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Bilateral Prefrontal Cortex Activation During Ankle Sensorimotor Conditions in People with Subacute Stroke – an Exploratory fNIRS Study

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Health and Rehabilitation Sciences
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Abstract

The purpose of this exploratory study is to evaluate prefrontal cortex (PFC) activation patterns linked to active and passive paretic ankle dorsiflexion and plantarflexion and somatosensory stimulation (SS) using a reformed paperclip in people with subacute stroke. By using a neuroimaging tool called functional near-infrared spectroscopy (fNIRS) over the PFC, oxygenated and deoxygenated hemoglobin levels were collected in 9 participants. Objectives, including between-condition differences in PFC activation, interhemispheric asymmetry during conditions, and the relationship between interhemispheric asymmetry and clinical outcome measurement (Fugl-Meyer Lower Extremity Assessment, or FMLE), were evaluated using the fNIRS plots and Laterality Index (LI). Results showed that the active condition demonstrated the highest PFC activation, followed by the SS condition, then the passive condition. Two methods (LI and fNIRS plots) investigated interhemispheric asymmetry and divergent findings were found. Moreover, participants who have a higher score on the FMLE demonstrated bilateral PFC activation during active and SS conditions but contralesional activation during the passive condition. Overall, our study provided exploratory results that assist in understanding the role of PFC in ankle sensorimotor functions in people with subacute stroke.

Keywords: Neuroimaging, Stroke, Functional near-infrared spectroscopy, Ankle dorsiflexion and plantarflexion, Prefrontal Cortex, Somatosensation

Summary for Lay Audience

Walking is an essential part of people's lives. In order to walk, the ability to move the ankle up and down and to feel the contact with the ground is important. However, these functions can be impacted after a stroke. Stroke damages the brain. Many people experience challenges regarding movement and sensation in one of their ankles after a stroke. Recent research has highlighted the relationship between brain activity and its role in arm and hand rehabilitation after a stroke. However, the role of brain activity in ankle functions is less well understood. Hence, this study intended to clarify the role of the prefrontal cortex (PFC) during ankle movement and sensory conditions. To measure brain activation, functional near-infrared spectroscopy (fNIRS) was placed on the forehead of 9 participants with subacute stroke during three conditions: 1) the active condition: participants moved their ankle up and down on their own; 2) the passive condition: the researcher moved their ankle up and down for them; 3) the SS condition: ankle stimulation using a reformed paperclip. We investigated the differences between conditions, the asymmetrical activation between the affected and unaffected sides of the brain and if there is a relationship between the activation patterns in the brain and their leg functions. Our results indicated that the active condition has the strongest relationship with the PFC, followed by the SS condition and then the passive condition. Two methods that we used to examine the brain activation asymmetry showed us contrary findings. Furthermore, participants who have better functions in the ankle demonstrated a similar amount of PFC activation on both affected and unaffected sides of the brain during the active and the SS condition, but the unaffected side of the brain was more activated during the passive condition. Ultimately, this study can help us understand how the PFC connects with ankle movements and sensation to inform future stroke rehabilitation and better interpretation of recovery outcomes for individuals who have experienced a stroke.

Acknowledgment

I wanted to take a moment to express my heartfelt gratitude toward two of my supervisors, Dr. Sue Peters and Dr. Susan Hunter. Dr. Peters, your guidance, support, and belief in my abilities have made an immeasurable difference in my academic and personal growth. I am deeply grateful for the countless hours you spent helping me navigate through difficult concepts and research. Your invaluable words of wisdom guided me toward a clearer career path and future aspirations. The nurturing lab environment you cultivated made my time in the lab truly enjoyable and rewarding. I cannot be more grateful for this journey with you as my mentor. Dr. Hunter, your expertise in academic writing and your keen eye for detail have greatly enhanced my writing skills and overall academic performance. Your constructive feedback and thoughtful critiques have been instrumental in helping me grow as a scholar and improve the quality of my work. I am truly grateful for the time and effort you invested in reviewing my papers and providing comprehensive feedback. I thank you immensely for your mentorship.

I would like to thank the study team. Nathan Durand, I have learned so much during our data collection. Thank you for always being supportive and seizing any opportunity to deepen my knowledge of the clinical population. Thank you, Sarthak Kohli, we struggled together and succeeded together. I am grateful that I gained a friend along my MSc journey. Thank you, Dr. Ricardo Viana and Dr. Jamie Fleet, for your clinical expertise in helping me design the study and with recruitment. Thank you to all members of the NRP lab, I look forward to working with all of you again. Thank you to all the physiotherapists in the stroke unit at the Parkwood Hospital for your engagement in our research study and for thinking of us with every new patient that was admitted.

Thank you to all of the participants who volunteered to take part in this study. You were all welcoming and provided us with support through the data collection section. This study would not be possible without your contribution.

This thesis is dedicated to my family, my mother (姜晶 Jing), my father (栾晓辉 XiaoHui), and my sister (栾惠竹 HuiZhu). Mom and Dad, you have been my unwavering champion and biggest supporter since the very beginning. You have respected my decisions and trusted me as an adult to embark on my own adventure. You have created an environment where the possibilities for my achievements are boundless and limitless. Your guidance has taught me the virtues of strength, independence, grit, and warrior-like determination. I am grateful eternally for both of you and all the sacrifices you have done for me. To my sister, you have always got my back since we were kids. I am proud of you for all of your achievement, and I am so lucky to have you as my big sister. To my nephew, I hope you can grow up to be as awesome as your favourite aunt. To Teofilo Calatre, your love and support have empowered me to overcome every challenge I encounter. You have illuminated my world in ways words can't capture. Thank you for being my guiding light and filling every moment with laughter and warmth. To my friends Wenqi, Jamie, Emma, Maadeha, and more. Thank you for being the source of my joy. Finally, to all the dreamers.

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List of Abbreviations

LI: Laterality Index

PFC: Prefrontal Cortex

Active: Active ankle plantarflexion and dorsiflexion condition

Passive: Passive ankle plantarflexion and dorsiflexion condition

SS: Somatosensory stimulation

FMLE: Fugl Meyer Lower Extremity Assessment

FMUE: Fugl-Meyer Upper Extremity Assessment

FMLE-M: The motor portion of the Fugl-Meyer Lower Extremity Assessment

FMLE-S: The sensory portion of the Fugl-Meyer Lower Extremity Assessment

FMLE-T: The total score of the Fugl-Meyer Lower Extremity Assessment

fNIRS: Functional Near-Infrared Spectroscopy

fMRI: Functional Magnetic Resonance Imaging

HbO: Oxygenated Hemoglobin

HbR: Deoxygenated Hemoglobin

Hb: Hemoglobin

SL: Siying Luan

ND: Nathan Durand

IQR: Interquartile range

SD: Standard Deviation

1 CHAPTER 1

1.1 Introduction

A cerebrovascular accident or stroke occurs every 5 minutes in Canada.[1] Current estimates indicate that more than 878,000 people in Canada have experienced a stroke.[1,2] Stroke is the major cause of short-term motor and sensory impairment, which can lead to substantial long-term impairments with the lack of adequate treatment and rehabilitation.[3–5] Both short-term and long-term motor and sensory impairment can contribute to factors such as muscle weakness, poor motor control, reduced sensation and balance instability.[6–8] These factors can further impact the person's ability to perform daily activities, such as walking, bathing, toileting and social interactions.[9–12] The ability to walk (either independently or by using assistive devices) enables individuals to move around freely, navigate their environment, and engage in social activities.[13] Subsequently, a restriction in walking contributes to diminished social interactions and self-care activities and further leads to decreased quality of life among people who have had a stroke.[14–16]

Restoring the ability to walk has been rated as a high priority among survivors of stroke.[17,18] However, more than half of individuals who have experienced a stroke experience difficulty walking with or without assistive devices.[19,20] The control of movement for the execution of walking requires sensorimotor functions, which is a complex interplay between sensory and motor functions. Sensorimotor functions are supported by the central nervous system and the somatosensory system.[21] The central nervous system consists of the brain and the spinal cord, and it plays a fundamental role in coordinating and controlling movements involved in walking.[22] The somatosensory system in the periphery includes proprioception (limb position sense) and cutaneous somatosensation, which provides the senses of touch, pressure, vibration,

and others. [23] The somatosensory system is one of the key components for providing input to the central nervous system to enable coordinated motor output.[23] Generally, disruption in either the somatosensory system or the central nervous system can result in sensorimotor impairments including somatosensation deficits (difficulty to feel the ground or their limb position) and motor deficits (difficulty to move their ankle voluntarily), which subsequently affects walking. [24–27] After a stroke, direct damage to the central nervous system can impact motor function and the perception of peripheral sensation due to disrupted communications within the brain and between the central nervous system and the somatosensory system.[28] Because the severity of impairment after a stroke can vary across individuals and may also fluctuate over time within the same individual, examining brain activations individually holds the potential to enhance the effectiveness of gait rehabilitation. [29–31] The concept of personalized medicine has emerged in gait rehabilitation and has been identified by the Canadian Institute of Health Research as a research priority.[30–32] An important starting point in understanding poststroke gait recovery is to explore how brain activation can serve as an indicator of recovery during the rehabilitation process through the assessment of its correlation with ankle sensorimotor functions.

In contrast to the rich body of research detailing the neural mechanisms driving hand and arm functional recoveries after stroke, the cortical activation patterns underlying the recovery of ankle functions are less well understood. Current stroke literature recognizes the interplay between cortical activation and performance on outcome measures in the lower extremity after rehabilitation.[33–35] Specifically, rehabilitation (e.g., physiotherapy) results in increased cortical activity, which is associated with better motor recovery in the leg.[36,37] However, few studies have explored the cortical activation of sensorimotor functions in the ankle. The existing literature has explored the relationship between cortical activation and ankle functions poststroke either in a single domain (e.g., solely sensory or motor), during dynamic movements (e.g., sit to stand) or

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other non-somatosensory aspects of sensation (e.g., visual or auditory condition). To fully understand cortical activation patterns related to ankle sensorimotor functions, ankle sensorimotor conditions (e.g., somatosensory or motor conditions) should be investigated in a supine position to control for the additional effort needed with maintaining upright posture in standing and sitting.[38,39] Understanding cortical activity during ankle sensorimotor conditions can provide valuable insights into stroke rehabilitation. Hence, to explore the interplay of cortical activation with sensorimotor functions in the ankle, individuals' cortical activation patterns must be observed during the execution of active and passive ankle dorsiflexion and plantarflexion and cutaneous somatosensory (e.g., light touch) stimulation (SS) in a supine position.

1.2   Stroke

Stroke is the leading cause of adult-onset disability and the third leading cause of death in adults in Canada.[40] The economic impact of stroke is significant in the Canadian healthcare system, resulting in a direct cost of 3.6 billion dollars.[41] Since the early 1990s, the number and rate of hospitalizations and deaths have steadily declined in all age groups for both men and women despite the continued aging of the population.[42] The reduction in hospitalizations and deaths could be attributed to the successful implementation of preventive measures. [42]

A stroke happens when blood flow in the brain is suddenly disrupted (ischemic stroke) or a blood vessel in the brain ruptures (hemorrhagic stroke) leading to the lack of oxygen and nutrients to the brain, which can irreversibly damage nerve cells that are responsible for bodily functions.[43] Risk factors for stroke include non-modifiable risk factors, such as an increasing age, a family history of strokes, and being a female. Modifiable risk factors include hypertension, cardiovascular disease, diabetes, and cigarette smoking.[44] Neurological deficits caused by a stroke influence a variety of functions including cognition, sensation, mobility and communication.[34]

One of the most common impairments after stroke is hemiparesis, weakness on one side of the body, and it contributes significantly to decreased gait performance when the lower extremity is significantly impacted. [45] Hemiparesis affects around 65% of survivors of stroke.[46] When a stroke happens on the right cerebral hemisphere in the area responsible for motor function, the left side of the body can have hemiparesis.[47] Hemiparesis differs from hemiplegia, which is a complete loss of strength leading to paralysis on one side of the body.[48] The two terms imply reduced capacity of movement and possibly sensation on one side of the body; however, they differ in severity and are not interchangeable.[49] People with hemiplegia can have severe impairment of both gross (e.g., walking) and fine (e.g., writing) motor skills and drastically impaired sensation. In contrast, people with hemiparesis experience weakened muscle strength and relatively less severely impaired sensation in affected limbs.[46,48–50]

To improve affected motor and sensory functions, people need rehabilitation after experiencing a stroke. [51] The timing of rehabilitation interventions is relevant to the outcomes of stroke recovery. The clinical staging of stroke follows the following timelines: the acute stage is 1-7 days from the onset of the stroke, the subacute stage ranges from 7 days to 6 months (early subacute: 7 days-3 months, late subacute: 3-6 months), and the chronic stage is classified at and beyond 6 months poststroke.[52] Most of the recovery after a stroke (48-91%) occurs through and to the end of the subacute stroke stage. [53] Rehabilitation during the subacute stage has been shown to improve mobility, independence, neurological deficits and activities of daily living, especially for those with a moderate to severe stroke.[54]

Following a stroke, rehabilitation can stimulate sprouting from surviving neurons resulting in new connections with other neurons.[55] This rewiring of brain circuits, neuroplasticity, recruits existing neurons to perform functions that were previously controlled by the now damaged neurons.[55,56] Subacute stroke rehabilitation happens when optimal recovery can be facilitated

with neuroplasticity.[34] The majority of stroke rehabilitation protocols rely on motor learning principles to induce neuroplasticity.[37] The effectiveness of rehabilitation in the subacute stage can vary depending on individual-level factors of the stroke (e.g., severity of stroke).[30,57] Hence, observing the relationship between brain activation and function in the subacute stage can help to understand mechanisms of recovery and their association with recovery of function in the subacute stage.

