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Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA,
IRVINE

An experimental and modeling framework for neurophysiological characterization of stroke
injury and ankle rehabilitation

DISSERTATION

submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Biomedical Engineering

by

Piyashi Biswas

Dissertation Committee:
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DEDICATION

To my family and friends for supporting me through this journey.

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Johnson, C. A., **Biswas, P.**, Tapia, R., See, J., Dodakian, L., Chan, V., Wang, P. T., et al. *Neurorehabilitation and Neural Repair*, 39(12), 1031–1045.

A Single-Center, Assessor-Blinded, Randomized Controlled Clinical Trial to Test the Safety and Efficacy of a Novel Brain-Computer Interface Controlled Functional Electrical Stimulation (BCI-FES) Intervention for Gait Rehabilitation in the Chronic Stroke Population **2024**

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Venkatesan, D., Krishna, T. S., **Biswas, P.**, & Dey, R. *Journal of Molecular Liquids*, 299, 112221.

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Sandhya, M. S., **Biswas, P.**, Vinay, N. R., Sivakumar, K., & Dey, R. *Journal of Molecular Liquids*, 278, 219–225.

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Dey, R., & **Biswas, P.** *Journal of Molecular Liquids*, 265, 356–360.

**Using a Robotic Device to Quantify the Impact of Con-
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Johnson, C. A., **Biswas, P.**, See, J., Briendel, O., Chan, V., Dodakian, L., Wang, P. T., et al. *2025 International Conference on Rehabilitation Robotics (ICORR)*, pp. 1473–1478.

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**Early Detection of Acute Exacerbation of Chronic Ob-
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Hickman, N., Hughes, A. L., **Biswas, P.**, et al., & Biswas, R. In *C15. Emerging COPD Diagnostics and Treatments*, pp. A4499–A4499. American Thoracic Society.

**Dissecting Vascular and Platelet Function in Ovarian
Cancer With Organ-on-a-Chip Methodology** **Jul 2019**

Saha, B., Bui, J., **Biswas, P.**, Sood, A. K., Afshar-Kharghan, V., & Jain, A. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 39(Suppl.1), A554–A554.

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ABSTRACT OF THE DISSERTATION

An experimental and modeling framework for neurophysiological characterization of stroke injury and ankle rehabilitation

By

Piyashi Biswas

Doctor of Philosophy in Biomedical Engineering

University of California, Irvine, 2026

Professor Zoran Nenadic, D.Sc., Chair

Stroke is the leading cause of long-term disability, and many survivors are left with chronic gait impairments. These can limit societal ambulation and lead to a multitude of health complications, making gait rehabilitation a major priority in stroke recovery. Decades of research have focused on addressing post-stroke gait impairment caused by foot-drop. Still, there have been no breakthroughs, leaving clinicians and patients with limited options that often provide only temporary effects. Therefore, novel therapies, based on neurobiological principles of stroke recovery, should be developed to provide long-lasting improvements. Brain-computer interfaces (BCIs) have been suggested as a method of harnessing the brain's neuroplasticity via the Hebbian mechanism. BCIs can directly access the brain, and when paired with other rehabilitation modalities such as functional electrical stimulation (FES) and robotics, Hebbian-like changes can strengthen connections between neural populations, leading to long-lasting improvements. While BCI-based therapies are being developed, the mechanisms underlying them have been challenging to demonstrate in clinical trials. Clinical assessments such as the Fugl-Meyer, stroke scales, gait velocity, and gait endurance have been developed to assess an individual's stroke-related disability and quantify recovery during the rehabilitation process. However, these assessments do not capture the neurophysiological changes that accompany rehabilitation, making it difficult to determine whether neuroplas-

ticity has indeed occurred. While some efforts have tried to include neurological assessments that may provide insight into the brain-muscle connection, most of these assessments are either static or do not involve volitional movement. In this work, we develop a novel assessment framework that addresses these challenges.

We use a computational model of the human motor control system to identify the potential impact of post-stroke injury and targets of rehabilitation strategies. This allows us to understand the potential and expected impact of BCI-based rehabilitation specifically, and test that theory. With this knowledge, we then design an assessment method using noninvasive electrophysiological recording systems that utilize EEG, EMG, and kinematic data during dynamic tasks to provide a personalized, comprehensive understanding of neuromuscular connections. We collect baseline data from 19 able-bodied participants and recruit 10 chronic stroke participants who undergo 4 weeks of BCI-FES or BCI-robotic rehabilitation interventions. Based on these experimental datasets, we identify and model how injury impacts different aspects of movement. We then study how these change after rehabilitation and whether we can estimate neuroplastic changes using our novel assessment. This work establishes a neurophysiological assessment framework that can quantify personalized rehabilitation-induced neuroplastic changes, offering new insights into the mechanisms of BCI-based stroke recovery.

Chapter 1

Introduction and Background

One in four adults experiences at least one stroke in their lifetime [129]. It is the leading cause of long-term disability, with an estimated 7 million survivors of chronic stroke just in the United States. This number is projected to increase substantially with a growing population, rising life expectancy, and improving acute survival rates [58, 130, 123, 137]. The economic implications of managing stroke-related care are estimated at over \$100B annually [62, 119]. These costs extend beyond healthcare expenses and include loss of productivity as well as associated caregiver burden.

Despite the best physical therapy and spontaneous recovery that occurs during the acute phase post-stroke, progress often plateaus as patients enter the chronic phase (> 6 months), with 30-60% of survivors experiencing long-term gait-related disability [37, 55]. One of the most prevalent and functionally limiting gait impairments is foot drop, characterized by weakness or paralysis of the ankle dorsiflexors. This prevents the foot from clearing the ground during the swing phase, resulting in toe drag, compensatory movement patterns (such as hip hiking and circumduction), and significantly higher metabolic cost of walking.

These gait deficits are particularly debilitating, reducing mobility, independence, and quality of life, thereby increasing reliance on caregivers and assistive devices, directly impacting social reintegration [63, 7, 131]. This can lead to further health complications, including increased risk of falls [38, 91, 125], osteoporosis [39, 91], cardiovascular deconditioning [29, 69], deep vein thrombosis [81, 26], and pressure ulcers [106, 140, 121]. Given these impacts, gait rehabilitation after stroke remains a high therapeutic priority among survivors [55, 84].

Currently, physical therapy is the primary and most effective approach for gait rehabilitation after stroke [133, 135]. Traditional physical therapy relies on repetitive movement and high-volume exercise to improve motor function. Specifically, to address foot drop, exercise plans are designed to focus on recovering ankle function [82, 1]. However, its efficacy is often limited by insufficient motivation and motor engagement, particularly during long-term rehabilitation [93, 66, 93, 79]. The challenge is further compounded by practical barriers to ongoing care. Continued physical therapy beyond the acute phase is often not covered by insurance, imposing a significant financial burden on patients and families [67, 98]. Additionally, the existence of a rehabilitative plateau in the chronic phase (> 6 months post-stroke) [141], where the patient is unable to benefit from further physical therapy, while debated [16, 80], can render continued efforts in conventional physical therapy futile. Therefore, given the high clinical need and these practical barriers, it is critically important to develop alternative rehabilitation approaches that are both effective and accessible.

Over the last few decades, rehabilitation research has focused on developing technologies to address the limitations of traditional physical therapy. These novel interventions also offer potential alternate avenues of improvement for patients experiencing the rehabilitative plateau and may be the answer to continued improvements by engaging newer pathways of recovery [80].

One primary focus has been on robotic systems that can mimic and enhance therapeutic exercises. Robotic methods offer several advantages: they provide repeatable, consistent

fatigue-free movements, can assist movement across multiple degrees of freedom, target multiple joints, and enable closed-loop rehabilitation by recording performance data and adjusting assistance in real time. Several robotic systems have been developed for gait rehabilitation, including the Lokomat [31], G-EO gait trainer [27], EksoGT [77], ReWalk [21], and HAL [42]. These systems, many of which are body weight-supported treadmill-based, target specific gait parameters such as cadence, endurance, and symmetry while incorporating task-specific training principles. One challenge with robotic rehabilitation is the brain’s tendency to become dependent on assistance, a phenomenon known as slacking, particularly in passive designs [95, 19]. Researchers have implemented assist-as-needed paradigms and other integrated motivational elements, such as virtual reality and gamification, to promote active engagement. Exoskeleton-based robots face additional practical challenges, including bulky designs that require supervision to prevent injuries and exorbitant costs [99].

Functional electrical stimulation (FES) is another established intervention that has shown potential for improving ankle movement and foot clearance after stroke [105, 61, 111]. FES delivers electrical pulses to peripheral nerves that lead to muscle contractions. For foot drop, the peroneal nerve is stimulated, targeting the activation of the tibialis anterior (TA) muscle, producing dorsiflexion. It has been shown to enhance muscle strength, reduce spasticity, improve range of motion, and promote more natural activation patterns [83]. Additionally, when combined with voluntary movement, it has also been hypothesized to drive neuroplastic changes in cortical and spinal circuits via antidromic impulses, promoting long-term gait recovery [103].

While these technology-based approaches have shown promise in smaller studies, none have established themselves as superior to conventional physical therapy [8, 40]. Large-scale clinical trials remain limited, and available evidence has not identified a clear advantage for these as stand-alone interventions over conventional therapy. These technologies appear most effective when combined with traditional physical therapy, providing a more com-

prehensive rehabilitation experience. However, despite that, clinical trial outcomes remain highly variable, with many studies showing that conventional therapy performs equally well or better [3]. In cases where technological interventions appear superior, the advantage may be confounded by differences in treatment dosage rather than true mechanistic benefits.

A critical limitation is the incomplete understanding of how these interventions drive recovery. Given that neuroplasticity may be the primary mechanism of motor recovery after stroke, understanding and targeting neuroplastic changes are hypothesized to be essential for achieving sustained rehabilitation outcomes [59, 47]. Hence, there is a need for interventions explicitly conceptualized around neurobiological principles, with neuroplasticity as the central therapeutic mechanism.

Brain-computer Interfaces (BCIs) are hypothesized to offer one such neuroplasticity-centered approach [3]. BCIs provide direct access to neural activity by recording and decoding neurophysiological signals in real time. When combined with other rehabilitation modalities, BCIs can facilitate motor rehabilitation through Hebbian learning mechanisms [48, 72]. According to Hebbian theory, “neurons that fire together, wire together”, meaning that synchronized activation of neural populations strengthens their connectivity. Foot drop after stroke may result from disruption of the corticospinal pathway [30], thereby weakening the connection between the motor cortex and the lower motor neurons that control ankle dorsiflexion. BCI-based therapies aim to restore this connectivity by synchronizing cortical activity with either peripheral muscle activation or providing sensory feedback, reinforcing the damaged neural circuits through repeated, temporally coordinated activity.

Table 1.1: Summary of BCI-based stroke rehabilitation studies.

Study	N	Population	Target	Intervention	Control	Dosage	Main Finding
Ramos-Murguialday 2013 [92]	32	Chronic stroke	UE	BCI-Robot + CT	Robot + CT	17 sessions, 60 mins	Improved FM scores than control

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Study	N	Population	Target	Intervention	Control	Dosage	Main Finding
Pichiorri 2015 [90]	28	Subacute stroke	UE	BCI-Motor Imagery (MI) + CT	MI + CT	3 hrs CT + 30 min BCI/Sham, 12 sessions over 4 weeks	Multiple improved measures, increase in FM and MRC over control
Biasiucci 2018 [4]	27	Chronic stroke	UE	BCI-FES + CT	FES + CT	45 min CT + 60 min BCI/Sham, 10 sessions over 5 weeks	Multiple improved measures, increase in FM, MRC, and NIHSS over control
Cheng 2020 [9]	11	Chronic stroke	UE	BCI-Robot + CT	Robot + CT	30 min CT + 90 min BCI/Sham, 18 sessions over 6 weeks	Increase in FM but comparable between groups, ARAT increased more for BCI than control
Miao 2020 [68]	16	Chronic stroke	UE	BCI-FES + CT	CT	12 sessions over 4 weeks, 60 mins	Improved FM scores than control
Ji 2025 [32]	40	Acute stroke	UE	BCI-Robot	Robot	20 sessions over 4 weeks, 60 mins	Improved FM-UE scores than control
Sebastián- Romagosa 2023 [107]	22	Chronic stroke	LE + UE	BCI-FES	N/A	25 sessions over 3 months, 60 min	Multiple improved measures, including Gait Speed, Dorsiflexion, and FM
McCrimmon 2015 [65]	9	Chronic stroke	LE	BCI-FES	N/A	12 sessions over 4 weeks, 60 min	Multiple improved measures, including Gait Speed and Dorsiflexion
Mrachacz- Kersting 2016 [72]	22	Subacute and Chronic stroke	LE	BCI-FES	Sham FES	3 sessions over 1 week	Multiple improved measures including FM and Gait Speed
Chung 2020 [10]	26	Chronic stroke	LE	BCI-FES	CT	15 sessions over 5 weeks, 30 min	Improved Gait Speed over control
Luo 2024 [57]	64	Acute stroke	LE	BCI-FES + CT	CT	70 min CT + 30 min BCI (2× a day); 20 sessions over 2 weeks	Multiple improved measures, including FM and FAC over control

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Study	N	Population	Target	Intervention	Control	Dosage	Main Finding
Zhao 2022 [151]	28	Subacute stroke	LE	BCI-Robot + CT	Robot + CT	30 min CT + 30 min BCI/Sham, 24 sessions over 4 weeks	Multiple improved measures, but FM comparable between groups

Abbreviations: N: number of participants; UE: upper extremity; LE: lower extremity; BCI: brain-computer interface; CT: conventional therapy; MI: motor imagery; FES: functional electrical stimulation; FM: Fugl-Meyer Assessment; FM-UE: Fugl-Meyer Upper Extremity; MRC: Medical Research Council Scale; NIHSS: National Institutes of Health Stroke Scale; ARAT: Action Research Arm Test; FAC: Functional Ambulation Category; N/A: not applicable.

