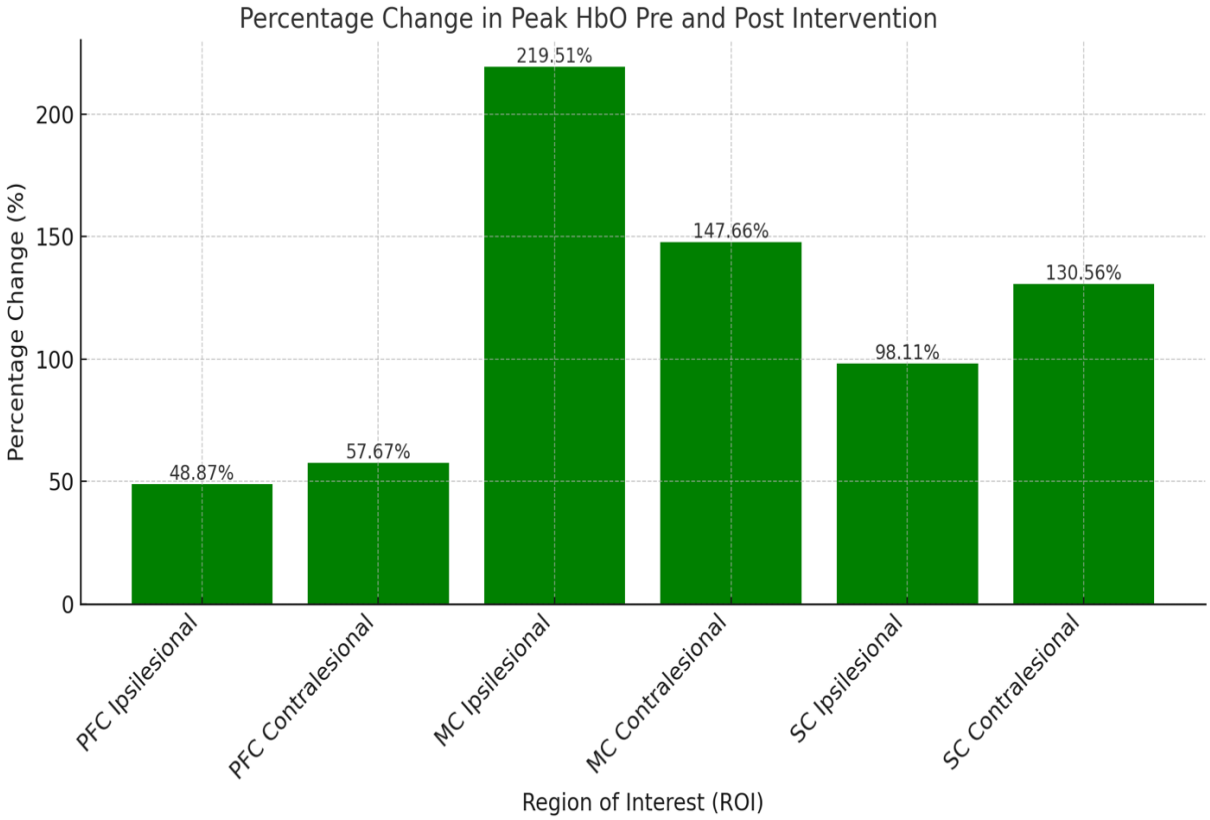

Figure 2-30 Participant Seven Percentage Change in Peak Oxyhemoglobin (HbO). The bar chart depicts the percentage change in peak HbO across several regions of interest (ROIs) between the pre- and post-intervention. The regions evaluated include the prefrontal cortex (PFC), motor cortex (MC), and somatosensory cortex (SC) for both the ipsilesional and contralesional hemispheres.

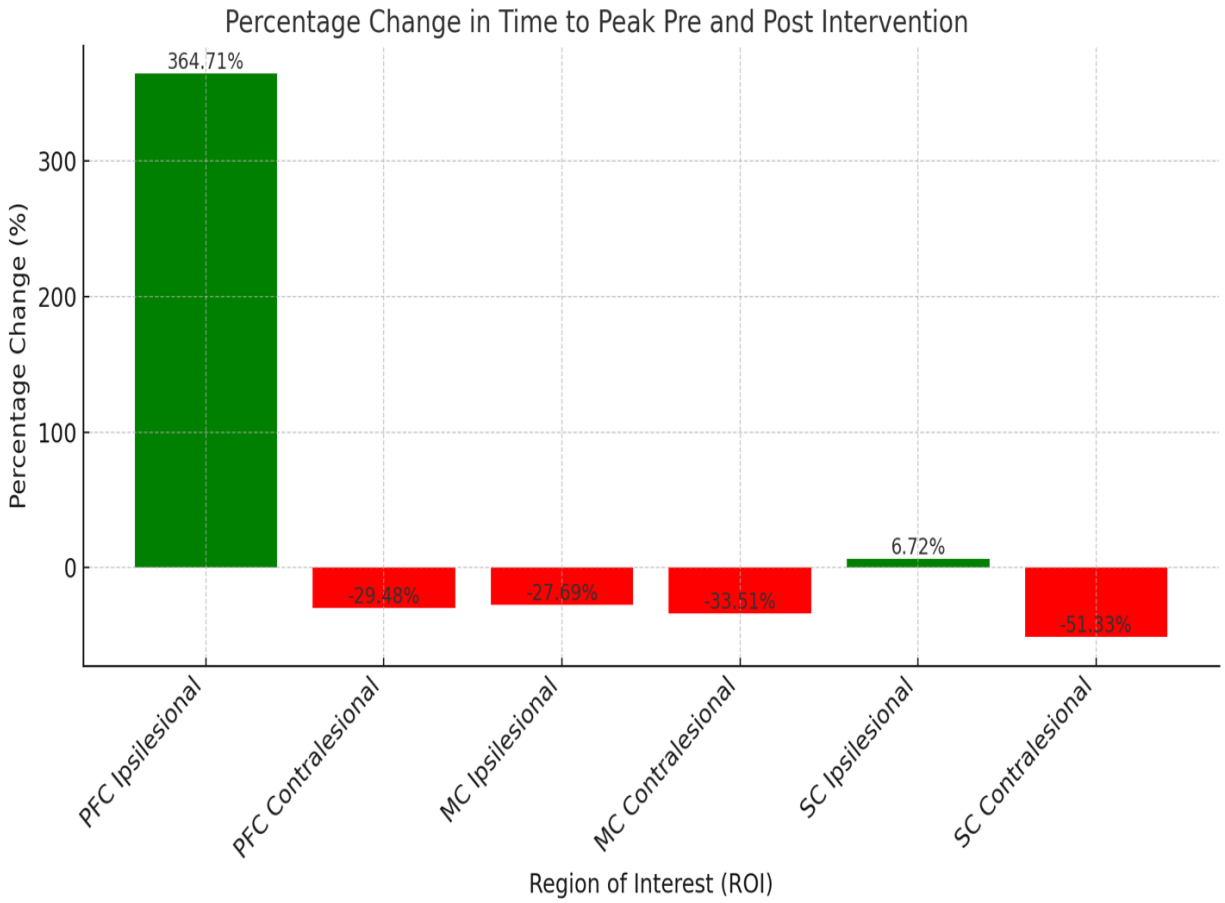

Figure 2-31 Participant Seven Percentage Change in Time-to-Peak. The bar chart depicts the percentage change in time-to-peak across several regions of interest (ROIs) between the pre-and post-intervention. The regions evaluated include the prefrontal cortex (PFC), motor cortex (MC), and somatosensory cortex (SC) for both the ipsilesional and contralesional hemispheres.

This participant presented with a Left-Sided Middle Cerebral Artery (LMCA) stroke, with an FMA-UE score of 50, indicating moderately severe motor impairment. The analysis revealed increases in peak HbO across most regions of interest (ROIs), with notable increases in the ipsilesional motor cortex (+219.51%) and contralesional motor cortex (+147.66%). The somatosensory cortex also exhibited increases, with the ipsilesional somatosensory cortex showing a +98.11% increase and the contralesional somatosensory cortex showing +130.56%.

The time-to-peak analysis showed mixed results, with some regions exhibiting delays in neural activation while others demonstrated faster processing times. The ipsilesional prefrontal cortex displayed a substantial increase (+364.71%), reflecting a delay in activation.

These trends suggest that the intervention may have enhanced neural activity in both motor and sensory regions, as indicated by the increases in peak HbO, particularly in the motor cortex. The mixed time-to-peak results suggest that some regions, such as the prefrontal cortex, experienced delayed activation, while others, like the contralesional somatosensory cortex, demonstrated faster processing times. The participant's moderately severe impairment, as indicated by the FMA-UE score, may have contributed to the differential patterns of neural activation and timing observed across cortical regions.

2.7.3 Group Analysis

This analysis examined time-to-peak and peak HbO across three key brain regions—the prefrontal cortex, motor cortex, and somatosensory cortex—for all participants (n=7) both pre- and post-intervention. Time-to-peak reflects the time required for each region of interest (ROI) to reach its maximum HbO level during the motor task, while peak HbO represents the highest concentration of oxygenated hemoglobin in each region. Data from both the ipsilesional and contralesional hemispheres were analyzed for these metrics.

To explore changes in brain activation patterns, paired t-tests were conducted to compare pre- and post-intervention values for each ROI across both hemispheres. To account for multiple comparisons, a Benjamini-Hochberg false discovery rate correction was applied, ensuring that significant findings reflect meaningful neurophysiological changes. While observable changes were noted in the mean values of both time-to-peak and peak HbO across various ROIs, these differences did not reach statistical significance at the $p < 0.05$ threshold. No significant changes were observed in the prefrontal cortex, motor cortex, or somatosensory cortex in either hemisphere. These results should be interpreted with caution, as the small sample size (n=7) limits statistical power. Despite the lack of statistically significant results, the observed trends suggest that the intervention may have influenced brain activation patterns, warranting further investigation in studies with larger cohorts.

To complement the statistical analysis, z-scores were calculated to standardize the peak HbO and time-to-peak values across participants. Box plots were generated to visualize the distribution of z-scores for each ROI under pre- and post-intervention conditions. These visualizations highlighted central tendencies, variability, and potential outliers in brain activation and response timing. While z-score and box plot analyses showed observable changes across

participants, these trends were also not statistically significant. The visualizations provide a qualitative understanding of brain activation patterns, suggesting possible effects of the intervention that may be further explored in larger-scale studies.

Table 2-11 Group Peak Oxyhemoglobin (HbO) Statistical Analysis

ROI	Mean Pre (e-05)	Mean Post (e-05)	T-Statistic	P-Value	Significant ($p < 0.05$)
PFC_Ipsilesional	**1.91**	**2.02**	**-0.06**	**00.953**	**No**
PFC_Contralesional	**3.05**	**3.08**	**-0.12**	**0.910**	**No**
MC_Ipsilesional	**2.86**	**3.13**	**-0.40**	**0.706**	**No**
MC_Contralesional	**2.61**	**2.89**	**-0.60**	**0.567**	**No**
SC_Ipsilesional	**2.19**	**3.06**	**-0.71**	**0.504**	**No**
SC_Contralesional	**2.67**	**3.49**	**-0.72**	**0.493**	**No**

This table summarizes the statistical results of the group peak HbO across three regions of interest (ROIs): the prefrontal cortex (PFC), the motor cortex (MC), and the somatosensory cortex (SC) for both ipsilesional and contralesional hemispheres. The group analysis includes the pre-and post-intervention mean values of HbO, the corresponding t-statistics, p-values, and the significance levels ($p < 0.05$).

Table 2-12 Group Time-to-Peak Statistical Analysis

ROI	Mean Pre (s)	Mean Post (s)	T-Statistic	P-Value	Significant ($p < 0.05$)
PFC_Ipsilesional	**4.03**	**4.84**	**-0.49**	**0.636**	**No**
PFC_Contralesional	**4.13**	**3.93**	**0.09**	**0.928**	**No**
MC_Ipsilesional	**4.16**	**5.97**	**-2.20**	**0.070**	**No**
MC_Contralesional	**4.14**	**5.46**	**-1.04**	**0.338**	**No**
SC_Ipsilesional	**3.09**	**5.81**	**-2.18**	**0.071**	**No**
SC_Contralesional	**4.05**	**3.94**	**0.10**	**0.919**	**No**

This table summarizes the statistical results of the time-to-peak across three regions of interest (ROIs): the prefrontal cortex (PFC), the motor cortex (MC), and the somatosensory cortex (SC) for both ipsilesional and contralesional hemispheres. The analysis includes the pre-and post-intervention mean values of HbO, the corresponding t-statistics, p-values, and the significance levels ($p < 0.05$).