1.2.1   Stroke-Induced Changes in the Body

The central nervous system controls movements through communication between neurons in cortical and subcortical structures.[58] After a stroke, alterations in cortical activation patterns in the relevant cortical and subcortical areas affected by the stroke can be observed.[59–61] Lesions in the central nervous system from the stroke lead to peripheral changes in structures not directly impacted by the stroke. Specifically, stroke induces the reorganization of the muscle fibres and motor neurons, which can lead to the inability to recruit motor units and lead to muscle weakness.[62–64] At the sensory level, stroke can disrupt sensory pathways that transmit sensory signals from the body to the brain, resulting in impaired transmission of sensory information and leading to reduction or loss of sensations.[64]

1.2.2   Interhemispheric Asymmetry Poststroke

Quantitative measures derived from neuroimaging studies during the early and late subacute stages of stroke reveal that stroke is linked to asymmetrical patterns of brain activation compared to individuals without a stroke.[30,65,66] This asymmetrical pattern of brain activation induced by stroke is referred to as interhemispheric asymmetry and can be characterized by a decrease in neural activation in the affected hemisphere and/or an increased neural activation in the unaffected hemisphere.[67] One of the numerical measures used to quantify the degree of

interhemispheric asymmetry is the laterality index (LI). The most favourable motor and sensory recovery outcomes are associated with a greater shift towards a more typical pattern of brain function, resembling that of individuals without a stroke.[68] For example, bilateral activation in the primary motor cortices is found in healthy adults during active plantarflexion and dorsiflexion of the right ankle, with more activation reported on the contralateral cortex.[58,69] This finding demonstrated that although contralateral activation is more pronounced, the primary motor cortices are bilaterally activated during unilateral ankle movement in healthy adults. [69] Though interhemispheric asymmetry is prevalent poststroke, it is ambiguous how it is presented (favouring contralesional or ipsilesional) during ankle sensorimotor conditions. In a case study of an individual with a subacute stroke, a statistically significant increase in the contralesional primary motor cortex and primary somatosensory cortex was observed during active paretic ankle dorsiflexion compared with the rest condition.[70] The findings of this study suggested the possibility of more contralesional activation in individuals with a subacute stroke during ankle sensorimotor conditions, despite the small sample size reported.[70] No other studies were found that compare interhemispheric asymmetry during active and passive paretic ankle dorsiflexion and plantarflexion, nor during SS around the paretic ankle in people with subacute stroke. Current findings demonstrated that interhemispheric asymmetry can be present in people with subacute stroke during ankle movements. However, there is insufficient evidence to comprehensively understand how interhemispheric asymmetry presents in people with subacute stroke during ankle sensorimotor conditions.

It is also ambiguous how interhemispheric asymmetry, namely ipsilesional and contralesional activation, contribute to recovery poststroke. Due to the limited number of studies investigating ankle sensorimotor functions, the existing research examining the relationship between interhemispheric asymmetry and gait performance can offer valuable background

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knowledge on this subject. Lim et al. found that greater levels of contralesional activation in the primary motor cortex and primary somatosensory cortex are related to faster gait speeds in people with chronic stroke.[71] Similarly, better walking outcomes were found to be associated with greater contralesional activation in the primary motor cortex and primary somatosensory cortex in people with chronic stroke.[72] In contrast, Enzinger et al. reported increased contralesional activation in the primary motor cortex and primary somatosensory cortex negatively correlated with the function of the paretic ankle and leg in individuals with chronic stroke.[73] Additionally, one study found no correlation between functional outcomes and activation in the primary motor cortex and the primary somatosensory cortex during voluntary ankle dorsiflexion in people with subacute and chronic stroke.[74] The divergent findings regarding lower extremity functional performances emphasize the complexity of defining the role of interhemispheric asymmetry in relation to functional recovery after stroke. Hence, it would be beneficial to investigate interhemispheric asymmetry relating to ankle sensorimotor functions to provide a more comprehensive understanding of functional recovery in the lower extremity in people with subacute stroke.

1.2.3   Functional Outcome Measures and Brain Activity Poststroke

Functional outcome measures (e.g., Fugl Meyer Lower Extremity Assessment) are commonly used in stroke rehabilitation. Typically, they are used to understand the effect of treatments, establish the functions of the individual at a single point in time, and determine the areas affected poststroke (e.g., knee joint, hip).[75] Fugl-Meyer Lower Extremity Assessment (FMLE) is a common outcome measure that is globally used among clinicians and researchers to assess sensorimotor impairments in people after stroke, including motor functioning, balance, sensation, and joint range of motion.[76] A higher FMLE score indicates better functions, meaning

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the individual is less impaired.[77] While the FMLE measures the functional ability of the lower extremity in people poststroke, it is undetermined if a relationship between FMLE and cortical activation exists. Research has shown that the Fugl-Meyer Upper Extremity Assessment (FMUE) score is negatively correlated with the interhemispheric asymmetry poststroke, which means motor functional improvement in the upper limbs correlates with less interhemispheric asymmetry.[78,79] Specifically, a study demonstrated a statistically significant negative correlation between interhemispheric asymmetry and FMUE scores at the subacute stage of stroke.[80] This evidence supported that the FMUE scores correlated negatively with interhemispheric asymmetry poststroke, but the relationship of the FMLE with interhemispheric asymmetry still requires a more thorough evaluation.

1.3   Ankle and Gait

Walking dysfunction occurs in more than 80% of survivors of stroke.[81] Mizukami et al. found in their cohort of people that immediately after a stroke, the majority (50%) of people cannot walk, 12% can walk with assistance, and 37% can walk independently.[82] After following the people for 11 weeks of rehabilitation, 18% of people still could not walk, 11% walked with assistance, and 50% walked independently.[82] Common alterations in gait performance poststroke include decreased gait speed, and increased gait asymmetry and energy cost.[82] These changes in gait and any accompanying muscle weakness are implicated in the high occurrence of falls in people after a stroke.[83]

The ankle plays a crucial role in the process of gait, also known as walking.[84] It contributes to the overall stability, control, and efficiency of movement during gait.[85] The ankle has multiple functions, such as absorbing the impact of each step, supporting the body's weight and contributing to stability.[86] The ankle joint has a large range of motion, including

dorsiflexion (moving the foot toward the shin) and plantarflexion (pointing the foot downward). [87] These movements are essential for smooth and efficient gait performance. Moreover, the ankle joint contains numerous sensory receptors that provide feedback to the central nervous system about the position, movement, and weight-bearing status of the foot.[88–91] This feedback is crucial for maintaining balance and coordinating muscle activity during gait.[91] Since the ankle has multiple functions contributing to gait performance, impairment in the ankle sensorimotor functions can negatively impact walking.

1.3.1   Ankle Dorsiflexion and Plantarflexion Impairment and Gait

As mentioned earlier, ankle dorsiflexion and plantarflexion are essential for walking. Research has demonstrated that restricted dorsiflexion and plantarflexion range of motion at the ankle joint has been associated with poor balance and an increased fall risk in older adults compared to healthy controls.[92] The risks of falls and poor balance control can be heightened after a stroke, as it is common for people with hemiparesis to experience difficulty or an inability to actively dorsiflex and plantarflex the ankle. [25]

Ankle dorsiflexion allows the foot to clear the ground, preventing tripping or falling. [93] It assists in proper foot placement for the next step and contributes to the forward body movement.[94] The importance of ankle dorsiflexion is also shown by two systematic reviews that state the strength of the ankle dorsiflexor muscles has a strong positive correlation with walking activity compared to other lower limb muscle groups.[95,96] A stroke can result in a condition known as foot drop, difficulty or inability to dorsiflex the ankle. [97] Foot drop affects 20%-30% of people after a stroke.[87] This can lead to difficulty in clearing the toe during the swing phase of walking, increasing the risk of falls.[87] Interventions to address foot drop include the

prescription of an ankle-foot orthosis which maintains a neutral position and prevents the ankle from going into plantarflexion.[98–100]

Ankle plantarflexion provides the necessary power for propulsion, helping to move the body forward.[101] The act of ankle plantarflexion enhances the efficiency of walking by reducing the energy required for each step.[102,103] Stroke with resulting motor deficits in the lower extremity can affect ankle plantarflexion, which leads to muscle weakness or reduced ability to generate the necessary force to move the body forward.[104] This can result in decreased walking speed as maximum walking speed is strongly related to the plantarflexor strength in the paretic ankle. [93,105] Other consequences of decreased ankle plantarflexion strength include increased energy expenditure during walking and altered gait patterns.[103] Rehabilitation addressing ankle plantarflexion impairments often includes muscle strengthening exercises, range of motion exercises, and gait training to support and optimize ankle function.[106–108]

Overall, both ankle dorsiflexion and plantarflexion are crucial components of gait.[87,92] By observing how stroke affects these movements and improving these movements through rehabilitation for people with stroke, it is possible to enhance their gait performance and increase overall mobility and functional independence.[98,106–108]

1.3.1.1   Ankle Dorsiflexion, Plantarflexion and Brain Activation Patterns

Gait patterns poststroke are often affected as a result of reduced central descending neural signals to the paretic ankle.[109] Informed by studies with healthy adults, active right ankle dorsiflexion is mainly controlled by cortical areas and plantarflexion activated more subcortical areas.[58] Active right ankle dorsiflexion activated areas such as bilateral primary motor cortices, bilateral primary somatosensory cortices, and bilateral secondary somatosensory cortices, whereas active plantarflexion activated areas such as the ipsilateral supplementary motor area and the basal

ganglia.[58] On the other hand, passive ankle dorsiflexion generated activation over bilateral secondary somatosensory cortices and contralateral primary motor cortex and passive plantarflexion is controlled by subcortical areas and frontal non-primary motor areas in healthy volunteers.[58,110] These findings showed that brain activation patterns vary during active and passive ankle dorsiflexion and plantarflexion. This difference raises the question of how active and passive ankle dorsiflexion and plantarflexion are associated with brain activation in individuals with stroke, specifically with interhemispheric asymmetry. However, no studies exist to address this question.

Although no studies were found to examine active and passive ankle dorsiflexion and plantarflexion in people with subacute stroke, the following studies conducted in other populations could inform the current understanding of the literature on this topic. Enzinger et al. reported increased activation in the primary motor cortex and primary somatosensory cortex during both active and passive ankle dorsiflexion and plantarflexion compared to rest in participants with chronic stroke and in healthy controls. [73] However, they did not investigate if active ankle dorsiflexion and plantarflexion elicit a different pattern of activation from passive ankle dorsiflexion and plantarflexion.[73] This comparison was investigated by Francis et al. in healthy adult volunteers, active dorsiflexion and plantarflexion of the right ankle resulted in more prefrontal cortex (PFC) activation compared to the passive conditions.[110] Drawing from the findings of studies conducted on both healthy individuals and people with chronic stroke, it can be concluded that brain activation is observable during active and passive ankle dorsiflexion and plantarflexion with the likelihood that active ankle movement elicits greater activation compared to passive movement. However, further research is needed to fully understand the nuances of this topic.[111]

1.3.2   Ankle Somatosensation and Gait

As an important aspect of sensorimotor functions, somatosensory input from the lower extremity is vital for gait.[30,112] During walking, somatosensation plays a crucial role in providing feedback about the position, movement, and stability of the body. [113,114] Somatosensory information from the ankle helps maintain balance and adaptation of the gait pattern to different surfaces.[115–117] It also contributes to the coordination of muscle activity and the regulation of step length and timing.[118–120] Impairment in foot or ankle somatosensation is related to a deterioration of postural control and may result in an increased risk for falls.[121]

In individuals who have experienced a stroke, ankle somatosensation may be affected due to damage to the brain. As a key component of somatosensation, cutaneous somatosensation contributes to gait by providing crucial sensory information and feedback. Impairments in processing cutaneous somatosensation in the ankle are prevalent poststroke.[122] Seven to fifty-three percent of people with subacute stroke reported having impaired cutaneous somatosensation in both the upper and lower limb on the affected side.[26] Stroke survivors with ankle cutaneous somatosensation deficits may experience problems with weight-bearing on the affected side, decreased ankle stability, and altered coordination during walking.[123,124] These impairments can affect the overall gait pattern, leading to compensatory movements, increased risk of falls, and reduced walking efficiency.[124,125]

1.3.2.1   Somatosensation and Brain Activation Patterns

The brain is responsible for processing and integrating sensory information, including somatosensation from the ankle and generating appropriate motor responses during walking.[126,127] Somatosensation deficits in the paretic ankle after a stroke can have significant

consequences on post-stroke functional outcomes. [115–117] These consequences manifest as difficulties in gait control and maintaining balance. [121]

Research in healthy adults demonstrated increased activation over the bilateral thalami and the primary somatosensory cortices during light touch in the foot.[128–131] Existing poststroke research targets other aspects of cutaneous somatosensation (e.g., pressure) and functional outcomes.[124] However, no studies were found to investigate how interhemispheric asymmetry after stroke correlates with the processing of ankle cutaneous somatosensation. Assessing brain activation during SS in the ankle poststroke can aid in understanding poststroke gait recovery.[124]

1.4   Prefrontal Cortex and Voluntary Control

Due to motor and sensory impairments associated with hemiparesis, many individuals post-stroke tend to rely on their non-paretic limb to complete daily conditions.[132] When the use of the paretic limb is neglected, the brain will tend to suppress or reduce the neural connections associated with the unused paretic limb.[132] Reduced usage of the paretic limb may result in decreased motor control, muscle strength, and coordination, as well as increased muscle atrophy and joint stiffness.[133–136] To promote neuroplasticity and maximize functional recovery, it is crucial to actively engage the paretic limb in rehabilitation activities. [132,136]

The prefrontal cortex (PFC) covers the front part of the frontal lobe of the cerebral cortex.[137] The PFC contributes to the control of ankle functions and gait due to its involvement in cognitive processing and motor control. [138,139] Cognitive processing refers to the mental activities involved in acquiring, processing, storing, and utilizing information.[140] To perform gait activities, cognitive processing is crucial for analyzing sensory input, coordinating movements, and adjusting motor responses based on the environment.[141,142] Thus, PFC helps integrate sensory information about foot placement, ground contact, and balance from sensory receptors and

the environment to make informed decisions about maintaining stability and adjusting movements as needed.[143]

The PFC is also involved in motor planning and coordination during gait, evidenced by significant activation present in the PFC before the onset of and during walking.[144] The PFC has connections with multiple brain regions involved in motor control, including the premotor cortex and the supplementary motor area. [145,146] While there is no direct connection between the PFC and the primary motor cortex, studies indicate the presence of anatomical links between the PFC and the premotor area. The premotor area, in turn, projects to both the primary motor cortex and the spinal cord, facilitating the transmission of motor commands.[145] The connection between the PFC and the primary motor cortex and the primary somatosensory cortex has also been identified.[147] Through these connections, the PFC can contribute to the precise coordination of ankle movements and ensures the execution of walking.[144,148,149]

Despite the importance of PFC in controlling ankle sensorimotor movement, few studies examined interhemispheric asymmetry between the right and left PFC and its effects on ankle sensorimotor function poststroke. To inform the current understanding of this topic, gait research poststroke provided valuable insights.[150–152] For instance, Al-Yahya et al. observed increased bilateral PFC activation in individuals with chronic stroke compared to healthy controls under both single-condition and dual-condition (e.g., walking paired with a cognitive condition) walking conditions.[153] Similarly, Hawkins et al. demonstrated greater bilateral PFC activation in people with chronic stroke during walking compared to both young and older healthy adults.[151] On the contrary, Lim et al. found greater ipsilesional PFC activation compared to contralesional PFC activation during walking in people with chronic stroke.[71] These findings suggest discrepancies in the literature regarding interhemispheric asymmetry in the PFC during gait. Hence, further

research should be conducted to fully understand the role of interhemispheric asymmetry in the PFC poststroke.

