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# Exploring the relationship between hemispheric prefrontal cortex activation, standing balance, and fatigue in individuals post-stroke: A fNIRS study

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# Abstract

Balance impairments are common after stroke. Reasons for this are multifactorial and include motor dysfunction and fatigue. Limited research has explored the combined effects of post-stroke fatigue and balance on brain activation patterns. Research has shown that prefrontal cortex (PFC) activation may be involved in both motor control and fatigue throughout the recovery process post-stroke. The aim of this thesis was to determine whether: (1) PFC activation levels change between standing balance tasks, (2) PFC hemispheric activation is asymmetric during standing balance tasks, and (3) fatigue levels are associated with task-based activation. Patients with hemiparesis were recruited from the inpatient stroke unit at Parkwood Institute. Functional near-infrared spectroscopy was applied bilaterally over the PFC to measure brain activation during balance tasks. Fatigue was assessed using the Fatigue Severity Scale (FSS). Nine patients were included. Measures of PFC activation during the semi-tandem stance showed a greater amplitude than the double-leg stance, indicating more brain activation during this activity. Participants with greater fatigue (higher score on FSS) showed more activation in the ipsilesional PFC compared to the contralesional PFC. Greater ipsilesional PFC activation may occur when performing more challenging balance positions, potentially indicating compensatory activation.

## Keywords

Stroke; Sub-acute; Brain activation; Balance; Fatigue; Self-perceived fatigue; Prefrontal Cortex (PFC); Mobile neuroimaging; Functional Near-Infrared Spectroscopy; Portalite

# Summary for Lay Audience

Problems with maintaining balance are common after stroke since some people can have difficulties performing voluntary movements possibly due to muscle weakness or fatigue. Individuals can also experience a change in brain activation patterns as the stroke can disrupt blood flow to the affected areas. Previous research has focused on balance issues and fatigue after stroke; however, their combined effects and relationship with brain activation have not been previously examined. Prefrontal cortex (PFC) activation has been evident while learning action sequences and has a relationship with fatigue throughout the recovery process after stroke. Thus, the purpose of this thesis was to determine whether PFC activation levels change between balance tasks, if PFC activation is asymmetrical during standing balance tasks, and if fatigue levels correlate with task-based activation. Patients after stroke with weakness on one side of their body participated from the inpatient stroke unit at Parkwood Institute. We used functional near-infrared spectroscopy (fNIRS) to observe PFC activation during standing balance tasks. fNIRS uses near-infrared light to determine the oxy- and-deoxy-hemoglobin concentration in a specific region. The increase of blood flow to an area may indicate brain activation since the tissue would require more oxygen to function. Two balance tasks were used to evoke PFC activation: (1) double-leg stance (feet shoulder width apart) and (2) semi-tandem stance (one foot in front of the other). Using the oxy-hemoglobin concentration as measured by fNIRS, we determined the asymmetry of PFC activation during both tasks. We also utilized a questionnaire to quantify self-perceived fatigue levels among participants. Nine participants were included in the study. PFC activation during the semi-tandem stance, as measured by the change in oxy-hemoglobin and deoxy-hemoglobin, was higher compared to the double-leg stance. Similarly, PFC activation in the stroke hemisphere was greater during the semi-tandem stance, potentially because this

task was more challenging. Individuals with higher fatigue levels also showed more PFC activation on the stroke hemisphere. Considering task-difficulty during rehabilitation may help increase activation in the PFC in the stroke-affected hemisphere, which has been linked to better recovery.

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# List of Abbreviations

fMRI: Functional magnetic resonance imaging

fNIRS: Functional near-infrared spectroscopy

HRF: Hemodynamic response function

LI: Laterality Index

PET: Positron emission tomography

PFC: Prefrontal cortex

# Chapter 1 : Balance and Fatigue after a stroke

## 1 General Introduction

### 1.1 Stroke

Stroke is a neurological condition resulting from blockage of blood flow (ischemic stroke) or bleeding in the brain (hemorrhagic stroke) and is one of the leading causes of physical disability, with 62 000 new strokes occurring every year in Canada (Bindawas et al., 2017; Canadian Institute for Health Information, 2021). Lack of blood flow or hemorrhage prevents the brain from receiving oxygen and nutrients to respond to the body's metabolic demands, subsequently triggering the death of brain cells and resulting in loss of brain function (Foucher & Faure, 2020). The altered neuronal activity in the affected brain region may result in weakness in one side of the body, known as hemiparesis (Lin et al., 2013).

Hemiparesis refers to weakness or mild to moderate loss of strength, whereas hemiplegia is a severe or complete loss of strength (Biller et al., 2011). Approximately 80% of stroke survivors experience some degree of hemiparesis and may show associated dysfunction with one (unilateral) or both sides (bilateral) of the body based on the location and severity of the stroke (Bindawas et al., 2017; Street et al., 2018). Patients with hemiparesis involving the lower extremity can present with balance abnormalities which may increase fall risk (Wei et al., 2019). These balance impairments may also lead to fear of participating in social activities and a compromised ability to independently perform activities of daily living (De Oliveira et al., 2008; Wei et al., 2019). In addition to balance deficits, fatigue can significantly impact people after stroke. Fatigue is related to poor quality of life, with approximately 51% of patients reporting it as one of their most challenging symptoms after stroke (Mutai et al., 2017). Moreover, fatigue affects many patients after a stroke, with prevalence rates between 23% and 75% (Wu et al., 2015). This widespread occurrence of fatigue after stroke emphasizes its additional negative influence on self-perceived physical health (Kutlubaev et al., 2015). Other consequences of stroke may include decreased range of motion or coordination, and altered cognition, all of which may contribute to the increased fatigability frequently reported by stroke survivors (Cumming et al., 2016; De Oliveira et al., 2008).

## 1.2 The brain after stroke

The brain is a highly complex organ responsible for controlling many bodily functions (Bindawas et al., 2017). In the human central nervous system, approximately 90% of the motor and sensory nerve tracts crossover from one side to the other to connect the brain with motor neurons and sensory receptors in the body (Kinsbourne, 2013; Natali et al., 2022). This crossover, or decussation, connects each brain hemisphere to the opposite side of the body (Kinsbourne, 2013). So, following a stroke in the left hemisphere, the right side of the body can show functional deficits (Bindawas et al., 2017). Due to the variation in stroke location among individuals, some people may exhibit functional deficits on the same side as the lesion (ipsilesional side) (Schaefer et al., 2007). Research by Nayar et al., (2016) found that individual outcomes after stroke may depend on the brain hemisphere in which the stroke occurred.

This variability in stroke outcomes is reflected in the timeline of stroke recovery, which can be differentiated into phases. The Stroke Recovery and Rehabilitation Roundtable Taskforce outlined the timing of recovery across the first six months after a stroke (Bernhardt et al., 2017). They characterized the first 24 hours as the hyperacute phase, the first seven days as the acute phase, seven days to three months as the early sub-acute phase, months 3-6 as late subacute, and anything after six months was deemed the chronic phase of stroke recovery (Bernhardt et al., 2017). The first weeks to months post-stroke (acute and early sub-acute phase) represent a critical window and may be a crucial time for the reorganization of brain activation patterns which is often targeted for restorative interventions (Bernhardt et al., 2017; Grefkes & Fink, 2020).

## 1.3 Balance after stroke

Balance impairments and falls are common after stroke since patients may experience motor dysfunction, possibly due to altered brain activation. These factors not only increase the risk of injury but can also result in hospitalizations which may lead to impaired quality of life (Basso Moro et al., 2014; Cumming et al., 2016). Therefore, focusing on balance impairments during rehabilitative interventions is essential to improve mobility and prevent further injury after stroke. People post-stroke may have difficulty maintaining balance when correcting for a destabilizing perturbation or voluntarily performing movements (Basso Moro et al., 2014). For activities of daily living, such as reaching for objects, moving from a seated to a standing position, and walking, the ability to maintain static or dynamic balance is fundamental for postural control and can be necessary to complete tasks independently (Basso Moro et al., 2014). Static balance refers to the control of the center of mass in relation to the base of support during a stationary stance, whereas dynamic balance refers to the active correction to maintain or re-establish the center of mass within the base of support (Cohen et al., 2020; Schmidt et al., 2021). Postural control, however, can be defined as the overall achievement, reestablishment, or maintenance of balance during different postures or tasks (Pollock et al., 2000). The maintenance of postural control after stroke may be decreased due to the altered ability to select relevant information from the visual, vestibular, and somatosensory systems to elicit appropriate motor functions to maintain static and dynamic balance (Bayouk et al., 2006). Patients post-stroke can have difficulty with balance but can often perform the double-leg stance comfortably and, to a lesser degree, the tandem stance (one foot in front of the other) (Bayouk et al., 2006). These two tasks are especially important as they may represent foundational positions that are precursors for the ability to walk or maintain more complex balance positions. Bayouk et al., (2006) also noted that when attempting to perform more challenging tasks like a single-leg stance or rising from a chair without using arm support, patients after stroke can often have difficulties (Bayouk et al., 2006). These findings indicate that individual’s post-stroke can encounter challenges while maintaining and adapting to different balance positions after a stroke.

A diminished ability to maintain balance is particularly concerning, considering that individuals have an estimated 7% risk of falling in the first week and 73% during the first year after stroke (Denissen et al., 2019). Apart from physical injury, a fall could decrease independence, impair physical activity levels, and lead to depressed mood (Persson & Hansson, 2021). Prevalence rates of sedentary behavior after stroke are high in inpatient settings, with 94% of the day spent sitting in acute stroke units (Hall et al., 2020; Mattlage et al., 2015). Individuals with low functional ability post-stroke may exhibit higher levels of sedentary behavior than those with higher functional status. As a result, people with low functional status may be more susceptible to injury when attempting to regain or improve mobility (Wei et al., 2019). Furthermore, individuals’ post-stroke with higher functional status may be able to maintain their balance and independence during activities and, are therefore, less likely to fall (Teasell et al., 2002). People with moderate functional status may experience a combination of these factors, as they can have a compromised ability to balance yet still maintain some functional mobility (Wei et al., 2019). Thus, for the purpose of this study, people with moderate functional status after stroke will be included since they may be able to perform different balance tasks repetitively.

## 1.4 Prefrontal Cortex (PFC)

The prefrontal cortex (PFC) is a large brain area with multiple subdivisions and is located on the rostral regions in the frontal cortices (Carlén, 2017; Suzuki et al., 2004). The PFC can flexibly adapt behavior based on current goals and context, also known as cognitive control. Studies have demonstrated the PFC's crucial role in decision-making and combining cognition and action through its structural connections that reach multiple motor areas in the brain (Cao et al., 2018). Specifically, dorsolateral prefrontal cortex (DLPFC) activation has been documented in healthy individuals and after stroke during the cognitive control of task planning and learning of action sequences (Schulz et al., 2019). This may reinforce the PFC as a possible region of interest for continuously relearning lost motor functions during rehabilitation. The PFC may affect the output signal from motor areas like the primary motor and premotor cortex to the spinal cord motor neurons, affecting motor function for people post-stroke(Schulz et al., 2019). This highlights the complex nature of movement control, as evidenced by the activation of the PFC not only when healthy participants perform different tasks (Khan et al., 2023; Suzuki et al., 2004) but also during the recovery process of stroke (Hermand et al., 2019; Ward et al., 2003).