Over the past few decades, researchers have successfully developed BCI-based interventions, combining them with robotic systems, exosuits, and FES, consistently demonstrating superiority over these modalities used in isolation (see Table 1.1). However, large-scale clinical trials remain scarce, and existing evidence has not yet established clear superiority over dose-matched conventional therapy. Additionally, several of these studies lack proper randomized controls, diluting the impact of their findings. This limited evidence base makes it difficult to confidently determine whether BCI-based interventions offer meaningful improvements over standard physical therapy approaches.

A fundamental challenge is that, despite being explicitly designed to induce neuroplasticity, the precise mechanisms underlying BCI-mediated recovery remain poorly understood [134, 127]. Depending on the neural populations and pathways targeted, BCI therapies may facilitate recovery through different mechanisms. Some may enhance the efferent (motor) pathway, improving movement execution and muscle activation. Others may restore or strengthen afferent (sensory) feedback, which is critical for motor learning [134]. Given that these mechanisms likely operate simultaneously and interact dynamically, isolating their individual contributions to functional improvement has proven extremely difficult. This mechanistic complexity, combined with the heterogeneous nature of stroke injuries and variability

in patient response, makes predicting treatment efficacy a pressing challenge that must be addressed to advance the clinical translation of BCI-based gait rehabilitation.

While BCI-based rehabilitation is hypothesized to promote neuroplasticity, limited clinical studies provide neurophysiological evidence to support this. Most gait rehabilitation studies rely on functional assessments such as the 10-meter walk test (10MWT) and 6-minute walk distance (6MWD). Some studies incorporate instrumented gait analysis to capture additional parameters, including step width, stride length, and cadence [3]. However, gait is a complex sensorimotor process involving multiple interacting systems, including coordinated joint kinematics, ankle dorsiflexion and plantarflexion, hip and knee flexion, spinal central pattern generators, and proprioceptive feedback [100, 64]. Furthermore, post-stroke impairments such as muscle spasticity, compensatory movement patterns, abnormal muscle co-contraction, impaired balance, and reduced force generation can all significantly compromise gait function [124, 51]. To assess lower extremity motor function more comprehensively, studies may include the Fugl-Meyer lower extremity scale, manual muscle testing, active and passive range-of-motion measurements, the Timed Up and Go test, and the modified Ashworth Scale for spasticity.

These assessments are clinical, functional, and biomechanical measures that quantify impairment severity and functional capacity. While some combination of these tests is standard practice in most clinical rehabilitation trials, they may not directly measure neuroplasticity [12]. Long-term improvements in these functional outcomes may suggest that neural reorganization has occurred, but they do not constitute direct evidence of cortical or spinal plasticity. Therefore, although many technology-based rehabilitation interventions claim to induce neuroplasticity, evidence in gait rehabilitation remains largely indirect, inferred from functional improvements rather than demonstrated through direct neurophysiological measurement. This gap between claimed mechanisms and available evidence highlights the

need for more rigorous assessment of neural changes underlying functional recovery in gait rehabilitation.

Studies have attempted to assess neuroplasticity by pairing neurophysiological measures such as functional near-infrared spectroscopy (fNIRS), functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI), electroencephalography (EEG), motor evoked potentials (MEP via transcranial magnetic stimulation, TMS), or blood biomarkers with behavioral and functional gait outcomes (see Table 1.1). These assessments can provide evidence of brain and spinal changes that evolve alongside improvements in walking function following rehabilitation. In upper extremity BCI studies, Ramos-Murguialday et al. [92] observed increased EMG waveform length and fMRI activation shifts in the BCI group, with fMRI laterality index and EMG measures correlating with Fugl-Meyer scores. Pichiorri et al. [90] found greater motor imagery-induced EEG desynchronization in the BCI group post-therapy, though MEP responses did not differ between groups. Biasiucci et al. [4] reported that EEG-based functional connectivity differed between groups, with the BCI group exhibiting enhanced connectivity post-therapy. Ji et al. [32] observed a stronger fNIRS response in the BCI group compared to controls.

For lower extremity rehabilitation, McCrimmon et al. [65] observed increased movement-related desynchronization and post-movement resynchronization after four weeks of BCI-FES therapy. Similarly, Mrachacz-Kersting et al. [72] recorded increased tibialis anterior MEP amplitude in the BCI group but not in controls. However, DTI metrics of the corticospinal tract did not correlate with functional outcomes. Zhao et al. [151] observed higher blood serum BDNF levels in the BCI group, though MEP amplitudes were comparable between groups.

While these results are promising, the neurophysiological assessments employed remain incomplete. fMRI and EEG capture only changes occurring in the brain, whereas MEP measurements using TMS assess corticospinal pathway integrity, but in the absence of volitional

movement. Additionally, corticomuscular coherence (CMC), while revealing relationships between neural and muscular activity [147, 120], is typically measured under static, isometric conditions. CMC has been shown to poorly reflect neuromuscular coupling during dynamic movement [115, 24], which is central to gait function. Therefore, more comprehensive methods are needed to understand the mechanisms underlying rehabilitation-induced recovery.

Computational models are emerging as valuable tools for understanding neurorehabilitation mechanisms after stroke [96]. By integrating experimental data with computational approaches, these models can predict outcomes, optimize rehabilitation strategies, and provide evidence of neuroplastic changes that may occur during rehabilitation. Importantly, computational models can guide the design of more targeted assessments to reveal the mechanisms underlying functional recovery.

In this dissertation, we use a computational model based on human motor control theory to investigate the neural targets of BCI-based stroke rehabilitation and leverage these insights to design a novel dynamic neurophysiological assessment. We collect data from a small cohort of able-bodied participants and chronic stroke participants with foot drop as they undergo four weeks of BCI-based rehabilitation. Using data acquired at multiple time points, we first estimate baseline parameters from able-bodied data and then compare them with stroke parameters to characterize and quantify the impact of injury. Finally, we examine how model parameters change during rehabilitation and compare these changes with the functional and biomechanical improvements observed over the course of therapy.

Chapter 2

Motor control framework for studying post-stroke motor deficits and rehabilitation

2.1 Motivation

Rehabilitation after stroke involves complex neuroplastic changes in the brain and spinal cord. As discussed in Chapter 1, BCI-based rehabilitation techniques are hypothesized to induce neuroplasticity via Hebbian learning mechanisms, potentially leading to longer-lasting functional improvements. However, even within this Hebbian framework, there are competing hypotheses about the specific mechanisms through which BCI therapies facilitate recovery [134]. BCI interventions are thought to primarily strengthen efferent motor pathways by reinforcing cortical motor commands paired with muscle activation [18, 65]. BCIs may also restore afferent sensory feedback that is critical for motor learning and cortical reorganization [112, 149]. Given that these mechanisms likely operate simultaneously during rehabilitation, experimental studies alone cannot easily decouple their individual

contributions to functional improvement. Understanding which neural pathways and control mechanisms are targeted by different rehabilitation strategies is essential for designing more effective therapies and establishing evidence-based treatment selection criteria.

Computational models provide a powerful approach to address these challenges [96]. In the context of BCI-based rehabilitation, computational models can simulate movement generation and sensory processing under ideal conditions, replicate stroke-induced disruptions to these pathways, and predict how specific interventions influence recovery. This approach enables testing mechanistic hypotheses, predicting intervention outcomes based on individual impairment profiles, and identifying optimal therapeutic targets before conducting resource-intensive clinical trials.

In this chapter, we present a computational framework based on human motor control theory that models the sensorimotor control loop governing ankle dorsiflexion during gait. The model incorporates both feedforward motor commands and proprioceptive feedback pathways, allowing us to simulate different sites of neurological injury that lead to foot drop after stroke. We use this model to investigate which specific pathway disruptions produce clinically observed impairment patterns, identify potential therapeutic targets for recovery, and predict how BCI-based interventions may differentially affect motor versus sensory pathways. The insights gained from these simulations guide the design of neurophysiological assessments and inform hypotheses tested in subsequent experimental chapters.

2.2 Background

Foot drop is caused by impaired ankle dorsiflexion due to disruption of the neural pathways controlling the tibialis anterior and other dorsiflexor muscles [30]. To investigate the mechanisms through which rehabilitation interventions facilitate recovery, it is essential to understand the sensorimotor control system underlying voluntary movement generation. Human

motor control involves both descending motor commands and ascending sensory feedback pathways operating through interconnected cortical, spinal, and peripheral networks [49]. Motor commands originate in cortical planning and execution areas, including the premotor cortex, supplementary motor area, and primary motor cortex. These signals are transmitted through descending pathways, primarily the corticospinal tract, to lower motor neurons that innervate and activate muscle fibers. Simultaneously, sensory pathways carry proprioceptive information from muscle spindles and Golgi tendon organs back to the central nervous system, providing feedback about muscle length, velocity, tension, and joint position. This sensory information is integrated at both spinal and supraspinal levels to modulate ongoing motor commands and correct movement errors in real time.

At a systems level, motor control can be conceptualized as the integration of two complementary mechanisms: feedforward and feedback control [108, 139]. Feedforward control generates motor commands based on the desired movement goal and learned models of body dynamics, enabling rapid execution of movement without waiting for sensory confirmation. In contrast, feedback control uses sensory information to detect and correct deviations from the intended movement trajectory.

According to the inverse dynamics model hypothesis [145, 43, 144], feedforward control may be implemented in our body via “internal models” maintained in the cerebellum, which are essentially neural representations of the motor signals/commands required to generate the desired movement. Ideally, that would mean that if the desired trajectory is input to the internal model, the signals generated from it would lead to actual movement that is close to the desired trajectory. Simultaneously, forward models, which are paired with the inverse models and receive an efference copy of the generated motor commands, predict the expected sensory feedback. This prediction allows the system to anticipate movement outcomes, bypassing the delay caused by sensory information processing, which is particularly critical for rapid, coordinated movements. These internal models are hypothesized to reside

in cerebellar circuits, which interface with cortical motor planning areas to refine motor commands.

In parallel, the motor cortex and supplementary motor area integrate information from the internal model system to generate motor commands that descend through the corticospinal tract to spinal motor neurons, ultimately producing muscle activation and movement. Once movement is initiated, sensory feedback from proprioceptors is compared against the forward model’s predictions, and any mismatch between predicted and actual sensory feedback is used to update motor commands, completing the sensorimotor control loop.

2.3 The dorsiflexion control model

Inspired by the motor control theories, we developed a nonlinear computational model (see Fig. 2.1), focusing specifically on ankle dorsiflexion motor control, that captures the essential interactions between central motor areas (supplementary motor area: SMA and primary motor cortex: M1), spinal motor neurons, the tibialis anterior muscle, and primary somatosensory cortex (S1). The model simplifies the complex network of neural interactions while preserving anatomically informed connectivity between these functional components. The input to the model is a high-level, volitional dorsiflexion trajectory represented as a step function. The inverse model converts this signal into a neural representation of a command that, when passed down to the end-effector, produces the desired output. Specifically, the motor cortex generates the required neural signals using information from these models and sends them down the spinal cord to the α motor neurons (MNs). The α MNs recruit the muscles to produce the force required for dorsiflexion (TA muscle), and the ankle moves with this force. Hence, the measurable outputs are tibialis anterior muscle activity, ankle joint angle trajectory, and ankle torque. The sensation produced with this movement is then fed back to the spinal cord and brain. The error signal from the actual sensation and the expected sensation estimated by the forward model, ε , is used to correct motor commands [43].

The activating projections from S1 to M1 [109, 14, 117, 28] are represented by the positive feedback. Each functional element representing a distinct neuronal population is modeled using a sigmoid activation function with population-level synaptic weights, w , that model the strength of signal transmission between components. High synaptic weights represent strong, intact connections characteristic of the healthy motor system. Stroke-induced lesions are modeled by reducing these synaptic weights, effectively weakening specific pathways and reproducing clinically observed functional deficits. Conversely, rehabilitation-induced recovery can be represented as increases in these weights toward values observed in the uninjured system, reflecting potential mechanisms of neural repair and reorganization.