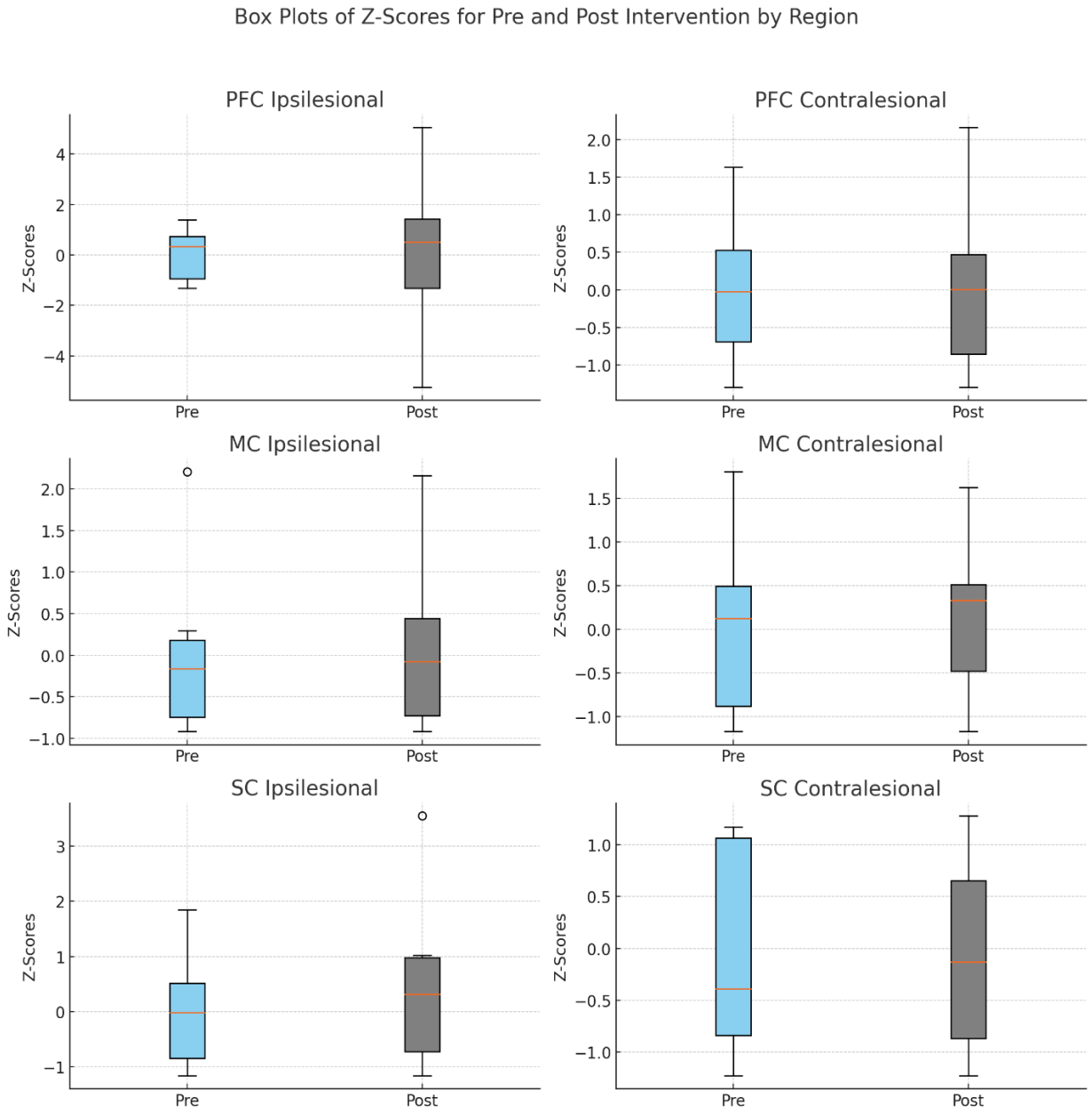

Figure 2-32 Group-level Visual Comparison of the Z–scores for Peak Oxyhemoglobin (HbO). The box plots presented in the image provide a visual comparison of Z-scores for the peak of HbO for pre- and post-intervention data across three regions of interest: the prefrontal cortex (PFC), motor cortex (MC), and somatosensory cortex (SC) in both the ipsilesional and contralesional hemispheres.

Each plot illustrates the distribution of z-scores for the pre- and post-intervention periods, providing insights into changes in brain activity across regions. In the ipsilesional prefrontal cortex, the box plot shows an increase in variability in z-scores post-intervention, with a noticeable upward shift in the median value. This trend may indicate increased brain activity following the intervention. Similar patterns are observed in the ipsilesional motor cortex and somatosensory cortex, where post-intervention z-scores exhibit greater variability and higher ranges, suggesting possible increases in activation post-intervention. Outliers in regions such as the ipsilesional motor cortex and somatosensory cortex highlight individual differences in response to the intervention.

In contrast, the contralesional hemisphere shows less pronounced changes between pre- and post-intervention periods. In the contralesional prefrontal cortex and motor cortex, the distribution of z-scores remains relatively consistent, with only slight shifts in median values. This suggests a more stable activation pattern in the contralesional hemisphere.

Overall, the box plots suggest increased activation in the ipsilesional regions post-intervention, particularly in the motor and somatosensory cortices, with notable variability among participants. The relatively stable patterns in contralesional regions may reflect that the intervention had a more pronounced effect on the ipsilesional hemisphere, which was more affected by the stroke. The presence of outliers underscores the importance of considering individual differences in brain activation patterns, which may warrant further investigation in future studies.

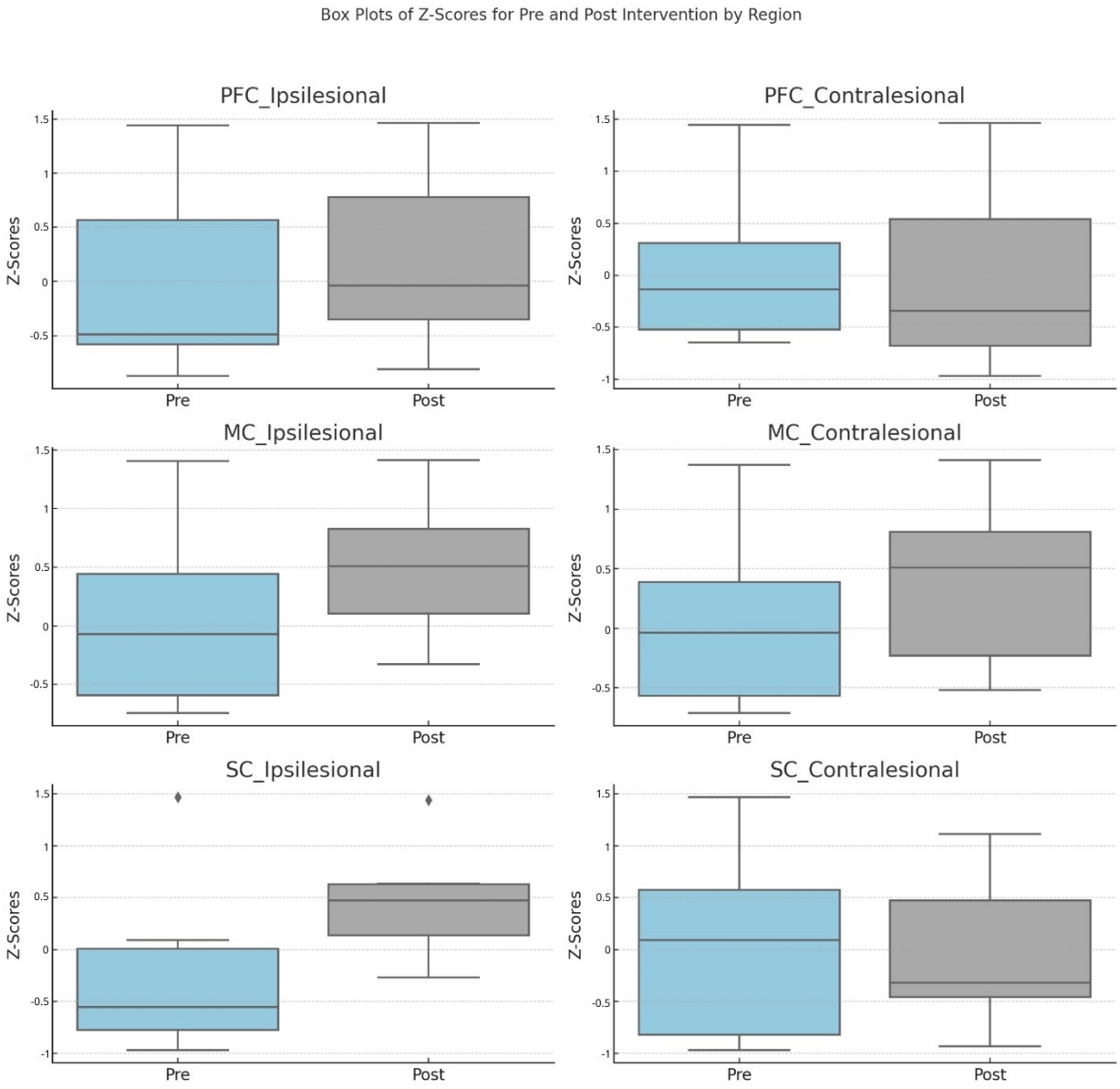

Figure 2-33 Group-level Visual Comparison of The Z – Scores for Time-to-Peak. The box plots presented in the image provide a visual comparison of the Z-scores for time-to-peak values pre- and post-intervention across three regions of interest: the prefrontal cortex (PFC), motor cortex (MC), and somatosensory cortex (SC) in both the ipsilesional and contralesional hemispheres. The central line in each box plot represents the median Z-score for time-to-peak.

The box plot (Figure 2.33) shows a slight upward shift in the median z-scores post-intervention in the ipsilesional prefrontal cortex. This trend may suggest that brain activation timing in this region became slower after the intervention, as higher z-scores correspond to longer time-to-peak values, indicating delayed activation. Post-intervention variability of z-scores increased in some regions, such as the ipsilesional somatosensory cortex, reflecting a broader range of activation responses among participants. This variability may represent differences in activation levels rather than changes in the speed of activation. A similar pattern is observed in the ipsilesional motor and somatosensory cortices, where post-intervention median z-scores shifted slightly but do not clearly indicate faster activation timing. Instead, these shifts might reflect changes in activation patterns within these regions, accompanied by greater variability.

In contrast, the contralesional hemisphere shows more stable patterns in z-scores across regions (Figure 2.33). The median and spread of z-scores in the contralesional prefrontal cortex and motor cortex remain relatively unchanged between the pre- and post-intervention periods, suggesting minimal shifts in the timing or intensity of neural activity in these regions. In the contralesional somatosensory cortex, a slightly wider spread of z-scores is observed post-intervention, indicating increased variability in sensory processing responses. However, these changes do not reflect notable shifts in activation timing compared to the ipsilesional hemisphere.

Overall, the box plots (Figure 2.33) illustrate changes in z-scores post-intervention, particularly in the ipsilesional motor and sensory cortices. The shifts in z-scores suggest changes in the range and intensity of activation responses rather than a consistent trend toward faster activation timing. These patterns highlight variability in how participants responded to the intervention, with some showing more pronounced changes in activation timing or levels. In contrast, the relatively stable z-scores in the contralesional hemisphere suggest that the

intervention may have had a more pronounced effect on the hemisphere directly affected by the stroke. These findings highlight the potential of the intervention to influence neural activation in the ipsilesional hemisphere, although individual differences in response emphasize the need for further investigation in larger studies.

2.8 SUMMARY OF FINDINGS

This study aimed to explore the feasibility of using fNIRS as a biomarker of neuroplasticity to measure rehabilitation-induced changes in brain activity in chronic stroke patients. The primary goal was to observe how brain activation patterns in the ipsilesional and contralesional hemispheres change before and after a motor learning intervention, considering the severity of upper limb motor dysfunction. Given the increasing interest in non-invasive techniques to measure neuroplasticity, this study contributes to the field by providing insights into the potential of fNIRS to assess brain activation changes associated with rehabilitation in stroke patients.

2.8.1 Key Findings

Several key findings, which offer significant insights into using fNIRS to map stroke rehabilitation-induced motor learning and neuroplasticity, emerged from this detailed study and warrant further investigation to fully understand their potential clinical applications recovery.

1. Individual Variability in Recovery Patterns: Participants demonstrated significant variability in recovery patterns, even among those with similar levels of upper limb paralysis and chronicity beyond the typical six-month post-stroke recovery period. Participants 1, 2, and 3 had FM-UE scores indicating severe impairment with limited gross motor control of the affected shoulder and elbow. Participants 1 and 3 exhibited decreases in HbO, while Participant 2 showed

increases. Participants 4, 5, 6, and 7, who had some control over the affected wrist but minimal hand function, exhibited increases in HbO in both ipsilesional and contralesional hemispheres, though to varying degrees. Time-to-peak changes were also highly variable across participants, hemispheres, and brain regions. Each participant demonstrated unique brain activity profiles pre- and post-intervention, with heterogeneous changes in activation patterns. The observed variability highlights the limitations of group-level analyses in capturing the nuanced, individualized responses to rehabilitation interventions

2. Changes in HbO and Time-to-Peak in the Ipsilesional Hemisphere: Participants exhibited unique patterns of change in brain activity within the ipsilesional hemisphere across the prefrontal cortex, motor cortex, and somatosensory cortex. Below is a summary of findings for each participant, with references to corresponding figures:

Participant One (Figure 2.4, Figure 2.5, Table 2.4): Exhibited a general decrease in peak HbO across all ipsilesional regions post-intervention, with the most pronounced reductions in the somatosensory and prefrontal cortices. Additionally, a substantial increase in time-to-peak, particularly in the somatosensory and motor cortices, suggests delayed neural activation post-intervention.

Participant Two (Figure 2.8, Figure 2.9, Table 2.5): The ipsilesional motor cortex showed an increase in peak HbO (+248.15%) post-intervention, with moderate increases in the prefrontal and somatosensory cortices. Time-to-peak increased across regions, reflecting slower response times.

Participant Three (Figure 2.12, Figure 2.13, Table 2.6): The ipsilesional prefrontal cortex demonstrated a marked increase in peak HbO (+95.47%), while the somatosensory cortex exhibited delayed activation, with a +1613.16% increase in time-to-peak.

Participant Four (Figure 2.16, Figure 2.17, Table 2.7): Peak HbO levels remained relatively stable across ipsilesional regions, but there were significant increases in time-to-peak across all regions, indicating delayed neural responses.

Participant Five (Figure 2.20, Figure 2.21, Table 2.8): The ipsilesional motor cortex showed a substantial increase in peak HbO (+100.00%), while the prefrontal cortex exhibited a decrease (-336.40%). Time-to-peak increased notably in the somatosensory and motor cortices.

Participant Six (Figure 2.24, Figure 2.25, Table 2.9): Large increases in peak HbO were observed in most ROIs, including the ipsilesional motor cortex (+688.65%) and somatosensory cortex (+511.11%). Time-to-peak showed substantial delays in the ipsilesional motor cortex (+327.66%).

Participant Seven (Figure 2.28, Figure 2.29, Table 2.10): Peak HbO increased across ipsilesional regions, particularly in the motor cortex (+219.51%). Most ROIs exhibited shorter time-to-peak post-intervention, except for the ipsilesional prefrontal and somatosensory cortices, which showed delays.ipsilesional prefrontal cortex and ipsilesional somatosensory cortex which showed delayed activation.

Group Results (Table 2.11, Table 2.12, Figure 2.32, Figure 2.33):

Across the group, the ipsilesional hemisphere showed trends of increased peak HbO in the motor cortex and somatosensory cortex post-intervention. Box plots (Figure 2.32) illustrate an upward shift in z-scores for peak HbO post-intervention in these regions, highlighting variability among participants, with some exhibiting increased activation.

For time-to-peak, the group-level analysis revealed longer time-to-peak values post-intervention in the motor cortex and somatosensory cortex, as shown in Figure 2.33. This trend suggests slower activation timing in these regions, which may reflect processing inefficiencies. The variability in

z-scores across participants underscores individual differences in response to the intervention, with some participants showing more pronounced changes than others.

This aligns with previous studies where increased activity in the ipsilesional hemisphere has been associated with motor recovery post-stroke (Calautti & Baron, 2003; Zhang et al., 2024). The heightened activation could indicate compensatory mechanisms crucial for regaining motor control in the affected upper limb.