In healthy young and older adults, PFC activation has been evident while compensating for motor and sensory changes to maintain balance (St George et al., 2021). However, there is a notable difference in PFC activation pattern during balance tasks for young and older adults. While healthy young adults tend to demonstrate right PFC activation during balance tasks that disrupt visual or sensory cues, older adults often exhibit bilateral activity, reflecting age-related changes in activation patterns while maintaining balance (St George et al., 2021; Teo et al., 2018). These age-related changes in older adults may reduce the available cognitive resources required to maintain balance resulting in more bilateral PFC activity (St George et al., 2021).

PFC activation has also been evident while performing balance tasks in patients with stroke (St George et al., 2021; Ward et al., 2003). Researchers have noted that before rehabilitation, PFC activation increased in the ipsilesional compared to the contralesional hemisphere when postural perturbations are introduced post-stroke (Fujimoto et al., 2014). However, like healthy older adults, a more bilateral PFC activation pattern is observed during postural perturbation following intensive rehabilitation post-stroke (Fujimoto et al., 2014). This supports the importance of PFC in maintaining postural control and displays its significance for further investigation to explore potential variations in PFC activation patterns across different standing balance tasks.

The extent to which PFC may contribute neuronal output for the postural control of standing balance in motor areas is unknown. While research shows detectable changes in the activation pattern of the ipsilesional and contralesional PFC during postural perturbation (Fujimoto et al., 2014; Schulz et al., 2019; St George et al., 2021), less is understood regarding PFC activation during static balance post-stroke. In addition, increased fatigue can negatively impact the cognitive control process regulated by the PFC (Pires et al., 2018). As the PFC plays a crucial role in goal-directed exercises and learning of action sequences, increased fatigue levels may compromise its functioning, resulting in less efficient behaviors for maintaining postural balance and potentially increasing the risk of falls (Pires et al., 2018).

## 1.5 Fatigue after stroke

Fatigue is common following a stroke, and the presentation of fatigue can vary significantly among individuals (Wu et al., 2015). Researchers have not agreed on a single description of fatigue after a stroke (Aarnes et al., 2019); however, a modified definition of fatigue based on previous work in other medical conditions can be described as ‘‘*a subjective lack of physical or mental energy (or both) that is perceived by the individual to interfere with* *usual or desired activities.*'' (Cumming et al., 2016; Kuppuswamy et al., 2015). The persistence of fatigue varies among individuals, and in some cases, it can interfere with the progress of regaining function during rehabilitation (Glader et al., 2002; Naess et al., 2012; Wu et al., 2015). Increased fatigue may also limit participation in everyday life, with negative effects on return to work and social interactions and decreased independence for activities of daily living (Aarnes et al., 2019; De Oliveira et al., 2008). Comparing fatigue levels between healthy adults, patients with other chronic diseases, and individuals' post-stroke, research by Zedlitz et al., (2011) found that compared to the other groups, only cognitive and somatic (mentally focusing on physical symptoms) issues were related with fatigue post-stroke. This finding suggests that fatigue may partly result from the lack of proper adaptation to less efficient neural resources, possibly because of altered blood flow, as activation in affected areas may have been altered post-stroke (Zedlitz et al., 2011).

Understanding the underlying mechanism of fatigue after stroke is crucial, as it may involve changes and damage to existing brain activation patterns (Kutlubaev et al., 2015; Zedlitz et al., 2011). Altered brain activation resulting from reduced neural firing rates in the brain may be responsible for fatigue after stroke, with its extent likely differing between patients (Kuppuswamy et al., 2015). Furthermore, fatigue post-stroke could also result from a combination of psychosocial stress and alterations in brain activation patterns leading to the dysfunction of motor pathways (Kutlubaev et al., 2015). Various psychosocial factors such as sleep disturbances, pain, depression, and adjustment to post-stroke symptoms may be associated with self-reported fatigue (Appelros, 2006; Paciaroni & Acciarresi, 2019; Zhang et al., 2021). Although researchers have conducted multiple studies to identify factors contributing to fatigue post-stroke, the relationship between fatigue and brain activation during tasks remains understudied. Understanding the interaction between fatigue and hemispheric activation patterns could provide valuable insights into the underlying mechanism of post-stroke impairments and potentially guide future interventions.

## 1.6 Interhemispheric competition model

The imbalance between the ipsilesional and contralesional hemispheres, often described by the interhemispheric competition model, may partially be responsible for the persistent functional deficits often observed in people post-stroke (Cunningham et al., 2019). According to this proposed model, the increased activation in the contralesional compared to the ipsilesional hemisphere might limit post-stroke recovery (Abualait, 2019; Gomez Palacio Schjetnan et al., 2013). The potential increase in activation of the contralesional hemisphere after stroke, possibly influenced by fatigue, may result in asymmetrical activation patterns in the brain, potentially influencing motor function during recovery (Abualait, 2019). Several studies use the laterality index (LI) to examine the interhemispheric asymmetry of regional activation, which relies on the oxygenated hemoglobin concentration in the blood between the ipsilesional and contralesional hemispheres (Lin et al., 2013; Sukal-Moulton et al., 2018; Yamazaki et al., 2022). The main rationale for assessing asymmetry of brain activation using LI is to determine the degree of relative dominance of each hemisphere during specific tasks or conditions (Borrell et al., 2023; Seghier, 2008). Understanding brain asymmetry can provide insights into the altered pattern of brain activation in relation to balance and fatigue in individuals' post-stroke.

The interhemispheric competition model is debated in the literature, with conflicting evidence emerging. Some argue the model only holds true during specific tasks and may only be applicable to a subset of the chronic stroke population (Cunningham et al., 2019). For instance, Calautti et al. (2007) used the LI to assess the relative activation of each hemisphere. They found that with increased contralesional primary motor cortex (M1) activation post-stroke, participants were slower in the number of times they were able to tap their finger in 15 seconds. This finding suggests a possible link between increased activation in the contralesional hemisphere and impaired motor performance post-stroke. On the other hand, Schaechter and Perdue (2008) demonstrated that increased activation of the contralesional M1 during a finger-tapping task in patients with chronic stroke is correlated with good motor recovery. Research has also found that an increase in ipsilesional activation have been correlated with better functional outcomes when performing tasks involving the upper and lower extremities (Dodd et al., 2017; Lim et al., 2022). Considering this conflicting research, increased activation in the contralesional hemisphere post-stroke may hinder motor function for some patients while potentially facilitating continued recovery for others (Dodd et al., 2017). Increased activation of the contralesional in comparison to ipsilesional hemisphere may recruit additional neural resources to compensate for the damaged ipsilesional motor system (Dodd et al., 2017). Irregular brain activation patterns like an increase in contralesional activation post-stroke may contribute to the increasing self-perceived fatigue, as the brain's metabolic demand increases to accomplish activities (Boksem & Tops, 2008; Dodd et al., 2017; Pinti et al., 2020). Using the LI, research shows that the activation pattern for the ipsilesional and contralesional primary motor cortex change after stroke; however, it is unknown if the same is true for PFC during standing balance (Calautti et al., 2010; Johansen-Berg et al., 2002; Kraft et al., 2015).

## 1.7 Outcome measures

Fatigue can be assessed subjectively through questionnaires, diaries, and interviews or objectively through physiological processes and performance (Sharma & Sheth, 2019). Based on previous research, self-reported questionnaires, such as the Fatigue Severity Scale (FSS), have predominantly been used to study fatigue post-stroke (Drummond et al., 2017; Mutai et al., 2017; Naess et al., 2012; Tang et al., 2014) and have been shown to be useful (Wang et al., 2018). The FSS is a simple, unidimensional scale most frequently used for measuring fatigue in people with chronic illnesses (Learmonth et al., 2013). It was initially developed by Krupp et al. (1989) for use with patients diagnosed with multiple sclerosis and systemic lupus erythematosus. The FSS is a self-administered nine-item questionnaire rated on a seven-point Likert scale, where one indicates strong disagreement and seven indicates strong agreement. A score is obtained through an average of the nine items (Valko et al., 2008). Researchers found that the FSS demonstrated excellent test-retest reliability and internal consistency (similar items on the test) in people after a stroke (Nadarajah et al., 2017). The FSS also showed good agreement with other fatigue measures and could distinguish patients after stroke from healthy controls based on fatigue (Nadarajah et al., 2017). Finally, the FSS takes minimal time to administer and can be used to compare results with other studies (Aali et al., 2020).

Balance ability for patients changes with rehabilitation and stages of post-stroke recovery, so clinicians require a quantifiable measure to monitor these changes (Blum & Korner-Bitensky, 2008). One commonly used measurement is the Berg Balance Scale (BBS), which provides a quantitative assessment for balance (Liao et al., 2021). The BBS was originally developed for use with older adults and has excellent validity and reliability (Berg et al., 1992; Liao et al., 2021; Pickenbrock et al., 2016). It is a 14-item scale that assesses balance and risk for falls through observation of patient performance (Blum & Korner-Bitensky, 2008). Each item is scored from 0 to 4, with 0 representing an inability to complete tasks and 4 representing total independence (Berg et al., 1992). The total score ranges from 0 to 56, with higher scores indicating better balance outcomes (Berg et al., 1992; Huang et al., 2020). The BBS has been shown to be reliable and valid in assessing balance for people post-stroke (Huang et al., 2020; Liao et al., 2021; Mao et al., 2002). Generally, the scale takes minimal time to administer and is performed by trained healthcare professionals (Stevenson, 2001).

## 1.8 Functional near-infrared spectroscopy (fNIRS)

Brain imaging has enhanced the ability to analyze brain activation patterns that facilitate reorganization after stroke (Schulz et al., 2019). Imaging techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) are reliable tools to map activity for the somatosensory, cognitive, and motor tasks of the upper extremities; however, they are susceptible to motion artifacts and unable to analyze brain activation during upright, dynamic tasks, like standing (Miyai et al., 2001). Several studies emphasized functional near-infrared spectroscopy (fNIRS) as an alternative imaging technique for mapping brain functions in healthy participants and patients during static and dynamic tasks (Basso Moro et al., 2014; Chen et al., 2022; Fujimoto et al., 2014; St George at al., 2021). fNIRS is a non-invasive neuroimaging technique that detects changes in oxygenated (oxy-Hb) and deoxygenated (deoxy-Hb) hemoglobin in the blood and has good test-retest reliability during motor tasks for healthy adults (Fujimoto et al., 2014; Pinti et al., 2020; Rond et al., 2023). fNIRS devices use continuously emitted near-infrared light, some of which scatters and absorbs into the tissue resulting in light attenuation (Pinti et al., 2020). This attenuation because of tissue scattering and absorption can be estimated through the ratio of light input to output (Pinti et al., 2020). fNIRS uses these changes in attenuation through a source-detector pairing (a channel) to measure relative hemoglobin concentration changes in a localized region using the modified Beer-Lambert Law (Rea et al., 2014).

When a specific brain region has increased neuronal activity, cerebral blood flow will temporarily increase to meet the oxygen demands of neural cells (Phillips et al., 2016). This neurovascular coupling maintains the metabolic demand of cerebral blood flow for appropriate brain activity (Phillips et al., 2016). fNIRS uses this neurovascular coupling to identify neural activity changes represented by changes in blood oxygenation in the activated cortical region (Basso Moro et al., 2014). This is characterized by the increase in oxy-Hb and decrease in deoxy-Hb, represented by a hemodynamic response function (HRF) (Basso Moro et al., 2014). Previous work by Lin et al. (2013) and Teo et al. (2018) show that the oxy-Hb and deoxy-Hb concentrations are sensitive to movement-related changes and may be used as identifiers for regional activation during different tasks.