1.5 Assessing Prefrontal Cortex Activity Using Neuroimaging

Neuroimaging modalities assist researchers to visualize and quantify cortical activation and further our knowledge of how the brain contributes to functional outputs.[146] In stroke, functional neuroimaging has emerged as a useful tool, unveiling the pathophysiological aspects of brain damage and enabling the assessment of functional-structural relationships during poststroke recovery. [154] Integrating neuroimaging tools into stroke rehabilitation can be beneficial in delineating the mechanisms underlying poststroke recovery.

1.5.1 fNIRS VS. fMRI

Neuroimaging techniques such as functional Near-Infrared Spectroscopy (fNIRS) and functional Magnetic Resonance Imaging (fMRI) are commonly used to evaluate cortical activation. fNIRS is a non-invasive optical neuroimaging tool to assess cortical activation by observing changes in oxygenated (HbO) and deoxygenated (HbR) hemoglobin (Hb) levels.[155] fNIRS and fMRI both measure the hemodynamic response to neural activity, though use different approaches. fMRI relies on blood oxygen level dependent contrast to visualize active brain regions. [156] More specifically, it utilizes the magnetic properties of Hb, especially HbR.[156] fMRI has contributed greatly to the understanding of functional neuroanatomy in both healthy younger and older adults.[157] It is non-invasive and boasts exceptional spatial resolution.[158] However, fMRI has some practical constraints that can limit its usage such as participant claustrophobia, movement restrictions (e.g., supine position), and contraindications to being in a magnetic field (e.g., surgical metal in the body).[158] Furthermore, fMRI has lower temporal resolution than fNIRS. fMRI also

requires expensive equipment, maintenance and highly trained and specialized personnel, accounting for a greater cost to perform an fMRI scan.[156]

On the other hand, fNIRS uses low levels of near-infrared light (between 700 nm and 900 nm wavelength) to record changes in cerebral blood flow through optical sensors placed on the surface of the scalp. [156] fNIRS relies on the process of neurovascular coupling, which refers to the mechanism by which changes in neural activity lead to corresponding adjustments in cerebral blood flow to meet the metabolic demands of active brain regions.[159] For example, when neurons become active, increased demand for oxygenated blood (and therefore HbO) will be observed in the activated brain areas. Optical sensors of fNIRS detect these changes and consequently interpret the concentration of HbO and HbR with excellent spatial resolution.[156] fNIRS is relatively inexpensive and suitable for a wide range of people (i.e., infants to older adults). fNIRS has a higher temporal resolution than fMRI, typically between 1 to 10Hz.[160] Its portability allows neuroimaging research to be conducted with participants performing conditions such as standing or walking and in many environments, including in inpatient settings.[160,161] Compared to fMRI, fNIRS is not sensitive to common electrical or magnetic devices, such as pacemakers and hearing aids, therefore there are fewer restrictions on whom the equipment can be used safely.[162]

1.5.2   fNIRS and Stroke

Research has demonstrated that fNIRS can be used in a clinical setting due to its usability and reduced sensitivity to head motion artifacts.[35] The portability of fNIRS allows it to be an effective neuroimaging tool in investigating cortical activity in different environments, such as an inpatient setting.[156] In the existing literature, fNIRS has been used to study cortical activation during gait with the stroke population, but not with sensorimotor functions of the

ankle.[151,163,164] The advantages of fNIRS allow investigations of dorsiflexion, plantarflexion and somatosensation of the paretic ankle in people with subacute stroke in more realistic and clinical environments.

1.6   Rationale for Thesis Research Project

Restoring the ability to walk has been rated as a high priority among stroke survivors.[17,18] The ankle plays a crucial role in the execution of walking, also known as gait.[84] Its functions of plantarflexion, dorsiflexion and somatosensation contribute significantly to the overall stability, control, and efficiency of movement during gait.[85] However, these functions are often affected poststroke due to interhemispheric asymmetry, which is the asymmetrical activation patterns in the contralesional and ipsilesional hemispheres.[165] The loss of or weakened ankle functions can result in gait asymmetry and contributes to falls.[109,121] Despite the prevalence of interhemispheric asymmetry poststroke, few studies have investigated how it affects ankle sensorimotor functions.

1.6.1   Purpose

The purpose of this exploratory study is to examine the prefrontal cortex (PFC) activation patterns during active ankle plantarflexion and dorsiflexion, passive ankle plantarflexion and dorsiflexion, and somatosensory stimulation (SS) around the ankle in people with subacute stroke. The objectives of this study are:

1. To examine between-condition differences in both HbO and HbR concentration

2. To investigate interhemispheric asymmetry using concentration differences in both HbO and HbR for each condition

3. To determine the relationship between interhemispheric asymmetry (represented by LI) and clinical outcome measurement (represented by FMLE)

1.6.2   Hypotheses

It was hypothesized that:

1. The order of HbO concentration, from highest to lowest, would be as follows: the active condition, then the passive condition, and last, the SS condition. HbR concentration would stay relatively similar between conditions

2. Greater contralesional activation would be found compared to ipsilesional activation in all conditions

3. Participants with a higher score on the FMLE would be found to have more bilateral PFC activation compared to those with a lower score

2   CHAPTER 2

2.1   Introduction

A stroke occurs every 5 minutes in Canada.[1] Stroke is a leading cause of adult-onset disability in Canada and impairments in sensorimotor functions commonly occur among people after stroke.[166] These impairments encompass a range of sensorimotor functions, including somatosensation deficits (difficulty to feel the ground or their limb position) and motor deficits (difficulty to move their limb voluntarily).[24–27] Due to sensorimotor impairments poststroke, more than half of individuals who have experienced a stroke are unable to walk independently without assistive devices.[19,20] Consequently, the restriction on walking can result in diminished social interactions and self-care activities and further leads to decreased quality of life among people who have had a stroke.[14–16] The foot directly contacts with the environment during walking, making foot/ankle sensorimotor functions crucial to numerous components of walking.[167] Specifically, ankle plantarflexion (pointing the foot downward), dorsiflexion (lifting the foot upward) and somatosensation (e.g., light touch) contribute significantly to the overall stability, control, and efficiency of movement during walking.[85] Since a stroke directly damages the brain, examining brain activation is beneficial in understanding the impact of stroke on ankle sensorimotor functions. Addressing impairments in ankle sensorimotor functions is not only related to the motor and sensory cortices but also extends to the involvement of the prefrontal cortex (PFC). The PFC contributes to the analysis of sensory input, coordination of movements, and adjustment of motor responses based on the environment in the ankle according to its functions of cognitive processing and motor control. [138,139,141,142] As a result of a stroke, the functions of the PFC can be disrupted, which can potentially contribute to impairments in sensorimotor functions in the ankle. Hence, discovering the relationship between PFC and ankle sensorimotor functions poststroke can be beneficial to understand poststroke recovery.[24–27]

Quantitative measures derived from neuroimaging studies during the early and late subacute stages of stroke reveal that stroke is linked to asymmetrical patterns of brain activation compared to individuals without a stroke.[30,65,66] This asymmetrical pattern of brain activation induced by stroke is referred to as interhemispheric asymmetry and can be characterized by a decrease in neural activation in the affected hemisphere and an increased neural activation in the unaffected hemisphere.[67] Informed by studies conducted on healthy adults, bilateral activation in the primary motor cortices is found during active plantarflexion and dorsiflexion of the right ankle, with more activation reported on the contralateral cortex.[58,69] However, in a case study of an individual with a subacute stroke, a statistically significant increase in the contralesional primary motor cortex and primary somatosensory cortex was observed during active paretic ankle dorsiflexion compared with the rest condition.[70] The findings of this study suggested the possibility of a more contralesional activation in individuals with a subacute stroke during ankle sensorimotor conditions, despite the small sample size reported.[70] Furthermore, drawing from the findings of studies conducted on healthy adults, it can be concluded that active ankle movement elicits greater activation compared to passive movement. [73] For example, Francis et al. reported that active dorsiflexion and plantarflexion of the right ankle resulted in more PFC activation compared to the passive condition in healthy adults.[110] However, this relationship was not investigated among people after a stroke. Lastly, despite the importance of ankle somatosensory functions, few studies examined cortical activation during ankle somatosensory conditions poststroke. Research in healthy adults reported increased activation over the bilateral thalami and the primary somatosensory cortex during light touch SS in the foot.[128–131] However, no studies investigated how the perception of ankle cutaneous somatosensation changes poststroke.

To measure cortical activity, functional near-infrared spectroscopy (fNIRS) can be used to quantify changes in the PFC by measuring oxygenated (HbO) and deoxygenated (HbR)

hemoglobin (Hb) levels.[155] fNIRS relies on the process of neurovascular coupling, which refers to the mechanism by which changes in neural activity lead to corresponding adjustments in cerebral blood flow to meet the metabolic demands of active brain regions.[159] This process supports that changes in Hb concentration (increased HbO and decreased HbR) indicate brain activation.[168,169] The portability of fNIRS allows it to be an effective neuroimaging tool in investigating cortical activity in different environments, such as inpatient settings.[156]

In conclusion, the existing literature has explored cortical activation during ankle sensorimotor conditions in healthy adults, but few studies were conducted with people after stroke. In the stroke literature, PFC activation during ankle functions was explored either in a single domain (e.g., solely sensory or motor), during dynamic movements (e.g., walking) or other non-somatosensory aspects of sensation (e.g., visual or auditory condition). To fully understand PFC activation patterns during ankle sensorimotor functions, this study aims to examine bilateral PFC activation patterns during ankle sensorimotor conditions (e.g., somatosensory or motor conditions) in people with subacute stroke. Understanding PFC activation during ankle sensorimotor conditions can provide valuable insights into gait rehabilitation poststroke.

2.1.1   Purpose

The purpose of this exploratory study is to examine the prefrontal cortex activation patterns during active ankle plantarflexion and dorsiflexion, passive ankle plantarflexion and dorsiflexion, and somatosensory stimulation (SS) around the ankle in people with subacute stroke. The objectives of this study are:

1. To examine between-condition differences in both HbO and HbR concentration

2. To investigate interhemispheric asymmetry using concentration differences in both HbO and HbR for each condition

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3. To determine the relationship between interhemispheric asymmetry (represented by LI) and clinical outcome measurement (represented by FMLE)

2.1.2 Hypothesis

It was hypothesized that:

1. The order of HbO concentration, from highest to lowest, would be as follows: the active condition, then the passive condition, and last, the SS condition. HbR concentration would stay relatively similar between conditions.

2. Greater contralesional activation would be found compared to ipsilesional activation in all conditions.

3. Participants with a higher score on the FMLE would be found to have more bilateral PFC activation compared to those with a lower score.

2.2 Methodology

2.2.1 Participants

We used a convenience sample of participants recruited from the inpatient stroke unit at Parkwood Institute in London, Ontario, Canada between May 2022 and May 2023. This study was approved by the University of Western Ontario Health Sciences Ethics Review Board, London, Canada (HSREB#119880) and by the Clinical Resources Impact Committee of Lawson Health Research Institute (Appendix A).

2.2.2 Inclusion & Exclusion Criteria

Individuals were recruited and screened by their physician and physiotherapist at admission into the hospital. Individuals were eligible to participate if they were medically stable (able to participate in the inpatient stroke rehabilitation programs), age greater than or equal to 19 years, displayed hemiparesis after the stroke, were an independent community ambulator prior to the

stroke, were able to understand and follow instructions in English, and were able to provide

informed consent. Individuals were excluded if they were unable to communicate in English,

presented other chronic health conditions that would adversely affect participation (e.g.,

Parkinson's disease, multiple sclerosis, cancer, orthopedic limitation, recent myocardial infarct)

and/or directly affected hemoglobin levels, or had a cerebellar stroke. Each participant provided

written informed consent prior to data collection.