3. Contralesional Hemisphere Activation: The contralesional hemisphere generally showed increases in HbO levels post-intervention for most participants, mirroring the ipsilesional hemisphere. This trend was observed in five out of seven participants, suggesting coordinated activation increases across hemispheres. However, individual differences were notable, with Participants 1 and 3 displaying reductions in HbO levels in the contralesional hemisphere, particularly in the somatosensory cortex. This reduction may indicate greater engagement of the ipsilesional hemisphere, potentially reducing the need for contralesional compensatory activation. These findings align with the concept that contralesional overactivity, often observed in the early stages post-stroke, diminishes as recovery progresses and ipsilesional networks regain function (Arshad, 2017; Rehme et al., 2012).

4. Time-to-Peak Patterns and Bilateral Involvement: A key observation was the similarity in time-to-peak values between ipsilesional and contralesional hemispheres during motor recovery tasks. This synchronization may reflect bilateral cortical involvement in motor control and reorganization following stroke(Dancause & Nudo, 2011). Early in recovery, the contralesional hemisphere often exhibits increased activity as a compensatory mechanism when the ipsilesional hemisphere is compromised (Marshall et al., 2000). As recovery progresses, ipsilesional activation tends to increase, reflecting improved outcomes. This study observed bilateral engagement during

motor tasks, with similar time-to-peak values across hemispheres in some regions, supporting previous findings on synchronized activity during recovery (Grefkes et al., 2008; Rehme et al., 2011).

Compared to previous studies, such as Rehme et al. (2011) and Grefkes & Ward (2014), as we report individual data at the ROI level, our findings provide a nuanced perspective on the role of both hemispheres in post-stroke recovery. While Rehme et al. observed increased recruitment of frontal areas and basal ganglia in response to motor tasks during early recovery (Rehme et al., 2011), the present study highlights specific changes in hemispheric activity beyond the typical window of spontaneous recovery (>6 months). We observed increased HbO levels in both the ipsilesional and contralesional hemispheres in most participants, indicating bilateral engagement in motor tasks. Additionally, time-to-peak values suggested a gradual synchronization of activation timing between hemispheres, especially in participants with greater functional recovery. These findings align with Grefkes & Ward's (2014) observations of functional reorganization, wherein coordinated activity across hemispheres supports motor recovery. This bilateral reorganization in our study suggests that both hemispheres dynamically contribute to motor function improvements, even in the chronic stage post-stroke (Grefkes & Ward, 2014).

Furthermore, this study provides a contrasting perspective to Carter et al. (2012), which reported decreased activation in the contralesional motor cortex following stroke recovery.(Carter et al., 2012). However, Carter et al. examined a heterogeneous stroke population at different recovery stages, including the subacute phase, whereas our study focuses specifically on chronic stroke patients (>6 months post-stroke) undergoing a structured motor learning intervention. Additionally, Carter et al. used resting-state functional connectivity MRI (rs-fcMRI), which assesses network-level reorganization at rest, while our study measured task-related HbO

activation using fNIRS during active motor performance. These methodological differences may explain why we observed bilateral increases in activation post-intervention, suggesting greater reliance on both hemispheres for motor compensation in our chronic stroke cohort.

Our findings underscore that the degree of motor impairment and time since stroke may significantly influence the extent and direction of hemispheric activation changes. This highlights the importance of tailoring rehabilitation approaches based on patient-specific factors, such as severity and chronicity, to optimize neural reorganization outcomes. Future research is needed to further distinguish how different rehabilitation interventions impact hemispheric activity in patient subgroups to better understand the mechanisms underlying diverse recovery trajectories.

2.8.2 Limitations

While this study provides valuable insights into the neuroplastic mechanisms underlying stroke recovery, several limitations should be acknowledged.

1. Small Sample Size: The sample size (n=7) was small, limiting the findings' generalizability. Future studies should include more significant, diverse populations to validate these results and explore how stroke severity and chronicity influence brain activation patterns.

2. Lack of Long-Term Follow-Up: This study only assessed brain activity immediately before and after the intervention. A longer-term follow-up would provide more information on the durability of the observed neuroplastic changes and whether these improvements in brain activation are sustained over time.

3. Absence of a Control Group: With a control group, it is easier to definitively attribute the observed changes in brain activity to the intervention alone. Future research could benefit from

including a control group that undergoes a different or placebo intervention to more clearly isolate the effects of motor learning on brain activation.

4. Despite its advantages, fNIRS has several limitations in stroke rehabilitation. One significant issue is its sensitivity to motion artifacts, which can compromise data accuracy during motor tasks. This limitation is particularly relevant for stroke patients, who may exhibit involuntary movements. Furthermore, the limited penetration depth of 1-3 cm restricts fNIRS's ability to monitor deeper brain structures, and variability in hemoglobin concentration among individuals can affect the reliability of measurements.

5. Whether participants attempted to engage the less affected hand during fNIRS data capture: People with stroke may involuntarily or voluntarily activate the less affected (good, or 'sound') hand when attempting to move their affected hand. This is called 'mirror movement'. Although we monitored the hand tapping task during fNIRS data capture and did not observe mirror movement, we are not able to know for sure whether participants activated muscles in their sound side. We would have to employ electromyography on the sound side to know for sure, which we did not do.

2.8.3 Conclusion

In conclusion, this study demonstrates the feasibility of using fNIRS to track neuroplastic changes in brain activity following motor learning interventions in stroke patients. The findings highlight the potential of fNIRS as a non-invasive tool for monitoring rehabilitation progress and offer insights into unique inter-individual patterns of changes in brain activity. Although the study has some limitations, it provides a solid foundation for future research to optimize stroke rehabilitation strategies and enhance our understanding of neuroplasticity in recovery.

3 CHAPTER THREE: SUMMARY OF FINDINGS AND FUTURE DIRECTIONS

3.1 DISCUSSION

This study aimed to evaluate functional near-infrared spectroscopy (fNIRS) as a biomarker for neuroplasticity in stroke rehabilitation, precisely measuring changes in brain activity before and after a motor learning intervention targeting upper limb function. The focus was on motor cortex, somatosensory cortex, and prefrontal cortex activity, analyzing how the intervention modulated Oxyhemoglobin (HbO) concentrations in these brain regions.

This chapter presents a comparative analysis of our findings with previous studies reviewed in section 2.4.3. Through this comparison, we aim to situate our results within the broader context of fNIRS research in stroke rehabilitation. By comparing our study to Kim et al. (2022), Xie et al. (2022), Liu et al. (2022), Delorme et al. (2019), Muller et al. (2024), and Kim et al. (2024), we explore similarities and differences in participant characteristics, intervention types, and outcomes. This approach reveals insights into hemispheric activation, neuroplasticity, and the nuanced interactions between ipsilesional and contralesional regions in chronic stroke recovery. Additionally, this discussion identifies areas where our understanding remains incomplete, such as neurovascular coupling and time-to-peak variability. intervention.

3.1.1 Comparison with Kim et al. (2022): Bilateral Motor Cortex Activation

Kim et al. (2022) demonstrated that integrating visual, somatosensory feedback, and motor intention significantly enhanced ipsilesional motor cortex activation in chronic stroke survivors during motor tasks (Kim et al., 2022). Our study aligns with these findings but further extends them by showing increased activation not only in the ipsilesional motor cortex but also in contralesional regions post-intervention. This bilateral engagement suggests that both hemispheres

contribute to motor recovery, potentially reflecting compensatory mechanisms in chronic stroke rehabilitation. However, while Kim et al. focused on stroke patients in the early recovery phase and healthy participants, our study examines individuals beyond six months post-stroke, when spontaneous recovery is generally minimal.

The ipsilesional activation observed in our study suggests that targeted interventions can engage motor cortex areas actively, even in the chronic stage of recovery. This finding supports the idea that visual and somatosensory feedback mechanisms, though not a focus in our intervention, may enhance motor recovery in chronic stroke patients by engaging the ipsilesional hemisphere. The differences in recovery timing suggest that more intensive or varied feedback mechanisms may be required for sustained ipsilesional activation in the chronic phase.

While Kim et al. emphasize combining feedback mechanisms (Kim et al., 2022), our study indicates that isolated motor interventions may still promote ipsilesional activation. Future research could investigate the individual and combined effects of different feedback types on motor cortex activation across varying post-stroke durations to determine which factors most effectively drive motor reactivation.

3.1.2 Comparison with Xie et al. (2022): Neuroplasticity and Severity-Based Responses

Xie et al. (2022) reported neuroplastic responses in the ipsilesional superior frontal cortex particularly in patients with mild motor dysfunction (manual muscle test score ≥4). Increased bilateral superior frontal cortex activation was observed in patients with moderate motor impairment (manual muscle test scores of 2–3) during robot-assisted task-oriented upper limb motor training. In contrast, our study included participants with moderate to severe upper limb impairment, as indicated by FM-UE scores. Our findings showed increased HbO levels in both

ipsilesional and contralesional cortices across participants, with variations in the extent of change at the individual level. This distinction highlights differences in participant severity and chronicity between studies, emphasizing the importance of tailoring neuroplasticity interventions to these factors. Our findings suggest that bilateral cortical engagement may persist as a compensatory strategy in chronic stroke patients. This contrasts with Xie's results, where lateralization decreased as impairment severity decreased. The chronicity of our participants may explain this stable bilateral engagement, as the brain may have reached a plateau in functional reorganization in which both hemispheres contribute to motor function.

Xie's study highlights the potential of fNIRS for real-time neuroplastic monitoring during rehabilitation (Xie et al., 2022). While our study underscores this potential in chronic stroke, it also suggests that different neuroplastic trajectories may emerge across phases of recovery. Future studies could use real-time fNIRS to personalize interventions based on neuroplastic capacity, possibly revealing more distinct activation patterns between chronic and acute phases.

3.1.3 Comparison with Liu et al. (2022): Brain-Computer Interface and Enhanced Connectivity

Liu et al. (2022) reported enhanced connectivity between ipsilesional and contralesional motor cortices following brain-computer interface (BCI) training, suggesting increased cortical engagement in patients with moderate to severe impairment (Liu et al., 2022). In our study, we observed bilateral increases in HbO levels, indicating similar involvement from both hemispheres. However, our study did not specifically assess connectivity between these regions, focusing instead on overall activation levels and time-to-peak values.

Liu's study shows the benefits of targeting connectivity as a specific outcome (Liu et al., 2022). Future research on chronic stroke could assess connectivity patterns between hemispheres to better understand how hemispheric coordination supports recovery. Understanding these connectivity patterns could also clarify the functional significance of HbO increases in relation to motor gains.

3.1.4 Comparison with Delorme et al. (2019): Early Recovery and Lateralization

Delorme et al. (2019) observed a shift from bilateral to ipsilesional activation over two months in early post-stroke patients with mild to severe hemiparesis (Delorme et al., 2019). This reorganization coincided with significant improvements in motor function, as evidenced by increased FM-UE scores. In contrast, our study included chronic stroke participants with moderate to severe upper limb impairment, as indicated by FM-UE scores and found persistent bilateral activation in the motor and somatosensory cortices. Specifically, our study demonstrated sustained bilateral activation with time-to-peak values indicating a more stable activation pattern across participants. This consistent bilateral engagement suggests that, in the chronic post-stroke phase, bilateral activation may serve as a stable compensatory strategy. Unlike the early post-stroke stage, where neuroplastic changes are more dynamic, this persistence of bilateral activation in chronic stroke participants likely reflects an adaptive mechanism. Such a mechanism may be particularly important for individuals with moderate to severe impairment, who continue to rely on both hemispheres to support motor function.

Delorme's findings imply that early recovery allows for greater specialization in the ipsilesional hemisphere (Delorme et al., 2019). Future studies are needed to assess if targeted interventions could facilitate a similar ipsilesional shift in chronic patients, particularly those with

greater impairment. Exploring time-to-peak changes across recovery phases could also enhance our understanding of neurovascular coupling adaptation over time.

3.1.5 Comparison with Muller et al. (2024): Motor Cortex Overactivation and Compensatory Strategies

Muller et al. (2024) noted ipsilesional motor cortex overactivation associated with compensatory trunk movements in chronic stroke patients (Muller et al., 2024). In our study, we similarly observed increased HbO levels in motor cortices, particularly among participants with better functional recovery (Participants six and seven), who exhibited faster time-to-peak values in certain regions. Unlike Muller's study, which links overactivation with physical compensations, our study focuses on activation patterns without directly measuring compensatory physical movements.

The increased activation in motor cortices observed in our study aligns with Muller et al.'s findings on motor overactivation, suggesting that bilateral cortical activity may play a role in supporting movement in chronic stroke patients. Furthermore, the faster time-to-peak in participants with improved function could indicate refined neurovascular responses and more efficient motor control. However, since we did not assess physical compensatory movements in our study, we cannot determine whether increased activation is directly correlated with compensatory strategies. Integrating kinematic measurements, as employed in Muller et al.'s study, could offer valuable insights into the relationship between cortical overactivation and physical compensation strategies in chronic stroke.

3.1.6 Comparison with Kim et al. (2024): Ipsilesional and Contralesional Cortical Activation

Kim et al. (2024) conducted a cross-sectional study with 18 chronic stroke patients (mean age: 67 ± 7.1 years, 13 men) to explore the potential of functional near-infrared spectroscopy (fNIRS) for monitoring cortical activation during upper limb rehabilitation using a digital therapeutic program called MotoCog® (Kim et al., 2024). Participants exhibited a range of motor function levels, as assessed by the FMA-UE, grip and pinch strength tests, and the box and block test. Significant cortical activation was observed in the ipsilesional primary motor cortex, ipsilesional primary somatosensory cortex, and contralesional prefrontal cortex during the rehabilitation program. The activation patterns varied according to FMA-UE scores, with positive correlations observed between FMA-UE scores and activation in the ipsilesional motor cortex, while negative correlations were noted in the ipsilesional somatosensory cortex, frontal lobe, and parietal lobe.

These findings align with our results, which also showed increased HbO levels in both the ipsilesional motor and somatosensory cortices, emphasizing that both hemispheres contribute to motor tasks in chronic stroke patients. Our study further supports Kim et al.'s observation that chronic stroke patients rely on bilateral cortical resources for motor tasks, reflecting a different neuroplastic profile compared to earlier post-stroke stages.

Kim et al. highlight the need for more specific investigation into how activation patterns vary across stroke types and recovery durations (Kim et al., 2024). Our findings underscore this need by demonstrating that participant characteristics, such as motor impairment levels and recovery duration, significantly influence cortical activation. Future research should explore these variables in relation to neuroplasticity and functional outcomes.