Several advantages of fNIRS make it a suitable neuroimaging technique to study relationships between brain activation and mobility. Like fMRI, fNIRS measures the hemodynamic response due to neurovascular coupling and has a good temporal resolution (Scarapicchia et al., 2017). Commonly, fNIRS measures at 10 Hz compared to 0.5 Hz in fMRI, allowing for better HRF tracking because of a higher sampling rate (Herold et al., 2018; Pinti et al., 2020; Scarapicchia et al., 2017). Recent advancements in neuroimaging technology have pushed fNIRS systems to become smaller, wireless, and battery-operated, increasing their portability (Scarapicchia et al., 2017). Additionally, fNIRS devices also have better tolerance to motion artifacts than fMRI, as they do not require complete stillness to certify data quality (Pinti et al., 2020; Scarapicchia et al., 2017). This advantage has allowed researchers to use fNIRS devices in ambulatory settings, including walking, engaging in conversations, and dancing (Pinti et al., 2020). With its portability and reduced restrictions on motion, fNIRS is well-suited for use during standing balance tasks.

## 1.9 Objective

Measures of PFC activation during balance tasks with different fatigue levels may provide valuable information to further understand post-stroke recovery. Although many studies have independently explored the effects of post-stroke fatigue and postural instability on cortical activation for patients' post-stroke, the brain activity patterns underlying fatigue levels and standing balance control remain unknown. This thesis aims to determine whether cortical activation (using oxy-Hb and deoxy-Hb concentration) in bilateral PFCs differ in patients with different fatigue levels (based on the FSS) during two standing balance tasks. Using the LI, this study will look at hemispheric activation between the ipsilesional and contralesional PFC during standing balance tasks. The main questions this thesis will address are as follows:

1. In individuals' post-stroke, do oxy-Hb and deoxy-Hb levels change for standing balance tasks based on difficulty?
2. Is hemispheric PFC activation asymmetrical during standing balance tasks in individuals' post-stroke?
3. Do fatigue levels have a relationship with task-based activation in individuals' post-stroke?

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# Chapter 2 : Relationship between balance, fatigue, and PFC activation in individuals' post-stroke

## 2 Introduction

Stroke is one of the leading causes of long-term disability and is prevalent in the Canadian population (Canadian Institute for Health Information, 2021). Stroke can alter neuronal activity in the affected region since a lack of blood flow or hemorrhage can interrupts the brain's ability to receive essential oxygen and nutrients to meet its metabolic demands (Foucher & Faure, 2020; Lin et al., 2013). As a result of the altered neuronal activity after a stroke, individuals may experience hemiparesis, characterized by weakness on one side of the body (Lin et al., 2013). Specifically, hemiparesis affecting the lower extremity can result in balance abnormalities, potentially increasing the risk of falls (Wei et al., 2019). Consequently, individuals may fear participating in social activities, and potentially experience compromised independence while performing everyday tasks (De Oliveira et al., 2008). In addition to balance deficits, increased fatigue is a significant concern for people after a stroke. Increased fatigue may impact patients' quality of life, with approximately 51% reporting fatigue as one of the most challenging aspects after stroke (Mutai et al., 2017). Furthermore, fatigue is a widespread issue among patients' post-stroke, with prevalence rates ranging from 23% to 75% (Wu et al., 2015). Fatigue after stroke has a widespread impact on self-perceived physical health, as it may be associated with decreased range of motion, coordination, and altered cognition (Kutlubaev et al., 2015). These aspects can contribute to the increased fatigability frequently reported by individuals after stroke.

Balance impairments and falls are frequent following a stroke, as patients often experience motor dysfunction, potentially attributed to altered brain activation (Basso Moro et al., 2014). These factors not only increase the chance of sustaining injuries but can also result in hospitalizations which can impair quality of life (Basso Moro et al., 2014; Cumming et al., 2016). In a study by Persson and Hansson (2021) aimed at determining factors associated with the risk of falls prior to and shortly after stroke found that the strongest determinant of falls during inpatient stay was impaired postural control. A diminished ability to balance can be particularly concerning, given that people post-stroke have a high risk of falling (73%) during the first year after stroke (Denissen et al., 2019). Beyond the physical injuries that may result from a fall, people post-stroke may also experience declines in physical activity levels and decreased independence (Persson & Hansson, 2021). Therefore, prioritizing balance recovery during rehabilitation interventions is crucial to increase mobility and reduce the risk of injury in people post-stroke.

Measuring cortical activation during a standing balance task may provide valuable information to investigate the neural mechanisms for balance control. Using conventional imaging techniques, including functional magnetic resonance imaging (fMRI) or positron emission tomography (PET), is not feasible due to the nature of the standing task (Fujimoto et al., 2014). However, functional near-infrared spectroscopy (fNIRS) is suitable to assess cortical activation during standing balance, given its good test-retest reliability during motor tasks for healthy adults and high tolerance to motion artifacts (Pinti et al., 2020; Rond et al., 2023; Suzuki et al., 2004). Several studies have used fNIRS to observe cortical activation patterns for healthy adults and patients during different tasks (Basso Moro et al., 2014; Chen et al., 2022; Fujimoto et al., 2014; St George at al., 2021). For example, St George et al. (2021) used fNIRS to investigate cortical activity during standing balance for healthy individuals and found evident activation of the prefrontal cortex (PFC). While maintaining balance, young healthy adults have more right

PFC activation, while older adults display bilateral PFC activity, potentially reflecting age-related changes (Teo et al., 2018). Age-related changes in older adults may decrease the cognitive resources available to maintain balance leading to more a bilateral PFC activation pattern (St George et al., 2021). PFC activation has also been evident during balance for people post-stroke (Ward et al., 2003). After introducing postural perturbations, researchers have noted an increase in ipsilesional PFC activation compared to the contralesional PFC in people performing dynamic balance tasks after a stroke (Fujimoto et al., 2014). While research shows detectable changes in the activation pattern of the ipsilesional and contralesional hemisphere during postural perturbation, less is understood about PFC activation during standing balance post-stroke (Fujimoto et al., 2014; Schulz et al., 2019; St George et al., 2021).

Fatigue is prevalent after stroke, with its frequency and duration varying significantly among individuals (Wu et al., 2015). There is no agreed upon description of fatigue post-stroke; however, it can be described as a lack of physical or mental energy that prevents the individual to perform activities of daily living (Cumming et al., 2016; Kuppuswamy et al., 2015). Increased fatigue can negatively impact the cognitive control process regulated by the PFC (Pires et al., 2018). Due to the PFC’s essential role in execution of goal-directed exercise and learning of action sequences, increased fatigue levels may impact its efficiency, resulting in a reduced ability to maintain balance (Pires et al., 2018). Fatigue post-stroke can persist at varying degrees among individuals, and in some cases, it can hinder the progress of regaining function during rehabilitation (Glader et al., 2002; Wu et al., 2015). Fatigue may be an ongoing symptom throughout stroke recovery potentially because of the lack of proper adaptation to less efficient neural resources post-stroke (Zedlitz et al., 2011). Investigating the interaction between fatigue and the maintenance of balance may help further understand the principal mechanism of post-stroke impairments while potentially informing rehabilitative interventions.

This study aims to determine the potential changes in oxy-Hb and deoxy-Hb levels in the PFC as measured by fNIRS during standing balance tasks, whether hemispheric PFC activation is symmetrical during these tasks, and the potential link between self-perceived fatigue and task-based activation in people after stroke.

## 2.1 Methods

### 2.1.1 Participants

Participants were recruited from the inpatient stroke unit at Parkwood Institute in London, ON. The study included individuals with lower limb hemiparesis who were medically stable, had the ability to understand and follow instructions, and could maintain a standing position for up to 20 seconds. Patients were excluded from the study if the lesion was in the cerebellum, as it can cause impaired coordination of movements and limit their ability to complete balance tasks. Individuals with any other chronic health condition that would affect participation (Parkinson's disease, MS, Cancer) or any condition that directly affects hemoglobin were also not included. Additional information, including age in years, sex, time since stroke, type of stroke, location of the stroke, and functional ability, was also recorded. All participants provided informed written consent, and the study was approved by Western University, Health Sciences Research Ethics Board (Appendix B).

### 2.1.2 Balance tasks

Participants were asked to perform two different balance tasks with the aim of producing activation in the PFC that was recorded using fNIRS. For the current study, recognizing that participants with lower leg hemiparesis were included and they may not be able to maintain complex stances, ensuring all participants can complete the tasks was imperative. In a study conducted by Bayouk et al. (2006), researchers found that double leg stance was the only task that was able to be completed by all participants after stroke. Tandem stance had the second-highest completion rate of 87.5%. Based on data from Bayouk et al. (2006), and to ensure data collection sessions did not exceed 1.5 hours, two balance tasks were used. Double-leg and semi-tandem stance modified from the tandem stance was used to ensure participants could perform all tasks. A visual representation of the approximate foot placements for participants during both tasks is shown in Figure 1. Participants were asked to avoid moving their heads during tasks to minimize motion interference, as head movements can distort the accuracy of the fNIRS data. A licensed physiotherapist was present during all data collection sessions to ensure participant safety. Additionally, participants had a bed in front of them and a chair behind them, ensuring that support was available in case they needed to rest during the session (Figure 2 & 3). Using a random number generator, the task order was randomized between and within participants. Each task included a 30s baseline period followed by 20s of the balance tasks and 30s of rest, repeated five times (Figure 4).

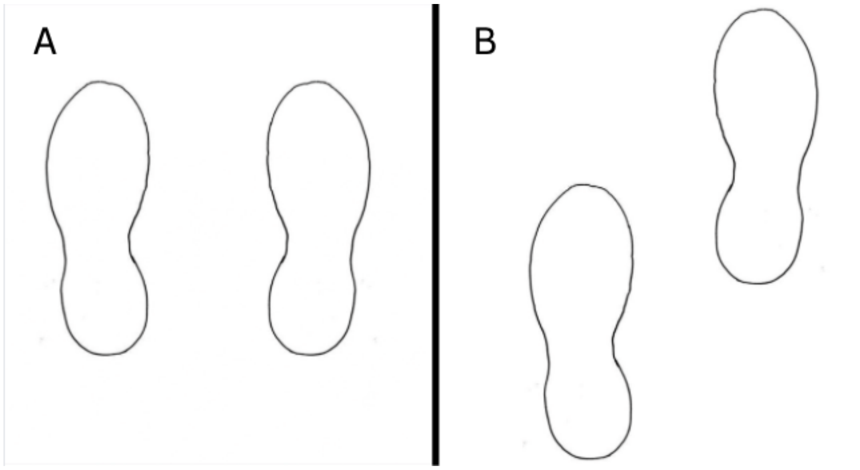


**Figure 1: Visual representation of foot placement during balance tasks. (A) Double-leg stance (DL), (B) Semi-tandem stance (ST).**