2.2.3 Experimental Protocol

2.2.3.1 fNIRS System and Placement

The continuous wave fNIRS system (PortaLite, Artinis Medical Systems, Elst, The

Netherlands, www.artinis.com, see Figure 1) with LED optodes (wavelengths of 759 and 841nm)

was used to measure functional brain activity at a sampling rate of 50 Hz through Oxysoft 1.3.1

software. Each device contained one source and three detectors (**Figure 1A**). Prior to the

experiment, nasion-inion distance, ear-to-ear distance (between preauricular points), and the head
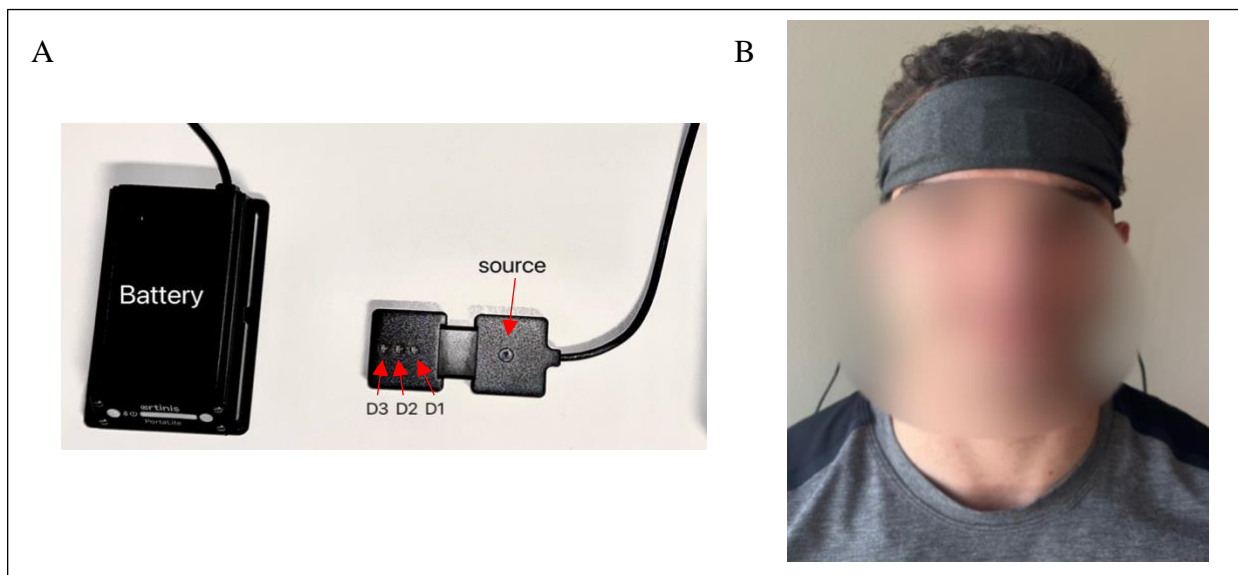
Figure 1. (A). fNIRS system -- PortaLite Artinis Medical System; D1, D2, D3: Detector 1, 2, 3 and (B). Example of a participant wearing two fNIRS devices on the forehead with the headband over the devices.

circumference of the participants were measured to ensure consistent placement among participants. Two fNIRS devices were placed over the bilateral PFC in accordance with the international 10-20 landmarking system [170]. A headband affixed the sensors to the head to ensure minimal light pollution to the signals (**Figure 1B**).

2.2.3.2   Condition Procedures

Data collections were completed on the inpatient stroke unit and conditions were administered by two members of the study team (SL or ND). All participants were asked to lie in a supine position on a plinth in the inpatient stroke unit gym or in their hospital bed allowing the ankle to be moved freely. The protocol was 5 trials for each of three conditions on the paretic ankle: (1) active ankle plantarflexion and dorsiflexion, (2) passive ankle plantarflexion and dorsiflexion, and (3) the SS condition using a reformed paperclip to stimulate the ankle. Condition order was randomized using a web randomization tool (www.randomizer.org) with the experimenter triggering the start of each trial.[171] Each trial lasted 20s and the rest time between trials varied from 15s to 30s to minimize the physiological effects of breathing and heart rate on the condition hemodynamic responses.[172] All conditions were performed under metronome guidance at a frequency of 0.33 Hz (20BPM) and the metronome was on during conditions and rest periods to control for the effects of the auditory stimulus. The pace was visually monitored by the experimenter to ensure that participants adhered to the 0.33 Hz tempo. Pillows were placed under the knee and gastrocnemius muscles to ensure the ankle can move freely. The verbal instructions to start the conditions was "Start" and the instruction to stop the conditions was "Stop." Participants were blinded to the order of the conditions, number of total trials and length of each trial and were instructed not to count the number of total trials or their movement repetitions in each trial. During the testing, participants were instructed to relax, not to close their eyes, refrain

from moving, and not think about anything in particular. Participants were asked to look at a visual

fixation point on the ceiling during conditions and rest periods to minimize head movements. A

licenced physiotherapist was present at all times during the entire data collection to ensure the

safety of the participant.

For the active ankle plantarflexion and dorsiflexion condition, participants were instructed

to move their paretic ankle through the range of motion they can achieve in time to the metronome.

They were asked to relax their non-paretic leg and focus on only moving the paretic ankle.

Participants were told to only move their ankle once they hear a beat from the metronome to avoid

anticipation (e.g., beat – dorsiflex – beat – plantarflex). Due to diverse degrees of impairments in

ankle sensorimotor functions, the degree of range of motion was not restricted during this condition.

More importantly, participants were instructed to focus on voluntarily moving their ankles, rather

than achieving a certain degree of movement.
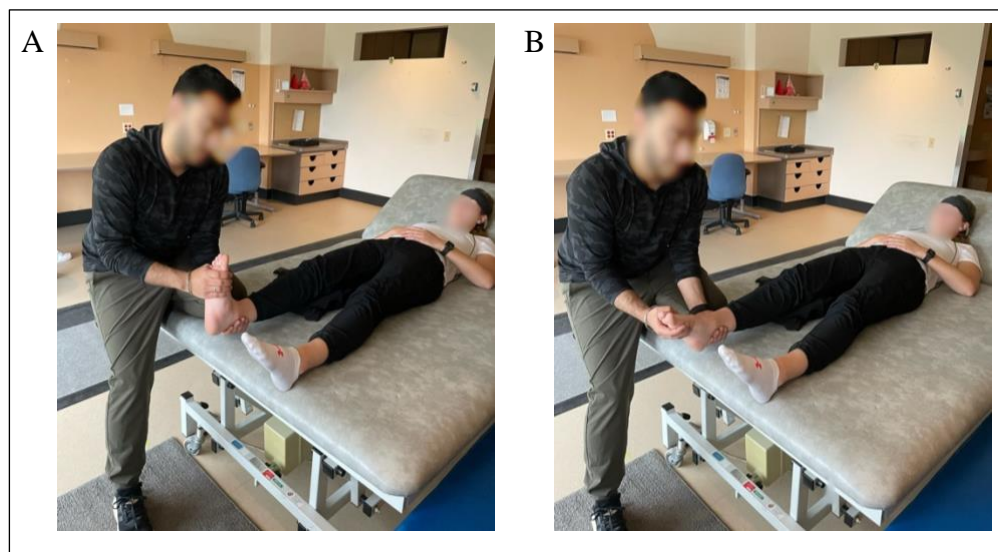
**Figure 2. (A) An example of passive ankle dorsiflexion of the paretic
ankle and (B). Example of passive ankle plantarflexion of the
paretic ankle.**

During the passive ankle dorsiflexion **(Figure 2A)** and plantarflexion **(Figure 2B)** condition, the experimenter moved the participants' paretic ankle through the achievable range of motion they could tolerate. Participants were instructed to be as relaxed as possible and to allow the experimenter to complete each movement. The researcher placed one hand around the metatarsal heads and the other hand cupped under the heel proximal to the malleoli. The researcher maintained continuous hand contact with the foot throughout all trials to regulate and account for any potential impact of additional somatosensory input resulting from touching the foot. The comfortable range of motion was determined by a physiotherapist prior to the condition in each participant. The patient's leg was supported by pillows allowing the ankle to move freely.

For the SS condition, the experimenter applied light touch somatosensation using a reformed paperclip for all but one participant (reformed safety pin used for the first participant) in accordance with the metronome (**Figure 3A**). The change from a safety pin to a paperclip was due to slight twitching induced by the sharpness of the safety pin. The same sensory stimulation site, L4 (ankle dorsiflexors), was selected for all participants according to the American Spinal Injury
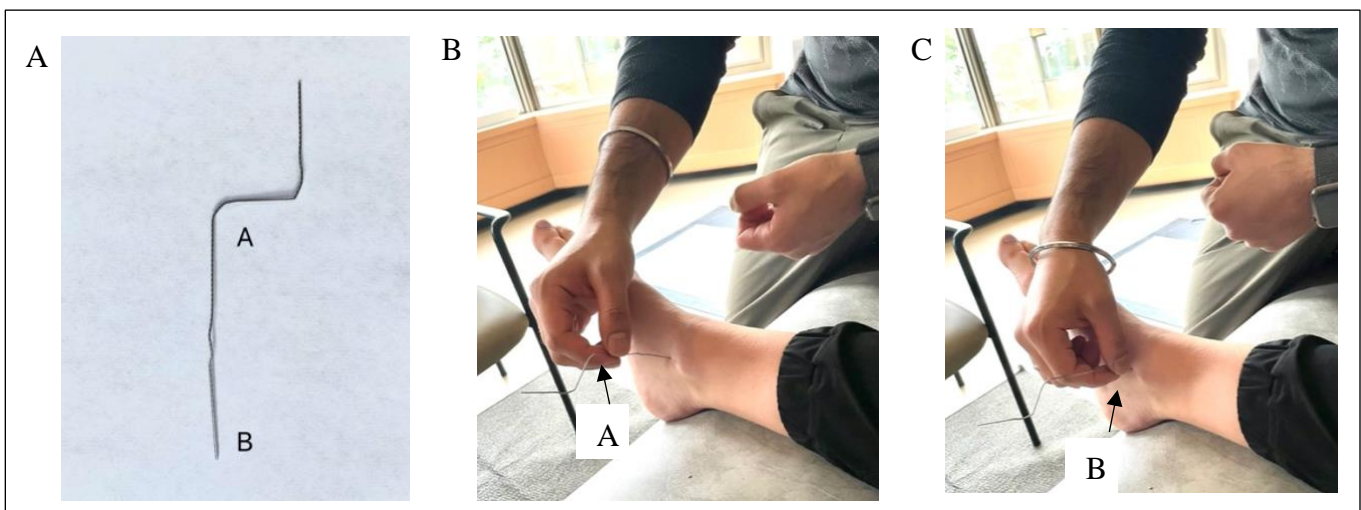
Figure 3. (A). Reformed paperclip tool used for SS with point A and point B, (B). An example of how a researcher starts the application of SS around the ankle at point A and (C). An example of how a researcher ends the application of SS around the ankle at point B.

Association (ASIA) impairment scale.[173] The experimenter placed their thumb and index finger at point A of the SS tool and slid down to point B to apply even pressure to the skin of all participants (**Figure3B, Figure 3C**). The experimenter avoided any part of their hand touching the participant's skin to avoid additional somatosensory input.

2.2.4   Outcome Measures

Demographic and medical history information was obtained prior to data collection through data extraction from medical charts, which included age, sex, lesioned hemisphere, depth of lesion (cortical or subcortical), type of stroke, time since stroke, stroke location and the Berg Balance Scale score. The Berg Balance Scale score were collected to quantify balance functions.

2.2.4.1   Fugl-Meyer Lower Extremity Assessment

The Fugl-Meyer Lower Extremity Assessment (FMLE) was conducted by a trained physiotherapist within 7 days of the fNIRS assessment. FMLE assesses sensorimotor impairments in the stroke population, including motor functioning, balance, sensation, and joint functioning, and is a recommended outcome measure for individuals living after stroke.[76] FMLE is proven to have a high inter- and intra-rater reliability and can reliably assess poststroke sensorimotor impairment severity for clinical practice or rehabilitation research.[77] The sensory and motor function evaluations of the FMLE assessment were completed. (Appendix B)

2.2.4.2   Laterality Index

The laterality index (LI) represents interhemispheric asymmetry and is commonly used in people who have had a stroke.[174] Many recent fNIRS studies have involved LI to address interhemispheric asymmetry, ranging from testing the agreement between LI from fMRI and fNIRS to assessing interhemispheric asymmetry in the patient population (e.g., subcortical stroke).[175,176]

To measure interhemispheric asymmetry during sensorimotor conditions, we have calculated the LI for both HbO and HbR using the following equation[177]:

$$LI = \frac{\Delta Ipsi - \Delta Contra}{\Delta Ipsi + \Delta Contra}$$

ΔIpsi and ΔContra represent the Hb concentration change within the PFC in the ipsilesional and contralesional hemispheres, respectively.[178] The change in concentration is determined by subtracting the mean of baseline values (measured before the start of the condition: -2s to -0.02s) from the mean condition values (measured throughout condition performance: 0 to 20s).[179] This equation yields a value for LI between -1 < LI < +1, where a negative value of LI indicates more contralesional activation and a positive value indicates more ipsilesional activation.[180] An LI value of "− 1" indicates complete contralesional hemisphere dominance, an LI value of "+ 1" indicates complete ipsilesional hemisphere dominance, and an LI value between "+ 0.2" and "− 0.2" indicates bilateral activation.[178,181] Furthermore, the LI was plotted against the FMLE to visually display the relationship between interhemispheric asymmetry and clinical outcome measures.

2.2.5   Data Analysis

2.2.5.1   fNIRS data analysis

fNIRS data were processed by using open-source software HOMER3 [182], which is implemented in MATLAB (Mathworks, 2017b, Natick, MA, USA). All HOMER3 functions and corresponding parameters are indicated within square brackets. The raw fNIRS intensity data were first converted to optical density [hmrR_Intesnity2OD] and a lowpass filter of 0.15 Hz was applied to the data to remove high-frequency noise [hmrR_BandpassFilt:Bandpass_Filter_OpticalDensity: lpf = 0.15].[163,183] Optical density data was then converted into relative concentration changes of oxy-hemoglobin (HbO) and deoxy-hemoglobin (HbR) based on the modified Beer-Lambert law

[hmrR_OD2Conc: ppf = 6.0 6.0].[184–186] Last, the hemodynamic response was estimated using the general linear model [hmrR_GLM_old] with an ordinary least squares approach [glmSolveMethod = 1], and consecutive sequence of gaussian functions [idxBasis = 1] as the type of basis function [trange = − 5.0 30.0, paramsBasis = 0.5 0.5, rhoSD_ssThresh = 0, flagNuisanceRmethod = 1, driftOrder = 3, c_vector = 0].[163,187]

After processing the fNIRS signal, we exported the data into Excel spreadsheets. Because our sample size is small (n=9), we did not proceed with statistical analysis. Instead, we inspected each figure visually for results. We calculated the mean and standard deviation of both HbO and HbR during the baseline and condition period for each condition and participant. We then plotted the line charts for objectives 1&2, and scatter plots for objective 3. LI values were also calculated for objective 2.