3.2 Implications for Rehabilitation

This study underscores the importance of considering chronicity, severity, and hemispheric interaction when designing rehabilitation programs for stroke patients. The observed bilateral activation patterns and time-to-peak variability suggest that individualized rehabilitation approaches could optimize outcomes by leveraging both hemispheres' involvement in motor function. Using fNIRS to monitor these patterns could allow clinicians to adapt interventions to patients' neuroplastic potential.

3.3 Future Research Directions

Our study suggests several avenues for future research. First, the functional significance of bilateral activation in chronic stroke patients, especially concerning time-to-peak values, warrants further exploration. Additionally, multimodal approaches combining fNIRS with Electroencephalography or kinematic data could provide a comprehensive view of compensatory strategies and cortical reorganization. Expanding studies to larger, diverse populations will be essential to standardize neuroplasticity markers and enhance fNIRS as a tool for personalized rehabilitation.

4 REFERENCES

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. https://doi.org/10.1152/japplphysiol.00515.2006

Aguirre, G. K., Detre, J. A., Zarahn, E., & Alsop, D. C. (2002). Experimental design and the relative sensitivity of BOLD and perfusion fMRI. *Neuroimage*, *15*(3), 488-500. https://doi.org/10.1006/nimg.2001.0990

Alawieh, A., Zhao, J., & Feng, W. (2018). Factors affecting post-stroke motor recovery: Implications on neurotherapy after brain injury. *Behav Brain Res*, *340*, 94-101. https://doi.org/10.1016/j.bbr.2016.08.029

Almajidy, R. K., Mankodiya, K., Abtahi, M., & Hofmann, U. G. (2020). A Newcomer's Guide to Functional Near Infrared Spectroscopy Experiments. *IEEE Rev Biomed Eng*, *13*, 292-308. https://doi.org/10.1109/RBME.2019.2944351

Anwer, S., Waris, A., Gilani, S. O., Iqbal, J., Shaikh, N., Pujari, A. N., & Niazi, I. K. (2022). Rehabilitation of Upper Limb Motor Impairment in Stroke: A Narrative Review on the Prevalence, Risk Factors, and Economic Statistics of Stroke and State of the Art Therapies. *Healthcare (Basel)*, *10*(2). https://doi.org/10.3390/healthcare10020190

Arshad, Q. (2017). Dynamic interhemispheric competition and vestibulo-cortical control in humans; A theoretical proposition. *Neuroscience*, *353*, 26-41. https://doi.org/10.1016/j.neuroscience.2017.04.013

Auriat, A. M., Neva, J. L., Peters, S., Ferris, J. K., & Boyd, L. A. (2015). A Review of Transcranial Magnetic Stimulation and Multimodal Neuroimaging to Characterize Post-Stroke Neuroplasticity. *Front Neurol*, *6*, 226. https://doi.org/10.3389/fneur.2015.00226

Austin, M. W., Ploughman, M., Glynn, L., & Corbett, D. (2014). Aerobic exercise effects on neuroprotection and brain repair following stroke: a systematic review and perspective. *Neurosci Res*, *87*, 8-15. https://doi.org/10.1016/j.neures.2014.06.007

Ayaz, H., Onaral, B., Izzetoglu, K., Shewokis, P. A., McKendrick, R., & Parasuraman, R. (2013). Continuous monitoring of brain dynamics with functional near infrared spectroscopy as a tool for neuroergonomic research: empirical examples and a technological development. *Front Hum Neurosci*, *7*, 871. https://doi.org/10.3389/fnhum.2013.00871

Babalola, M. (2023). *The feasibility of measuring rehabilitation-induced changes in upper limb movement and cognition using robotic kinematics in chronic stroke* . In.

Balardin, J. B., Zimeo Morais, G. A., Furucho, R. A., Trambaiolli, L., Vanzella, P., Biazoli, C., & Sato, J. R. (2017). Imaging Brain Function with Functional Near-Infrared Spectroscopy in Unconstrained Environments. *Front Hum Neurosci*, *11*, 258. https://doi.org/10.3389/fnhum.2017.00258

Barbay, M., Diouf, M., Roussel, M., Godefroy, O., & GRECOGVASC study group. (2018). Systematic Review and Meta-Analysis of Prevalence in Post-Stroke Neurocognitive Disorders in Hospital-Based Studies. *Dement Geriatr Cogn Disord*, *46*(5-6), 322-334. https://doi.org/10.1159/000492920

Barsi, G. I., Popovic, D. B., Tarkka, I. M., Sinkjaer, T., & Grey, M. J. (2008). Cortical excitability changes following grasping exercise augmented with electrical stimulation. *Exp Brain Res*, *191*(1), 57-66. https://doi.org/10.1007/s00221-008-1495-5

Bernhardt, J., Hayward, K. S., Kwakkel, G., Ward, N. S., Wolf, S. L., Borschmann, K., Krakauer, J. W., Boyd, L. A., Carmichael, S. T., Corbett, D., & Cramer, S. C. (2017). Agreed definitions and a shared vision for new standards in stroke recovery research: The Stroke Recovery and Rehabilitation Roundtable taskforce. *Int J Stroke*, *12*(5), 444-450. https://doi.org/10.1177/1747493017711816

Bindawas, S. M., & Vennu, V. S. (2016). Stroke rehabilitation. A call to action in Saudi Arabia. *Neurosciences (Riyadh)*, *21*(4), 297-305. https://doi.org/10.17712/nsj.2016.4.20160075

Bleyenheuft, Y., & Gordon, A. M. (2014). Precision grip in congenital and acquired hemiparesis: similarities in impairments and implications for neurorehabilitation. *Front Hum Neurosci*, *8*, 459. https://doi.org/10.3389/fnhum.2014.00459

Boehme, A. K., Esenwa, C., & Elkind, M. S. (2017). Stroke Risk Factors, Genetics, and Prevention. *Circ Res*, *120*(3), 472-495. https://doi.org/10.1161/CIRCRESAHA.116.308398

Byblow, W. D., Stinear, C. M., Barber, P. A., Petoe, M. A., & Ackerley, S. J. (2015). Proportional recovery after stroke depends on corticomotor integrity. *Ann Neurol*, *78*(6), 848-859. https://doi.org/10.1002/ana.24472

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

Carbajal-Galarza, M. M., Chinchihualpa-Paredes, N. O., Abanto-Perez, S. A., & Lazo-Porras, M. (2020). Effectiveness of technological interventions to improve upper limb motor function in people with stroke in low- and middle-income countries: Protocol for a systematic review and meta-analysis. *medRxiv*.

Carey, L. M., Matyas, T. A., & Oke, L. E. (1993). Sensory loss in stroke patients: effective training of tactile and proprioceptive discrimination. *Arch Phys Med Rehabil*, *74*(6), 602-611. https://doi.org/10.1016/0003-9993(93)90158-7

Carmichael, S. T., Kathirvelu, B., Schweppe, C. A., & Nie, E. H. (2017). Molecular, cellular and functional events in axonal sprouting after stroke. *Exp Neurol*, *287*(Pt 3), 384-394. https://doi.org/10.1016/j.expneurol.2016.02.007

Carmichael, S. T., Wei, L., Rovainen, C. M., & Woolsey, T. A. (2001). New patterns of intracortical projections after focal cortical stroke. *Neurobiol Dis*, *8*(5), 910-922. https://doi.org/10.1006/nbdi.2001.0425

Carter, A. R., Shulman, G. L., & Corbetta, M. (2012). Why use a connectivity-based approach to study stroke and recovery of function? *Neuroimage*, *62*(4), 2271-2280. https://doi.org/10.1016/j.neuroimage.2012.02.070

Chen, W. L., Wagner, J., Heugel, N., Sugar, J., Lee, Y. W., Conant, L., Malloy, M., Heffernan, J., Quirk, B., Zinos, A., Beardsley, S. A., Prost, R., & Whelan, H. T. (2020). Functional Near-Infrared Spectroscopy and Its Clinical Application in the Field of Neuroscience: Advances and Future Directions. *Front Neurosci*, *14*, 724. https://doi.org/10.3389/fnins.2020.00724

Cheng, S., Xin, R., Zhao, Y., Wang, P., Feng, W., & Liu, P. (2023). Evaluation of fMRI activation in post-stroke patients with movement disorders after repetitive transcranial magnetic stimulation: a scoping review. *Front Neurol*, *14*, 1192545. https://doi.org/10.3389/fneur.2023.1192545

Chohan, S. A., Venkatesh, P. K., & How, C. H. (2019). Long-term complications of stroke and secondary prevention: an overview for primary care physicians. *Singapore Med J*, *60*(12), 616-620. https://doi.org/10.11622/smedj.2019158

Chow, B. W., Nuñez, V., Kaplan, L., Granger, A. J., Bistrong, K., Zucker, H. L., Kumar, P., Sabatini, B. L., & Gu, C. (2020). Caveolae in CNS arterioles mediate neurovascular coupling. *Nature*, *579*(7797), 106-110. https://doi.org/10.1038/s41586-020-2026-1

Cirillo, J., Mooney, R. A., Ackerley, S. J., Barber, P. A., Borges, V. M., Clarkson, A. N., Mangold, C., Ren, A., Smith, M. C., Stinear, C. M., & Byblow, W. D. (2020). Neurochemical balance and inhibition at the subacute stage after stroke. *J Neurophysiol*, *123*(5), 1775-1790. https://doi.org/10.1152/jn.00561.2019

Coderre, A. M., Zeid, A. A., Dukelow, S. P., Demmer, M. J., Moore, K. D., Demers, M. J., Bretzke, H., Herter, T. M., Glasgow, J. I., Norman, K. E., Bagg, S. D., & Scott, S. H. (2010). Assessment of upper-limb sensorimotor function of subacute stroke patients using visually guided reaching. *Neurorehabil Neural Repair*, *24*(6), 528-541. https://doi.org/10.1177/1545968309356091

Collaborators, G. S. (2019). Global, regional, and national burden of stroke, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*, *18*(5), 439-458. https://doi.org/10.1016/S1474-4422(19)30034-1

Connell, L. A., Lincoln, N. B., & Radford, K. A. (2008). Somatosensory impairment after stroke: frequency of different deficits and their recovery. *Clin Rehabil*, *22*(8), 758-767. https://doi.org/10.1177/0269215508090674

Coscia, M., Wessel, M. J., Chaudary, U., Millán, J. D. R., Micera, S., Guggisberg, A., Vuadens, P., Donoghue, J., Birbaumer, N., & Hummel, F. C. (2019). Neurotechnology-aided interventions for upper limb motor rehabilitation in severe chronic stroke. *Brain*, *142*(8), 2182-2197. https://doi.org/10.1093/brain/awz181

Cotman, C. W., & Berchtold, N. C. (2002). Exercise: a behavioral intervention to enhance brain health and plasticity. *Trends Neurosci*, *25*(6), 295-301. https://doi.org/10.1016/s0166-2236(02)02143-4

Coupland, A. P., Thapar, A., Qureshi, M. I., Jenkins, H., & Davies, A. H. (2017). The definition of stroke. *J R Soc Med*, *110*(1), 9-12. https://doi.org/10.1177/0141076816680121

Cramer, S. C. (2004). Functional imaging in stroke recovery. *Stroke*, *35*(11 Suppl 1), 2695-2698. https://doi.org/10.1161/01.STR.0000143326.36847.b0

Cramer, S. C. (2008). Repairing the human brain after stroke: I. Mechanisms of spontaneous recovery. *Ann Neurol*, *63*(3), 272-287. https://doi.org/10.1002/ana.21393

Cramer, S. C., Nelles, G., Benson, R. R., Kaplan, J. D., Parker, R. A., Kwong, K. K., Kennedy, D. N., Finklestein, S. P., & Rosen, B. R. (1997). A functional MRI study of subjects recovered from hemiparetic stroke. *Stroke*, *28*(12), 2518-2527. https://doi.org/10.1161/01.str.28.12.2518

Csipo, T., Mukli, P., Lipecz, A., Tarantini, S., Bahadli, D., Abdulhussein, O., Owens, C., Kiss, T., Balasubramanian, P., Nyúl-Tóth, Á., Hand, R. A., Yabluchanska, V., Sorond, F. A.,

Csiszar, A., Ungvari, Z., & Yabluchanskiy, A. (2019). Assessment of age-related decline of neurovascular coupling responses by functional near-infrared spectroscopy (fNIRS) in humans. *Geroscience*, *41*(5), 495-509. https://doi.org/10.1007/s11357-019-00122-x

Cui, X., Bray, S., & Reiss, A. L. (2010). Functional near infrared spectroscopy (NIRS) signal improvement based on negative correlation between oxygenated and deoxygenated hemoglobin dynamics. *Neuroimage*, *49*(4), 3039-3046. https://doi.org/10.1016/j.neuroimage.2009.11.050

Dancause, N., & Nudo, R. J. (2011). Shaping plasticity to enhance recovery after injury. *Prog Brain Res*, *192*, 273-295. https://doi.org/10.1016/B978-0-444-53355-5.00015-4

Dasso, N. A. (2019). How is exercise different from physical activity? A concept analysis. *Nurs Forum*, *54*(1), 45-52. https://doi.org/10.1111/nuf.12296

Davidson, B., Bhattacharya, A., Sarica, C., Darmani, G., Raies, N., Chen, R., & Lozano, A. M. (2024). Neuromodulation techniques - From non-invasive brain stimulation to deep brain stimulation. *Neurotherapeutics*, *21*(3), e00330. https://doi.org/10.1016/j.neurot.2024.e00330

Delorme, M., Vergotte, G., Perrey, S., Froger, J., & Laffont, I. (2019). Time course of sensorimotor cortex reorganization during upper extremity task accompanying motor recovery early after stroke: An fNIRS study. *Restor Neurol Neurosci*, *37*(3), 207-218. https://doi.org/10.3233/rnn-180877

Doyle, S., Bennett, S., Fasoli, S. E., & McKenna, K. T. (2010). Interventions for sensory impairment in the upper limb after stroke. *Cochrane Database Syst Rev*, *2010*(6), CD006331. https://doi.org/10.1002/14651858.CD006331.pub2

Dukelow, S. P., Herter, T. M., Moore, K. D., Demers, M. J., Glasgow, J. I., Bagg, S. D., Norman, K. E., & Scott, S. H. (2010). Quantitative assessment of limb position sense following stroke. *Neurorehabil Neural Repair*, *24*(2), 178-187. https://doi.org/10.1177/1545968309345267