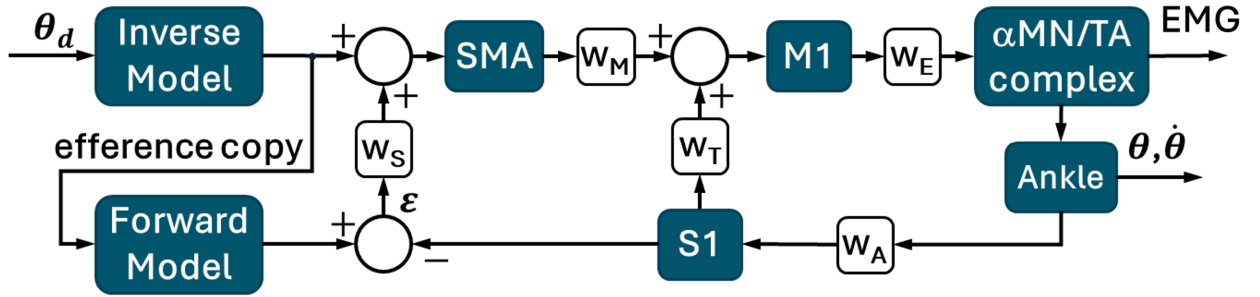


Figure 2.1: Simplified diagram of ankle dorsiflexion within the sensorimotor loop. SMA: supplementary motor area, M1: primary motor cortex, α MN: alpha motor neuron, TA: tibialis anterior muscle, S1: primary sensory cortex, EMG: electromyogram. The input to the Inverse Model is a desired dorsiflexion angle, θ_d , and its output is a neural representation of this intention. The input to the Forward Model is the efference copy, and its output is the sensory consequence of this intention. The error signal, ε , is the sensory representation of the discrepancy between θ_d and the dorsiflexion angle θ . It is added to the feedforward path to correct motor commands. The “synaptic” weights, w , are coupling coefficients between different elements.

2.4 Simulink implementation

To quantitatively test model predictions about impairment mechanisms and rehabilitation targets, we implemented the dorsiflexion control model from Fig. 2.1 in a simulation environment that enables systematic manipulation of pathway-specific parameters (see Fig. 2.2).

The control model was implemented in MATLAB Simulink 2024b (The MathWorks Inc., Natick, MA).

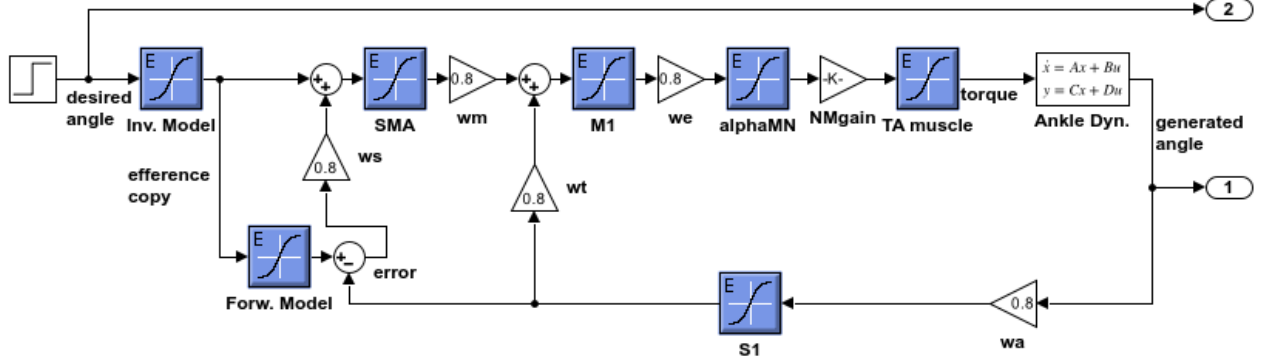


Figure 2.2: Simulink Implementation of motor control model. This representation transforms the motor control model presented in Fig. 2.1 by replacing the functional elements with a sigmoid activation function (Elliot sigmoid Eq. 2.1). The Ankle is represented by a 2nd order dynamic system adjusted for stability. Weights are represented by tunable constants, and all the values were first chosen nominally to output an ideal condition representation of dorsiflexion action simulated as a step function.

Each functional element representing neuronal populations (SMA, M1, MN, muscle, S1) and internal models (Inverse and Forward), was modeled using a sigmoid activation function known as the Elliot sigmoid:

$$y = \left(\frac{1}{1 + |x|} \right) \quad (2.1)$$

It should be noted that our findings are independent of the choice of the sigmoid model. The function above represents a particularly simple model. The α MN/TA complex was represented by a serial connection of two Elliot sigmoids with a neuromuscular gain in between. The ankle is modeled as a second-order dynamic system with inertia (J), viscosity (B), and elasticity (K) coefficients. These values were chosen to satisfy $B^2 > 4KJ$ to avoid oscillatory responses. To simulate the ideal condition of output trajectory (θ) matching the desired trajectory (θ_d), all weights were chosen at a nominal value of 0.8, and the neuromuscular

gain was adjusted accordingly (see Fig. 2.3). This results in the output achieving a complete match to the desired trajectory as the sensorimotor loop processes the desired signal.

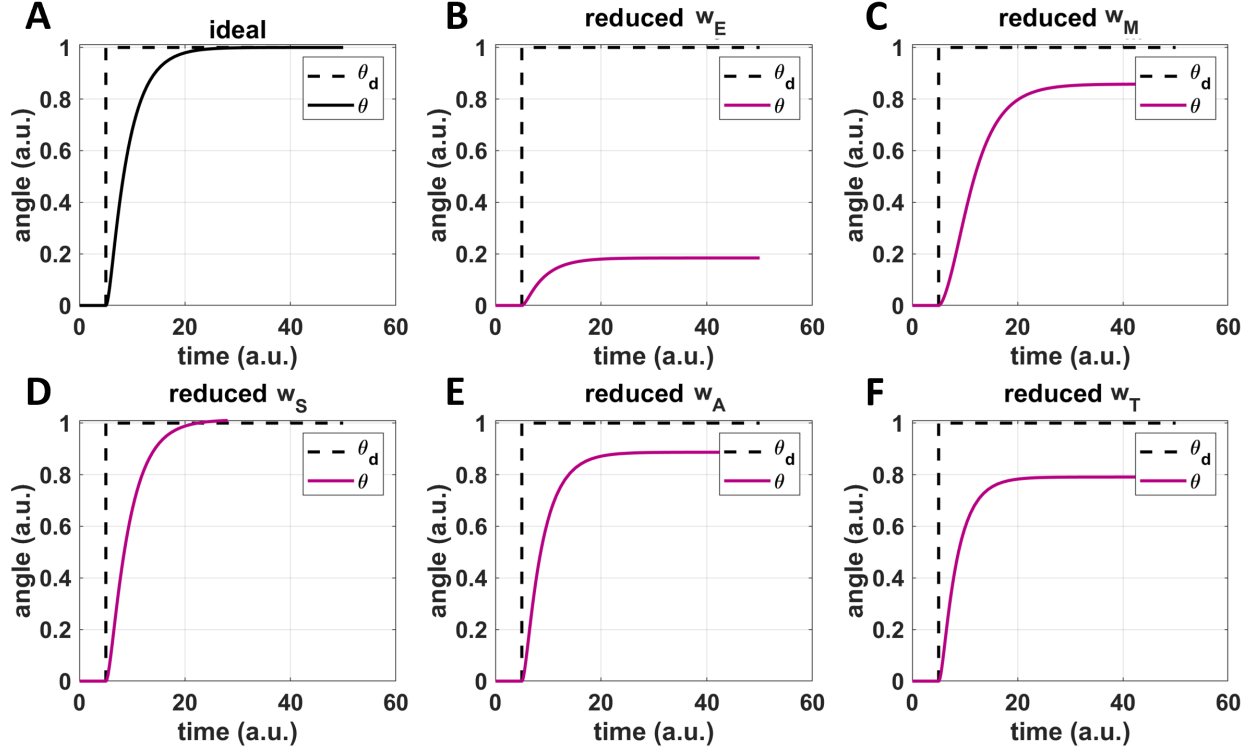


Figure 2.3: Simulation results from weight perturbations. A. Ideal condition (all weights set to nominal values representing an uninjured system). B. C. D. E. and F. Equivalent graphs when w_E , w_M , w_S , w_A , and w_T are reduced by 90% of their nominal value, respectively. These examples show that different weights affect the system differently, suggesting a greater influence of weights more proximal to the output (ankle), such as w_E .

To simulate injury within the loop, the weights can be adjusted and reduced. For example, Fig. 2.3 shows how the output, θ , is affected by reducing each weight by 90% of its nominal value. Based on these examples, weight w_E seems to have the most drastic impact on the output, followed by w_T , w_M , w_A , and w_S . To investigate the contribution of each of these parameters more formally, a local sensitivity analysis is conducted by perturbing each weight one at a time, keeping the rest of the weights at their nominal values. We quantify these dependencies by calculating the normalized sensitivity coefficient defined as $S_w^\theta = \frac{d\theta/\theta}{dw/w}$. The coefficient associated with loss of function is calculated by starting at the nominal value of 0.8 and reducing each weight by 1%, resulting in the following sensitivity coefficients:

$S_{w_E}^\theta = 0.42$, $S_{w_T}^\theta = 0.16$, $S_{w_M}^\theta = 0.11$, $S_{w_A}^\theta = 0.06$, and $S_{w_S}^\theta = -0.01$. Hence, the output is most impacted by $w_E > w_T > w_M > w_A > w_S$. Similarly, to understand the impact of each of these parameters in the context of restoration of function, we set the starting values of the parameters at 0.4 and increase the weights one by one to calculate the sensitivity coefficient. This results in sensitivity coefficient values: $S_{w_E}^\theta = 0.83$, $S_{w_T}^\theta = 0.48$, $S_{w_M}^\theta = 0.18$, $S_{w_A}^\theta = 0.14$, and $S_{w_S}^\theta = 0.02$. This implies that when it comes to restoration of function, the output is more sensitive to $w_E > w_M > w_T > w_A > w_S$. The difference in the order of sensitivity between the loss and restoration of functions highlights that rehabilitation targets may not necessarily correspond to injury targets.

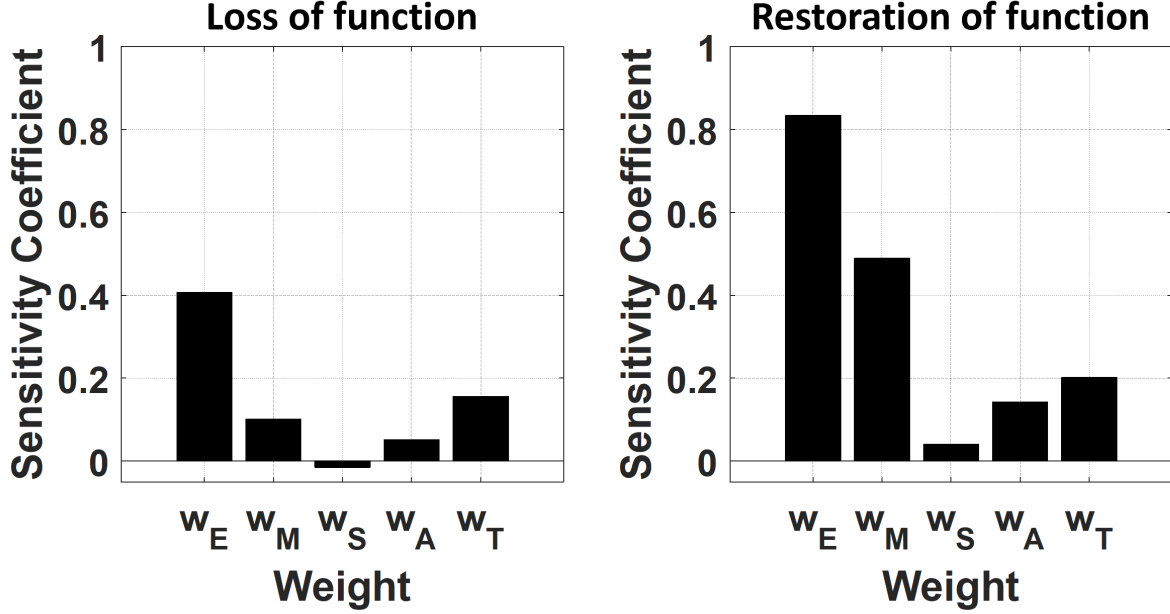


Figure 2.4: Sensitivity analysis results: loss and restoration of function. The results rank the weights by impact on output and highlight the importance of w_E (efferent weight), followed by the sensory (afferent weight), w_T for loss of function and motor cortex weight, w_M for restoration of function, respectively.

Based on this analysis, the loss and restoration of the motor output are most sensitive to changes in cortico-muscular coupling (w_E), followed by cortico-cortico coupling (w_M and w_T) and finally by sensory feedback (w_A and w_S).