2.2.5.2   Outliers

Outlier calculation was applied to the LI values by determining the interquartile range (IQR). Outliers were defined using the follower equation where Q1 represents the first quartile and Q3 represents the third quartile: outlier < Q1 - 1.5*(IQR) or outlier > Q3 + 1.5*(IQR).[188]

2.3   Results

2.3.1   Overall Flow of the Study

Overall, the study protocol was straightforward. Since the equipment preparation was completed prior to the participant's arrival, the fNIRS device was ready for immediate use after placing the device on the participant. The duration for data collection was about 1 hour. No participants reported discomfort while wearing the fNIRS device. Our first participant displayed slight twitching and reported minor discomfort due to the use of the sharp end of a safety pin during

the SS condition, so we modified the stimulation tool to a reformed paperclip for all the other participants. Participants have all completed all conditions as described.

The results came from nine participants who completed the assessment. Thirteen individuals were enrolled in the study. Four participants were not able to complete the data collection session and the reasons for dropouts include diagnoses of neurological disorders identified after consent, chronic health problems hindering participation, and incompatible placement of the fNIRS device. More details can be found in Appendix C. Enrollment was affected due to the COVID-19 pandemic. When the stroke unit was on outbreak, researchers were not allowed to be on the unit until the outbreak was over. Since the stroke unit experienced multiple outbreaks, enrollment in this study was restricted.

Table 1| Summary of participant demographic and clinical characteristics. (n=9)

Age	**65.2 ± (14.4) Years**
Sex (Female/Male)	**5/4**
Time Since Stroke (Days)	**38.9 ± (28.1)**
Lesion Depth (Cortical/Subcortical/Unknown)	**1/7/1**
Lesion Side (Left/Right)	**3/6**
Stroke Type (Ischemic/Hemorrhagic/Unknown)	**7/1/1**
Berg Balance Scale (/56 Max)	**23.3 ± (20.0)**
FMLE-Motor (/34 Max)	**17.9 ± (6.8)**
FMLE-Sensory (/12 Max)	**10.8 ± (2.3)**
FMLE-Total (/46 Max)	**29.0 ± (7.0)**

Values are presented as [Mean ± (SD)]. Abbreviations: FMLE, Fugl-Meyer Lower Extremity Assessment.

2.3.2   Demographic and Clinical Characteristics

Table 1 shows a summary of participant demographics. Detailed individual participant data are presented in Appendix D. All nine participants completed the active, passive and SS conditions. Two participants had fewer repetitions for the active or the SS conditions due to signal pollution. Details are demonstrated in Appendix E.

2.3.3   Objective 1: PFC Activation During Ankle Conditions

An increase in HbO concentration was observed in all conditions for the bilateral PFC (**Figure 4**). Active, passive and SS conditions all peaked around a similar amplitude for the ipsilesional HbO. In the contralesional PFC, the active condition had the most changes in amplitude in HbO, followed by the SS condition and then the passive condition. The active condition showed an initial decrease in ipsilesional PFC at approximately 0-5s followed by an increase starting at 5s and peaking around 10s. The ipsilesional PFC HbO concentration started to decrease after around 18s. Similar patterns were shown in the contralesional PFC with the distinction of an initial increase between 0-3s instead of a decrease. The HbO activation patterns were similar for the passive and the SS condition in both hemispheres. The passive condition displayed an initial decrease from 0 to approximately 5 seconds followed by an increase. This increase in HbO concentration remained elevated until around 20s. Furthermore, the HbO values for the active condition peaked about 5s earlier than both the passive and SS conditions. The active condition reached its maximum concentration value at around 8-13s while both passive and SS conditions reached their maximum concentration value around 13-18s. Similar results across conditions were found bilaterally for HbR. All conditions stayed relatively close to 0. Increasing HbR patterns in the SS and the passive condition were observed in contrast with a decreasing pattern in the active condition. Ipsilesional HbR showed greater differences between conditions than contralesional HbR.

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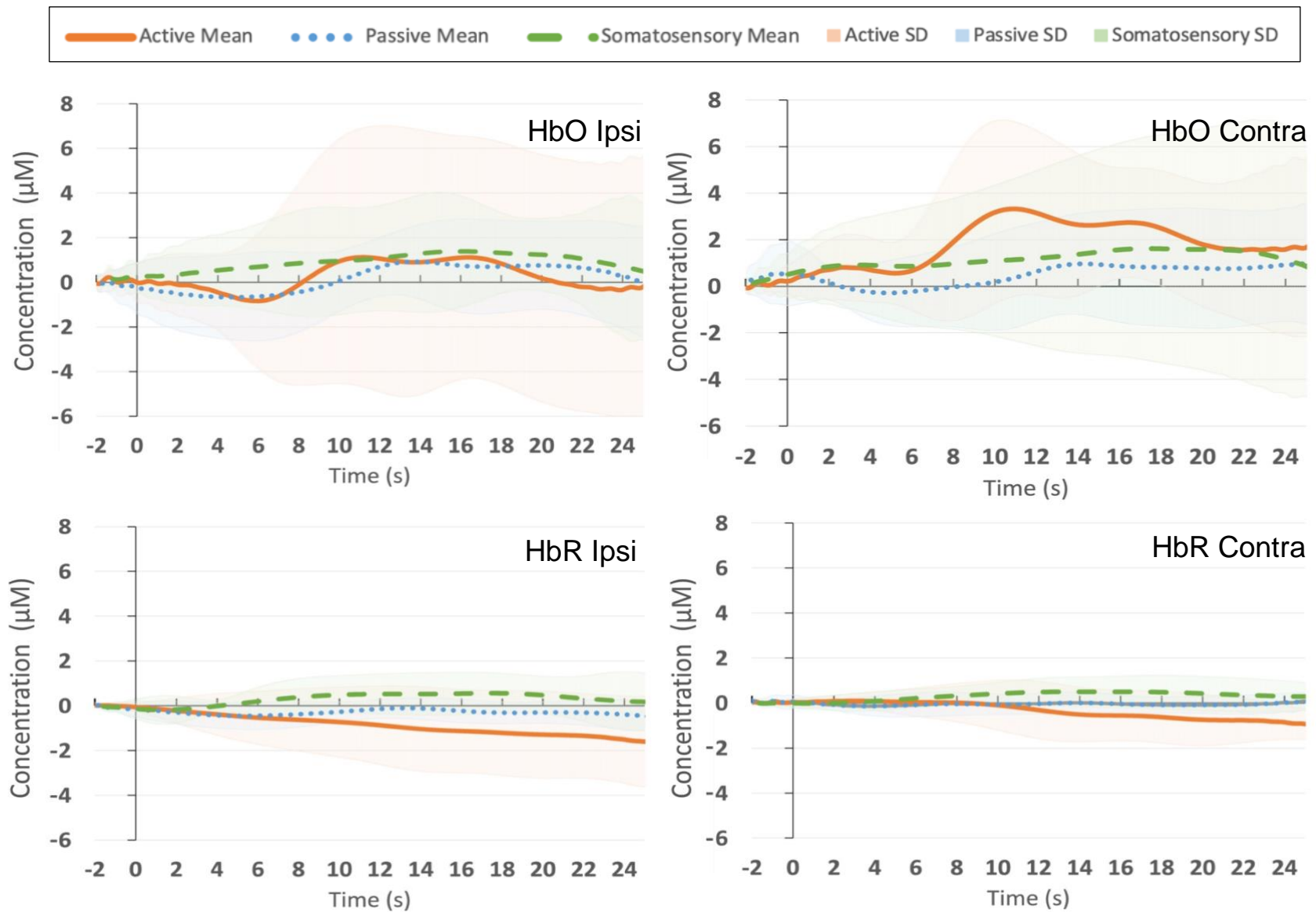
Figure 4. Mean and SD (shaded) of PFC activation during three conditions: active and passive ankle dorsiflexion and plantarflexion and SS.

Legend for Figure 4: Solid line represents the active condition; dotted line represents the passive condition; dashed line represents the SS condition. HbO, oxygenated hemoglobin; HbR, deoxygenated hemoglobin; HbO Ipsi, HbO ipsilesional; HbO Contra, HbO Contralesional; HbR Ipsi, HbR ipsilesional; HbR Contra, HbR Contralesional; SD, Standard Deviation
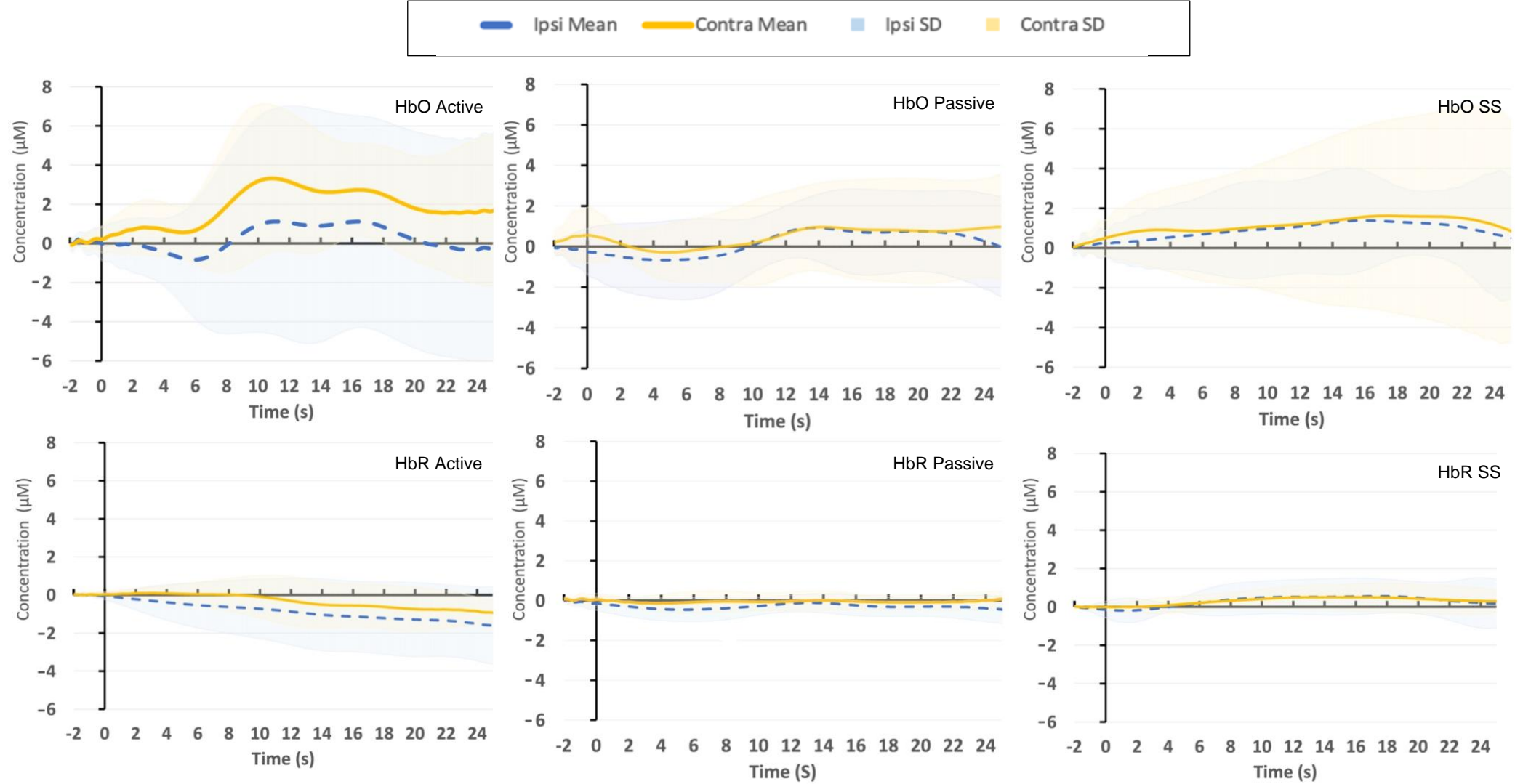
Figure 5. Mean and SD (shaded) of PFC activation for ipsilesional and contralesional hemisphere during three conditions: active and passive ankle dorsiflexion and plantarflexion and SS.

Legend: Solid line represents contralesional PFC activation and dashed line represents ipsilesional PFC activation. Ipsi, ipsilesional; Contra, Contralesional; SD, Standard Deviation; HbO, oxygenated hemoglobin; HbR, deoxygenated hemoglobin; SS, somatosensory stimulation.

2.3.4 Objective 2: PFC Activation Between Hemispheres During Ankle Conditions

Based on visual inspection (**Figure 5**), the contralesional hemisphere showed greater HbO concentration than the ipsilesional in the active conditions and bilateral activation for the passive and SS conditions. In the active condition, the difference between hemispheres was more visually apparent than in the passive and SS conditions. The contralesional HbO concentration increased after the start of the active condition and peaked at around 10s. The decrease in HbO values initiated after the peak and continued to decrease until the active condition was finished. The ipsilesional HbO data showed similar patterns as contralesional but with a smaller amplitude of change, indicating more contralesional PFC activation during the active condition. For the passive and SS conditions, the bilateral activation was found as both ipsilesional and contralesional activation overlapped each other. The amplitude of increase in HbO from the contralesional PFC was the highest in active conditions compared to that of the passive and SS conditions. For HbR, the active condition displayed a decrease in both ipsilesional and contralesional PFC. In the passive and the SS conditions, contralesional and ipsilesional PFC activation stayed relatively unchanged compared to the baseline.

To compare interhemispheric asymmetry, LI was calculated for each participant during each condition (**Table 2**). Three numbers were identified as outliers and were excluded from the calculation of the mean and SD. Aside from outliers, 3 LI values from each group of HbO active, HbR active and HbR passive and 1 value from each group of HbO passive and HbO SS were outside of the expected range of -1 to +1.[174,181] **Table 3** listed the mean and SD of LI during each condition. The LI values (mean ± SD) were 0.7±0.9 for HbO active, -0.2±0.7 for HbO passive, -0.5±0.7 for HbO SS in the PFC. This result may indicate more ipsilesional PFC activation for the

Table 2| LI and FMLE scores for each participant during three conditions using both HbO and HbR concentration.