Duncan, P. W., Goldstein, L. B., Horner, R. D., Landsman, P. B., Samsa, G. P., & Matchar, D. B. (1994). Similar motor recovery of upper and lower extremities after stroke. *Stroke*, *25*(6), 1181-1188. https://doi.org/10.1161/01.str.25.6.1181

Duncan, P. W., Zorowitz, R., Bates, B., Choi, J. Y., Glasberg, J. J., Graham, G. D., Katz, R. C., Lamberty, K., & Reker, D. (2005). Management of Adult Stroke Rehabilitation Care: a clinical practice guideline. *Stroke*, *36*(9), e100-143. https://doi.org/10.1161/01.STR.0000180861.54180.FF

Duret, C., Grosmaire, A. G., & Krebs, H. I. (2019). Robot-Assisted Therapy in Upper Extremity Hemiparesis: Overview of an Evidence-Based Approach. *Front Neurol*, *10*, 412. https://doi.org/10.3389/fneur.2019.00412

Edwards, D. F., Lang, C. E., Wagner, J. M., Birkenmeier, R., & Dromerick, A. W. (2012). An evaluation of the Wolf Motor Function Test in motor trials early after stroke. *Arch Phys Med Rehabil*, *93*(4), 660-668. https://doi.org/10.1016/j.apmr.2011.10.005

Erecińska, M., & Silver, I. A. (1989). ATP and brain function. *J Cereb Blood Flow Metab*, *9*(1), 2-19. https://doi.org/10.1038/jcbfm.1989.2

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., Kim, J. S., Heo, S., Alves, H., White, S. M., Wojcicki, T. R., Mailey, E., Vieira, V. J., Martin, S. A., Pence,

B. D., Woods, J. A., McAuley, E., & Kramer, A. F. (2011). Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A*, *108*(7), 3017-3022. https://doi.org/10.1073/pnas.1015950108

Esquenazi, A., & Packel, A. (2012). Robotic-assisted gait training and restoration. *Am J Phys Med Rehabil*, *91*(11 Suppl 3), S217-227; quiz S228-231. https://doi.org/10.1097/PHM.0b013e31826bce18

Falk, T. H., Guirgis, M., Power, S., & Chau, T. T. (2011). Taking NIRS-BCIs outside the lab: towards achieving robustness against environment noise. *IEEE Trans Neural Syst Rehabil Eng*, *19*(2), 136-146. https://doi.org/10.1109/TNSRE.2010.2078516

Feigin, V. L., Brainin, M., Norrving, B., Martins, S., Sacco, R. L., Hacke, W., Fisher, M., Pandian, J., & Lindsay, P. (2022). World Stroke Organization (WSO): Global Stroke Fact Sheet 2022. *Int J Stroke*, *17*(1), 18-29. https://doi.org/10.1177/17474930211065917

Feigin, V. L., Forouzanfar, M. H., Krishnamurthi, R., Mensah, G. A., Connor, M., Bennett, D. A., Moran, A. E., Sacco, R. L., Anderson, L., Truelsen, T., O'Donnell, M., Venketasubramanian, N., Barker-Collo, S., Lawes, C. M., Wang, W., Shinohara, Y., Witt, E., Ezzati, M., Naghavi, M.,...Global Burden of Diseases, I. j., and Risk Factors Study 2010 (GBD 2010) and the GBD Stroke Experts Group. (2014). Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet*, *383*(9913), 245-254. https://doi.org/10.1016/s0140-6736(13)61953-4

Ferrari, M., & Quaresima, V. (2012). A brief review on the history of human functional near-infrared spectroscopy (fNIRS) development and fields of application. *Neuroimage*, *63*(2), 921-935. https://doi.org/10.1016/j.neuroimage.2012.03.049

Fugl-Meyer, A. R., Jääskö, 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.

Ghosh, A., Elwell, C., & Smith, M. (2012). Review article: cerebral near-infrared spectroscopy in adults: a work in progress. *Anesth Analg*, *115*(6), 1373-1383. https://doi.org/10.1213/ANE.0b013e31826dd6a6

Globas, C., Becker, C., Cerny, J., Lam, J. M., Lindemann, U., Forrester, L. W., Macko, R. F., & Luft, A. R. (2012). Chronic stroke survivors benefit from high-intensity aerobic treadmill exercise: a randomized control trial. *Neurorehabil Neural Repair*, *26*(1), 85-95. https://doi.org/10.1177/1545968311418675

Goljar, N., Burger, H., Vidmar, G., Marincek, C., Krizaj, J., Chatterji, S., Raggi, A., Leonardi, M., & Bickenbach, J. E. (2010). Functioning and disability in stroke. *Disabil Rehabil*, *32 Suppl 1*, S50-58. https://doi.org/10.3109/09638288.2010.517598

Gómez-Palacio-Schjetnan, A., & Escobar, M. L. (2013). Neurotrophins and synaptic plasticity. *Curr Top Behav Neurosci*, *15*, 117-136. https://doi.org/10.1007/7854_2012_231

Gramfort, A., Luessi, M., Larson, E., Engemann, D. A., Strohmeier, D., Brodbeck, C., Parkkonen, L., & Hämäläinen, M. S. (2014). MNE software for processing MEG and EEG data. *Neuroimage*, *86*, 446-460. https://doi.org/10.1016/j.neuroimage.2013.10.027

Grefkes, C., & Fink, G. R. (2020). Recovery from stroke: current concepts and future perspectives. *Neurol Res Pract*, *2*, 17. https://doi.org/10.1186/s42466-020-00060-6

Grefkes, C., Nowak, D. A., Eickhoff, S. B., Dafotakis, M., Küst, J., Karbe, H., & Fink, G. R. (2008). Cortical connectivity after subcortical stroke assessed with functional magnetic resonance imaging. *Ann Neurol*, *63*(2), 236-246. https://doi.org/10.1002/ana.21228

Grefkes, C., & Ward, N. S. (2014). Cortical reorganization after stroke: how much and how functional? *Neuroscientist*, *20*(1), 56-70. https://doi.org/10.1177/1073858413491147

Grotta, J. C. (2016). *Stroke : pathophysiology, diagnosis, and management* (Sixth edition. ed.). Elsevier.

Hallett, M. (2001). Plasticity of the human motor cortex and recovery from stroke. *Brain Res Brain Res Rev*, *36*(2-3), 169-174. https://doi.org/10.1016/s0165-0173(01)00092-3

Hama, S., Yoshimura, K., Yanagawa, A., Shimonaga, K., Furui, A., Soh, Z., Nishino, S., Hirano, H., Yamawaki, S., & Tsuji, T. (2020). Relationships between motor and cognitive functions and subsequent post-stroke mood disorders revealed by machine learning analysis. *Sci Rep*, *10*(1), 19571. https://doi.org/10.1038/s41598-020-76429-z

Hankey, G. J., & Blacker, D. J. (2015). Is it a stroke? *BMJ*, *350*, h56. https://doi.org/10.1136/bmj.h56

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

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. *Front Hum Neurosci*, *10*, 442. https://doi.org/10.3389/fnhum.2016.00442

Heller, A., Wade, D. T., Wood, V. A., Sunderland, A., Hewer, R. L., & Ward, E. (1987). Arm function after stroke: measurement and recovery over the first three months. *J Neurol Neurosurg Psychiatry*, *50*(6), 714-719. https://doi.org/10.1136/jnnp.50.6.714

Helm, E. E., Matt, K. S., Kirschner, K. F., Pohlig, R. T., Kohl, D., & Reisman, D. S. (2017). The influence of high intensity exercise and the Val66Met polymorphism on circulating BDNF and locomotor learning. *Neurobiol Learn Mem*, *144*, 77-85. https://doi.org/10.1016/j.nlm.2017.06.003

Hernández, E. D., Galeano, C. P., Barbosa, N. E., Forero, S. M., Nordin, Å., Sunnerhagen, K. S., & Alt Murphy, M. (2019). Intra- and inter-rater reliability of Fugl-Meyer Assessment of Upper Extremity in stroke. *J Rehabil Med*, *51*(9), 652-659. https://doi.org/10.2340/16501977-2590

Hodics, T. M., Nakatsuka, K., Upreti, B., Alex, A., Smith, P. S., & Pezzullo, J. C. (2012). Wolf Motor Function Test for characterizing moderate to severe hemiparesis in stroke patients. *Arch Phys Med Rehabil*, *93*(11), 1963-1967. https://doi.org/10.1016/j.apmr.2012.05.002

Horgan, N. F., O'Regan, M., Cunningham, C. J., & Finn, A. M. (2009). Recovery after stroke: a 1-year profile. *Disabil Rehabil*, *31*(10), 831-839. https://doi.org/10.1080/09638280802355072

Hoshi, Y. (2003). Functional near-infrared optical imaging: utility and limitations in human brain mapping. *Psychophysiology*, *40*(4), 511-520. https://doi.org/10.1111/1469-8986.00053

Hoshi, Y. (2005). Functional near-infrared spectroscopy: potential and limitations in neuroimaging studies. *Int Rev Neurobiol*, *66*, 237-266. https://doi.org/10.1016/s0074-7742(05)66008-4

Housman, S. J., Scott, K. M., & Reinkensmeyer, D. J. (2009). A randomized controlled trial of gravity-supported, computer-enhanced arm exercise for individuals with severe hemiparesis. *Neurorehabil Neural Repair*, *23*(5), 505-514. https://doi.org/10.1177/1545968308331148

Hsieh, Y. W., Lin, K. C., Wu, C. Y., Lien, H. Y., Chen, J. L., Chen, C. C., & Chang, W. H. (2014). Predicting clinically significant changes in motor and functional outcomes after robot-assisted stroke rehabilitation. *Arch Phys Med Rehabil*, *95*(2), 316-321. https://doi.org/10.1016/j.apmr.2013.09.018

Hu, Z., Liu, G., Dong, Q., & Niu, H. (2020). Applications of Resting-State fNIRS in the Developing Brain: A Review From the Connectome Perspective. *Front Neurosci*, *14*, 476. https://doi.org/10.3389/fnins.2020.00476

Huang, V. S., & Krakauer, J. W. (2009). Robotic neurorehabilitation: a computational motor learning perspective. *J Neuroeng Rehabil*, *6*, 5. https://doi.org/10.1186/1743-0003-6-5

Hunter, J. V. (2002). Magnetic resonance imaging in pediatric stroke. *Top Magn Reson Imaging*, *13*(1), 23-38. https://doi.org/10.1097/00002142-200202000-00003

Huo, C. (2021). A review on functional near-infrared spectroscopy and application in stroke rehabilitation. In (Vol. 11): Medicine in Novel Technology and Devices.

Huo, C., Xu, G., Li, W., Xie, H., Zhang, T., Liu, Y., & Li, Z. (2021). A review on functional near-infrared spectroscopy and application in stroke rehabilitation. *Medicine in Novel Technology and Devices*, *11*, 100064. https://doi.org/https://doi.org/10.1016/j.medntd.2021.100064

Hussain, A., Lee, M., Rana, J., & Virani, S. S. (2021). Epidemiology and risk factors for stroke in young individuals: implications for prevention. *Curr Opin Cardiol*, *36*(5), 565-571. https://doi.org/10.1097/HCO.0000000000000894

Isabel, C., Calvet, D., & Mas, J. L. (2016). Stroke prevention. *Presse Med*, *45*(12 Pt 2), e457-e471. https://doi.org/10.1016/j.lpm.2016.10.009

Izzetoglu, M., Chitrapu, P., Bunce, S., & Onaral, B. (2010). Motion artifact cancellation in NIR spectroscopy using discrete Kalman filtering. *Biomed Eng Online*, *9*, 16. https://doi.org/10.1186/1475-925X-9-16

Jia, B., Lv, C., Li, D., & Lv, W. (2024). Cerebral cortex activation and functional connectivity during low-load resistance training with blood flow restriction: An fNIRS study. *PLoS One*, *19*(5), e0303983. https://doi.org/10.1371/journal.pone.0303983

Jia, F., Zhao, Y., Wang, Z., Chen, J., Lu, S., & Zhang, M. (2024). Effect of Graded Motor Imagery Combined With Repetitive Transcranial Magnetic Stimulation on Upper Extremity Motor Function in Stroke Patients: A Randomized Controlled Trial. *Arch Phys Med Rehabil*, *105*(5), 819-825. https://doi.org/10.1016/j.apmr.2023.12.002

Jöbsis, F. F. (1977). Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. *Science*, *198*(4323), 1264-1267. https://doi.org/10.1126/science.929199

Johansen-Berg, H., Dawes, H., Guy, C., Smith, S. M., Wade, D. T., & Matthews, P. M. (2002). Correlation between motor improvements and altered fMRI activity after rehabilitative therapy. *Brain*, *125*(Pt 12), 2731-2742. https://doi.org/10.1093/brain/awf282

Jokinen, H., Melkas, S., Ylikoski, R., Pohjasvaara, T., Kaste, M., Erkinjuntti, T., & Hietanen, M. (2015). Post-stroke cognitive impairment is common even after successful clinical recovery. *Eur J Neurol*, *22*(9), 1288-1294. https://doi.org/10.1111/ene.12743

Jones, T. A., & Adkins, D. L. (2015). Motor System Reorganization After Stroke: Stimulating and Training Toward Perfection. *Physiology (Bethesda)*, *30*(5), 358-370. https://doi.org/10.1152/physiol.00014.2015

Kaminski, E., Maudrich, T., Bassler, P., Ordnung, M., Villringer, A., & Ragert, P. (2022). tDCS over the primary motor cortex contralateral to the trained hand enhances cross-limb transfer in older adults [Original Research]. *Frontiers in Aging Neuroscience*, *14*. https://doi.org/10.3389/fnagi.2022.935781

Kasner, S. E. (2006). Clinical interpretation and use of stroke scales. *Lancet Neurol*, *5*(7), 603-612. https://doi.org/10.1016/s1474-4422(06)70495-1

Kasner, S. E., Chalela, J. A., Luciano, J. M., Cucchiara, B. L., Raps, E. C., McGarvey, M. L., Conroy, M. B., & Localio, A. R. (1999). Reliability and validity of estimating the NIH stroke scale score from medical records. *Stroke*, *30*(8), 1534-1537. https://doi.org/10.1161/01.str.30.8.1534

Kim, D. H., Lee, K. D., Bulea, T. C., & Park, H. S. (2022). Increasing motor cortex activation during grasping via novel robotic mirror hand therapy: a pilot fNIRS study. *J Neuroeng Rehabil*, *19*(1), 8. https://doi.org/10.1186/s12984-022-00988-7

Kim, J., Kim, E., Lee, S. H., Lee, G., & Kim, Y. H. (2024). Use of cortical hemodynamic responses in digital therapeutics for upper limb rehabilitation in patients with stroke. *J Neuroeng Rehabil*, *21*(1), 115. https://doi.org/10.1186/s12984-024-01404-y

Kleim, J. A., & Jones, T. A. (2008). Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. *J Speech Lang Hear Res*, *51*(1), S225-239. https://doi.org/10.1044/1092-4388(2008/018)

Knecht, S., Hesse, S., & Oster, P. (2011). Rehabilitation after stroke. *Dtsch Arztebl Int*, *108*(36), 600-606. https://doi.org/10.3238/arztebl.2011.0600

Ko, J. H., Tang, C. C., & Eidelberg, D. (2013). Brain stimulation and functional imaging with fMRI and PET. *Handb Clin Neurol*, *116*, 77-95. https://doi.org/10.1016/B978-0-444-53497-2.00008-5

Krakauer, J. W. (2006). Motor learning: its relevance to stroke recovery and neurorehabilitation. *Curr Opin Neurol*, *19*(1), 84-90. https://doi.org/10.1097/01.wco.0000200544.29915.cc

Krakauer, J. W., & Carmichael, S. T. (2017). Broken Movement: The Neurobiology of Motor Recovery after Stroke.