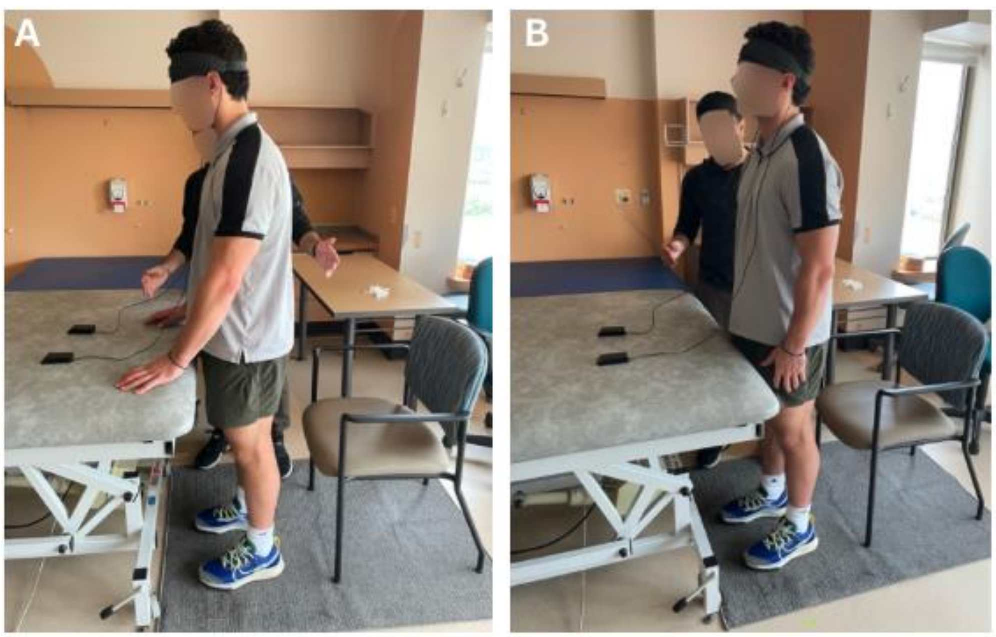


**Figure 2: Representation of participant position during rest and task for the double-leg stance during fNIRS recording. A: participant maintaining contact with a bed for support during rest; B: performing the double leg stance independently.**

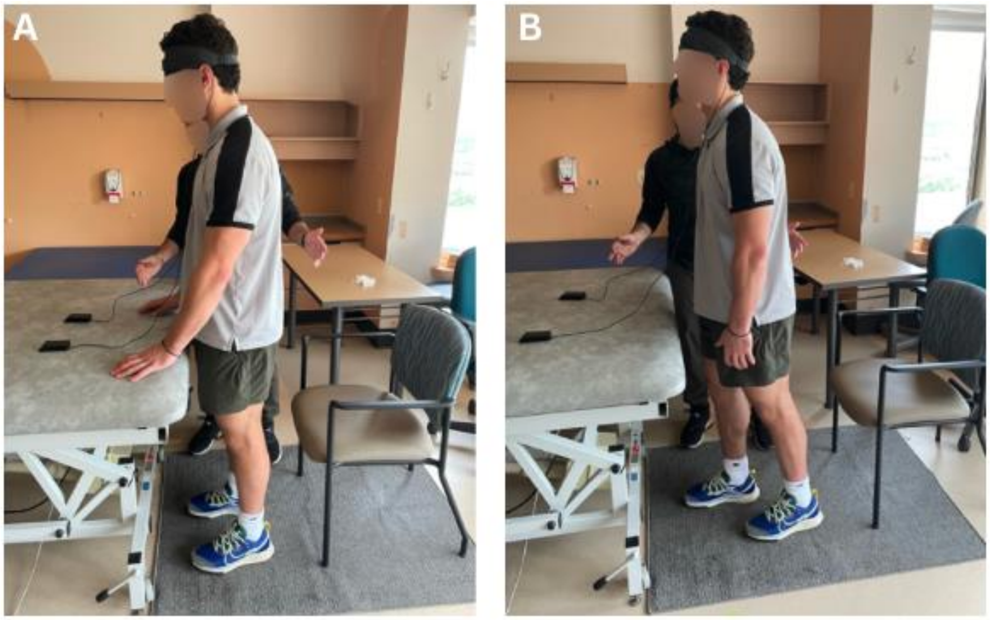


**Figure 3: Representation of participant position during rest and task for semi-tandem stance during fNIRS recording. A: participant maintaining contact with a bed for support during rest; B: participant performing the semi-tandem stance independently.**

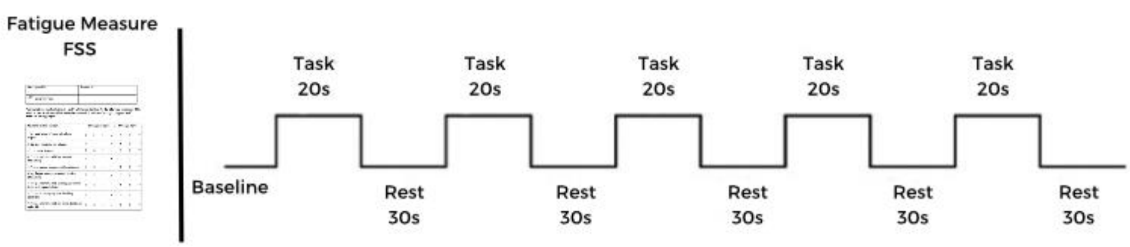


**Figure 4: Fatigue questionnaires preceding block design displaying five repetitions of each task during fNIRS collection.**

### 2.1.3 Berg Balance Scale (BBS)

The BBS provided a quantifiable measure of balance (Blum & Korner-Bitensky, 2008). The BBS was initially developed for older adults and has excellent validity and reliability (Liao et al., 2021; Pickenbrock et al., 2016). The BBS has also been shown to be a reliable and valid measure to assess balance for people post-stroke (Huang et al., 2020; Liao et al., 2021; Mao et al., 2002). The BBS has 14 items that assess balance and risk for falls by observing patient performance (Blum & Korner-Bitensky, 2008). Each item is scored from 0 to 4, with 0 representing an inability to complete tasks and 4 representing complete independence (Stevenson, 2001). The BBS was administered by a licensed physiotherapist upon the patient's initial admission to the inpatient stroke unit.

### 2.1.4 Fatigue Severity Scale (FSS)

The FSS was used to assess fatigue in individual's post-stroke. The FSS questionnaire is commonly used to measure subjective fatigue (Learmonth et al., 2013). The questionnaire is a unidimensional scale consisting of nine items that participants rate on a seven-point Likert scale ranging from one (strong disagreement) to seven (strong agreement). A score is obtained by averaging the responses across the nine items, with higher FSS score indicating greater self-perceived fatigue (Sharma & Sheth, 2019; Valko et al., 2008). The FSS has demonstrated excellent test-retest reliability and internal consistency among individuals' post-stroke (Nadarajah et al., 2017). To minimize the documentation of fatigue resulting from engagement of the balance tasks, the FSS was administered prior to initiating the fNIRS session (Figure 4). After the fNIRS session, the Fugl-Meyer Lower Extremity assessment was administered by a licensed physiotherapist to measure the level of motor impairment post-stroke (Gladstone et al., 2002).

### 2.1.5 fNIRS System

Changes in oxy-Hb and deoxy-Hb concentrations in the PFC were measured during both balance tasks using the PortaLite fNIRS system (Artinis Medical Systems, the Netherlands) (Figure 5). The PortaLite has 3 light sources and 1 detector, with source-detector distances of 30, 35, and 40 mm (Figure 6). Two devices were positioned bilaterally over the PFC, placed according to the international 10-20 EGG system at the height of 10% of the nasion-inion distance from the nasion and 10% of the head circumference to the left and right from the midline (Herbert H. Jasper, 1958; Huo et al., 2023; Mirelman et al., 2017). These locations roughly target the prefrontal cortex. The devices were covered using a dark headband to prevent noisy signals attributed to ambient light. Real-time neural activation in the form of oxy-Hb and deoxy-Hb was recorded at a frequency of 50hz. The Portalite uses Bluetooth technology, allowing participants to maintain balance without the constraint of wires. Besides feeling pressure from the device being placed on the forehead, participants were expected not to feel any discomfort from the fNIRS system. The placement of the device was adjusted during the session to be more comfortable for the participant if necessary. The PortaSync MKII trigger indicated the beginning and end of each task repetition and differentiated the raw data between tasks (Figure 7). The raw file was marked with a high trigger (H) and low trigger (L) denoted by a 5.0mV and 2.5mV signal, respectively. Oxysoft version 3.2.72 x64 (Artinis Medical Systems, the Netherlands) was used for data collection.


**Figure 5: fNIRS system - PortaLite, Artinis Medical Systems with the battery pack.**


**Figure 6: Close-up of source-detector parings on the Portalite fNIRS system. D1: Detector 1, S1: Source 1 (30mm), S2: Source 2 (35mm), S3: Source 3 (40mm).**


**Figure 7: PortaSync MKII – Trigger used to mark the beginning and end of tasks on the raw fNIRS file. H: high trigger (5.0 mV), L: low trigger (2.5 mV).**

### 2.1.6 fNIRS data processing

The concentrations of oxy-Hb and doxy-Hb were exported to Homer3 software for further data processing (Figure 8) (Tucker et al., 2022). First, the raw intensity data was converted to optical density using hmR_Intensity2OD. A bandpass filter with frequencies of 0.01 to 0.14 Hz was then used to reduce physiological noise such as heartbeat, respiration, and signal drift (Maidan et al., 2016). The data were then converted from optical density to concentration changes using hmR_OD2Conc, which utilizes the modified Beer-Lambert law (partial pathlength factor = 1.0) (Hocke et al., 2018). To remove motion artifacts and improve the signal, a correlation-based signal improvement (CBSI) filter was used (Maidan et al., 2016). Finally, a block average filter was used by taking the baseline period (5s before task onset) and the task period (0s to 35s) to calculate a hemodynamic response for both tasks (Hocke et al., 2018). Concentration changes for oxy-Hb and deoxy-Hb from the first channel (S1 to D1) was used from each device, resulting in four hemodynamic response functions (ipsilesional and contralesional) for each task. Task-based activation was determined by subtracting the average oxy-Hb concentration during baseline performance from the average oxy-Hb concentration during the task period (Maidan et al., 2016). This calculation allowed for the assessment of specific changes in oxy-Hb concentration attributed to task participation relative to the baseline (Maidan et al., 2016). Oxy-Hb concentration was used in this calculation since it is more sensitive than deoxy-Hb to motor tasks in the HRF response (Borrell et al., 2023; He et al., 2022).