	HbO			HbR			FMLE		
Participant No.	Active	Passive	SS	Active	Passive	SS	Motor (/34)	Sensory (/12)	Total (/46)
1	0.03	<u>-1.67</u>	<u>-1.85</u>	0.21	<u>-1.74</u>	0.22	24	10	34
2	0.08	-0.31	-0.33	<u>1.30</u>	-0.15	0.20	11	12	23
3	0.36	0.57	-0.48	-0.39	0.13	0.17	6	11	17
4	<u>1.32</u>	0.06	-0.76	0.66	<u>1.49</u>	0.23	19	12	31
5	<u>1.17</u>	-0.13	0.35	0.28	<u>-1.19</u>	0.68	22	11	33
6	0.57	0.87	0.12	<u>2.94</u>	0.34	-0.34	14	12	26
7	-0.09	-0.36	<u>22.28</u>*	0.20	<u>29.87</u>*	0.06	26	12	38
8	0.37	-0.71	0.03	0.64	-0.60	0.38	24	12	36
9	<u>2.74</u>	-0.40	-0.78	<u>3.33</u>	-0.05	<u>-1.26</u>*	15	5	20

*A positive number indicates more ipsilesional PFC activation and a negative number indicates more contralesional PFC activation; * indicates outliers; <u>Underline</u> indicates LI values that are beyond the expected range of -1 to +1. Abbreviations: LI, Laterality index; FMLE, Fugl-Meyer Lower Extremity; HbO, Oxygenated hemoglobin; HbR, Deoxygenated hemoglobin.*

Table 3| Mean ± SD of LI for three conditions: active, passive, and SS and Mean ± SD of FMLE-M, FMLE-S, FMLE-T.

	HbO	HbR	FMLE-M	FMLE-S	FMLE-T
Active	0.7±0.9	1.0±1.3			
Passive	-0.2±0.7	-0.2±1.0*	17.9 ± (6.8)	10.8 ± (2.3)	29.0 ± (7.0)
SS	-0.5±0.7*	0.2±0.3*			

* indicates n=8 for the calculation of LI due to excluded values of outliers; Abbreviations: HbO, oxygenated hemoglobin; HbR, deoxygenated hemoglobin; FMLE-M, the motor portion of the Fugl-Meyer Lower Extremity Assessment; FMLE-S, the sensory portion of the Fugl-Meyer Lower Extremity Assessment; FMLE-T, the total score of the Fugl-Meyer Lower Extremity Assessment

active condition, bilateral PFC activation for the passive condition and more contralesional activation for the SS condition.

The LI values (mean ± SD) were 1.0±1.3 for HbR in the active condition, -0.2±1.0 for HbR in the passive condition, and 0.2±0.3for HbR in the SS condition. This result might suggest an ipsilesional dominance in the active condition, and bilateral activation in the passive condition and the SS condition.

Comparing **Figure 5** and the LI value from **Table 3**, the results appeared to display both agreement and disagreement with each other. They potentially indicated bilateral activation for the passive condition. However, **Figure 5** showed an increase in contralesional PFC activation as opposed to the LI values, which could indicate more ipsilesional PFC activation. **Figure 5** also showed bilateral PFC activation for the SS condition, but the LI implied contralesional activation for the SS HbO and bilateral for SS HbR.

2.3.5   Objective 3: Relationship Between LI and FMLE

We evaluated the relationship between interhemispheric asymmetry of the PFC activity during the conditions and FMLE scores. Sensorimotor conditions (active and passive ankle plantarflexion and dorsiflexion) were plotted with FMLE-M and SS was plotted with FMLE-S. HbO SS, HbR passive and HbR SS were plotted with 8 individuals instead of 9 due to outliers. **Figure 6A** showed the scatter plot of LI against FMLE-M for all 9 participants for the active condition. The results may have indicated a negative relationship between active LI and FMLE-M for both HbO and HbR. This suggested that higher scores on the FMLE-M (better functioning) relate to LI values closer to zero, indicating more bilateral PFC activation during active ankle movements. A negative relationship between passive LI and FMLE-M also appeared (**Figure 6B**). A higher score on the FMLE-M would be related to a more negative LI value or more

contralesional PFC activation. This could imply that individuals with better functions poststroke display an asymmetry that favours contralesional PFC during passive ankle conditions. **Figure 6C** showcased a positive relation between HbO LI with FMLE-S and a negative relation between HbR LI with FMLE-S during SS. In both cases, a higher score on the FMLE-S could be related to a LI value closer to 0 (bilateral PFC activation). This explained individuals with better sensory functions could present bilateral PFC activation during the SS conditions.
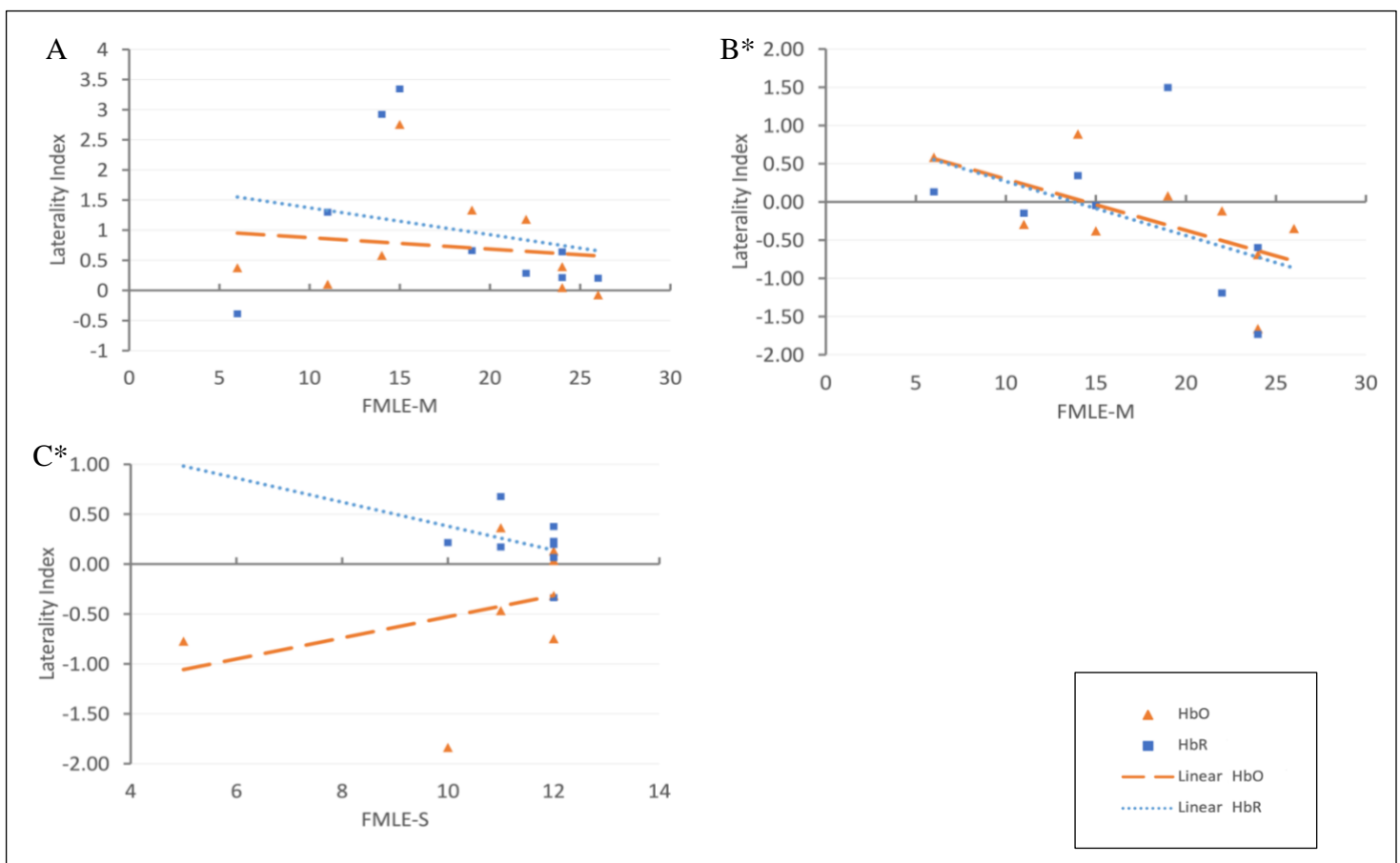
Figure 6. (A) Relation between LI during the active condition and FMLE-M. (B) Relation between LI during the passive condition and FMLE-M. (C) Relation between LI during SS and FMLE-S.

Legend: * indicates outliers existed and excluded within the group (HbO SS, HbR passive and HbR SS were plotted with n=8 and all other conditions contain n=9). Abbreviations: LI, Laterality Index; FMLE-M, the motor portion of the Fugl-Meyer Lower Extremity Assessment; FMLE-S, the sensory portion of the Fugl-Meyer Lower Extremity Assessment; FMLE-T, the total score of the Fugl-Meyer Lower Extremity Assessment; HbO, Oxygenated hemoglobin; HbR, Deoxygenated hemoglobin.

2.4 Discussion

This is the first fNIRS study completed in people with a subacute stroke that compared the hemodynamic response profiles across the bilateral PFC during active ankle dorsiflexion/plantarflexion, passive ankle dorsiflexion/plantarflexion and a light touch somatosensory condition, as well as the relationship between PFC activation and FMLE. Our descriptive results partially supported our hypotheses and are in line with previous work.

2.4.1 Activation of PFC: Active versus Passive versus SS

Our result showed that there was a difference in PFC activation between the active condition, the passive condition, and the SS condition. This result partially supported our hypothesis that the greatest PFC activation would be found during the active condition. Contrary to our hypothesis, higher activation in the PFC was observed during the SS condition than the passive condition. The following are possible explanations for the results. First, compared with the passive and the SS conditions, active ankle movement requires voluntary motor control to execute the condition. Previous studies have found the PFC is the main brain region responsible for voluntary motor control.[138,139] Hence, it is logical that the PFC will be activated further to complete the active condition compared to passive and SS conditions. Secondly, the cognitive processing of passive ankle sensorimotor movements may be limited by somatosensory impairment. Impairment in somatosensation includes diminished somatosensory perception and proprioception and is common in people with subacute stroke.[26] While the participant may be able to feel SS, it is possible that their proprioception is not intact or is impaired. This could potentially explain how SS elicits a higher amplitude than passive conditions. Because proprioception was not assessed in the current study, we suggest that future studies could document both cutaneous somatosensation and proprioception during somatosensory assessments. Finally, the differences between the results in the studies that informed our hypothesis, and the current

study may be explained by the study population (i.e., people with chronic stroke compared to people with subacute stroke).[73,110] Brain recovery poststroke is progressive and varies across individuals.[189] Hence, it is possible that people with subacute stroke and people with chronic stroke display different brain activation patterns that contribute to distinct research findings during the performance of the same conditions.

Of note, a decrease in HbR, which also indicates increased neural activation, was observed during active conditions in PFC. Previous fNIRS studies in walking poststroke have primarily reported findings in HbO concentrations.[31] Although reporting of HbR is recommended, few studies report these findings and further interpretation of the current findings is limited. [164,190]

2.4.2 Atypical Laterality Index Values Among People with Stroke

In both active and passive conditions, the LI findings from HbO are consistent with the LI results from HbR. They both presented that the active condition could elicit more ipsilesional PFC activation and the passive condition can activate the PFC bilaterally. However, LI results from HbO for the SS condition contradicted the LI values from HbR in that HbO LI suggested more contralesional PFC activation, whereas HbR LI may have demonstrated bilateral PFC activation. We speculate that this result may be attributed to the lack of guidelines in interpreting LI values from HbR concentrations. Moreover, interpreting the LI values from HbR is challenging since most studies solely report and interpret LI values calculated from HbO concentration.[177,191] It is possible that LI values from the HbR concentration follow a different threshold that indicates interhemispheric asymmetry. Further research on this topic is needed to fully understand the values of the current study.

With the exception of outliers, a total of 10 LI values fell beyond the expected range of -1 to +1 for HbO and HbR. A common characteristic observed among these values is that they have

different directions of change for the hemispheres meaning that positive values for one hemisphere and negative values for the other hemisphere. This could be explained by Borrell et al. who found that the General Linear Model analysis pipeline produced more inaccurate measures of brain laterality compared to other analysis methods such as block average.[181] Moreover, existing studies utilizing LI have primarily relied on fMRIs conducted on both clinical populations and healthy individuals.[178] There have been limited instances where fNIRS has been employed in LI calculations, particularly in the context of stroke-related research.[177] For example, He et al. used fNIRS to assess LI during walking in people with subacute stroke.[177] All LI values displayed were within the range of +1 and -1. We believe that the dissimilarity of results from He et al. and the current study could attribute to the nature of the conditions. The current study uses conditions that require more isolated movement rather than compound movements such as walking and standing. Walking or standing usually require the collective contribution of the entire body, whereas ankle sensorimotor functions are limited to peripheral joints and require engagement from one part of the body. This means the changes are more subtle and we may observe smaller changes in Hb amplitudes, subsequently affecting the values for LI. This suggests that future studies may consider incorporating conditions with a higher pace, faster tempo, or more repetitions.

2.4.3   Different Ways to Investigate Interhemispheric Asymmetry

We employed two methods to examine the interhemispheric asymmetry: visualizing Hb through plotting and utilizing the LI. Our plots may have indicated that the contralesional hemisphere showed greater PFC activation in active conditions and bilateral activation for passive and SS conditions. Interestingly, LI calculations yield a divergent outcome. LI calculation presented potentially more ipsilesional PFC activation for the active condition, bilateral activation for the passive condition, and contralesional or bilateral PFC activation for SS. These results

partially substantiated our hypothesis as supported by current literature.[70] The disparity in results can be attributed to variations in the specific brain regions of interest (primary motor cortex compared to PFC).[70]

In healthy adults, the typical hemodynamic response to neural activation consists of increased HbO concentration and decreased HbR concentration compared to the baseline.[192] This assumes activation values will be positive for HbO and negative for HbR. However, our finding suggests that we should refrain from making such an assumption, considering that brain recovery happens in various ways poststroke. There is limited information regarding changes in Hb differences in atypical brains, such as the brain after a stroke.[192] We believe the underlying assumption regarding cortical activation needs to be revisited, as well as the approach researchers employ to investigate interhemispheric asymmetry. LI may not be the best approach to consider when assessing interhemispheric asymmetry, particularly in individuals who have experienced a stroke.