2.5 Rehabilitation approaches and impact on model parameters

Based on this model and analysis, we can hypothesize the effect of different rehabilitation interventions and Hebbian plasticity mechanisms on the parameters of the model. Starting with conventional or robot-based therapy, the coincident activation of M1 and S1 would primarily strengthen the weight w_T . In interventions that are purely passive and lack voluntary drive, this coincident activation is absent, and Hebbian plasticity would not be expected. BCIs, being critically dependent on brain activity, could ensure the coactivation of M1 and S1 during interventions, provided movement intentions are accurately decoded with appropriate latencies. This co-activation may be enhanced further via BCI-driven FES, as the pulses can travel antidromically along motor nerve fibers. Hence, BCI-FES systems may have the best chance of strengthening w_E and w_T , making them a potentially superior intervention target compared with other rehabilitation mechanisms.

In summary, the computational model identified the efferent pathway weight (w_E) as the most impactful for dorsiflexion motor output and generated testable predictions about rehabilitation mechanisms. To validate these predictions and estimate model parameters using human participants data, we developed an experimental infrastructure and a parameter estimation framework described in the following chapter.

Chapter 3

Experimental Infrastructure and System Development

3.1 Motivation

To experimentally validate the insights from the computational model, we need to collect data representing the functional blocks of the sensorimotor loop (see Fig. 2.1) and quantify their interactions. This chapter describes the design of a dynamic neurophysiological assessment and the infrastructure required to collect this experimental data. We identified the neurophysiological signals and conditions under which to record them, and designed a custom robotic system, the Ankle Measuring Proprioceptive Device (version 2) or 2AMPD, that records continuous ankle movement trajectories and synchronizes with commercially available EEG and EMG recording systems. To study the sensory pathway, 2AMPD has been designed to produce passive ankle movements, thereby mimicking sensations similar to those observed during voluntary movements. Furthermore, the system enables the collection of standardized clinical measurements, including range of motion and maximum voluntary contraction, and facilitates novel proprioception assessments. Finally, 2AMPD can deliver

BCI-Robot therapy that is analogous in design to our existing BCI-FES therapy. This chapter presents an overview of the experimental design, 2AMPD system design, and BCI-Robot therapy implementation.

3.2 Experimental design requirements

From our computational modeling, we identified w_E , which adjusts/controls the connectivity from M1 to the α MNs, as a key parameter that could influence the loss of function after a stroke (see Fig. 3.1). Our sensitivity analysis also suggests that if w_E is strengthened via rehabilitation, it could maximally improve motor function output when compared to the other parameters. Therefore, this dissertation is primarily concerned with experimentally estimating, quantifying, and interpreting this parameter and the associated coupling parameters from the motor cortex and the muscle. The general nature of our approach and the breadth of the collected data permit the estimation of other parameters, which will be pursued in the subsequent studies.

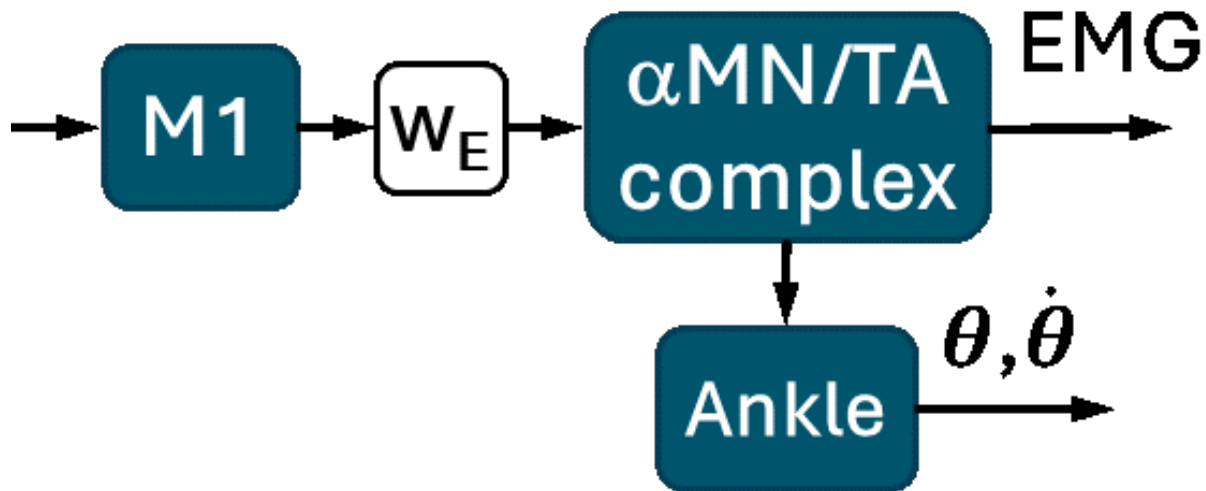


Figure 3.1: Subset of the sensorimotor loop model (Fig. 2.1) focusing on the efferent pathway of motor control.

To estimate these parameters, ideally, we would want to collect data from the M1 region corresponding to the leg or foot, tap into the α MN/TA complex, and then map the connectivity between the two functional blocks. We would also further expand this to collect ankle trajectory data to map the downstream relationship to the ankles. Given the challenges of recording data invasively, researchers have proposed noninvasive methods of characterizing these connections.

MEPs are one way to measure the corticomuscular integrity. It involves stimulating the brain using a TMS machine and recording the produced twitch. While this can simulate movement production, which can be useful in studying the impact on the descending pathways from the brain, given its external stimulation component, it may not accurately capture the essence of complete volitional motor control. Additionally, TMS can be challenging to localize and is impacted by several factors, such as the excitation threshold of competing pathways, wave characteristics, and directional sensitivity of the current [113]. Finally, MEPs may be impacted by a combination of multiple neurophysiological processes ongoing in the brain, leading to large variability in results [114].

Corticomuscular coherence (CMC) is another noninvasive measure of corticomuscular connectivity. Unlike TMS-induced MEPs, it does involve volitional movement and has been used as a functional indicator of this connectivity. CMC involves collecting EEG and EMG data during isometric contraction at a force level that does not induce fatigue. While some studies have shown a relationship between CMC and functional ability [147, 120], CMC for stroke often fails to reach statistical significance, making it an unreliable indicator that is difficult to track within the stroke population [70, 147]. Additionally, the quasi-static nature of CMC experiments challenges its applicability to dynamic conditions [115, 24].

With these observations in mind, we sought to design an experiment that maps the brain activity to muscle activity under dynamic foot/ankle movement conditions. Just like in CMC, we propose to record EEG to capture motor activity-related changes while simultaneously

recording EMG data from the TA muscle as a α MN/TA complex output surrogate. To synchronize these physiological signals with the behavior, we also propose to record ankle trajectory data, utilizing 2AMPD’s features.

Sensorimotor rhythms in EEG are observed in the form of power decreases during movement execution or motor imagery (event-related desynchronization: ERD) and rebound post-movement (event-related synchronization: ERS) [87]. Literature suggests that the magnitude of these measures may represent cortical activation [76, 88]. There is evidence that these measures increase with the increase in the level of motor engagement and output, including movement force and kinematic demands [116, 73, 2]. Additionally, these measures have been shown to be weaker in stroke than in able-bodied participants, potentially indicating stroke-related injuries impacting the ability to produce sensorimotor rhythms [15, 20, 85]. Conversely, that improvements in these measures could result in improved motor output [17, 78, 122]. On this basis, we hypothesize that ERD and ERS could be used as measures of cortical activity to quantify the strength of the cortical drive necessary to produce requisite movement.

Based on this hypothesis, we seek to quantify the characteristics of EEG, EMG, and movement trajectory signals, and model their interactions with the goal of understanding the underlying relationships. Our approach is rooted in combining statistical and biophysical modeling. Depending on the model choice, we can model the transformations cortical signals undergo as they pass through the α MN-TA-ankle cascade (Fig. 2.1), and factor out parameters, such as the putative cortico-spinal weight, w_E , and the gain of the α MN/TA complex, termed neuromuscular gain.

In summary, conducting these experiments requires the collection of synchronized neural, muscular, and kinematic data during continuous ankle movements. For this purpose, we employed the previously introduced 2AMPD custom robotic device, which could record ankle trajectories and produce synchronized time series with commercially available EEG and

EMG systems. Additionally, 2AMPD is designed to collect standardized clinical measurements, including range of motion, maximum voluntary contraction, and novel proprioception measures [35, 36]. This improved design is based on the previous version of AMPD [34] and extensive feedback from stroke survivors, physical therapists, and research personnel.

3.3 Infrastructure building

2AMPD is a multi-sensor platform robot designed to quantify ankle sensorimotor function in human participants (see Fig. 3.2). The system features bilateral foot pedals mounted on a rigid frame, enabling simultaneous or independent control of dorsiflexion and plantarflexion movements for both ankles. 2AMPD can span multiple experimental modalities, including active volitional movement, passive proprioceptive movement, and isometric force generation.

2AMPD’s mechanical design incorporates two switchable impedance states. In the zero-impedance mode, participants execute volitional ankle movements freely, enabling natural dorsiflexion-plantarflexion-related tasks. The system transitions to rigid mode for passive movement tasks, with pedals locked and controlled by integrated ACME lead screw actuators (Progressive Automations, PA-04-8-400-HS-24VDC). High-resolution angular quadrature encoder (E6B2-C, 1024 P/R) continuously records the pedal angular position, providing kinematic data. In rigid mode, tension load cells (Interface, SMA-200) measure ankle torque and capture force profiles during isometric contractions.

The 2AMPD control firmware is coded in C++ on a Teensy 4.0 microcontroller (ARM Cortex-M7, 600 MHz), implementing real-time sensor acquisition, motor control, and bidirectional communication with the host computer. The code architecture prioritizes safety through redundant “abort” mechanisms and enforces hardware limits and overrides to prevent participant injury while maintaining precise position and temporal control.

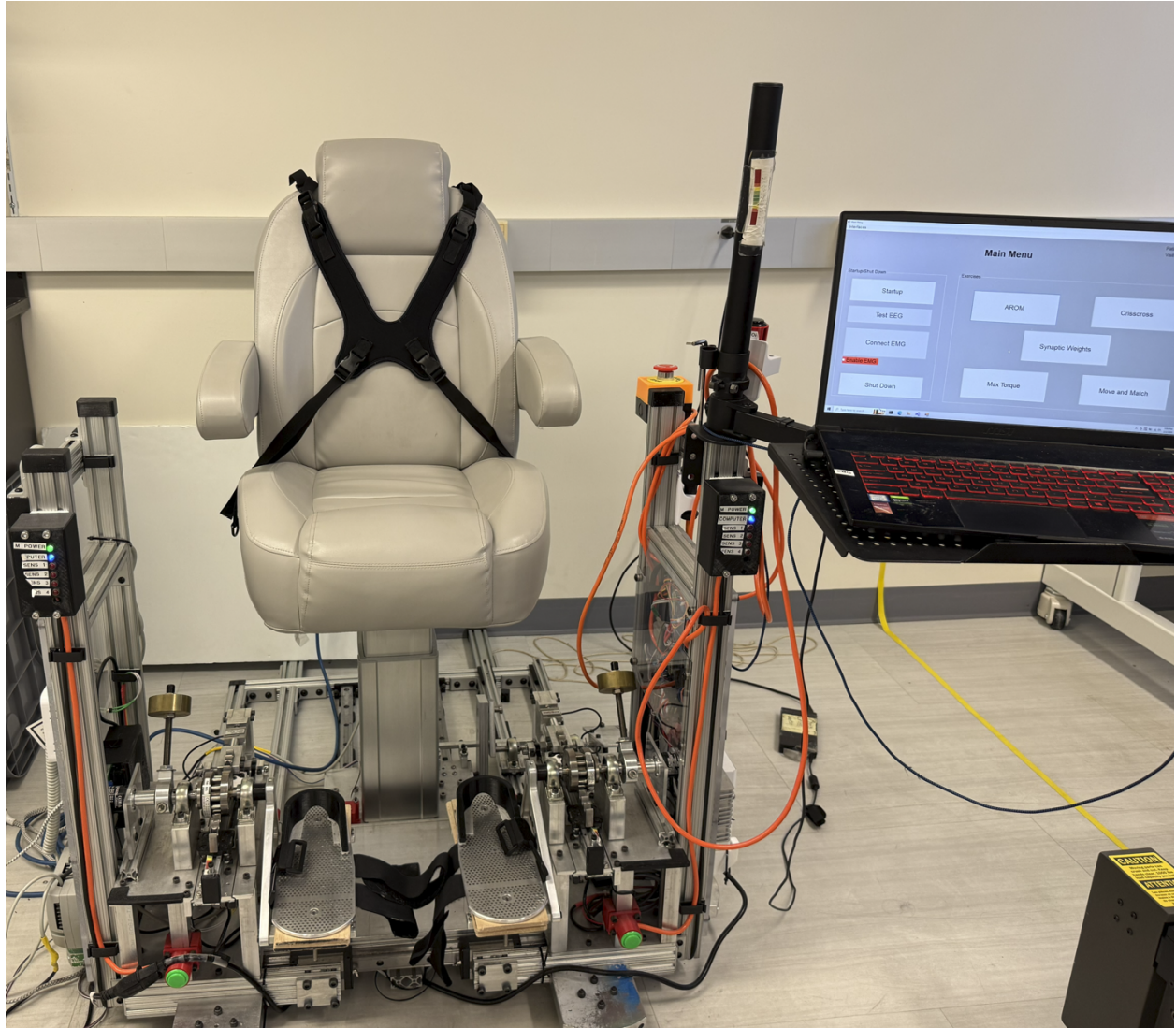


Figure 3.2: Custom-made 2AMPD [36] with the ability to record continuous ankle dorsiflexion and plantarflexion movement and synchronized with EEG and EMG data systems.