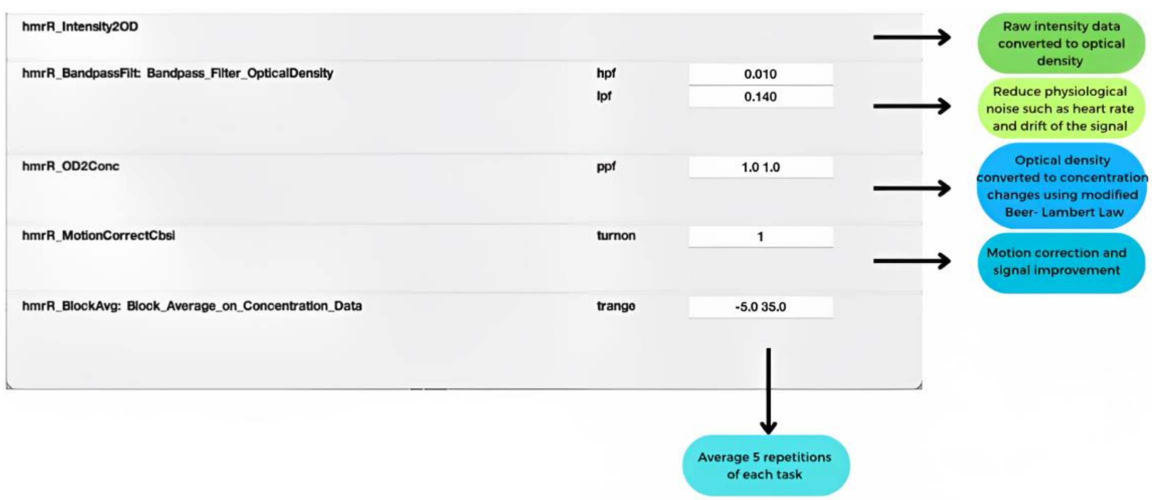


**Figure 8: Processing stream to analyze raw fNIRS data during standing balance in Homer3.**

### 2.1.7 Laterality Index (LI)

The laterality index (LI) was used to evaluate the asymmetry between the ipsilesional and contralesional PFC. LI values range from -1 to 1, with negative (-1 to 0) and positive values (1 to 0) representing contralesional and ipsilesional PFC activation, respectively (Jia et al., 2022). The predetermined LI threshold is usually set to -0.2 ≥LI ≤ 0.2, with values in this range indicating bilateral activation (Borrell et al., 2023; Hyeon Jin et al., 2020; Seghier, 2008). The formula for LI is as follows:

$$LI = \frac{oxyHb\ in\ the\ ipsilesional\ PFC - oxyHb\ in\ the\ contralesional\ PFC}{oxyHb\ in\ the\ ipsilesional\ PFC + oxyHb\ in\ the\ contralesional\ PFC}$$

## 2.2 Results

### 2.2.1 Demographics

Table 1 shows the clinical and demographical characteristics of all participants. Participants ranged in age from 48 to 87, with an average age of 65 years (SD= 14 years). Five females and four males were included in this study. All participants were in the sub-acute stage of stroke recovery, with an average of 39 days (SD= 28 days) since the stroke. One of the participants could not communicate in English, so informed consent and data collection were done with the help of a translator app and assistance from the patient’s family. Six of the nine participants had a stroke in the right hemisphere and three in the left hemisphere. Seven participants had an ischemic stroke, one had a hemorrhagic stroke, and one participant’s stroke type was unknown. Similarly, seven participants presented with a subcortical lesion, one with a cortical lesion, and one participants’ stroke location was unknown. The BBS score ranged from 3 to 52, averaging 20 (SD= 17) out of 56. The FSS score ranged from 1.70 to 4.66, with an average score of 3.52 (SD= 0.90). The Fugl-Meyer was also completed by a licensed physiotherapist with scores ranging from 17 to 38, with an average score of 29 (SD= 7) out of 46.

**Table 1: Participant characteristics**

| Participant | Age (yrs) | Sex | Time since stroke (days) | Lesion Hemisphere (Right/Left) | Type of Stroke | Location of Stroke | BBS (/56) | FSS (/7) | FM Total (/46) |
|---|---|---|---|---|---|---|---|---|---|
| S01 | 48 | F | 45 | Right | Ischemic | Subcortical | 52 | 1.77 | 34 |
| S02 | 69 | F | 45 | Left | Ischemic | Subcortical | 5 | 3.77 | 23 |
| S03 | 56 | F | 18 | Right | Ischemic | Subcortical | 29 | 3.55 | 17 |
| S04 | 52 | F | 16 | Left | Ischemic | Subcortical | 6 | 4.66 | 31 |
| S05 | 50 | M | 20 | Left | Ischemic | Subcortical | 12 | 1.70 | 33 |
| S06 | 68 | F | 31 | Right | Ischemic | Subcortical | 3 | 4.44 | 26 |
| S07 | 87 | M | 25 | Right | Unknown | Unknown | 46 | 3.11 | 38 |
| S08 | 81 | M | 43 | Right | Ischemic | Subcortical | 46 | 3.77 | 36 |
| S09 | 76 | M | 107 | Right | Hemorrhagic | Cortical | 11 | 3.88 | 20 |

*Note*. n=9. BBS: Berg Balance Scale, FSS: Fatigue Severity Scale. FM: Fugl Meyer, F: female, M: male.

### 2.2.2 Aim 1: Do oxy-Hb and deoxy-Hb levels change for standing balance tasks?

An average activation pattern in the PFC for all participants is included in Figure 9. An inverse relationship between oxy-Hb and deoxy-Hb was observed for all conditions, indicating that as oxy-Hb increased, deoxy-Hb decreased, and vice versa. Both tasks (0 to 20 seconds) produced an increase in activation (an increase in oxy-Hb concentration and a decrease in deoxy-Hb) compared to rest (-5 to 0 seconds). During both tasks, the HRF takes approximately 25 seconds after task onset to reach peak activation levels and approximately 5 to 10 seconds to return to baseline levels. The semi-tandem stance displayed a greater increase in amplitude (oxy-Hb) in the ipsilesional and contralesional PFC compared to the double-leg stance. PFC activation was greater in the ipsilesional than the contralesional hemisphere during both tasks, although bilateral activation occurred. The contralesional deoxy-Hb concentration during the semi-tandem stances slightly increases, with an inverse relationship with oxy-Hb at approximately 12 seconds after task onset. A larger variability in the standard deviation of the oxy-Hb concentration of the ipsilesional PFC during the double leg stance was observed. Both tasks show an m-shaped pattern in the oxy-Hb concentration with an initial peak at approximately 7 seconds and the second peak around 25 seconds. Figures 10 and 11 present the hemodynamic changes in the oxy-Hb and deoxy-Hb for the ipsilesional and contralesional PFC during both tasks. All participants show an inverse relationship between oxy-and-deoxy-Hb during both tasks.

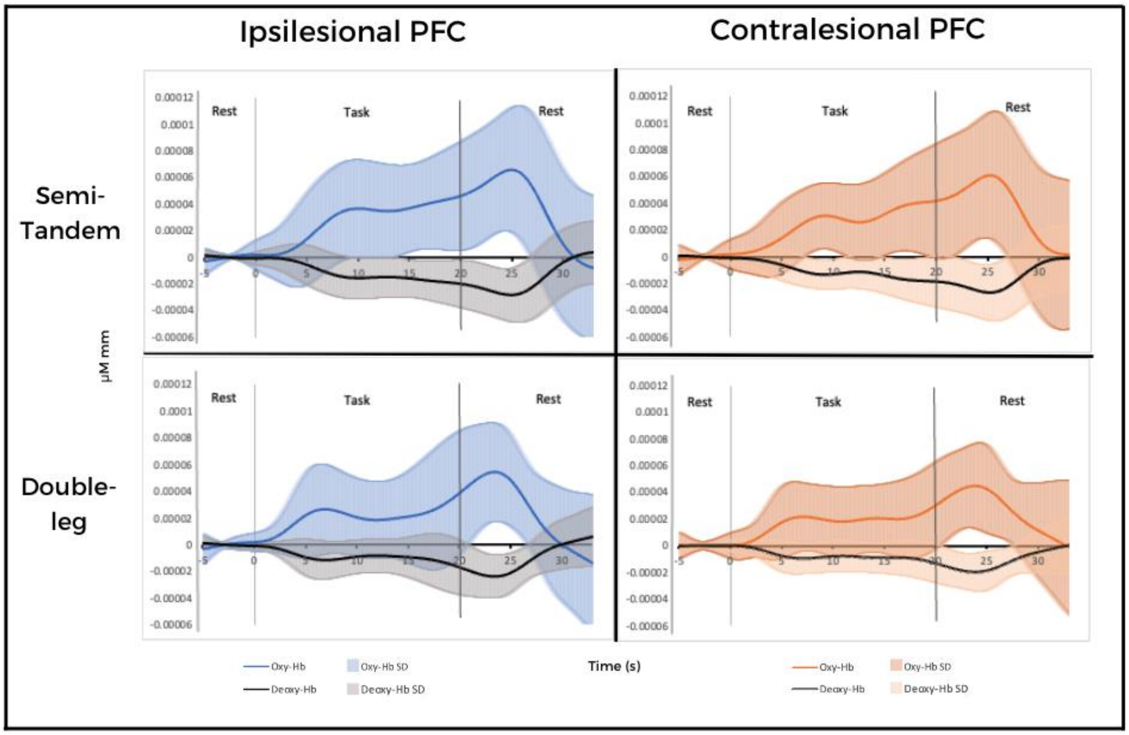


**Figure 9: Average and standard deviation for ipsilesional and contralesional PFC activation during both tasks. The top two graphs display PFC activation during the semi-tandem stance, while the bottom two graphs show PFC activation for the double-leg stance. The graphs on the left represent ipsilesional PFC activation, while the graphs on the right show contralesional PFC activation for both tasks. Markers at 0 and 20 seconds indicate the start and end of the task, respectively. Solid lines represent average oxy-Hb and deoxy-Hb, with shaded areas displaying standard deviation. Oxy-Hb: oxygenated hemoglobin, deoxy-Hb: deoxygenated hemoglobin, oxy-Hb SD: oxygenated hemoglobin standard deviation, deoxy-Hb SD: deoxygenated hemoglobin standard deviation, PFC: prefrontal cortex. X-axis: time (seconds), y-axis: concentration (µM mm).**

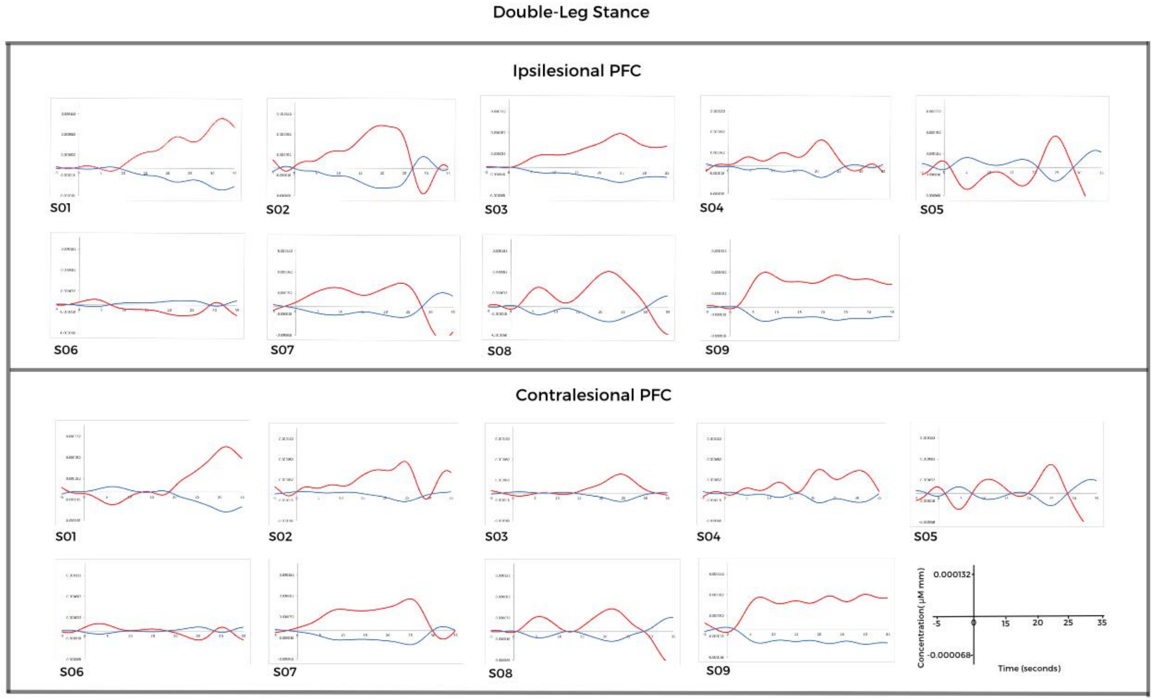


**Figure 10: Individual HRF for all participants for ipsilesional and contralesional PFC during the double-leg stance. The oxy-Hb and deoxy-Hb are indicated by the red and blue lines, respectively. HRF: hemodynamic response function, PFC: prefrontal cortex, oxy-Hb: oxygenated hemoglobin, deoxy-Hb: deoxygenated hemoglobin. X-axis: time (seconds), y-axis: relative concentration (µM mm).**