We recognize the significance of interhemispheric asymmetry in exploration and the importance of examining it. However, we are uncertain if LI is the most accurate method to investigate laterality. Due to this concern, we believe that visualizing through plotting the hemodynamic response function could potentially provide a more accurate method for our study to examine interhemispheric asymmetry. Future research should explore alternative approaches for investigating interhemispheric asymmetry poststroke.

2.4.4   FMLE and PFC Activation

Although FMLE has not commonly been assessed during the investigation of cortical activation in previous research, our study showed similar results as the richer body of literature that assessed upper extremity FM. Our result showcased that bilateral PFC activation was found

in better-functioning individuals with subacute stroke for SS conditions. This observation is logical since healthy adults typically exhibit bilateral activation in brain regions (e.g., the primary somatosensory cortex) during cutaneous somatosensation stimulation in the lower extremity.[128–131] Consequently, improved sensory functions in the lower extremity in people with subacute stroke are thought to resemble similar brain activation patterns of a healthy adult. Similarly, for the active condition, bilateral PFC activation was found in our study. Our result corresponded with previous findings in people with chronic stroke during walking.[153] This result was coherent as active ankle movement is involved in walking, which is bilaterally activated.

On the other hand, contralesional activation was associated with better functioning in passive ankle movements. We presume that our result can relate to unilateral (left PFC) activation observed during passive gait in healthy volunteers.[163] Consequently, the unilateral activation we are witnessing in individuals with higher functionality poststroke might resemble the brain activity patterns documented in healthy individuals.

2.5   Limitations

Our study had certain limitations. Overall, this protocol can be easily adhered to with potential modifications (e.g., faster tempo) regarding recruitment strategies. We think the major obstacle that resulted in the small sample size was restricted access to the inpatient stroke unit due to the COVID-19 outbreaks. We were solely recruiting participants from the inpatient stroke unit of a hospital that experienced ongoing outbreaks throughout the data collection period. It is crucial to acknowledge that certain individuals may not attend inpatient rehabilitation following a stroke due to various factors, such as limited access to healthcare and higher/lower levels of functions than the admission requirements. This circumstance may result in a potential limitation of our participant pool by excluding these individuals, which means our participants do not represent

everyone who has had a stroke. Future studies should consider these factors during the recruitment process. Because of our small sample size, the between-participant variability is likely high within the PFC.[193] This large between-subject variability likely contributes to the variation in results. Hence, we opted to visualize the results through plots instead of statistical analysis, as we believe this approach best suits the objectives of our study. This limitation should also inform future studies to have a potentially bigger sample size by recruiting from multiple sites or longer recruitment periods.

Second, this study solely focused on PFC, while the role of the primary motor cortex and primary somatosensory cortex in ankle sensorimotor control was not investigated. This is a limitation of the fNIRS device that we used. The placement of our fNIRS device is limited to the PFC since it cannot be used on hair-covered areas of the scalp. However, other brain regions are worth investigating during ankle sensorimotor conditions. Previous fNIRS studies showed increased activation in the primary motor cortex and the primary somatosensory cortex during walking in people with hemiparesis compared with during healthy gait.[177] This suggests that future studies should investigate these areas in addition to PFC during ankle sensorimotor conditions with a whole-cap fNIRS device. Third, the interpretation of LI values calculated from HbR concentration changes is limited due to underreported HbR LI values in the current literature. Most studies only report LI values calculated from HbO concentration changes, and they report that HbO is more sensitive than HbR to changes in hemodynamic response.[181,194] However, we think that both HbO LI and HbR LI values should be reported regardless of the significance of the values. We have also encountered values that fall outside the expected range, limiting our ability to interpret them. It is important to note that other studies either did not report such values or did not have any values outside the expected range. We are confident that the data analysis process itself did not introduce these outliers, affirming the reliability of our results. To address

this issue, we believe that increasing the sample size and employing conditions with a faster tempo or pace may offer a potential solution as these changes to the conditions may produce larger signals. Finally, leg dominance was not documented in this study. We did not consider leg dominance to be relevant to cortical changes because walking involves bilateral and whole-body movement, unlike upper-body activities that tend to be more specific and complex. Additionally, individuals commonly exhibit a preference for using one hand over the other; whereas it is less common for people to identify a favourable leg to utilize.[195] Leg dominance was typically not recorded in lower-extremity studies, but future studies could potentially record this information to investigate if a difference could be observed.[31]

2.6   Conclusion

In conclusion, this is the first exploratory study that utilized fNIRS to assess PFC activation during active and passive ankle dorsiflexion and plantarflexion and SS conditions in people with subacute stroke. Our results showed that there was more PFC activation in the active condition compared to the passive condition and the SS condition around the ankle. Two methods which investigated interhemispheric asymmetry in people with subacute stroke provided similar findings for the active and passive conditions and divergent findings for the SS condition. Specifically, both methods demonstrated that active ankle movement was related to asymmetrical PFC activation and passive elicited bilateral activation. The plotting method showed that SS was related to bilateral PFC activation, while the LI values indicated SS was related to more contralesional PFC activation from HbO values and bilateral activation from HbR values. Future research is needed to verify this finding and to improve methods used to address interhemispheric asymmetry. Participants who had better lower extremity functions showed bilateral PFC activation during active and SS conditions, whereas more contralesional PFC activation is found in the passive

condition. Overall, our study provided exploratory results that assist in understanding the role of PFC in ankle sensorimotor functions in people with subacute stroke. This also provides a theoretical basis for a better understanding of post-stroke ankle sensorimotor deficits and the development of strategies to optimize safe mobility after stroke.

3   CHAPTER 3

The main objective of the thesis was to understand PFC activation during active and passive ankle plantarflexion and dorsiflexion and somatosensory stimulation (SS) around the ankle among people with subacute stroke, as well as its relationship with FMLE. We discovered most PFC activation during the active condition, followed by the SS condition and the passive condition. However, the activation amplitude was relatively smaller compared to walking or standing conditions reported in the literature. Hence, we recommend future studies to employ more repetitions or faster pace for ankle sensorimotor conditions. Interhemispheric asymmetry was evaluated using plotting and LI. The results from LI were consistent with results from plots that active ankle movement was related to asymmetrical PFC activation; passive elicited bilateral activation; SS was related to asymmetrical but close to bilateral PFC activation. However, divergent findings were found between the two methods regarding the type of asymmetry (either more ipsilesional or contralesional activation) in active and SS conditions. We speculate that this discrepancy may be attributed to the lack of guidelines in interpreting LI values using fNIRS, especially from HbR concentrations. Interpreting the LI values from HbR is challenging since most studies solely report and interpret LI values calculated from HbO concentration.[177,191] It is possible that LI values from HbR concentration follow a different threshold that indicates bilateral activation, ipsilesional activation and contralesional activation. Further research on this topic is needed to comprehensively understand the values of the current study.

Our result also attempted at clarifying the relationship between FMLE and PFC activation. Our results indicated that bilateral PFC activation were found in participants with better functions during active and SS conditions, and contralesional PFC activation during passive conditions. The findings of this thesis are novel additions to the current stroke literature and provide the fundamental knowledge of the connection between PFC activation and ankle sensorimotor

functions poststroke. Poststroke recovery varies among individuals, which means brain activation should be monitored individually to aid in understanding recovery.

The results of this study can help inform the protocol for assessing cortical activation during ankle sensorimotor conditions in a clinical setting with people with subacute stroke. One area that can be developed from the work of this thesis to effectively address variability in brain activation among people with subacute stroke during ankle sensorimotor conditions is to understand how Canadian healthcare professionals address brain recovery in clinical practice. It is recommended to practise personalized care and that would be best achieved through the use of a portable and affordable neuroimaging device to monitor brain activation, such as fNIRS.

To continue to comprehensively understand cortical activities during ankle sensorimotor conditions among people with subacute stroke, expanding research to include other brain regions can use the findings that emerged from this thesis as a comparator to identify the brain regions that exhibit the most significant activation during ankle sensorimotor conditions. Future research that uses fNIRS should be aware of the duration of the study as a longer setup contributes to a longer time wearing the device, which could potentially be uncomfortable for some participants. Future studies that investigate people with chronic stroke or use other functional movements could potentially use the PFC activation figures within the present studies for comparison across study samples. Additionally, future studies should also attempt to clarify interhemispheric asymmetry during ankle sensorimotor conditions as this study found divergent results from two methods (LI and plotting). This contributes to the ongoing debate in the literature regarding the significance of asymmetrical patterns of activation in functional recovery. The introduction of fNIRS as a monitoring tool can potentially benefit recovery poststroke and inform better rehabilitation strategies by providing more individualized care and more accurate prediction of recovery for people who have had a stroke.

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5   APPENDICES

Appendix A: Ethics Approval Documents

LAWSON FINAL APPROVAL NOTICE

LAWSON APPROVAL NUMBER: R-22-066

PROJECT TITLE: Neural activation changes linked to increased aerobic intensity

PRINCIPAL INVESTIGATOR: Dr. Sue Peters

LAWSON APPROVAL DATE: 4/02/2022

ReDA ID: 11729

Overall Study Status: Active

Please be advised that the above project was reviewed by Lawson Administration and the project was approved.

"COVID-19: Please note that Lawson is continuing to review and approve research studies. However, this does not mean the study can be implemented during the COVID-19 pandemic. Principal Investigators, in consultation with their program leader or Chair/Chief, should use their judgment and consult <u>Lawson's research directive and guidelines</u> to determine the appropriateness of starting the study. Compliance with hospital, Lawson, and government public health directives and participant and research team safety supersede Lawson Approval."

 Please provide your Lawson Approval Number (R#) to the appropriate contact(s) in supporting departments (eg. Lab Services, Diagnostic Imaging, etc.) to inform them that your study is starting. The Lawson Approval Number must be provided each time services are requested.

Dr. David Hill
V.P. Research

Date: 16 December 2021

To: Dr Sue Peters

Project ID: 119880

Study Title: Neural activation changes linked to increased aerobic intensity

Application Type: HSREB Initial Application

Review Type: Full Board

Meeting Date: 02/Dec/2021

Date Approval Issued: 16/Dec/2021

REB Approval Expiry Date: 16/Dec/2022

_____

Dear Dr Sue Peters

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above mentioned study as described in the WREM application form, as of the HSREB Initial Approval Date noted above. This research study is to be conducted by the investigator noted above. **All other required institutional approvals and mandated training must also be obtained prior to the conduct of the study**.

Documents Approved:

Document Name	Document Type	Document Date	Document Version
FESbike_data_form	Case Report Form	14/Sep/2021	1
fNIRS Assessments-v1	Case Report Form	14/Sep/2021	1
End of Study information form_v2	End of Study Letter	13/Dec/2021	2
Letter-of-Information-and-Consent_v2	Written Consent/Assent	13/Dec/2021	2
FES bike and fNIRS protocol_v2	Protocol	13/Dec/2021	2

Documents Acknowledged:

Document Name	Document Type	Document Date
Budget	Study budget	12/Oct/2021

No deviations from, or changes to, the protocol or WREM application should be initiated without prior written approval of an appropriate amendment from Western HSREB , except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the trial.

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Karen Gopaul , Ethics Officer on behalf of Dr. Philip Jones, HSREB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Date: 23 March 2022

To: Dr Sue Peters

Project ID: 119880

Study Title: Neural activation changes linked to increased aerobic intensity

Application Type: HSREB Amendment Form

Review Type: Delegated

Full Board Reporting Date: 12/Apr/2022

Date Approval Issued: 23/Mar/2022

REB Approval Expiry Date: 16/Dec/2022

Dear Dr Sue Peters ,

The Western University Health Sciences Research Ethics Board (HSREB) has reviewed and approved the WREM application form for the amendment, as of the date noted above.

Documents Approved:

Document Name	Document Type	Document Date	Document Version
FM-LE	Paper Survey	Received March 15, 2022	
MFIS	Paper Survey	15/Mar/2022	1
Rating of Perceived Exertion	Paper Survey	15/Mar/2022	1
Fatigue Severity Scale	Paper Survey	15/Mar/2022	1
Letter of Information and Consent - March 15th 2022	Consent Form	15/Mar/2022	4
FES bike and fNIRS protocol_v3-revised	Protocol	15/Mar/2022	3

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Karen Gopaul , Ethics Officer on behalf of Dr. Philip Jones, HSREB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

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Appendix B: Fugl-Meyer Assessment Lower Extremity Assessment

Rehabilitation Medicine, University of Gothenburg

FUGL-MEYER ASSESSMENT   **ID:**
LOWER EXTREMITY (FMA-LE)   **Date:**
Assessment of sensorimotor function   **Examiner**:

E. LOWER EXTREMITY

I. Reflex activity, supine position			none	can be elicited	
Flexors: knee flexors			0	2	
Extensors: patellar, achilles (at least one)			0	2	
		Subtotal I (max 4)			

II. Volitional movement within synergies supine position			none	partial	full
Flexor synergy: Maximal hip flexion (abduction/external rotation), maximal flexion in knee and ankle joint (palpate distal tendons to ensure active knee flexion).	Hip	flexion	0	1	2
	Knee	flexion	0	1	2
	Ankle	dorsiflexion	0	1	2
Extensor synergy: From flexor synergy to the hip extension/adduction, knee extension and ankle plantar flexion. Resistance is applied to ensure active movement, evaluate both movement and strength (compare with the unaffected side)	Hip	extension	0	1	2
		adduction	0	1	2
	Knee	extension	0	1	2
	Ankle	plantar flexion	0	1	2
		Subtotal II (max 14)			

III. Volitional movement mixing synergies sitting position, knee 10cm from the edge of the chair/bed		none	partial	full
Knee flexion from actively or passively extended knee	no active motion	0		
	less than 90° active flexion, palpate tendons of hamstrings		1	
	more than 90° active flexion			2
Ankle dorsiflexion compare with unaffected side	no active motion	0		
	limited dorsiflexion		1	
	complete dorsiflexion			2
	Subtotal III (max 4)			