The actuators of the robot are controlled via pulse width modulation (PWM). The pedals are independently controlled to allow for different variations of movement in terms of speeds and directions. This is particularly important for the proprioception assessments, as a wide range of variable parameters can be tested with this system. The quadrature encoders provide continuous position feedback via hardware interrupt-driven polling. Encoder readings are sampled asynchronously, preventing data loss during blocking operations. There is a calibration routine performed at startup to establish zero position references.

Dual independent velocity-controlled PID controllers are implemented for smooth movement and velocity regulation. A proportional-only configuration is implemented ($K_p = 2.5$) and can adequately provide velocity tracking for passive movement protocols. The control loops execute at 20 Hz with output limits of ± 20 PWM units per cycle to prevent abrupt accelerations and jerky movements. This velocity-based approach enables direct implementation of the desired speed rather than the target position. A minimum PWM threshold (30) ensures sufficient torque to overcome resistance. An initial “boost” parameter (30-75, depending on direction and load) is set to provide additional starting torque given the limited workspace and decays once the desired speed is achieved.

The main control loop is a character-based command structure that communicates with the custom computer graphical user interface (GUI). Single-set character commands correspond to different functions and assessment tests that are hard-coded into the system, with potentially variable parameters. These include calibration tests, biomechanical tests, proprioception assessment tests, and even rehabilitation implementation. Additional parameters to adjust the chosen function are communicated from the GUI as a string of characters, parsed in the order received.

2AMPD transmits tab-delimited sensor packets at a 200Hz sampling rate with the following information: encoder values, load cell values, sensitivity levels, PWM, speed, motor states, participant button state, time, TTL sync pulse, slide positions, TTL stop pulse, and

proprioception assessment information and event-related flags. The TTL pulse is used to synchronize to peripheral devices like commercial EEG and EMG recording systems.

Additionally, a multi-layer safety architecture is implemented via four independent mechanisms. The first is the physical EMERGENCY stop button that triggers an interrupt service routine to safely back out of the current robot state to a known safe state. To avoid false positives, the button’s rising edge is combined with a debounce routine to determine a true call. A physical operator button is also used in conjunction with this system as an override function, allowing the operator to press the button to cancel the current state and return to the main loop safely. This cancel or override button can also be operated from the GUI, serving as the third safety mechanism. Finally, unplugging the USB connector between the robot and the computer automatically powers off the controllers and shuts down the operation. Operators or participants can use any of these mechanisms based on their preference, proximity, or reaction tendency.

3.4 BCI implementation

To implement a BCI-Robot rehabilitation protocol analogous to our BCI-FES intervention [5], we use the same BCI system and connect it to 2AMPD. 2AMPD takes binary input to either switch on or off, and translates this command into passive assistive robotic ankle movements for stroke rehabilitation. Specifically, when the BCI decoder [13] detects motor execution and/or intent from EEG signals, the system initiates the movement of the corresponding side pedal to dorsiflexion. The pedal trajectory is controlled using PID-controlled motor commands with real-time encoder position feedback, with the movement continuing until the ankle reaches the prescribed target, while monitoring the **Abort** flag for safety violations. Conversely, when the BCI decoder detects the lack of motor execution and/or intent, the function returns the pedal to neutral position (0°), creating a closed-loop paradigm where the robot amplifies volitional effort detected through EEG signals. This conditional

control structure enables participants to perform passively enhanced ankle movements with coincident neural control even when neuromuscular pathways are severely impaired. A more detailed description of this experimental paradigm can be found in [18, 65].

2AMPD is designed to perform clinical and biomechanical assessments like Active Range of Motion (AROM), Maximum Voluntary Contraction (MVC), Novel Proprioception Assessments [35, 36], BCI-Robotic Rehabilitation Intervention, and the novel dynamic Neurophysiological Assessment to estimate neuromuscular connectivity.

3.5 Experimental protocol

With our experimental setup meeting the requirements for conducting our novel neurophysiological assessment during dynamic (movement) conditions, we now turn to the design of an experimental paradigm to elicit measurable biomarkers. While there are several options for designing motor-related tasks to achieve this goal, a repetitive active dorsiflexion task was chosen to capture known volitional movement-related EEG features, such as ERD and ERS, muscle activity (EMG), and kinematics (ankle trajectory). To enhance proprioception and discourage reliance on visual feedback, a non-transparent board was placed over the participants' knees to occlude the view of their feet.

The paradigm was designed as a series of trials consisting of alternating relaxation and movement periods, as shown in Fig. 3.3. Each trial consisted of 5 states: Relax (baseline reference period), Slow (slow dorsiflexion movements), Relax (post-slow movement period to capture relaxation state after movement), Fast (fast dorsiflexion movements), and Relax (post-fast movement relaxation state), followed by a break lasting 10-20 seconds. In order to prevent prediction of movement cues, random short periods ranging from 0.5 to 2 seconds were incorporated into the baseline and post-slow Relax states. The repetitive slow and fast dorsiflexion movements were self-paced. For the Slow state, participants were directed to

perform slow, controlled movements, whereas for the Fast state, they were directed to move as fast as possible, producing a more ballistic movement. We designed the task to be analogous to repeated hand grasping, an upper-extremity motor ERD generation protocol [46, 146]. For both movement states, they were given specific instructions to try to traverse their entire dorsiflexion movement range. The post-movement relax states were introduced to capture ERS associated with cessation of movement. During these Relax states, the participants were directed to relax with their feet on the 2AMPD pedals at a neutral position (parallel to the ground). A stool was used to support the pedals and maintain the neutral position. This design was hypothesized to capture the modulation of the brain, muscle, and ankle activity during and after movement.

This dissertation uses data-driven mathematical modeling and parameterization to quantify and understand the nature of the relationship between the motor cortex, the TA muscle, and the ankle. This framework can be further extended to estimate other parameters in other pathways, like sensory (ankle - cortical connectivity), and cortico-cortical connectivity. In the following chapters, we use this framework to estimate this relationship in able-bodied and stroke participants as they go through 4 weeks of BCI-based rehabilitation.

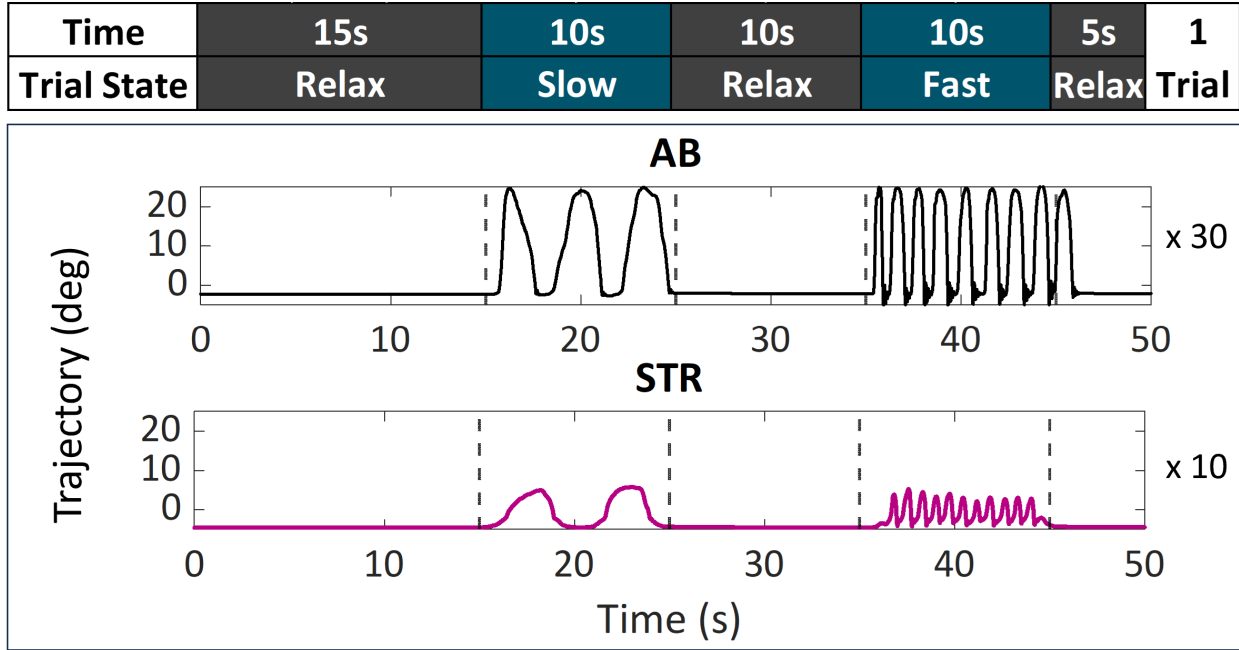


Figure 3.3: Experimental protocol used for dynamic neurophysiological assessment. The timeline shows a single experimental trial lasting ≈ 50 s. The able-bodied group and those with stroke performed respectively 30 and 10 trials, with a 10-20 s inter-trial break. Each trial begins with a no-movement (Relax) state to establish an EEG baseline. Next, the participants repetitively dorsiflexed their ankles at a self-selected slow pace (Slow). The traces show the ankle trajectories for two representative subjects from the AB and STR groups. This is followed by another no-movement period (Relax) to elicit a post-movement ERS. The participants then repetitively dorsiflexed their ankles at a fast pace (Fast), followed by another no-movement period (Relax). The state transitions were guided by computer-controlled visual cues.

Chapter 4

Baseline Study Experimental Methodology: Able-Bodied Participants

To estimate the baseline parameter values of our model, we first need to collect data from able-bodied (AB) participants. This chapter describes the recruitment and study design for this population.

4.1 Recruitment

The study was approved by the University of California, Irvine Institutional Review Board (IRB #20086432), and written informed consent was obtained from the subjects. The inclusion criteria for AB group included: 1) Age from 18 - 35, 2) No history of neurological conditions, 3) No history of gait impairments or musculoskeletal damage to ankles. The dominant side was determined by their preferred foot to kick a soccer ball.

4.2 Experimental protocol and setup

To collect experimental data for baseline estimation, the participants went through a series of biomechanical and neurophysiological assessments. The participants were seated on 2AMPD and commercial EEG, and EMG recording systems were connected for synchronized data collection as shown in Fig. 4.1. An LED display showing visual cues to guide task execution was positioned at the eye level of the participants, at a 3–4 ft distance. A 64-channel actively shielded EEG cap (Waveguard Original, ANT Neuro B.V., Hengelo, The Netherlands) with Ag/AgCl electrodes arranged according to the 10–20 international system was placed on the participants’ head, ensuring Cz was centered and electrodes were in the correct positions. A subset of 25 channels centered around Cz were gelled (SuperVisc, Brain Vision LLC, Morrisville, NC, USA) and prepared for data collection, comprising: Cz, F3, F1, Fz, F2, F4, FC3, FC1, FCz, FC2, FC4, C3, C1, Cz, C2, C4, CP3, CP1, CPz, CP2, CP4, P3, P1, Pz, P2, P4. To aid ocular artifact detection, 3 frontal electrodes (Fp1, Fpz, and Fp2) were included. A blunt needle was used to reduce the electrode-to-skin impedance by gentle abrasion of the scalp. An impedance measurement device was used to ensure the impedances were at values $< 10\text{ k}\Omega$ at 30 Hz. The cap was connected to two linked 32-channel bioamplifiers (NeXus-32, Mind Media, Roermond-Herten, The Netherlands) for data collection. The bioamplifiers band-pass filtered the recorded signals from 0.01 Hz to 50 Hz and sampled them at 256 Hz with a 22-bit resolution. A wireless surface EMG recording system (FREEEMG 1000, BTS Bioengineering, Milan, Italy) was used to collect EMG signals via self-adhesive EMG electrodes (3M™ Red Dot™, 2560, 3M Company, St. Paul, MN, USA) placed bilaterally over the TA muscle belly. The skin area for electrode placement was thoroughly cleansed with 70% isopropyl alcohol pads to reduce impedance, and the positioning was standardized by locating the TA belly during attempted dorsiflexion.