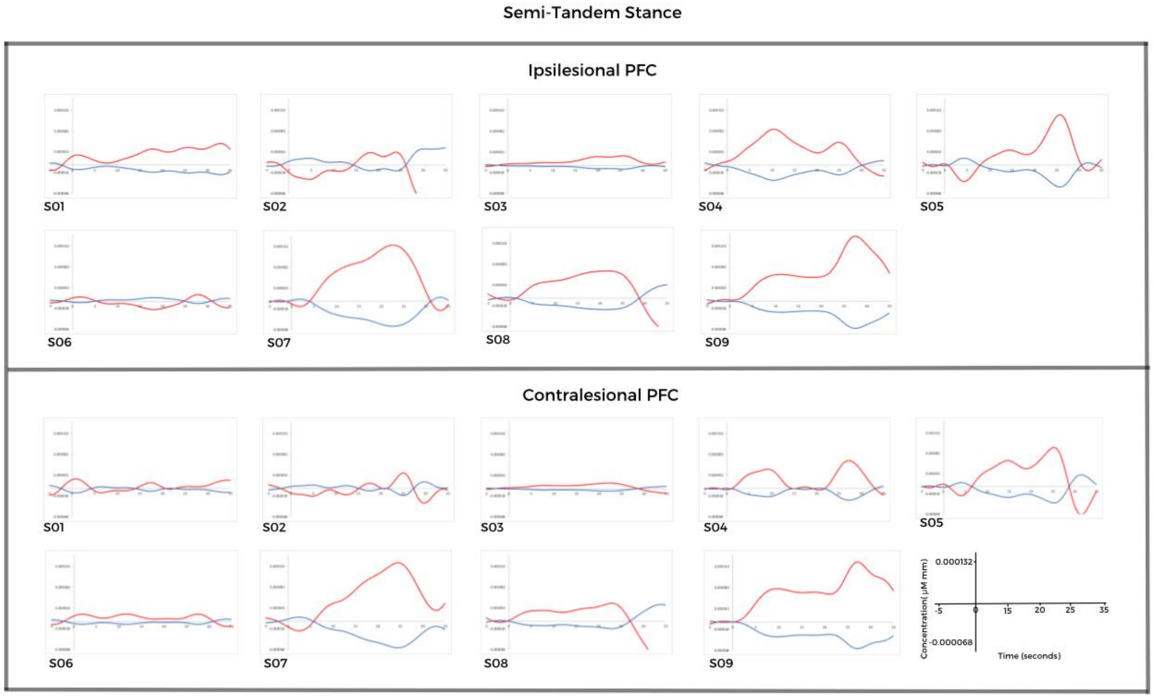


**Figure 11: Individual HRF for all participants for ipsilesional and contralesional PFC during the semi-tandem stance. The oxy-Hb and deoxy-Hb are indicated by the red and blue lines, respectively. HRF: hemodynamic response function, PFC: prefrontal cortex, oxy-Hb: oxygenated hemoglobin, deoxy-Hb: deoxygenated hemoglobin. X-axis: time (seconds), y-axis: concentration (µM mm).**

### 2.2.3 Aim 2: Is hemispheric PFC activation asymmetrical during standing balance tasks?

As shown in Table 2, all participants had a range of LI scores, with some showing bilateral activation during both tasks (-0.2 ≥LI≤0.2) (Borrell et al., 2023; Hyeon Jin et al., 2020; Seghier, 2008). The average LI during the double-leg stance was -0.201, indicating a slight preference for contralesional PFC activation. On the other hand, the average LI during the semi-tandem stance was 0.018, suggesting more bilateral PFC activation.

**Table 2: Laterality index values for both tasks.**

| Participants | LI for DL | LI for ST | Lesion Hemisphere (Right/Left) |
|---|---|---|---|
| S01 | 0.541 | 0.784 | Right |
| S02 | 0.171* | 0.528 | Left |
| S03 | 0.558 | 0.250 | Right |
| S04 | 0.002* | 0.301 | Left |
| S05 | -4.368** | -0.083* | Left |
| S06 | 1.180** | -1.976** | Right |
| S07 | -0.150* | 0.065* | Right |
| S08 | 0.283 | 0.326 | Right |
| S09 | -0.024* | -0.034* | Right |
| Average (SD) | -0.201* (1.614) | 0.018* (0.796) | 6 / 3 |

*Note.* LI: Laterality Index, DL: Double-leg, ST: Semi-tandem, * indicates bilateral PFC activation, ** indicates LI value not within expected range.

During the double leg stance, four participants showed bilateral PFC activation, while during the semi-tandem stance, five participants showed more ipsilesional than contralesional PFC activation. The LI value for S05 during the double leg stance and both LI values for S06 (double-leg and semi-tandem) were not within the expected range. Participants 7 and 9 showed bilateral PFC activation during both tasks. Bilateral PFC activation was also evident during the double leg stance for Participant 4, while Participant 5 showed bilateral PFC activation during the semi-tandem stance.

As seen in Figure 12, as the BBS score increased, participants displayed more ipsilesional PFC activation (positive LI values). Two participants with low BBS scores displayed more ipsilesional compared to contralesional PFC activation during the semi-tandem stance. Participants displayed more bilateral PFC activation during the double leg stance if they had low BBS scores.  Participants 1 and 3 displayed bilateral PFC activation during both tasks. Figure 12 also includes three laterality index scores that were not within the expected range.

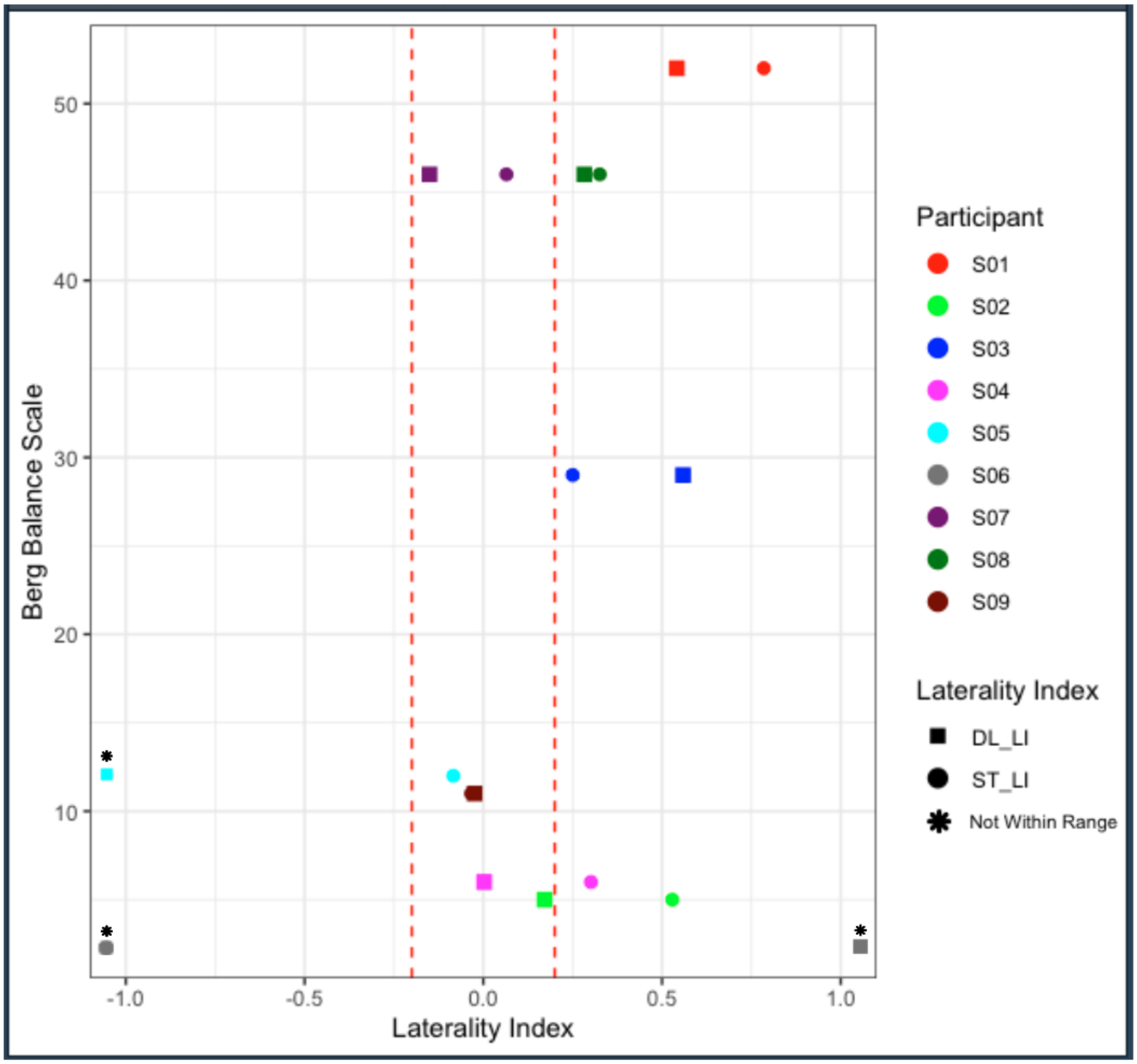


**Figure 12: Laterality index and Berg Balance Scale for all participants during both tasks. Values within the dashed red lines indicate bilateral activation (-0.2≥ LI ≤0.2). DL_LI (represented as squares): double-leg laterality index, ST_LI (represented as circles): semi-tandem laterality index.**

### 2.2.4 Aim 3: Do fatigue levels have a relationship with task-based activation?

As shown in Figure 13, two participants (S03 & S08) with scores higher than 3 on the FSS display more ipsilesional than contralesional PFC activation, with two participants (S07 & S09) showing bilateral activation ($-0.2 \geq LI \leq 0.2$) during both tasks. Four participants with a fatigue score higher than 3 show more ipsilesional than contralesional PFC activation during the semi-tandem stance.