Kumar, N., & Michmizos, K. P. (2020). Machine Learning for Motor Learning: EEG-based Continuous Assessment of Cognitive Engagement for Adaptive Rehabilitation

Robots. *2020 8th IEEE RAS/EMBS International Conference for Biomedical Robotics and Biomechatronics (BioRob)*, 521-526.

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.

Kwakkel, G., Kollen, B., & Twisk, J. (2006). Impact of time on improvement of outcome after stroke. *Stroke*, *37*(9), 2348-2353. https://doi.org/10.1161/01.STR.0000238594.91938.1e

Kwakkel, G., Kollen, B. J., van der Grond, J., & Prevo, A. J. (2003). Probability of regaining dexterity in the flaccid upper limb: impact of severity of paresis and time since onset in acute stroke. *Stroke*, *34*(9), 2181-2186. https://doi.org/10.1161/01.STR.0000087172.16305.CD

Lanctôt, K. L., Lindsay, M. P., Smith, E. E., Sahlas, D. J., Foley, N., Gubitz, G., Austin, M., Ball, K., Bhogal, S., Blake, T., Herrmann, N., Hogan, D., Khan, A., Longman, S., King, A., Leonard, C., Shoniker, T., Taylor, T., Teed, M.,...Consortium, i. c. w. t. C. S. (2020). Mood, Cognition and Fatigue following Stroke, 6th edition update 2019. *Int J Stroke*, *15*(6), 668-688. https://doi.org/10.1177/1747493019847334

Langhorne, P., Bernhardt, J., & Kwakkel, G. (2011). Stroke rehabilitation. *Lancet*, *377*(9778), 1693-1702. https://doi.org/10.1016/S0140-6736(11)60325-5

Langhorne, P., Coupar, F., & Pollock, A. (2009). Motor recovery after stroke: a systematic review. *Lancet Neurol*, *8*(8), 741-754. https://doi.org/10.1016/s1474-4422(09)70150-4

Lawlor, D. A., Smith, G. D., Leon, D. A., Sterne, J. A., & Ebrahim, S. (2002). Secular trends in mortality by stroke subtype in the 20th century: a retrospective analysis. *Lancet*, *360*(9348), 1818-1823. https://doi.org/10.1016/S0140-6736(02)11769-7

Lee, J. (**2024**). Data-Driven Stroke Classification Utilizing Electromyographic Muscle Features and Machine Learning Techniques. In: *Appl. Sci.* .

Lee, J., Kim, Y., & Kim, E. (2024). Data-Driven Stroke Classification Utilizing Electromyographic Muscle Features and Machine Learning Techniques. *Applied Sciences*.

Levi, F., Lucchini, F., Negri, E., & La Vecchia, C. (2002). Trends in mortality from cardiovascular and cerebrovascular diseases in Europe and other areas of the world. *Heart*, *88*(2), 119-124. https://doi.org/10.1136/heart.88.2.119

Li, X., Jin, M., Zhang, N., Hongman, W., Fu, L., & Qi, Q. (2024). Neural correlates of fine motor grasping skills: Longitudinal insights into motor cortex activation using fNIRS. *Brain Behav*, *14*(1), e3383. https://doi.org/10.1002/brb3.3383

Lim, S. B., & Eng, J. J. (2019). Increased Sensorimotor Cortex Activation With Decreased Motor Performance During Functional Upper Extremity Tasks Poststroke. *J Neurol Phys Ther*, *43*(3), 141-150. https://doi.org/10.1097/NPT.0000000000000277

Lin, S. H., & Dionne, T. P. (2018). Interventions to Improve Movement and Functional Outcomes in Adult Stroke Rehabilitation: Review and Evidence Summary. *J Particip Med*, *10*(1), e3. https://doi.org/10.2196/jopm.8929

Linder, S. M., Rosenfeldt, A. B., Davidson, S., Zimmerman, N., Penko, A., Lee, J., Clark, C., & Alberts, J. L. (2019). Forced, Not Voluntary, Aerobic Exercise Enhances Motor

Recovery in Persons With Chronic Stroke. *Neurorehabil Neural Repair*, *33*(8), 681-690. https://doi.org/10.1177/1545968319862557

Little, C. E., Emery, C., Black, A., Scott, S. H., Meeuwisse, W., Nettel-Aguirre, A., Benson, B., & Dukelow, S. (2015). Test-retest reliability of KINARM robot sensorimotor and cognitive assessment: in pediatric ice hockey players. *J Neuroeng Rehabil*, *12*, 78. https://doi.org/10.1186/s12984-015-0070-0

Liu, L., Jin, M., Zhang, L., Zhang, Q., Hu, D., Jin, L., & Nie, Z. (2022). Brain-Computer Interface-Robot Training Enhances Upper Extremity Performance and Changes the Cortical Activation in Stroke Patients: A Functional Near-Infrared Spectroscopy Study. *Front Neurosci*, *16*, 809657. https://doi.org/10.3389/fnins.2022.809657

Lo, A. C., Guarino, P. D., Richards, L. G., Haselkorn, J. K., Wittenberg, G. F., Federman, D. G., Ringer, R. J., Wagner, T. H., Krebs, H. I., Volpe, B. T., Bever, C. T., Bravata, D. M., Duncan, P. W., Corn, B. H., Maffucci, A. D., Nadeau, S. E., Conroy, S. S., Powell, J. M., Huang, G. D., & Peduzzi, P. (2010). Robot-assisted therapy for long-term upper-limb impairment after stroke. *N Engl J Med*, *362*(19), 1772-1783. https://doi.org/10.1056/NEJMoa0911341

Lo, J. W., Crawford, J. D., Desmond, D. W., Bae, H. J., Lim, J. S., Godefroy, O., Roussel, M., Kang, Y., Jahng, S., Köhler, S., Staals, J., Verhey, F., Chen, C., Xu, X., Chong, E. J., Kandiah, N., Yatawara, C., Bordet, R., Dondaine, T.,...Collaboration, S. a. C. S. (2022). Long-Term Cognitive Decline After Stroke: An Individual Participant Data Meta-Analysis. *Stroke*, *53*(4), 1318-1327. https://doi.org/10.1161/STROKEAHA.121.035796

Lum, P. S., Burgar, C. G., Shor, P. C., Majmundar, M., & Van der Loos, M. (2002). Robot-assisted movement training compared with conventional therapy techniques for the rehabilitation of upper-limb motor function after stroke. *Arch Phys Med Rehabil*, *83*(7), 952-959. https://doi.org/10.1053/apmr.2001.33101

MacKay-Lyons, M., Billinger, S. A., Eng, J. J., Dromerick, A., Giacomantonio, N., Hafer-Macko, C., Macko, R., Nguyen, E., Prior, P., Suskin, N., Tang, A., Thornton, M., & Unsworth, K. (2020). Aerobic Exercise Recommendations to Optimize Best Practices in Care After Stroke: AEROBICS 2019 Update. *Phys Ther*, *100*(1), 149-156. https://doi.org/10.1093/ptj/pzz153

Macko, R. F., Ivey, F. M., Forrester, L. W., Hanley, D., Sorkin, J. D., Katzel, L. I., Silver, K. H., & Goldberg, A. P. (2005). Treadmill exercise rehabilitation improves ambulatory function and cardiovascular fitness in patients with chronic stroke: a randomized, controlled trial. *Stroke*, *36*(10), 2206-2211. https://doi.org/10.1161/01.STR.0000181076.91805.89

Maejima, H., Inoue, T., & Takamatsu, Y. (2019). Therapeutic exercise accompanied by neuronal modulation to enhance neurotrophic factors in the brain with central nervous system disorders. *Phys Ther Res*, *22*(1), 38-43. https://doi.org/10.1298/ptr.R0004

Mang, C. S., Campbell, K. L., Ross, C. J., & Boyd, L. A. (2013). Promoting neuroplasticity for motor rehabilitation after stroke: considering the effects of aerobic exercise and genetic variation on brain-derived neurotrophic factor. *Phys Ther*, *93*(12), 1707-1716. https://doi.org/10.2522/ptj.20130053

Mang, C. S., Whitten, T. A., Cosh, M. S., Scott, S. H., Wiley, J. P., Debert, C. T., Dukelow, S. P., & Benson, B. W. (2018). Test-retest reliability of the KINARM end-point robot for assessment of sensory, motor and neurocognitive function in young adult athletes. *PLoS One*, *13*(4), e0196205. https://doi.org/10.1371/journal.pone.0196205

Marchal-Crespo, L., & Reinkensmeyer, D. J. (2009). Review of control strategies for robotic movement training after neurologic injury. *J Neuroeng Rehabil*, *6*, 20. https://doi.org/10.1186/1743-0003-6-20

Marendic, M., Bulicic, A. R., Borovina, T., Mise, N. I., Romac, R., Suljic, E., Titlic, M., & Milosevic, M. (2016). Categorization of Ischemic Stroke Patients Compared with National Institutes of Health Stroke Scale. *Med Arch*, *70*(2), 119-122. https://doi.org/10.5455/medarh.2016.70.119-122

Marshall, R. S., Perera, G. M., Lazar, R. M., Krakauer, J. W., Constantine, R. C., & DeLaPaz, R. L. (2000). Evolution of cortical activation during recovery from corticospinal tract infarction. *Stroke*, *31*(3), 656-661. https://doi.org/10.1161/01.str.31.3.656

McDonnell, M. N., Buckley, J. D., Opie, G. M., Ridding, M. C., & Semmler, J. G. (2013). A single bout of aerobic exercise promotes motor cortical neuroplasticity. *J Appl Physiol (1985)*, *114*(9), 1174-1182. https://doi.org/10.1152/japplphysiol.01378.2012

McKendrick, R., Mehta, R., Ayaz, H., Scheldrup, M., & Parasuraman, R. (2017). Prefrontal Hemodynamics of Physical Activity and Environmental Complexity During Cognitive Work. *Hum Factors*, *59*(1), 147-162. https://doi.org/10.1177/0018720816675053

McKendrick, R., Parasuraman, R., & Ayaz, H. (2015). Wearable functional near infrared spectroscopy (fNIRS) and transcranial direct current stimulation (tDCS): expanding vistas for neurocognitive augmentation. *Front Syst Neurosci*, *9*, 27. https://doi.org/10.3389/fnsys.2015.00027

McKendrick, R., Parasuraman, R., Murtza, R., Formwalt, A., Baccus, W., Paczynski, M., & Ayaz, H. (2016). Into the Wild: Neuroergonomic Differentiation of Hand-Held and Augmented Reality Wearable Displays during Outdoor Navigation with Functional Near Infrared Spectroscopy. *Front Hum Neurosci*, *10*, 216. https://doi.org/10.3389/fnhum.2016.00216

Medicine, A. C. o. S. (2009). American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. *Med Sci Sports Exerc*, *41*(3), 687-708. https://doi.org/10.1249/MSS.0b013e3181915670

Mehrholz, J., Pohl, M., Platz, T., Kugler, J., & Elsner, B. (2018). Electromechanical and robot-assisted arm training for improving activities of daily living, arm function, and arm muscle strength after stroke. *Cochrane Database Syst Rev*, *9*(9), CD006876. https://doi.org/10.1002/14651858.CD006876.pub5

Metcalf, C., Adams, J., Burridge, J., Yule, V., & Chappell, P. (2007). A review of clinical upper limb assessments within the framework of the WHO ICF. *Musculoskeletal Care*, *5*(3), 160-173. https://doi.org/10.1002/msc.108

Mihara, M., & Miyai, I. (2016). Review of functional near-infrared spectroscopy in neurorehabilitation. *Neurophotonics*, *3*(3), 031414. https://doi.org/10.1117/1.NPh.3.3.031414

Mintun, M. A., Lundstrom, B. N., Snyder, A. Z., Vlassenko, A. G., Shulman, G. L., & Raichle, M. E. (2001). Blood flow and oxygen delivery to human brain during functional activity:

theoretical modeling and experimental data. *Proc Natl Acad Sci U S A*, *98*(12), 6859-6864. https://doi.org/10.1073/pnas.111164398

Mooney, R. A., Ackerley, S. J., Rajeswaran, D. K., Cirillo, J., Barber, P. A., Stinear, C. M., & Byblow, W. D. (2019). The Influence of Primary Motor Cortex Inhibition on Upper Limb Impairment and Function in Chronic Stroke: A Multimodal Study. *Neurorehabil Neural Repair*, *33*(2), 130-140. https://doi.org/10.1177/1545968319826052

Moriai-Izawa, A., Dan, H., Dan, I., Sano, T., Oguro, K., Yokota, H., Tsuzuki, D., & Watanabe, E. (2012). Multichannel fNIRS assessment of overt and covert confrontation naming. *Brain Lang*, *121*(3), 185-193. https://doi.org/10.1016/j.bandl.2012.02.001

Moriarty, T. A., Mermier, C., Kravitz, L., Gibson, A., Beltz, N., & Zuhl, M. (2019). Acute Aerobic Exercise Based Cognitive and Motor Priming: Practical Applications and Mechanisms. *Front Psychol*, *10*, 2790. https://doi.org/10.3389/fpsyg.2019.02790

Morris, D. M., Uswatte, G., Crago, J. E., Cook, E. W., & Taub, E. (2001). The reliability of the wolf motor function test for assessing upper extremity function after stroke. *Arch Phys Med Rehabil*, *82*(6), 750-755. https://doi.org/10.1053/apmr.2001.23183