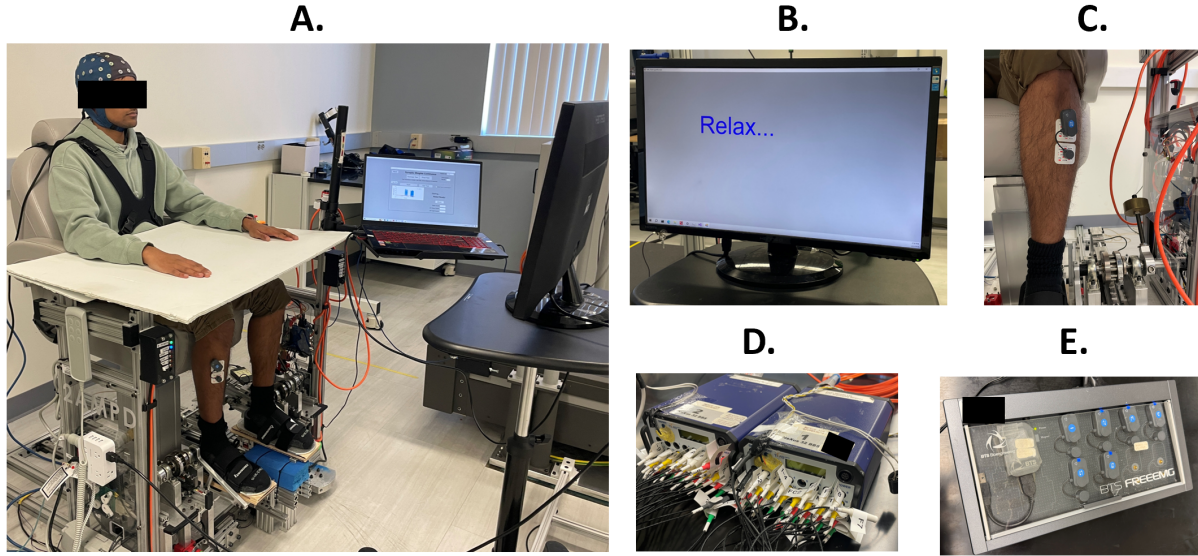


Figure 4.1: A: Experimental setup with the subject seated in the 2AMPD while donning the EEG cap and facing the LED display. B: LED display showing a visual cue. C: EMG electrode placement over the TA muscle. D: EEG amplifiers. E: FREEEMG 1000 wireless surface EMG system.

4.3 Assessments

Participants underwent biomechanical assessments with 2AMPD, including Active Range of Motion (AROM) and Maximum Voluntary Contraction (MVC) measurements. To obtain more reliable estimates, the assessments were repeated twice. EMG data were also recorded with the kinematic data for these assessments. For AROM, 2AMPD was in the 0-impedance state, with the starting position being the natural plantarflexed hanging of the foot. For MVC, 2AMPD was in the rigid state, allowing for force measurements that are later converted to torque following our previous protocol. All measurements were conducted bilaterally. To study the neurophysiological signals during ankle dorsiflexion movements, the AB group completed 30 trials of the assessment framework developed in Chapter 3 (see Fig. 3.3).

Additionally, a CMC estimation task was designed following a similar paradigm, where the participants contracted their ankle at 2 force levels, 30% MVC and 60% MVC, in place of the repeated dorsiflexion movements. Participants received visual feedback on the screen

showing both the target and their real-time torque output as a percentage of their maximum dorsiflexion torque during MVC. They were instructed to maintain the force level to the best of their ability throughout the trial state. A total of 15 trials were completed in this experiment.

Chapter 5

Rehabilitation Study Experimental Methodology: Chronic Stroke Participants

5.1 Recruitment

For this study, we recruited people with chronic stroke-related foot-drop (referred to as the STR group) to undergo 4 weeks of rehabilitation intervention. The study was approved by the local ethics committee (UCI IRB#20194936). The participants underwent screening and baseline visits that included several assessments to ensure their eligibility for the study. Those who qualified were consented to participate in the study. The inclusion criteria were as follows:

1. Age 18–80 years (inclusive) at the time of consent
2. Stroke, ischemic or intracerebral hemorrhagic (ICH) confirmed radiologically, with on-set date at least 26 weeks prior to day of randomization

3. Gait Velocity <0.8 m/s at both visits
4. Dorsiflexion Active Range of Motion (AROM) $<15^\circ$ (as measured by goniometer with feet dangling) and less than Passive Range of Motion (PROM)
5. Dorsiflexion PROM $\geq 0^\circ$ in subtalar neutral or with FES
6. Plantarflexors Spasticity (as measured by Modified Ashworth Scale) <3
7. Able to walk >10 m with supervision, and with or without AFO (cane or walkers permitted)
8. Can tolerate FES with pain <4 on the analog pain scale and produce muscle response $\geq 10^\circ$

5.2 Study design

The study was designed as a two-arm, parallel-group, assessor-blinded randomized clinical trial with 10 STR participants (see Fig. 5.1). Participants first underwent an initial phone screen, followed by informed consent to proceed with a screening visit. Once eligibility was confirmed based on all inclusion and exclusion criteria, participants provided a second informed consent and completed a baseline (BL) visit. Participants were then randomized into one of two intervention groups, stratified by age (≥ 65 or <65), gait speed ($0.40 - 0.80$ m/s and <0.40 m/s), after re-confirming that inclusion and exclusion criteria were still met.

Following the BL visit, participants began their assigned rehabilitation program. A weekly assessment was conducted on the first day of each intervention week throughout the 4-week BCI-based therapy period. Upon completion of the intervention, participants returned for a post-therapy visit (PT), 2 – 3 days after their final therapy session, followed by two additional follow-up visits at 1 month (1M) and 3 months (3M) post-intervention.

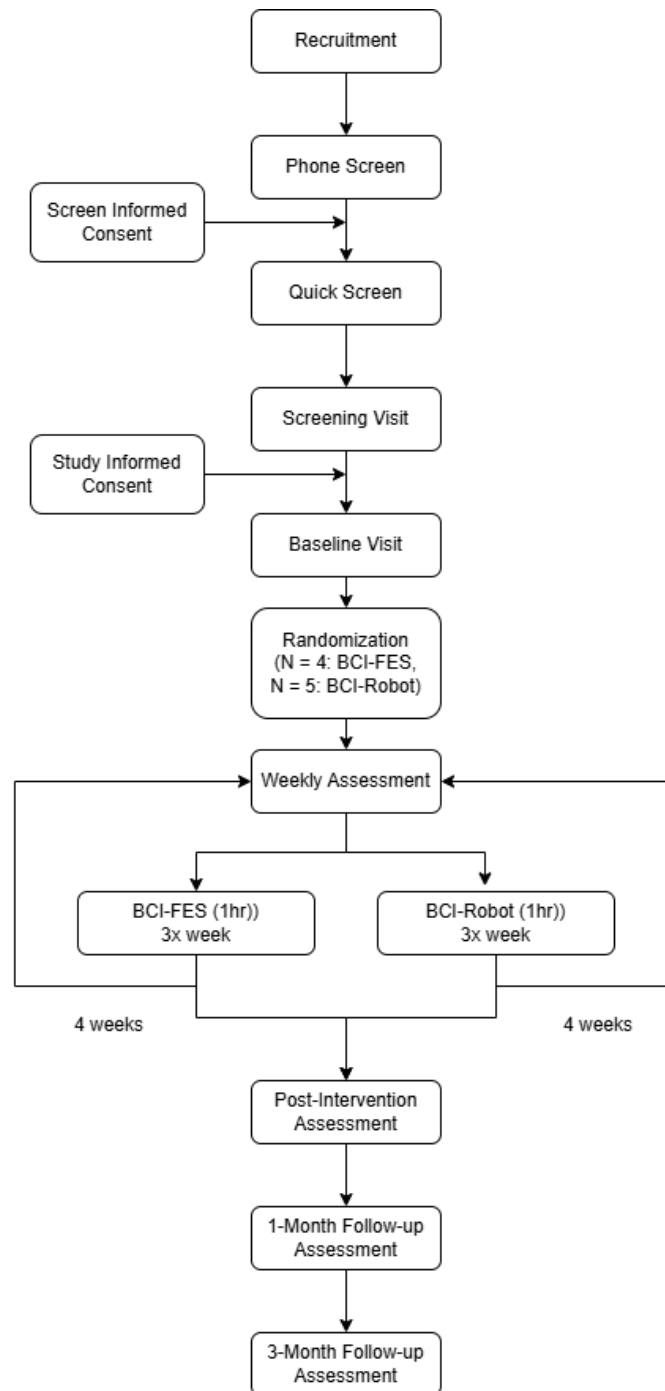


Figure 5.1: Design for BCI-FES and BCI-Robot Intervention study

5.3 Intervention

All participants were scheduled to receive 12 intervention sessions delivered 3 times per week over 4 weeks. Participants were requested to suspend any concurrent external therapy focused on the leg or walking until the 1M follow-up visit.

Participants were randomized to receive either BCI-FES or BCI-robotic therapy. Both interventions shared a common BCI unit consisting of a custom 8-channel EEG-based system capable of detecting movement execution in real time. At the start of each session, participants were seated on AMPD and fitted with a 64-channel EEG cap following the 10-20 system, with the 8 channels at and surrounding the Cz electrode gelled to capture EEG activity relevant to ankle dorsiflexion.

The BCI decoder was trained at the beginning of each session by recording 3 minutes of EEG data during alternating epochs of attempted or executed dorsiflexion and idling, which were used to build a personalized classification model. Once trained, the appropriate assistive device was connected depending on the group assignment. For the BCI-FES group, stimulation pads were placed over the shin of the affected leg to elicit peroneal nerve stimulation and subsequent tibialis anterior activation, with stimulation frequency and current adjusted to produce approximately 10 degrees of dorsiflexion. For the BCI-Robotic group, the affected ankle was strapped to the 2AMPD pedal with loosened straps to allow volitional movement, and the robot was configured to deliver a passive 10-degree dorsiflexion boost upon BCI decoding a dorsiflexion attempt from EEG data.

The main intervention consisted of 5-minute blocks, each comprising alternating 10-second epochs of idle and attempted dorsiflexion, as cued by computer-generated visual instructions. When the BCI system decoded a dorsiflexion state from the EEG signals, the assigned assistive device was activated, delivering either electrical stimulation or a passive dorsiflexion

boost in a closed-loop manner. Each 5-minute block was repeated 6 to 10 times with rest breaks between blocks, providing approximately 1 hour of total intervention per session.

5.4 Assessments

All participants underwent a series of assessments to characterize their ankle movement ability at each study visit. The screening visit included a more extensive battery of measures to confirm inclusion and exclusion criteria compatibility. Subsequent visits, including BL, weekly, PT, 1M, and 3M assessments, were condensed due to time constraints while retaining the primary outcome measures. Although additional clinical assessments were administered by trained physical therapists at select visits (refer Table 5.1), the present work focuses on results from the gait speed assessment, robot-based biomechanical assessments, and the dynamic neurophysiological tests.

Table 5.1: Visits and Assessments: Screening (Screen), Baseline (BL), Weekly 1-4 (Wk 1-4), Post Test (PT), 1 Month (1M), 3 Month (3M) visits

Visit	Screen	BL	Wk 1	Wk 2	Wk 3	Wk 4	PT	1M	3M
Consent (10 min)	X	X							
Medical History (20 min)	X								
Blood Pressure (5 min)	X	X	X	X	X	X	X	X	X
Montreal Cognitive Assessment (10 min)	X								
NIH Stroke Scale: language and inattention (2 min)	X								
Mod Ashworth Scale (3 min)	X								
Geriatric Depression Scale	X								
Gait Velocity (with/without AFO as needed) (5 min)	X	X	X	X	X	X	X	X	X
Fall frequency (1 min)	X	X	X	X	X	X	X	X	X
Dorsiflexion ROM (2 min)	X	X	X	X	X	X	X	X	X
DF/PF Manual Muscle Test (5 min)	X	X	X	X	X	X	X	X	X
Dynamic Neurophysiological Assessment (30-60 min)		X	X	X	X	X	X	X	X
FES Tolerance (5 min)	X								
Robot Assessments (Max Torque/AROM) (15 min)		X	X	X	X	X	X	X	X

Chapter 6

Data Analysis and Signal Processing

The entire data processing pipeline was implemented using custom scripts in MATLAB R2024b (The MathWorks, Inc., Natick, MA, USA).

6.1 Biomechanical assessments

For AROM and MVC assessments, trajectory and kinematic information were derived from 2AMPD encoder data. The load-sensor force data were used to estimate the torque during MVC using the method described in Johnson et al. [36]. A low-pass filter with a cutoff frequency of 5Hz was used to remove any high-frequency noise. For AROM assessments, the dorsiflexion and plantarflexion maximum positions were obtained by searching for a 1-s window with the highest mean value in the corresponding trajectory data. Similarly, the MVC maximum torque was estimated from a 1-s window with the highest mean in the load sensor data. An average was taken over all trials to obtain the final value.

The EMG data were preprocessed to obtain the EMG rectified envelope. First, a notch filter at 60Hz was applied, followed by a 4th-order, 20Hz high-pass, zero-phase-shift Butterworth filter. The signal was then rectified, and a 4th-order, 5Hz low-pass, zero-phase-shift Butter-

worth filter was used to remove high-frequency components and obtain the envelope. The EMG value for each trial was estimated as the average over a 1-s window identified in the 2AMPD data, and the final value was taken as the average across all trials.