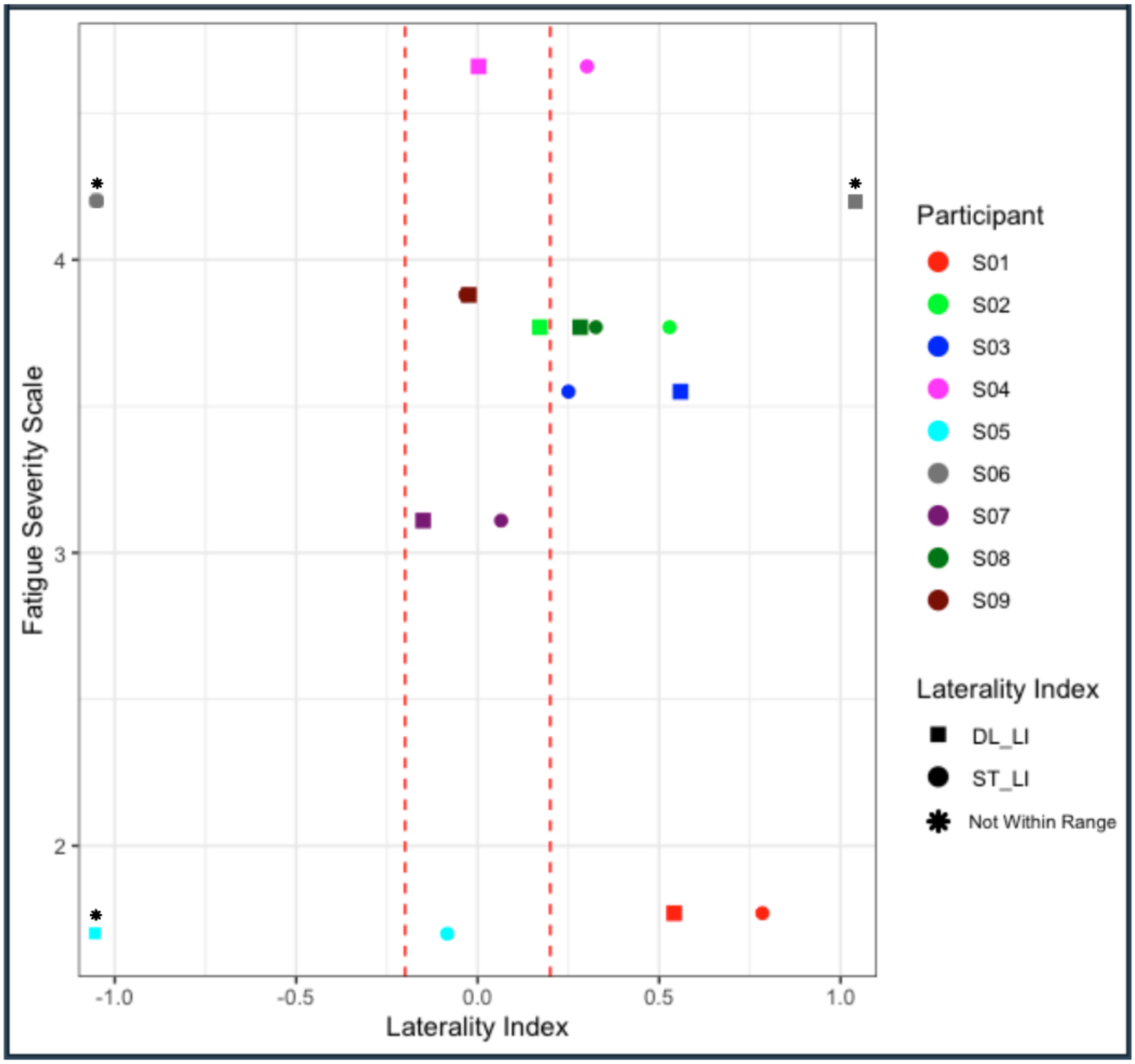


**Figure 13: Laterality index and fatigue severity scale for all participants during both tasks. Values within the dashed red lines indicate bilateral activation (-0.2 ≥ LI ≤ 0.2). DL_LI (represented as squares): double-leg laterality index, ST_LI (represented as circles): semi-tandem laterality index.**

## 2.3 Discussion

We sought to determine the potential changes in oxy-Hb and deoxy-Hb levels during standing balance tasks, the asymmetry of hemispheric PFC activation during these tasks, and the potential link between self-perceived fatigue and task-based activation in people post-stroke. To accomplish our objective, we utilized two standing tasks to evoke activation in the PFC, which was recorded bilaterally using fNIRS. We used the laterality index to examine the asymmetry of PFC activation, and the Fatigue Severity Scale was used to document fatigue.

*Changes in oxy-Hb and deoxy-Hb during tasks*

Our findings outline a slight increase in ipsilesional and contralesional PFC activation during the semi-tandem stance compared to the double-leg stance, although bilateral activation occurred during the semi-tandem stance (Figure 9). The increase in PFC activation was characterized by the increase in oxy-Hb and the decrease in deoxy-Hb (Yap et al., 2017; Yeung et al., 2018). Consistent with previous research findings, this study provides evidence that a more challenging balance task, like the semi-tandem stance, may evoke a higher level of PFC activation than the double-leg stance (Csipo et al., 2021; Moriarty et al., 2019). These results support prior research suggesting that increased task difficulty may be associated with the engagement of neural resources in the form of PFC involvement (Moriarty et al., 2019). The increase in PFC activation displayed during the semi-tandem stance may also indicate that the PFC plays a crucial role in the execution of complex motor tasks, potentially through an increase in cognitive control (Chen et al., 2022).

During gait, healthy adults can minimize the allocation of neural resources to walking (through automaticity) and have more resources to divert towards completing additional cognitive tasks (Wang et al., 2023). Automaticity refers to automatic or reflexive actions that do not require conscious effort, whereas executive control strategies involve goal-directed, conscious effort or cognitive resources to successfully complete a task (Clark, 2015). Healthy people can easily switch between automated and executive control strategies when executing a task (Clark, 2015). Since patients' post-stroke may have neurological damage, this process may change in motor strategy from automaticity to requiring more conscious effort, evident by the bilateral activation seen during the semi-tandem stance (Wang et al., 2023).

The large standard deviation around the mean in Figure 9 shows that there was not a uniform pattern of activation across all participants, potentially indicating the heterogeneity of post-stroke deficits. This variability may also be due to several other factors, including the location and severity of the lesion, individual differences in recovery potential, age, and pre-stroke functional levels (Cassidy et al., 2022; Goh & Stewart., 2019; Teo et al., 2018). These differences in fNIRS signals could also be attributed to the inter-subject variability in the placement of the Portalite device, participant motion, and signal processing techniques (Balters et al., 2021; Yap et al., 2017). The changes in oxy-Hb and deoxy-Hb highlight the importance of considering task difficulty when focusing on PFC activation during post-stroke recovery and may contribute to further understanding the neural mechanism underlying balance control.

*Asymmetry of PFC activation during tasks*

Our findings provide insights into the asymmetry of PFC activation during different standing balance tasks. The average LI during the double leg stance indicated a slight bias in activation towards the contralesional PFC compared to ipsilesional, suggesting that most participants exhibited an increase in activation of the contralesional PFC. However, this average is slightly biased as the LI value for Participant 5 (-4.368) was well out of the expected range and likely skewed the average towards contralesional PFC activation. Conversely, the average LI during the semi-tandem stance indicates balanced activation patterns, with more bilateral PFC activation evident. The average LI value for the semi-tandem stance may also be biased towards bilateral activation due to the LI value for Participant 6 (-1.976) falling outside of the expected range. The varied LI values during both tasks suggest that the extent of PFC contribution while maintaining balance may change depending on the task demands and difficulty.

Further investigation of the individual data shows interesting changes in PFC activation during both balance tasks. During the double-leg stance, approximately 44% of the participants demonstrated bilateral PFC activation, whereas, during the semi-tandem stance, a greater proportion (~55%) displayed more ipsilesional than contralesional PFC activation. Like the findings of oxy-Hb and deoxy-Hb, the evident variation within tasks may indicate that the activation level in ipsilesional and contralesional PFC may differ depending on the task difficulty and individual characteristics. In several of our participants, the increased ipsilesional PFC activation during the semi-tandem stance may reflect the involvement of additional cognitive processes essential for maintaining a more challenging standing balance position. Previous studies have shown that people post-stroke may display increased contralesional activation, which may be associated with poorer functional outcomes (Calautti et al., 2007; Grefkes & Fink, 2020). However, participating in challenging tasks like the semi-tandem stance may help to increase ipsilesional activation, which has been linked to better functional outcomes (Dodd et al., 2017). Furthermore, Lim et al., (2022) demonstrated that individuals post-stroke demonstrated more ipsilesional than contralesional PFC activation during walking tasks. Our study further supported this observation during balance tasks, as participants appear to display more ipsilesional PFC activation in relation to better balance scores on the BBS and more bilateral activation with lower BBS scores (Figure 12). These findings suggest that an increase in ipsilesional PFC activation after stroke could possibly serve as an indicator of better balance outcomes, although further investigation is required.

The LI value for Participant 5 during the double leg stance and both LI values for Participant 6 (double leg and semi-tandem) were not within the expected range. To examine the unexpected LI scores, we further explored the results for the two participants in depth. For Participant 5, the left hemisphere was affected after stroke, thus, the negative LI value during the double leg stance (-4.368) indicated increased contralesional (right PFC for this participant) activation. Previous research has indicated that healthy young adults often display increased right PFC activation, likely due to a predominance of this brain area during challenging balance tasks (Teo et al., 2018). Since the PFC is also responsible for inhibition (suppression of inappropriate responses) of unwanted movements, healthy young adults may require a greater involvement of the right PFC during balance to inhibit unwanted movements (Aron et al., 2004; Munakata et al., 2011; Teo et al., 2018). Like young healthy adults, younger patients' post-stroke may display a similar dominance of the right PFC activation during balance. Given that Participant 5 in our study was relatively young (age 50), it is possible that their age influenced their LI value during the double leg stance resulting in the LI score outside the expected range. For Participant 6, the right hemisphere was affected post-stroke, the negative LI value during the semi-tandem stance indicated increased activation in the contralesional hemisphere (left PFC in this case). Interestingly, Participant 6 experienced one of the highest fatigue levels among all participants, evidenced by a score of 4.44 on the FSS. Previous research has established a correlation between fatigue, depression, and anxiety (Radman et al., 2012; Snaphaan et al., 2011; Wu et al., 2015). Moreover, some studies have targeted the left PFC with repetitive transcranial magnetic stimulation to alleviate symptoms of depression in adults (Leggett et al., 2015). While we recognize that this speculation is outside the scope of this study, it is plausible that Participant 6 may have been experiencing not only high fatigue levels but also co-occurring depression or anxiety, which could influence the LI values during both tasks. Future studies accounting for factors like depression and anxiety in addition to fatigue may help to further contextualize our findings.

*Fatigue and task-based activation*

Fatigue is a common symptom experienced by individuals' post-stroke, and it can negatively influence overall quality of life and functional outcomes (Wu et al., 2015). Previous research has noted that increased fatigue may be associated with limited participation in everyday life and decreased independence (Aarnes et al., 2019). Furthermore, studies have shown that the persistence of fatigue can vary among individuals and may hinder the recovery process during stroke rehabilitation (Naess et al., 2012; Wu et al., 2015). One study by Goh and Stewart (2019) examined the relationship between post-stroke fatigue and motor and cognitive performance measures. They found that higher fatigue levels, as measured by the FSS, were associated with worse balance performance on the BBS. Another study by Christensen et al., (2008) explored the effects of fatigue on patients hospitalized, following their first stroke, and found that an increased level of fatigue was associated with poor functional outcomes.