Mukherjee, A., & Chakravarty, A. (2010). Spasticity mechanisms - for the clinician. *Front Neurol*, *1*, 149. https://doi.org/10.3389/fneur.2010.00149

Muller, C. O., Faity, G., Muthalib, M., Perrey, S., Dray, G., Xu, B., Froger, J., Mottet, D., Laffont, I., Delorme, M., & Bakhti, K. (2024). Brain-movement relationship during upper-limb functional movements in chronic post-stroke patients. *J Neuroeng Rehabil*, *21*(1), 188. https://doi.org/10.1186/s12984-024-01461-3

Murase, N., Duque, J., Mazzocchio, R., & Cohen, L. G. (2004). Influence of interhemispheric interactions on motor function in chronic stroke. *Ann Neurol*, *55*(3), 400-409. https://doi.org/10.1002/ana.10848

Murphy, T. H., & Corbett, D. (2009). Plasticity during stroke recovery: from synapse to behaviour. *Nat Rev Neurosci*, *10*(12), 861-872. https://doi.org/10.1038/nrn2735

Naseer, N., & Hong, K. S. (2015). fNIRS-based brain-computer interfaces: a review. *Front Hum Neurosci*, *9*, 3. https://doi.org/10.3389/fnhum.2015.00003

Nilsen, D. M., Gillen, G., Geller, D., Hreha, K., Osei, E., & Saleem, G. T. (2015). Effectiveness of interventions to improve occupational performance of people with motor impairments after stroke: an evidence-based review. *Am J Occup Ther*, *69*(1), 6901180030p6901180031-6901180039. https://doi.org/10.5014/ajot.2015.011965

Nudo, R. J., Plautz, E. J., & Frost, S. B. (2001). Role of adaptive plasticity in recovery of function after damage to motor cortex. *Muscle Nerve*, *24*(8), 1000-1019. https://doi.org/10.1002/mus.1104

O'Dwyer, N. J., Ada, L., & Neilson, P. D. (1996). Spasticity and muscle contracture following stroke. *Brain*, *119 (Pt 5)*, 1737-1749. https://doi.org/10.1093/brain/119.5.1737

Obrig, H. (2014). NIRS in clinical neurology - a 'promising' tool? *Neuroimage*, *85 Pt 1*, 535-546. https://doi.org/10.1016/j.neuroimage.2013.03.045

Otaka, E., Otaka, Y., Kasuga, S., Nishimoto, A., Yamazaki, K., Kawakami, M., Ushiba, J., & Liu, M. (2015). Clinical usefulness and validity of robotic measures of reaching movement in hemiparetic stroke patients. *J Neuroeng Rehabil*, *12*, 66. https://doi.org/10.1186/s12984-015-0059-8

Page, S. J., Gater, D. R., & Bach-Y-Rita, P. (2004). Reconsidering the motor recovery plateau in stroke rehabilitation. *Arch Phys Med Rehabil*, *85*(8), 1377-1381. https://doi.org/10.1016/j.apmr.2003.12.031

Penna, L. G., Pinheiro, J. P., Ramalho, S. H. R., & Ribeiro, C. F. (2021). Effects of aerobic physical exercise on neuroplasticity after stroke: systematic review. *Arq Neuropsiquiatr*, *79*(9), 832-843. https://doi.org/10.1590/0004-282X-ANP-2020-0551

Perrey, S. (2014). Possibilities for examining the neural control of gait in humans with fNIRS. *Front Physiol*, *5*, 204. https://doi.org/10.3389/fphys.2014.00204

Pinti, P., Tachtsidis, I., Hamilton, A., Hirsch, J., Aichelburg, C., Gilbert, S., & Burgess, P. W. (2020). The present and future use of functional near-infrared spectroscopy (fNIRS) for cognitive neuroscience. *Ann N Y Acad Sci*, *1464*(1), 5-29. https://doi.org/10.1111/nyas.13948

Piper, S. K., Krueger, A., Koch, S. P., Mehnert, J., Habermehl, C., Steinbrink, J., Obrig, H., & Schmitz, C. H. (2014). A wearable multi-channel fNIRS system for brain imaging in freely moving subjects. *Neuroimage*, *85 Pt 1*(0 1), 64-71. https://doi.org/10.1016/j.neuroimage.2013.06.062

Ploughman, M., Austin, M. W., Glynn, L., & Corbett, D. (2015). The effects of poststroke aerobic exercise on neuroplasticity: a systematic review of animal and clinical studies. *Transl Stroke Res*, *6*(1), 13-28. https://doi.org/10.1007/s12975-014-0357-7

Ploughman, M., Eskes, G. A., Kelly, L. P., Kirkland, M. C., Devasahayam, A. J., Wallack, E. M., Abraha, B., Hasan, S. M. M., Downer, M. B., Keeler, L., Wilson, G., Skene, E., Sharma, I., Chaves, A. R., Curtis, M. E., Bedford, E., Robertson, G. S., Moore, C. S., McCarthy, J., & Mackay-Lyons, M. (2019). Synergistic Benefits of Combined Aerobic and Cognitive Training on Fluid Intelligence and the Role of IGF-1 in Chronic Stroke. *Neurorehabil Neural Repair*, *33*(3), 199-212. https://doi.org/10.1177/1545968319832605

Pollock, A., Baer, G., Pomeroy, V., & Langhorne, P. (2003). Physiotherapy treatment approaches for the recovery of postural control and lower limb function following stroke. *Cochrane Database Syst Rev*(2), CD001920. https://doi.org/10.1002/14651858.CD001920

Pollock, A., Farmer, S. E., Brady, M. C., Langhorne, P., Mead, G. E., Mehrholz, J., & van Wijck, F. (2014). Interventions for improving upper limb function after stroke. *Cochrane Database Syst Rev*, *2014*(11), CD010820. https://doi.org/10.1002/14651858.CD010820.pub2

Pollock, M. L., Franklin, B. A., Balady, G. J., Chaitman, B. L., Fleg, J. L., Fletcher, B., Limacher, M., Piña, I. L., Stein, R. A., Williams, M., & Bazzarre, T. (2000). AHA Science Advisory. Resistance exercise in individuals with and without cardiovascular disease: benefits, rationale, safety, and prescription: An advisory from the Committee on Exercise, Rehabilitation, and Prevention, Council on Clinical Cardiology, American Heart Association; Position paper endorsed by the American College of Sports Medicine. *Circulation*, *101*(7), 828-833. https://doi.org/10.1161/01.cir.101.7.828

Pontzer, H., Brown, M. H., Raichlen, D. A., Dunsworth, H., Hare, B., Walker, K., Luke, A., Dugas, L. R., Durazo-Arvizu, R., Schoeller, D., Plange-Rhule, J., Bovet, P., Forrester, T. E., Lambert, E. V., Thompson, M. E., Shumaker, R. W., & Ross, S. R. (2016). Metabolic

acceleration and the evolution of human brain size and life history. *Nature*, *533*(7603), 390-392. https://doi.org/10.1038/nature17654

Prange, G. B., Jannink, M. J., Groothuis-Oudshoorn, C. G., Hermens, H. J., & Ijzerman, M. J. (2006). Systematic review of the effect of robot-aided therapy on recovery of the hemiparetic arm after stroke. *J Rehabil Res Dev*, *43*(2), 171-184. https://doi.org/10.1682/jrrd.2005.04.0076

Quaresima, V., & Ferrari, M. (2019). Functional Near-Infrared Spectroscopy (fNIRS) for Assessing Cerebral Cortex Function During Human Behavior in Natural/Social Situations: A Concise Review. *Organizational Research Methods*, *22*, 46 - 68.

Raghavan, P. (2015). Upper Limb Motor Impairment After Stroke. *Phys Med Rehabil Clin N Am*, *26*(4), 599-610. https://doi.org/10.1016/j.pmr.2015.06.008

Ramos-Lima, M. J. M., Brasileiro, I. C., Lima, T. L., & Braga-Neto, P. (2018). Quality of life after stroke: impact of clinical and sociodemographic factors. *Clinics (Sao Paulo)*, *73*, e418. https://doi.org/10.6061/clinics/2017/e418

Rech, K. D., Salazar, A. P., Marchese, R. R., Schifino, G., Cimolin, V., & Pagnussat, A. S. (2020). Fugl-Meyer Assessment Scores Are Related With Kinematic Measures in People with Chronic Hemiparesis after Stroke. *J Stroke Cerebrovasc Dis*, *29*(1), 104463. https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.104463

Rehme, A. K., Eickhoff, S. B., Rottschy, C., Fink, G. R., & Grefkes, C. (2012). Activation likelihood estimation meta-analysis of motor-related neural activity after stroke. *Neuroimage*, *59*(3), 2771-2782. https://doi.org/10.1016/j.neuroimage.2011.10.023

Rehme, A. K., Fink, G. R., von Cramon, D. Y., & Grefkes, C. (2011). The role of the contralesional motor cortex for motor recovery in the early days after stroke assessed with longitudinal FMRI. *Cereb Cortex*, *21*(4), 756-768. https://doi.org/10.1093/cercor/bhq140

Rehme, A. K., & Grefkes, C. (2013). Cerebral network disorders after stroke: evidence from imaging-based connectivity analyses of active and resting brain states in humans. *J Physiol*, *591*(1), 17-31. https://doi.org/10.1113/jphysiol.2012.243469

Rimmer, J. H., & Wang, E. (2005). Aerobic exercise training in stroke survivors. *Top Stroke Rehabil*, *12*(1), 17-30. https://doi.org/10.1310/L6HG-8X8N-QC9Q-HHM8

Rioult-Pedotti, M. S., Friedman, D., Hess, G., & Donoghue, J. P. (1998). Strengthening of horizontal cortical connections following skill learning. *Nat Neurosci*, *1*(3), 230-234. https://doi.org/10.1038/678

Roig, M., Skriver, K., Lundbye-Jensen, J., Kiens, B., & Nielsen, J. B. (2012). A single bout of exercise improves motor memory. *PLoS One*, *7*(9), e44594. https://doi.org/10.1371/journal.pone.0044594

Sabih, A. (2023). Stroke Prevention In A. K. Prasanna Tadi 2 (Ed.): StatPearls Publishing.

Scarapicchia, V., Brown, C., Mayo, C., & Gawryluk, J. R. (2017). Functional Magnetic Resonance Imaging and Functional Near-Infrared Spectroscopy: Insights from Combined Recording Studies. *Front Hum Neurosci*, *11*, 419. https://doi.org/10.3389/fnhum.2017.00419

Schaechter, J. D. (2004). Motor rehabilitation and brain plasticity after hemiparetic stroke. *Prog Neurobiol*, *73*(1), 61-72. https://doi.org/10.1016/j.pneurobio.2004.04.001

Schaechter, J. D., Kraft, E., Hilliard, T. S., Dijkhuizen, R. M., Benner, T., Finklestein, S. P., Rosen, B. R., & Cramer, S. C. (2002). Motor recovery and cortical reorganization after constraint-induced movement therapy in stroke patients: a preliminary study. *Neurorehabil Neural Repair*, *16*(4), 326-338. https://doi.org/10.1177/154596830201600403

Semenov, A. N., Yakimov, B. P., Rubekina, A. A., Gorin, D. A., Drachev, V. P., Zarubin, M. P., Velikanov, A. N., Lademann, J., Fadeev, V. V., Priezzhev, A. V., Darvin, M. E., & Shirshin, E. A. (2020). The Oxidation-Induced Autofluorescence Hypothesis: Red Edge Excitation and Implications for Metabolic Imaging. *Molecules*, *25*(8). https://doi.org/10.3390/molecules25081863

Semrau, J. A., Herter, T. M., Scott, S. H., & Dukelow, S. P. (2013). Robotic identification of kinesthetic deficits after stroke. *Stroke*, *44*(12), 3414-3421. https://doi.org/10.1161/STROKEAHA.113.002058

Shelton, F. N., & Reding, M. J. (2001). Effect of lesion location on upper limb motor recovery after stroke. *Stroke*, *32*(1), 107-112. https://doi.org/10.1161/01.str.32.1.107

Simmatis, L., Krett, J., Scott, S. H., & Jin, A. Y. (2017). Robotic exoskeleton assessment of transient ischemic attack. *PLoS One*, *12*(12), e0188786. https://doi.org/10.1371/journal.pone.0188786

Singh, A. M., Neva, J. L., & Staines, W. R. (2014). Acute exercise enhances the response to paired associative stimulation-induced plasticity in the primary motor cortex. *Exp Brain Res*, *232*(11), 3675-3685. https://doi.org/10.1007/s00221-014-4049-z

Singh, A. M., & Staines, W. R. (2015). The effects of acute aerobic exercise on the primary motor cortex. *J Mot Behav*, *47*(4), 328-339. https://doi.org/10.1080/00222895.2014.983450

Sivaramakrishnan, A., & Madhavan, S. (2021). Combining transcranial direct current stimulation with aerobic exercise to optimize cortical priming in stroke. *Appl Physiol Nutr Metab*, *46*(5), 426-435. https://doi.org/10.1139/apnm-2020-0677

Sood, M., Besson, P., Muthalib, M., Jindal, U., Perrey, S., Dutta, A., & Hayashibe, M. (2016). NIRS-EEG joint imaging during transcranial direct current stimulation: Online parameter estimation with an autoregressive model. *J Neurosci Methods*, *274*, 71-80. https://doi.org/10.1016/j.jneumeth.2016.09.008

Stefan, K., Kunesch, E., Cohen, L. G., Benecke, R., & Classen, J. (2000). Induction of plasticity in the human motor cortex by paired associative stimulation. *Brain*, *123 Pt 3*, 572-584. https://doi.org/10.1093/brain/123.3.572

Stinear, C. M., Smith, M. C., & Byblow, W. D. (2019). Prediction Tools for Stroke Rehabilitation. *Stroke*, *50*(11), 3314-3322. https://doi.org/10.1161/strokeaha.119.025696

Stoykov, M. E., & Madhavan, S. (2015). Motor priming in neurorehabilitation. *J Neurol Phys Ther*, *39*(1), 33-42. https://doi.org/10.1097/NPT.0000000000000065

Strangman, G., Boas, D. A., & Sutton, J. P. (2002). Non-invasive neuroimaging using near-infrared light. *Biol Psychiatry*, *52*(7), 679-693. https://doi.org/10.1016/s0006-3223(02)01550-0

Stucki, G., Cieza, A., Ewert, T., Kostanjsek, N., Chatterji, S., & Ustün, T. B. (2002). Application of the International Classification of Functioning, Disability and Health (ICF) in

clinical practice. *Disabil Rehabil*, *24*(5), 281-282. https://doi.org/10.1080/09638280110105222

Su, F., & Xu, W. (2020). Enhancing Brain Plasticity to Promote Stroke Recovery. *Front Neurol*, *11*, 554089. https://doi.org/10.3389/fneur.2020.554089

Sun, J., Pang, R., Chen, S., Chen, H., Xie, Y., Chen, D., Wu, K., Liang, J., Yan, K., & Hao, Z. (2021). Near-infrared spectroscopy as a promising tool in stroke: Current applications and future perspectives. *Journal of Innovative Optical Health Sciences*, *14*(06), 2130006. https://doi.org/10.1142/S1793545821300068

Tadi, P., & Lui, F. (2023). Acute Stroke. In *StatPearls*. StatPearls Publishing

Copyright © 2024, StatPearls Publishing LLC.