6.2 Neurophysiological assessments

6.2.1 Trajectory and kinematics feature extraction

For the dynamic experiment, position and speed features were obtained from the preprocessed trajectory data. A peak-detection algorithm (see Appendix A) was implemented to determine the peak position and velocity for each dorsiflexion movement. The instantaneous speed was calculated as the derivative of the trajectory during each movement. These peak values within a single trial were averaged to obtain the trial-wise features. For the Relax trial-states, the trial-wise features for both the position and velocity were simply estimated as the average values of the position and velocity over the state, as there were no movement peaks to detect.

6.2.2 EMG preprocessing and feature extraction

For the trial-wise features of the dynamic experiment, the EMG envelopes were preprocessed in the same way as the biomechanical assessments. A peak detector algorithm was used to find peak values corresponding to individual dorsiflexion movements within a trial state, and the results were averaged to obtain the mean EMG peak value. Since there were no peaks in the Relax trial states, the EMG was averaged over the entire period.

6.2.3 EEG preprocessing and artifact rejection

The raw EEG signals were preprocessed to enhance signal quality and reduce artifacts. A 60-Hz notch filter was applied, and the signals were further band-pass filtered between 0.1 Hz

and 50 Hz using a 4th-order zero-phase-shift Butterworth filter. After filtering, all trials were concatenated to form a continuous dataset. Independent Component Analysis (ICA) was performed using the “runica” algorithm implemented in the EEGLAB toolbox, and artifacts related to eye blinks, eye movements, and muscle activity were identified and removed. Any disconnected channels were also removed from the dataset. Finally, a surface Laplacian (spherical spline) filter was implemented to improve the spatial resolution and topographical localization of EEG features.

For the EEG data analysis, all trial states were divided into 1-s long epochs, and ankle trajectory data were used to ensure that the features reflected movement execution and not just visual cues. The features were further optimized by choosing the source electrode and finding personalized frequency bands corresponding to ERD and ERS activity within the 8Hz to 30Hz ranges corresponding to μ and β bands (see Appendix A).

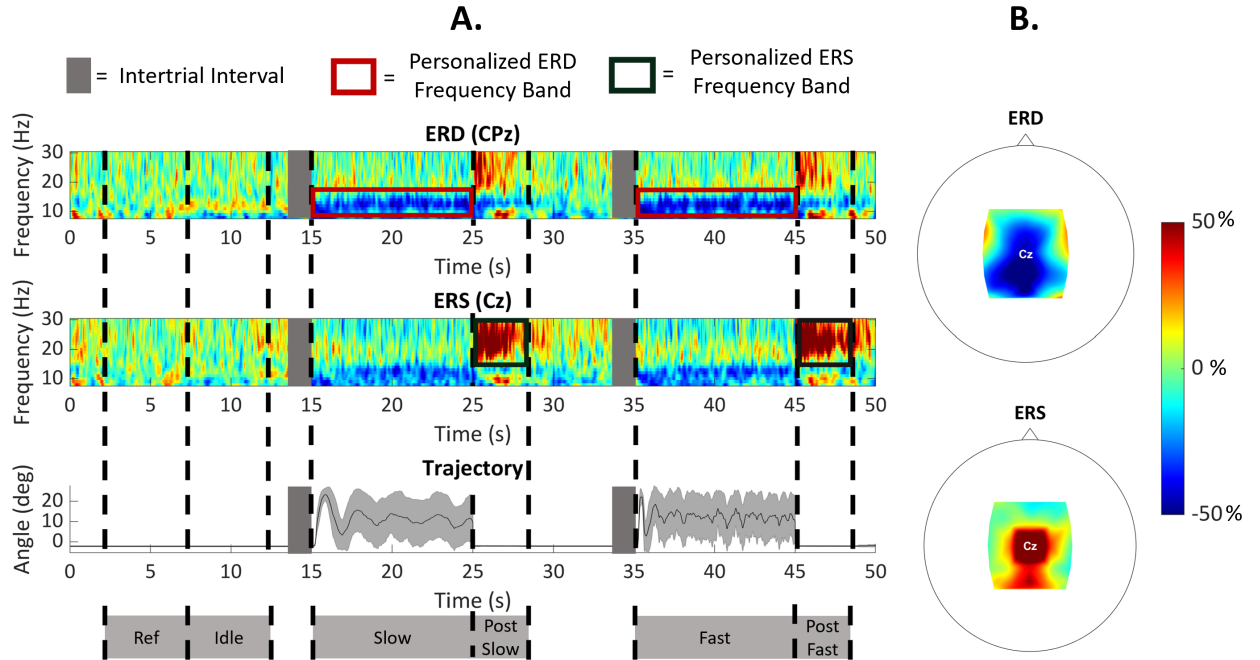


Figure 6.1: ERD and ERS estimation. A. Time-frequency plot of average EEG power changes and average ankle trajectory in the dynamic neurophysiological task for participant AB1, averaged over 30 trials, with movement-execution starts aligned. B. Topoplot representation of average power changes during movement execution, resulting in ERD (top) and post movement resynchronization, resulting in ERS (bottom).

The choice of subject personalized bands is practiced and recommended in literature, where task-specific, subject-specific, and body part-specific changes are reflected in the frequency representations of ERD and ERS [87],[75]. We observed the same trend with our data (shown in Fig. 6.1). Power spectral density (PSD) was computed for 1-s epochs. Signal power was computed in the chosen frequency band for each epoch and averaged over epochs for each trial in each trial state. Trial-wise ERD and ERS features were quantified as the percentage change of the averaged signal power from the baseline average.

6.2.4 Mapping of neurophysiological features and parameter estimation

To study the EEG-EMG relationship, trial-wise EEG and EMG features were extracted across Slow, Fast, and Post Movement periods. EEG features (ERD and ERS) were mapped against each other with EEG as the independent variable and EMG as the dependent variable. To ensure a positive-to-positive mapping (consistent with the sigmoid model), EEG features were sign-negated prior to model fitting, reflecting ERD, now positive, corresponding to movement onset, and ERS, now negative, corresponding to movement cessation. This mapping was subsequently extended to investigate the EEG-dorsiflexion position relationship.

To quantify these relationships as a measure of their coupling strength, a systematic model search was conducted to identify the most appropriate functional form that could fit this data. Given that the goal was to model the input-output relationship between neural populations, candidate models were drawn from those commonly used as activation functions in artificial neural networks: Sigmoid, Logistic, ReLU, and Exponential, with a Linear model included as a baseline comparator.

The two-parameter forms of these models were implemented as follows:

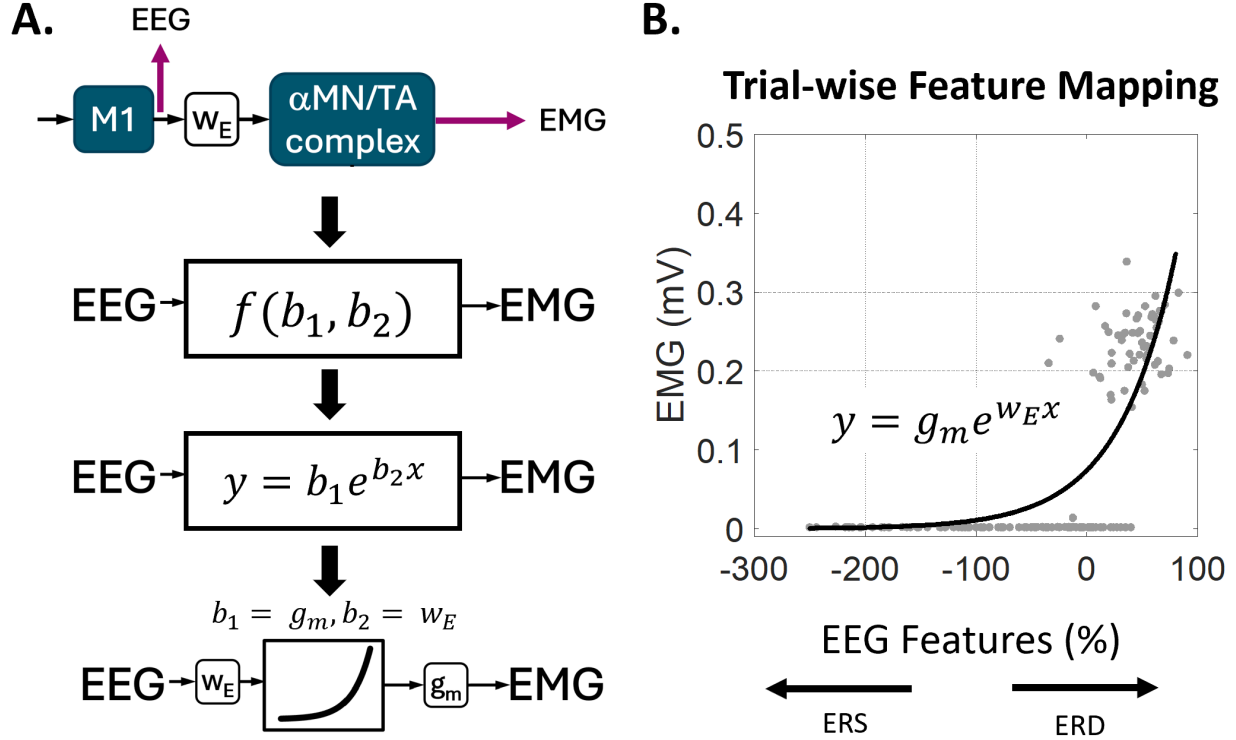


Figure 6.2: Modeling the functional relationship between EEG and EMG features. A. Model selection flowchart. The original model was adapted to use EEG and EMG features to represent cortical activation and resulting α MN/TA complex activity. A candidate model search was conducted among several 2-parameter nonlinear models, resulting in the final choice of the exponential model, with the two parameters representing neuromuscular gain (g_m) and neuromuscular coupling weight (w_E). B. Example of EEG-EMG feature mapping and subsequent modeling for one participant: A1, with $g_m = 0.07$ and $w_E = 0.02$.

$$\text{Sigmoid } y = \frac{b_1 x}{1 + b_2 |x|} + b_1$$

$$\text{Logistic } y = \frac{b_1}{1 + e^{b_2 x}}$$

$$\text{ReLU } y = \max(b_1 + b_2 x, 0)$$

$$\text{Exponential } y = b_1 e^{b_2 x}$$

$$\text{Linear } y = b_1 + b_2 x$$

Each candidate model was fit to the data using nonlinear least squares estimation, and the model performance was evaluated using the Akaike Information Criterion (AIC) and coefficient of determination (R^2). AIC was used as the primary selection criterion to penalize model complexity and prevent severe overfitting, with R^2 used as a secondary measure of goodness of fit. For each candidate model, parameter significance was assessed, and models with non-significant parameters were rejected in the selection process. The Logistic and Sigmoid models, despite being the expected best candidates, were rejected as they produced AIC values exceeding those of competing models by over 1000 points in several cases, and consistently yielded non-significant parameter estimates. The Linear model produced comparatively lower AIC values but demonstrated poor R^2 fit, indicating an inadequate characterization of the underlying relationship, specifically the post-movement and ERS mapping. The ReLU and Exponential models offered the best balance between model complexity and goodness of fit, achieving the lowest AIC values alongside acceptable R^2 values. The Exponential model (Eg. 6.1) was ultimately selected over ReLU as it allowed for parameter factorization into interpretable components, with a weight parameter represented by w_E as the coefficient of x (b_2), that scales the EEG features, and a gain parameter g_m , that scales the output (b_1), hypothesized to represent the weight and gain of the neuromuscular connection, respectively. A final model selection step was implemented at the individual fit level, where the Exponential model was compared against a constant model ($y = g_m$) based on

AIC and parameter significance, to determine the most appropriate representation for each observation.

$$\text{EMG} = \begin{cases} g_m e^{w_E \text{EEG}} \\ g_m \end{cases} \quad (6.1)$$

6.3 CMC calculation

For the CMC task, EEG data were preprocessed as described in Section 6.2.3. Each trial for the Low Force (0-10s of 30% MVC state) and High Force (0-10s of 60% MVC state) conditions was divided into 1-s-long epochs and stitched. EMG data were notch-filtered at 60Hz, segmented to match the EEG epochs, and then downsampled to 256Hz to align with the EEG sampling frequency. Corticomuscular coherence was calculated using magnitude-squared coherence with a window length of 1-s, 0 overlap, and sampling frequency of 256 Hz. The dynamic task data for both the AB and STR datasets, with slow and fast movements rather than static % MVC states, were processed similarly to estimate dynamic CMC for comparison. For all CMC calculations, the number of epochs was limited to the first 100 to maintain uniformity. The 95% confidence interval was calculated based on this using the formula 6.2 with $\alpha = 0.95$ and $N = 100$:

$$CI = 1 - (1 - \alpha)^{\frac{1}{N-1}} \quad (6.2)$$

6.4 Statistical analysis

Statistical analyses were conducted in MATLAB 2024b. Two primary datasets were analyzed: first, the AROM and MVC dorsiflexion data collected from AMPD, including max-

imum dorsiflexion positions, torque, and TA EMG; and second, the dynamic experiment data, including EEG, EMG, and AMPD signals.