IV. Volitional movement with little or no synergy standing position, hip at 0°		none	partial	full
Knee flexion to 90° hip at 0°, balance support is allowed	no active motion or immediate, simultaneous hip flexion	0		
	less than 90° knee flexion and/or hip flexion during movement		1	
	at least 90° knee flexion without simultaneous hip flexion			2
Ankle dorsiflexion compare with unaffected side	no active motion	0		
	limited dorsiflexion		1	
	complete dorsiflexion			2
	Subtotal IV (max 4)			

V. Normal reflex activity supine position, assessed only if full score of 4 points is achieved in part IV, compare with the unaffected side		hyper	lively	normal
Reflex activity knee flexors, Patellar, Achilles,	2 of 3 reflexes markedly hyperactive	0		
	1 reflex markedly hyperactive or at least 2 reflexes lively		1	
	maximum of 1 reflex lively, none hyperactive			2
	Subtotal V (max 2)			
	Total E (max 28)			

F. COORDINATION/SPEED, supine, after one trial with both legs, eyes closed, heel to knee cap of the opposite leg, 5 times as fast as possible		marked	slight	none
Tremor		0	1	2
Dysmetria	pronounced or unsystematic	0		
	slight and systematic		1	
	no dysmetria			2
		≥ 6s	2 - 5s	< 2s
Time	6 or more seconds slower than unaffected side	0		
	2-5 seconds slower than unaffected side		1	
	less than 2 seconds difference			2
Total F (max 6)				

H. SENSATION, lower extremity eyes closed, compare with the unaffected side		anesthesia	hypoesthesia or dysesthesia	normal
Light touch	leg	0	1	2
	foot sole	0	1	2
		less than 3/4 correct or absence	3/4 correct or considerable difference	correct 100%, little or no difference
Position small alterations in the position	hip	0	1	2
	knee	0	1	2
	ankle	0	1	2
	great toe (IP-joint)	0	1	2
Total H (max12)				

I. PASSIVE JOINT MOTION, lower extremity supine position, compare with the unaffected side		only few degrees (≤10° hip)	decreased	normal	J. JOINT PAIN during passive motion, lower extremity pronounced pain during movement or very marked pain at the end of the movement	some pain	no pain
Hip	Flexion	0	1	2	0	1	2
	Abduction	0	1	2	0	1	2
	External rotation	0	1	2	0	1	2
	Internal rotation	0	1	2	0	1	2
Knee	Flexion	0	1	2	0	1	2
	Extension	0	1	2	0	1	2
Ankle	Dorsiflexion	0	1	2	0	1	2
	Plantar flexion	0	1	2	0	1	2
Foot	Pronation	0	1	2	0	1	2
	Supination	0	1	2	0	1	2
Total (max 20)					**Total** (max 20)		

E. LOWER EXTERMTY	/28
F. COORDINATION / SPEED	/6
TOTAL E-F (motor function)	/34

H. SENSATION	/12
I. PASSIVE JOINT MOTION	/20
J. JOINT PAIN	/20

Appendix C: Reasons for Dropout

Participant No.	Reasons for dropout
S01	After consent, potential cognitive impairment identified
S02	After consent, diagnosed with Parkinson's Disease
S03	After consent, during device fitting, the participants' craniotomy affected the placement of the fNIRS devices
S04	After consent, chronic back pain was impacting their participation in data collection

Appendix D: Individual Characteristics

Participant ID	Age (years)	Sex	Time since stroke (Days)	Lesion Side	Lesion Depth	Type of Stroke	BBS (/56)	FMLE Motor (/34)	FMLE Sensation (/12)	FM Total (/46)
01	48	F	45	Right	Subcortical	Ischemic	52	24	10	34
02	69	F	45	Left	Subcortical	Ischemic	5	11	12	23
03	56	F	18	Right	Subcortical	Ischemic	29	6	11	17
04	52	F	16	Left	Subcortical	Ischemic	6	19	12	31
05	50	M	20	Left	Subcortical	Ischemic	12	22	11	33
06	68	F	31	Right	Subcortical	Ischemic	3	14	12	26
07	87	M	25	Right	Unknown	Unknown	46	26	12	38
08	81	M	43	Right	Subcortical	Ischemic	46	24	12	36
09	76	M	107	Right	Cortical	Hemorrhagic	11	15	5	20

FMLE=Fugl-Meyer Lower Extremity, BBS=Berg Balance Scale

Appendix E: Repetitions completed for each condition

Participants	Repetition completed for each condition		
	Active	Passive	Somatosensory
01	5	5	5
02	4 (Excluded one repetition due to movement on the non-paretic leg)	5	5
03	5	5	2 (Excluded three repetitions due to non-paretic leg movement, head movement and spasm)
04	5	5	5
05	5	5	5
06	5	5	5
07	5	5	5
08	5	5	5
09	5	5	5

6 Curriculum Vitae

<div align="center">

SIYING LUAN

</div>

EDUCATION

WESTERN UNIVERSITY London, Canada

Master of Health and Rehabilitation Science (MSc) 2021-2023
- Research in the field of physical therapy; Involved in the Neurorehabilitation Physiology Lab with Dr. Sue Peters & the Mobility in Ageing Lab with Dr. Susan Hunter
- Actively participated in academic conferences, such as *Neuroscience Research Day (NRD) at Western University and the 15th Health and Rehabilitation Graduate Research Conference* and 12 others; presented research findings to industry peers and experts.

Bachelor of Health Science (BHSc) 2017-2021
- Honors Specialization in Health Science; Minor in Psychology

CONFERENCE PRESENTATIONS AND PROCEEDINGS

***Bold** indicates S Luan, <u>underlined</u> indicates presenting author, *italic* indicates conference name

- <u>S Kohli</u>, **S Luan,** N Durand, J Fleet, R Viana, A Christie, R Teasell, L Brunton**,** S Peters. Cortical Activation, Standing Balance, and Fatigue - A Post-Stroke Explorative Study. *15th World Stroke Congress*, Toronto, Canada. October 10th, 2023. [Poster Presentation]
- <u>**S Luan**</u>, S Kohli, S Peters. Bilateral prefrontal cortex activation during lower extremity sensorimotor tasks in subacute stroke patients. *Parkwood Institute Research (PIR) Day - "Trauma-Informed Approaches to Research, Care, and Practice"*, Parkwood Institute, London, ON. April 27th, 2023. [Poster Presentation]
- S Kohli, <u>**S Luan,**</u> S Peters. Cortical activation, standing balance, and fatigue – a post stroke explorative study. *Parkwood Institute Research (PIR) Day - "Trauma-Informed Approaches to Research, Care, and Practice"*, Parkwood Institute, London, ON. April 27th, 2023. [Poster Presentation]
- <u>**S Luan**</u>, S Kohli, S Peters. Bilateral prefrontal cortex activation during lower extremity sensorimotor tasks in subacute stroke patients. *Neuroscience Research Day (NRD)*, Society of Neuroscience Graduate Student, Western University, London, ON. February 24th – 25th, 2023. [3 Minute Thesis Presentation]
- <u>**S Luan**</u>, S Peters. Cortical activation linked to sensorimotor functions post-stroke. *Health and Rehabilitation Graduate Research Conference*, Western University, London, ON. February 1st, 2023. [Oral presentation -- **Award of Achievement - Musculoskeletal Rehabilitation Research Network**]
- <u>**S Luan**</u>, F MacRae, J Watts, S Kohli, K Tsikrikis, S Peters. The Neurorehabilitation Physiology Lab. *Parkwood Institute Research Open House*, London, ON. December 2nd, 2022. [Virtual due to COVID-19, Video presentation]
- <u>**S Luan**</u>, S Kohli, S Peters. Discovering cortical activation associated with sensorimotor function after functional electrical stimulation cycling in patients with stroke: a pilot study. *London Health Research Day (LHRD),* Lawson Health Research Institute & Schulich School of Medicine & Dentistry, London, ON. May 30th, 2022. [Virtual due to COVID-19, Poster Presentation]
- <u>**S Luan**</u>, S Kohli, S Peters. Cortical activation associated with sensorimotor stimulation after functional electrical stimulation cycling in patients with stroke – a pilot study. *Parkwood Institute Research (PIR) Day - "Better Together: The Power of Partnership"*, Parkwood Institute, London, ON. April 21st, 2022. [Virtual due to COVID-19, Poster Presentation]
- <u>S Kohli</u>, **S Luan**, S Peters. Cortical activation, standing balance, and fatigue - a post-stroke explorative study. *Parkwood Institute Research (PIR) Day - "Better Together: The Power of Partnership"*, Parkwood Institute, London, ON. April 21st, 2022. [Virtual due to COVID-19, Poster Presentation]

- **S Luan**, S Peters. The change between cortical activation and somatosensory stimulation after functional electrical stimulation cycling in patients with stroke. *Neuroscience Research Day (NRD)*, Society of Neuroscience Graduate Student, Western University, London, ON. February 24th – 25th, 2022. [Virtual due to COVID-19, Oral Presentation]
- **S Luan**, S Peters. Discovering brain activation associated with sensorimotor stimulation after functional electrical stimulation cycling in patients with stroke. *Health and Rehabilitation Graduate Research Conference*, Western University, London, ON. February 2nd, 2022. [Virtual due to COVID-19, Poster presentation]
- S Kohli, **S Luan**, S Peters. Cortical activation, standing balance, and fatigue - a post-stroke explorative study. *Health and Rehabilitation Graduate Research Conference*, Western University, London, ON. February 2nd, 2022. [Virtual due to COVID-19, Poster presentation]
- **S Luan**, S Kohli, S Peters. Lab introduction and research proposal: discovering brain activation patterns associated with somatosensory stimulation in the lower extremity in stroke patients. *Parkwood Institute Research Open House*, London, ON. November 25th, 2021. [Virtual due to COVID-19, Video presentation]
- S Kohli, **S Luan**, S Peters. Effects of functional electrical stimulation on brain activation post-stroke. *Parkwood Institute Research Open House*, London, ON. November 25th, 2021. [Virtual due to COVID-19, Video presentation]
- **S Luan**, S Peters. Discovering the brain activation patterns associated with somatosensory stimulation in the lower extremity in healthy adults at rest: preliminary results for a systematic review. *Undergraduate Summer Research Internship Conference*, Western University, London, ON. August 24th, 2021. [Virtual due to COVID-19, Poster presentation]

PUBLICATION (Name bolded):
- **Luan S**, Kohli S, Peters S. Comparing prefrontal cortex activation using functional near-infrared spectroscopy with lower extremity sensorimotor movement before and after functional electrical stimulation cycling in patients with stroke.
- **Luan S**, Kohli S, Watts J, Peters S. Discovering brain activation patterns linked with lower extremity somatosensory stimulation using functional near-infrared spectroscopy and functional magnetic resonance imaging - a systematic review.
- **Luan S**, Kohli S, Peters S. The relationship between cortical activation patterns and sensorimotor functions in the lower extremity poststroke.
- **Luan S**, Kohli S, Lim SB, Yang CL, Wardhaugh E, Eng JJ, Peters S. Test-retest reliability of functional near-infrared spectroscopy during walking poststroke.
- Kohli S, **Luan S**, Peters S. Cortical activation patterns associated with static balance in the lower extremity post-stroke.
- Kohli S, **Luan S**, Peters S. Cortical activation changes associated with static balance before and after functional electrical stimulation cycling in patients with stroke.
- Kohli S, **Luan S**, Lim SB, Yang CL, Wardhaugh E, Eng JJ, Peters S. Sex differences in fNIRS signal in walking poststroke. [In preparation – manuscript writeup]
- Kohli S, **Luan S**, Ghatamaneni D, Brunton L, Peters S. Prevalence of fatigue between sexes in adult post-stroke—a systematic review

SCHOLARSHIPS, AWARDS AND OTHER ACCOLADES

- Certificate of Achievement - Musculoskeletal Rehabilitation Research Network, Health and Rehabilitation Graduate Research Conference, Western University, London, ON. February 1st, 2023. [Oral Presentation Award]

- Graduate Teaching Assistantship, HS 3240B: Environmental Health Promotion, School of Health Sciences, Western University, London, ON. January 4th – April 30th, 2022. [Amount: CAD 6,875.24]
- Graduate Teaching Assistantship, Health Science 2300A/Kinesiology 2222A: Systemic Approach to Functional Human Gross Anatomy. School of Health Sciences, Western University, London, ON. Sep 9th – December 20th, 2022. [Amount: CAD 6,875.23]
- Graduate Teaching Assistantship, Health Science 9601A/Applied Science 9011A: Introduction to Research Methods. School of Health Sciences, Western University, London, ON. Sep 9th – December 20th, 2022. [Amount: CAD 6,875.24]
- Graduate Teaching Assistantship, Health Science 2711B: Population Ageing and Health. School of Health Sciences, Western University, London, ON. January 10th – April 30th, 2022. [Amount: CAD 6,806.80]
- Summer Research Intern, Undergraduate Summer Research Internship. Western University, London, ON. May 2021– August 2021 [amount: CAD 7500]
- Dean's Honor Roll, Western University, London, ON. September 2020 – April 2021.
- Admission Scholarship, Western University, London, ON. August 2017 – September 2017. [Amount: CAD $1000]

CERTIFICATIONS & QUALIFICATIONS

- Possess the following certification: SOP, **TCPS-2, Good Clinical Practice (GCP),** Health Canada Division 5, Responsible Conduct of Research (RCR), Social and Behavioral Research, The Biomedical Research Ethics, and Transportation of Dangerous Goods (TDG), Workplace Hazardous Materials Information System (WHMIS), **Accessibility in Service (AODA),** Western Safe Campus Community, Worker Health and Safety Awareness, Equity, Diversity, and Inclusion (EDI), Responding to Disclosures of Gender-Based Violence, Indigenous Initiatives Content and Reflection, Building Inclusivity through Anti-Racism, Cyber Security Essentials

- Proficient in analyzing neuroimaging data using Homer3 and AtlasView; Completion of Homer3 training by Boston University (Instructors: Dr. David Boas)
- Completed the Leadership Education Program (2019-2020)