Takeuchi, N., & Izumi, S. (2012). Noninvasive brain stimulation for motor recovery after stroke: mechanisms and future views. *Stroke Res Treat*, *2012*, 584727. https://doi.org/10.1155/2012/584727

Takeuchi, N., Tada, T., Toshima, M., Matsuo, Y., & Ikoma, K. (2009). Repetitive transcranial magnetic stimulation over bilateral hemispheres enhances motor function and training effect of paretic hand in patients after stroke. *J Rehabil Med*, *41*(13), 1049-1054. https://doi.org/10.2340/16501977-0454

Taub, E., Miller, N. E., Novack, T. A., Cook, E. W., 3rd, Fleming, W. C., Nepomuceno, C. S., Connell, J. S., & Crago, J. E. (1993). Technique to improve chronic motor deficit after stroke. *Arch Phys Med Rehabil*, *74*(4), 347-354.

Terroni, L., Sobreiro, M. F. M., Conforto, A. B., Adda, C. C., Guajardo, V. D., de Lucia, M. C. S., & Fráguas, R. (2012). Association among depression, cognitive impairment and executive dysfunction after stroke. *Dement Neuropsychol*, *6*(3), 152-157. https://doi.org/10.1590/S1980-57642012DN06030007

Teyler, T. J., & DiScenna, P. (1987). Long-term potentiation. *Annu Rev Neurosci*, *10*, 131-161. https://doi.org/10.1146/annurev.ne.10.030187.001023

Timmermans, A. A., Lemmens, R. J., Monfrance, M., Geers, R. P., Bakx, W., Smeets, R. J., & Seelen, H. A. (2014). Effects of task-oriented robot training on arm function, activity, and quality of life in chronic stroke patients: a randomized controlled trial. *J Neuroeng Rehabil*, *11*, 45. https://doi.org/10.1186/1743-0003-11-45

Timmermans, A. A., Spooren, A. I., Kingma, H., & Seelen, H. A. (2010). Influence of task-oriented training content on skilled arm-hand performance in stroke: a systematic review. *Neurorehabil Neural Repair*, *24*(9), 858-870. https://doi.org/10.1177/1545968310368963

Trompetto, C., Marinelli, L., Mori, L., Pelosin, E., Currà, A., Molfetta, L., & Abbruzzese, G. (2014). Pathophysiology of spasticity: implications for neurorehabilitation. *Biomed Res Int*, *2014*, 354906. https://doi.org/10.1155/2014/354906

Urton, M. L., Kohia, M., Davis, J., & Neill, M. R. (2007). Systematic literature review of treatment interventions for upper extremity hemiparesis following stroke. *Occup Ther Int*, *14*(1), 11-27. https://doi.org/10.1002/oti.220

Veerbeek, J. M., Langbroek-Amersfoort, A. C., van Wegen, E. E., Meskers, C. G., & Kwakkel, G. (2017). Effects of Robot-Assisted Therapy for the Upper Limb After Stroke. *Neurorehabil Neural Repair*, *31*(2), 107-121. https://doi.org/10.1177/1545968316666957

Virani, S. S., Alonso, A., Aparicio, H. J., Benjamin, E. J., Bittencourt, M. S., Callaway, C. W., Carson, A. P., Chamberlain, A. M., Cheng, S., Delling, F. N., Elkind, M. S. V., Evenson, K. R., Ferguson, J. F., Gupta, D. K., Khan, S. S., Kissela, B. M., Knutson, K. L., Lee, C. D., Lewis, T. T.,...Subcommittee, A. H. A. C. o. E. a. P. S. C. a. S. S. (2021). Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association. *Circulation*, *143*(8), e254-e743. https://doi.org/10.1161/CIR.0000000000000950

Virani, S. S., Alonso, A., Benjamin, E. J., Bittencourt, M. S., Callaway, C. W., Carson, A. P., Chamberlain, A. M., Chang, A. R., Cheng, S., Delling, F. N., Djousse, L., Elkind, M. S. V., Ferguson, J. F., Fornage, M., Khan, S. S., Kissela, B. M., Knutson, K. L., Kwan, T. W., Lackland, D. T.,...Subcommittee, A. H. A. C. o. E. a. P. S. C. a. S. S. (2020). Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. *Circulation*, *141*(9), e139-e596. https://doi.org/10.1161/CIR.0000000000000757

von Luhmann, A., Wabnitz, H., Sander, T., & Muller, K. R. (2017). M3BA: A Mobile, Modular, Multimodal Biosignal Acquisition Architecture for Miniaturized EEG-NIRS-Based Hybrid BCI and Monitoring. *IEEE Trans Biomed Eng*, *64*(6), 1199-1210. https://doi.org/10.1109/tbme.2016.2594127

Wade, D. T., Langton-Hewer, R., Wood, V. A., Skilbeck, C. E., & Ismail, H. M. (1983). The hemiplegic arm after stroke: measurement and recovery. *J Neurol Neurosurg Psychiatry*, *46*(6), 521-524. https://doi.org/10.1136/jnnp.46.6.521

Wang, X., Ye, Z., Busse, J. W., Hill, M. D., Smith, E. E., Guyatt, G. H., Prasad, K., Lindsay, M. P., Yang, H., Zhang, Y., Liu, Y., Tang, B., Wang, Y., Couban, R. J., & An, Z. (2022). Endovascular thrombectomy with or without intravenous alteplase for acute ischemic stroke due to large vessel occlusion: a systematic review and meta-analysis of randomized trials. *Stroke Vasc Neurol*, *7*(6), 510-517. https://doi.org/10.1136/svn-2022-001547

Ward, N. S., Brown, M. M., Thompson, A. J., & Frackowiak, R. S. (2003). Neural correlates of motor recovery after stroke: a longitudinal fMRI study. *Brain*, *126*(Pt 11), 2476-2496. https://doi.org/10.1093/brain/awg245

Ward, N. S., & Cohen, L. G. (2004). Mechanisms underlying recovery of motor function after stroke. *Arch Neurol*, *61*(12), 1844-1848. https://doi.org/10.1001/archneur.61.12.1844

Wardlaw, J. M., Smith, C., & Dichgans, M. (2019). Small vessel disease: mechanisms and clinical implications. *Lancet Neurol*, *18*(7), 684-696. https://doi.org/10.1016/s1474-4422(19)30079-1

Weber, L. M., & Stein, J. (2018). The use of robots in stroke rehabilitation: A narrative review. *NeuroRehabilitation*, *43*(1), 99-110. https://doi.org/10.3233/NRE-172408

Wessel, M. J., Zimerman, M., & Hummel, F. C. (2015). Non-invasive brain stimulation: an interventional tool for enhancing behavioral training after stroke. *Front Hum Neurosci*, *9*, 265. https://doi.org/10.3389/fnhum.2015.00265

Wieloch, T., & Nikolich, K. (2006). Mechanisms of neural plasticity following brain injury. *Curr Opin Neurobiol*, *16*(3), 258-264. https://doi.org/10.1016/j.conb.2006.05.011

Winstein, C. J., Stein, J., Arena, R., Bates, B., Cherney, L. R., Cramer, S. C., Deruyter, F., Eng, J. J., Fisher, B., Harvey, R. L., Lang, C. E., MacKay-Lyons, M., Ottenbacher, K. J., Pugh,

S., Reeves, M. J., Richards, L. G., Stiers, W., Zorowitz, R. D., & American Heart Association Stroke Council, C. o. C. a. S. N., C.uncil on Clinical Cardiology, and Council on Quality of Care and Outcomes Research. (2016). Guidelines for Adult Stroke Rehabilitation and Recovery: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*, *47*(6), e98-e169. https://doi.org/10.1161/STR.0000000000000098

Wolf, S. L., Catlin, P. A., Ellis, M., Archer, A. L., Morgan, B., & Piacentino, A. (2001). Assessing Wolf motor function test as outcome measure for research in patients after stroke. *Stroke*, *32*(7), 1635-1639. https://doi.org/10.1161/01.str.32.7.1635

Wolf, S. L., Thompson, P. A., Morris, D. M., Rose, D. K., Winstein, C. J., Taub, E., Giuliani, C., & Pearson, S. L. (2005). The EXCITE trial: attributes of the Wolf Motor Function Test in patients with subacute stroke. *Neurorehabil Neural Repair*, *19*(3), 194-205. https://doi.org/10.1177/1545968305276663

Wong, A., Robinson, L., Soroush, S., Suresh, A., Yang, D., Madu, K., Harhay, M. N., & Pourrezaei, K. (2021). Assessment of cerebral oxygenation response to hemodialysis using near-infrared spectroscopy (NIRS): Challenges and solutions. *J Innov Opt Health Sci*, *14*(6). https://doi.org/10.1142/s1793545821500164

Wunder, M. L., & Staines, W. R. (2022). Chronic Exercise as a Modulator of Cognitive Control: Investigating the Electrophysiological Indices of Performance Monitoring. *Front Psychol*, *13*, 814199. https://doi.org/10.3389/fpsyg.2022.814199

Xie, H., Li, X., Huang, W., Yin, J., Luo, C., Li, Z., & Dou, Z. (2022). Effects of robot-assisted task-oriented upper limb motor training on neuroplasticity in stroke patients with different degrees of motor dysfunction: A neuroimaging motor evaluation index. *Front Neurosci*, *16*, 957972. https://doi.org/10.3389/fnins.2022.957972

Ye, S., Tao, L., Gong, S., Ma, Y., Wu, J., Li, W., Kang, J., Tang, M., Zuo, G., & Shi, C. (2024). Upper limb motor assessment for stroke with force, muscle activation and interhemispheric balance indices based on sEMG and fNIRS. *Front Neurol*, *15*, 1337230. https://doi.org/10.3389/fneur.2024.1337230

Yekutiel, M., & Guttman, E. (1993). A controlled trial of the retraining of the sensory function of the hand in stroke patients. *J Neurol Neurosurg Psychiatry*, *56*(3), 241-244. https://doi.org/10.1136/jnnp.56.3.241

Yoo, C., & Park, J. (2015). Impact of task-oriented training on hand function and activities of daily living after stroke. *J Phys Ther Sci*, *27*(8), 2529-2531. https://doi.org/10.1589/jpts.27.2529

Zhang, K., Ding, L., Wang, X., Zhuang, J., Tong, S., Jia, J., & Guo, X. (2024). Evidence of mirror therapy for recruitment of ipsilateral motor pathways in stroke recovery: A resting fMRI study. *Neurotherapeutics*, *21*(2), e00320. https://doi.org/10.1016/j.neurot.2024.e00320

Zhang, Y., Wang, D., Wang, D., Yan, K., Yi, L., Lin, S., Shao, G., Shao, Z., Sun, J., & Yang, A. (2023). Motor network reorganization in stroke patients with dyskinesias during a shoulder-touching task: A fNIRS study. *Journal of Innovative Optical Health Sciences*, *16*(06), 2340003. https://doi.org/10.1142/S1793545823400035

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. https://doi.org/10.1161/STROKEAHA.109.577023

Ziemann, U., & Siebner, H. R. (2008). Modifying motor learning through gating and homeostatic metaplasticity. *Brain Stimul*, *1*(1), 60-66. https://doi.org/10.1016/j.brs.2007.08.003

Zilles, K. (2018). Brodmann: a pioneer of human brain mapping-his impact on concepts of cortical organization. *Brain*, *141*(11), 3262-3278. https://doi.org/10.1093/brain/awy273

Zimeo Morais, G. A., Balardin, J. B., & Sato, J. R. (2018). fNIRS Optodes' Location Decider (fOLD): a toolbox for probe arrangement guided by brain regions-of-interest. *Sci Rep*, *8*(1), 3341. https://doi.org/10.1038/s41598-018-21716-z

Zimerman, M., Heise, K. F., Hoppe, J., Cohen, L. G., Gerloff, C., & Hummel, F. C. (2012). Modulation of training by single-session transcranial direct current stimulation to the intact motor cortex enhances motor skill acquisition of the paretic hand. *Stroke*, *43*(8), 2185-2191. https://doi.org/10.1161/STROKEAHA.111.645382

Zou, J., Yin, Y., Lin, Z., & Gong, Y. (2023). The analysis of brain functional connectivity of post-stroke cognitive impairment patients: an fNIRS study. *Front Neurosci*, *17*, 1168773. https://doi.org/10.3389/fnins.2023.1168773

Appendix A: HREB Ethics Approval Letter

HREB - Approval of Ethics Renewal 20210906
administrator@hrea.ca
Sent: Tuesday, November 26, 2024 11:06 AM
To: Ploughman Michelle(Principal Investigator) [mploughm@mun.ca]
Cc: Hreaadministrator

Researcher Portal File #: 20210906

Dear Dr. Michelle Ploughman:

This e-mail serves as notification that your ethics renewal for study HREB # 2020.273 – Optimizing the timing of priming exercise to boost motor learning and enhance motor and cognitive recovery from stroke - CPSR Exercise – has been **approved**. Please log in to the Researcher Portal to view the approved event.

Ethics approval for this project has been granted for a period of twelve months effective from 25 Nov 2024 to 25 Nov 2025.

Please note, it is the responsibility of the Principal Investigator (PI) to ensure that the Ethics Renewal form is submitted prior to the renewal date each year. Though the Research Ethics Office makes every effort to remind the PI of this responsibility, the PI may not receive a reminder. The Ethics Renewal form can be found on the Researcher Portal as an "Event".

The ethics renewal will be reported to the Health Research Ethics Board at their meeting dated 12 Dec 2024.

Thank you,

Research Ethics Office
Health Research Ethics Authority
760 Topsail Road
Mount Pearl, NL A1N 3J5
(e) info@hrea.ca
(t) 709-864-8871
(f) 709-864-8870
(w) www.hrea.ca