Our study shows that participants with fatigue scores higher than 3 on the FSS may display more ipsilesional PFC activation related to the semi-tandem stance, indicating a potential link between PFC activation and fatigue during challenging balance tasks. Around 40% of the participants with fatigue scores higher than 3 demonstrated increased ipsilesional PFC activation, further supporting that fatigue levels may influence the pattern of PFC activation observed in the semi-tandem stance. A study by Wolff et al., (2019) monitored changes in PFC activation while preforming a strenuous physical task for people with multiple sclerosis and found an increase in PFC activation may reflect as an aspect of fatigue. They proposed that an increase in PFC activation signifies the increased effort required to manage the accumulating fatigue instead of being representative of the level of self-perceived fatigue (Wolff et al., 2019). Like these results, participants in our study may show more ipsilesional PFC activation to manage the accumulation of fatigue rather than indicating the feeling of fatigue. It is important to note that in previous literature, an FSS score of above 4 indicates a significant level of perceived fatigue (Rosti-Otajärvi et al., 2017). The cut-off ≥4 on the FSS is used because less than 5% of healthy individuals rate their fatigue above this level, whereas a significant percentage of patients (60-90%) with medical disorders experience fatigue reaching or surpassing this score (Krupp et al., 1995; Rosti-Otajärvi et al., 2017). Given our study's small sample size, it is possible that we did not have enough participants to capture the full range of fatigue levels observed in previous research. If the cut-off score of 4 is considered as an indicator for significant levels of self-perceived fatigue, then our study shows a prevalence rate of ~22%. This prevalence rate of fatigue after stroke is considerably lower compared to previously reported rates of 68% (Lerdal et al., 2011) and 57% (Van de Port et al., 2007). A larger sample size may provide a wider range of fatigue levels and help to explain further potential factors contributing to the observed PFC activation pattern.

For Participants 7 and 9, a more bilateral activation pattern in the PFC was observed during both balance tasks, indicating the involvement of both hemispheres (Figure 13). Given that these two participants were among the oldest in our study, it is possible that age influenced the pattern of activation during both balance tasks. Previous research has demonstrated that older healthy adults exhibit more bilateral PFC activation compared to younger healthy adults while performing complex tasks, potentially because a greater allocation of resources is required to maintain balance performance (Teo et al., 2018). Visually exploring the individual HRF's (Figure 10 & 11) for participant 7 and 9, it is interesting to note that the change in oxy-Hb is greater during both tasks compared to younger participants in our study (Participant 1 & 2). This pattern of activation may be evident because like healthy older adults, older patients after stroke may require higher PFC activity for tasks with low physical demands compared to younger individuals to compensate for the age-related decline in cognitive and physical abilities (Baek et al., 2023). Age-related changes in PFC activation in addition to reduced automaticity may have contributed to the bilateral activation observed in these participants. Additionally, looking at the relationship with fatigue and LI (Figure 13), participants that showed more ipsilesional PFC activation experienced higher fatigue levels with two participants showing bilateral activity during both tasks. In this way, fatigue may influence the pattern of PFC activation, potentially contributing to balance impairments in people post-stroke.

*Limitations*

Some limitations of the present findings are worth considering. First, the sample included primarily patients with subcortical ischemic lesions; therefore, the extent to which our findings can be generalized to all patients in the sub-acute phase after stroke may be limited. However, considering that ischemic stroke represents most stroke cases, with approximately 87% being ischemic, while hemorrhagic strokes account for the remaining 13%, our findings provide valuable information to a significant portion of stroke cases (Salvadori et al., 2021). Second, the current study was limited by a small sample size because of low recruitment from the inpatient stroke unit. This was due to the occurrence of several COVID-19 outbreaks during participant recruitment that prohibited the research team from interacting with patients on the unit.

In addition, there were potential limitations in our study related to fNIRS as an imaging tool. This restriction was based on challenges associated with device placement because of hair in other regions of the scalp. Hair can disrupt the contact between the fNIRS sensors and the scalp, which may lead to a low signal-to-noise ratio in the data (Khan et al., 2012). By focusing on the forehead region, where hair disruption is low, we ensured that the fNIRS device made good contact with the skin. However, because of this limitation, the placement of the Portalite device was restricted to the forehead, excluding any additional brain regions from the measurement. Through observation of additional brain regions using fNIRS, we could further understand the underlying brain activity associated with balance and fatigue for individuals after stroke. Additionally, the Portalite fNIRS system does not include short channels, so the raw data may be contaminated by signals from other brain tissue, such as the scalp and cranium (Fujimoto et al., 2014). To mitigate potential contamination, we implemented a data processing approach where we subtracted the average oxy-Hb in the baseline from the task period. This subtraction was done assuming that scalp activation would be removed, allowing us to only focus on signals originating from the targeted brain region (Maidan et al., 2016). Our study then included the subtracted oxy-Hb concentration in the LI formula since it is more sensitive than deoxy-Hb to changes in the HRF response and has been used in previous LI analyses (Borrell et al., 2023; He et al., 2022).

Additionally, the literature focuses primarily on changes in oxy-Hb concentration compared to deoxy-Hb concentration (Yap et al., 2017; Yeung et al., 2018). The focus on oxy-Hb concentration may be because of near-infrared wavelengths from fNIRS devices displaying greater changes in oxy-Hb during tasks (Doi et al., 2013; Mihara et al., 2008). To ensure comparability with other fNIRS studies, we focused primarily on oxy-Hb concentration changes.

By aligning our approach with the literature and focusing on oxy-Hb-related changes, our findings can be readily compared and integrated with the broader scope of fNIRS research. However, deoxy-Hb changes may provide valuable information since an increase and subsequent decrease in deoxy-Hb concentration could also be considered as activation of the brain region (by using the oxygen available, the tissue would convert oxy-Hb into deoxy-Hb) (Hong & Zafar, 2018; Nakamura et al., 2020). This is reported in previous literature as the initial dip, where the initial oxygen requirement or deoxy-Hb increase may precede the cerebral blood flow to the brain region of interest (Kamran et al., 2018; Nakamura et al., 2020). Therefore, a separate analysis focusing only on deoxy-Hb may help to further explain differences in PFC activation for participants.

Lastly, fatigue can be an everchanging phenomenon, but this study only assessed self-rated fatigue at the one-time point. Measures of self-rated fatigue at different stages of stroke recovery may provide insights into how changes in PFC activation while maintaining balance are linked with fluctuating fatigue levels and recovery progression. Additionally, we did not account for depression or anxiety in this study. However, since fatigue is correlated with depression and anxiety, documenting these measures may help further explain differences in brain activation between individuals after stroke (Radman et al., 2012; Snaphaan et al., 2011; Wu et al., 2015). Without measuring these factors in our study, depression and anxiety levels among participants may have been a confounding variable influencing the pattern of PFC activation during balance.

## 2.4 Conclusion and future directions

Our study provides evidence of PFC activation during standing balance in people post-stroke. We observed a greater change in oxy-Hb than deoxy-Hb concentration during both tasks, with some participants showing bilateral activation. The observed asymmetry in PFC activation between tasks may indicate task-specific activation patterns. The increase in ipsilesional PFC activation during the semi-tandem stance for some participants may suggest a potential involvement of the ipsilesional hemisphere in maintaining challenging balance positions. These findings contribute to our understanding of PFC activation patterns during balance control and its relationship with fatigue for people post-stroke. However, further research is required to explore the clinical implications of these findings and their relationship with balance performance and recovery outcomes. Further studies could incorporate a larger sample size to explore the association between PFC activation and balance with longitudinal measures of fatigue. Additionally, a separate analysis focusing solely on deoxy-Hb concentration may also help to understand PFC activation and its relationship to balance and fatigue. Including different brain regions and dynamic balance tasks may also help to understand further changes in activation over time and their potential relationship with functional recovery.

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# Appendices

**Appendix A: Fatigue Severity Scale used to document self-perceived fatigue for people post-stroke.**

**Fatigue Severity Scale (FSS)**

| Participant ID: | Session #: |
|---|---|
| Date: ____/____/____ MONTH DAY YEAR | |

Please circle the number between 1 and 7 which you feel best fits the following statements. This refers to your usual way of life within the last week. 1 indicates "strongly disagree" and 7 indicates "strongly agree."

| Read and circle a number | Strongly Disagree → Strongly Agree | | | | | | |
|---|---|---|---|---|---|---|---|
| 1. My motivation is lower when I am fatigued. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 2. Exercise brings on my fatigue. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 3. I am easily fatigued. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 4. Fatigue interferes with my physical functioning. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 5. Fatigue causes frequent problems for me. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 6. My fatigue prevents sustained physical functioning. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 7. Fatigue interferes with carrying out certain duties and responsibilities. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 8. Fatigue is among my most disabling symptoms. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 9. Fatigue interferes with my work, family, or social life. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |

Version 1. March 15th, 2022

## Appendix B: Approval from the Western University Health Sciences Research Ethics Board.

Western 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

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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).***

Western Research

**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

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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).***

# Curriculum Vitae

## Sarthak Kohli

| | |
|---|---|
| **Post-secondary Education and Degrees:** | Dalhousie University<br>Halifax, Nova Scotia, Canada<br>2017-2021 B.Sc. Kinesiology<br><br>The University of Western Ontario<br>London, Ontario, Canada<br>2021-Present M.Sc. Health and Rehab Sci. (PT Field) Candidate |
| **Honours and Awards:** | Parkwood Institute Research Specific Endowment:<br>The London Life Stroke Rehabilitation Studentship<br>2022-2023 |
| **Related Work Experience** | Graduate Research Assistant<br>Neurorehabilitation Physiology Lab<br>The University of Western University<br>2021-Present<br><br>Teaching Assistant<br>The University of Western Ontario<br>2022-2023<br><br>Teaching Assistant<br>The University of Western Ontario<br>2021-2022 |

**Publications:**

Ghatamaneni D, **Kohli S**, MacDermid J, Peters S, Brunton L. Prevalence of Fatigue in Adolescents and Adults with Cerebral Palsy: A systematic review. [Provisionally Accepted at Fatigue: Biomedicine, Health & Behaviour]

**Research Presentations:**

***Kohli S***, Luan S, Durand N, Fleet J, Viana R, Christie A, Teasell R, Brunton L, Peters S. Cortical activation, standing balance, and fatigue - a post-stroke explorative study. 15$^{th}$ World Stroke Congress. Toronto ON, October 10-12$^{th}$, 2023. [Accepted poster presentation]

***Kohli S***, Luan S, Peters S. Cortical activation, standing balance, and fatigue - a post-stroke explorative study. 2022 Parkwood Institute Research Day. London ON, April 27, 2023. [Completed oral presentation]

***Kohli S***, Luan S, Peters S. Cortical activation, standing balance, and fatigue - a post-stroke explorative study. 2022 Parkwood Institute Research Day. London ON, April 21, 2022. [Completed oral presentation]

***Kohli S***, Luan S, Peters S. Cortical activation, standing balance, and fatigue - a post-stroke explorative study. 2022 Health and Rehabilitation Graduate Research Conference. UWO, Feb 2, 2022. [Completed oral presentation]

***Kohli S***, Luan S, Peters S. Effects of functional electrical stimulation on brain activation post-stroke. Parkwood Institute Research Open House 2021. Nov 25, 2021. [Completed oral presentation]