Prior to statistical testing, Shapiro-Wilk tests and QQ plots were used to assess normality of all datasets. If normality was not rejected, Welch’s two-sample t-test was applied for unpaired comparisons between the STR and AB groups, or a paired t-test for comparisons of different conditions within groups or between timepoints within the STR group, reporting the p-value and Cohen’s d. If normality was rejected, non-parametric equivalents were used: the Wilcoxon rank-sum test for unpaired data and the Wilcoxon signed-rank test for paired data, reporting the p-value and effect size r. Descriptive statistics were reported as mean and standard deviation (SD) for normally distributed data, and median and interquartile range (IQR) for non-normal data. To account for multiple comparisons, the Benjamini-Hochberg correction was applied to all p-values.

For the EEG data, personalized frequency bands and source channel locations were also investigated for group-level differences between STR and AB participants. Frequency bands were classified as μ -dominant (8–12 Hz), β -dominant (13–30 Hz), or mixed based on the proportion of each participant’s band overlapping with canonical μ and β ranges, and chi-square tests of independence were applied to contingency tables of group by band class for ERD and ERS separately. Band midpoints were additionally compared between groups using a Wilcoxon rank-sum test. For source channel analysis, the channel exhibiting the strongest ERD and the channel exhibiting the strongest ERS were identified for each participant. The frequency of selection for each channel was tallied separately for STR and AB participants, and chi-square tests of independence were applied to contingency tables of group by channel for ERD and ERS, respectively, to determine whether the spatial distribution of dominant source channels differed between groups.

To assess the consistency between the EEG–EMG and EEG–Dorsiflexion Position modeling frameworks, linear regressions were performed between corresponding parameter pairs (w_E

vs. w and g_m vs. g) across all participants. Additionally, linear regressions were performed between each parameter (w_E , g_m , w , g) and maximum dorsiflexion position and maximum dorsiflexion torque to quantify associations between model parameters and biomechanical capacity.

For the CMC analysis, isometric and dynamic CMC magnitudes were compared within AB participants using a Wilcoxon signed-rank test. Dynamic CMC was compared between STR and AB participants using a Wilcoxon rank-sum test. Linear regressions were also performed to assess the relationship between isometric and dynamic CMC within AB participants, and between slow and fast dynamic CMC and biomechanical outcomes across both groups. For all regressions, the coefficient of determination (R^2) and p-value are reported.

Chapter 7

Study of Stroke Injury via Biomechanical and Neurophysiological Assessments

7.1 Overview

Ten people with chronic stroke-related FD (STR group: 4 male, 6 female, age = 61 ± 12 yrs) and 19 able-bodied people (AB group: 8 male, 11 female, age = 24 ± 3 yrs), participated in ankle AROM, MVC, and neurophysiological assessments. All these measures were assessed using a multi-sensor robotic platform, AMPD. We will first present the biomechanical assessment results, followed by the neurophysiological and modeling results, and finally, the discussion of the interpretation of these results.

Table 7.1: Demographic Data for STR (I: Ischemic, H: hemorrhagic, L: left, R: right, AFO: Ankle Foot Orthosis)

Subject	Age/Sex	Time Since Stroke (mo)	Stroke Type	Stroke Location	Impaired Side	Gait Speed
STR1	F/77	70	I	R MCA territory	L	0.16
STR2	M/65	60	H	L basal ganglia	R	0.54 (AFO)
STR3	F/47	166	H	R basal ganglia, Wallerian degeneration	L	0.27
STR4	F/44	60	H	L cerebral peduncle, L thalamus	R	0.5
STR5	F/69	35	I + H	L basal ganglia hemorrhage, pons	R	0.16
STR6	M/69	82	H	L basal ganglia, parietal, frontal lobes	R	0.18 (AFO)
STR7	F/48	81	I	Bilateral corona radiata	L	0.54
STR8	M/74	74	H	L basal ganglia	R	0.22
STR9	F/50	49	H	R basal ganglia	L	0.14
STR10	M/64	38	I	Uncal herniation, R midbrain, L temporal-occipital	L	0.22

7.2 Biomechanical assessments

Two biomechanical assessments, AROM and MVC, were performed to quantify the impact of stroke injury on the ankle’s movement abilities, specifically the maximum ankle positions, maximum dorsiflexion torque, and maximum static TA EMG for both sides. Full descriptive statistics for all comparisons are presented in Table 7.2.

7.2.1 AROM: Injured ankle shows reduced range of motion and agonist activation

The injured ankle in STR participants demonstrated substantially reduced range of motion and agonist activation relative to both the uninjured side and AB participants, while the uninjured side remained comparable to AB participants.

The maximum dorsiflexion position for the injured ankle in STR participants was largely reduced compared to their uninjured side (adj. $p < 0.001$, $d = 2.04$) and AB participants (adj. $p < 0.001$, $d = 2.42$). The uninjured side was comparable to AB participants (adj. $p = 0.58$, $d = 0.25$; Fig. 7.1 (A)). TA EMG, measured at the maximum dorsiflexion position, followed the same pattern, with significantly reduced activation on the injured side relative to both the uninjured side (adj. $p = 0.006$, $r = 0.64$) and AB participants (adj. $p < 0.001$, $r = 0.69$), and a comparable activation on the uninjured side with AB participants (adj. $p = 0.116$, $r = 0.29$).

Additionally, we measured the maximum plantarflexion position. This was similarly reduced on the injured side relative to the uninjured side (adj. $p < 0.001$, $d = 3.00$) and AB participants (adj. $p < 0.001$, $d = 2.84$). However, unlike dorsiflexion, the uninjured side was also significantly reduced compared to AB participants (adj. $p = 0.0015$, $d = 1.21$), suggesting a bilateral plantarflexion deficit post-stroke.

Finally, the total ankle range, defined as the entire range from maximum dorsiflexion to maximum plantarflexion, showed the injured side substantially reduced relative to both the uninjured side (adj. $p < 0.001$, $d = 2.61$) and AB participants (adj. $p < 0.001$, $d = 3.50$), while the uninjured side remained comparable to AB participants (adj. $p = 0.15$).

7.2.2 MVC: Both ankles show reduced torque and activation

Unlike the primarily unilateral deficits observed in AROM, maximum dorsiflexion torque and TA activation during MVC revealed bilateral deficits post-stroke, with considerably larger impairments on the injured side.

The injured side demonstrated substantially lower torque than both the uninjured side (adj. $p < 0.001$, $d = 3.06$) and AB participants (adj. $p < 0.001$, $d = 3.94$), while the uninjured side also produced significantly lower torque than AB participants (adj. $p = 0.041$, $d = 0.94$; Fig. 7.1(B)). TA EMG during MVC mirrored this pattern, with the injured side showing reduced activation relative to both the uninjured side (adj. $p = 0.006$, $r = 0.64$) and AB (adj. $p = 0.001$, $r = 0.76$), and the uninjured side also exhibiting lower activation than AB participants (adj. $p = 0.044$, $r = 0.38$; Fig. 7.1(C)).

The results demonstrate a primarily unilateral effect on the ankle's maximum position ability, with bilateral effects on the maximum torque production and TA muscle activation ability during dorsiflexion post-stroke.

7.3 Neurophysiological assessments

Ankle kinematics, EMG activity, and EEG sensorimotor rhythms were recorded during the dynamic neurophysiological assessment to quantify ankle, muscle, and brain activity in dynamic conditions, in contrast to the static conditions covered in the biomechanical assessments. Full descriptive statistics for all comparisons are presented in Table 7.3.

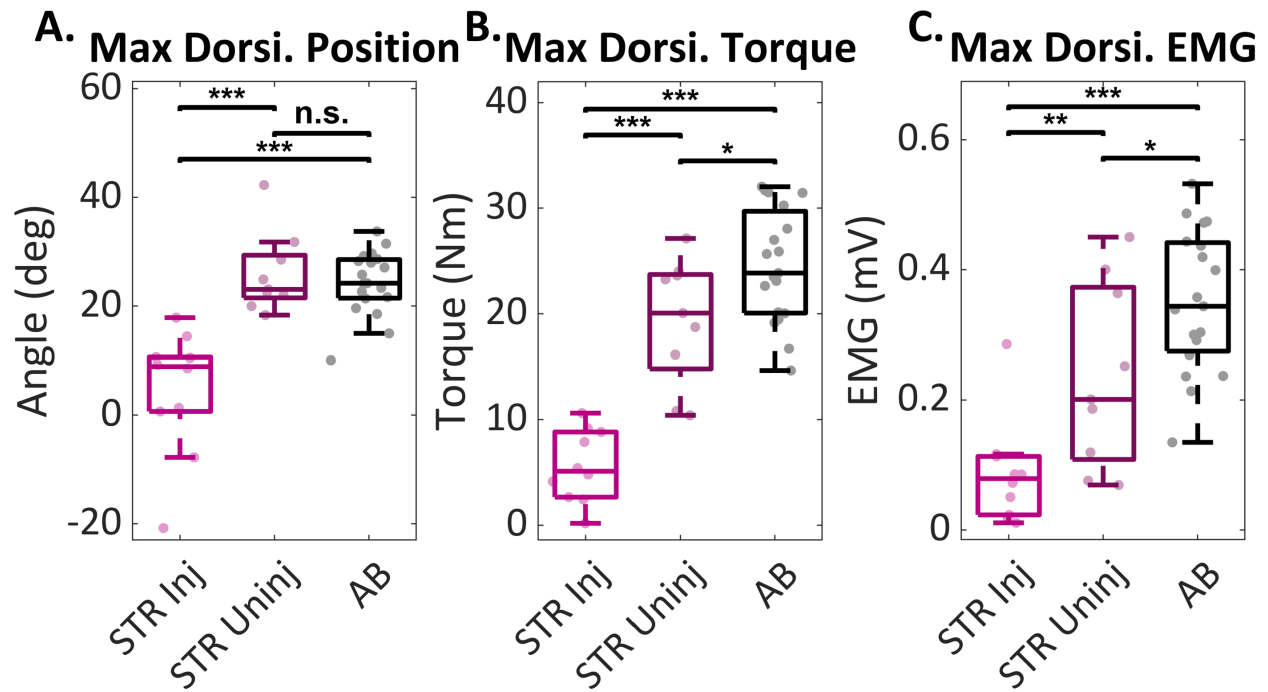


Figure 7.1: Comparison of A. Maximum Dorsiflexion Position during AROM (0° = parallel to ground), B. Maximum Dorsiflexion Torque during MVC, C. Maximum Dorsiflexion EMG during MVC. The injured and uninjured sides were compared via paired statistical tests, and the STR vs AB groups were compared via unpaired statistical tests. The cascade of deficit, i.e., the percentage change of values of the STR group from that of the AB group following the downstream connectivity, from the median Max Dorsi EMG (77.04%) to median Max Dorsi Torque (77.24%), and eventually the median Max Dorsi Position (82.48%).

Table 7.2: AROM and MVC Results

	Young Able Bodied	Stroke	
	Dominant	Injured	Uninjured
AROM Maximum Dorsiflexion Position ($^{\circ}$, mean $\pm$ SD)	24.3 $\pm$ 5.8	4.5 $\pm$ 11.6	25.9 $\pm$ 7.4
AROM Maximum Plantarflexion Position ($^{\circ}$, mean $\pm$ SD)	51.9 $\pm$ 7.6	32.1 $\pm$ 5.4	43.7 $\pm$ 4.4
AROM ($^{\circ}$, mean $\pm$ SD)	76.2 $\pm$ 8.1	36.6 $\pm$ 15.9	69.7 $\pm$ 11.3
TA EMG at AROM Maximum Dorsiflexion (mV, median [IQR])	0.374 [0.247 - 0.422]	0.075 [0.035 - 0.110]	0.223 [0.141 - 0.345]
Maximum Dorsiflexion Strength (N.m, mean $\pm$ SD)	24.6 $\pm$ 5.4	5.6 $\pm$ 3.4	19.4 $\pm$ 5.9
TA EMG at Maximum Dorsiflexion Strength (mV, median [IQR])	0.344 [0.275 - 0.442]	0.079 [0.023 - 0.113]	0.201 [0.108 - 0.373]

7.3.1 Dynamic ankle kinematics: Lower speeds and amplitudes produced by STR group

Both groups successfully produced distinct instantaneous speeds for Slow and Fast movements (STR: adj. $p = 0.010$, $r = 0.89$; AB: adj. $p < 0.001$, $r = 1.00$). However, the AB participants produced higher speeds than STR across both movement types (adj. $p < 0.001$, $r = 0.65$; Fig. 7.2 (A)). Dorsiflexion amplitudes were comparable across speeds in the STR group (adj. $p = 0.439$), whereas AB participants produced smaller amplitudes during Fast movements (adj. $p < 0.001$). The overall amplitudes were substantially larger in the AB participants than in the STR participants (adj. $p < 0.001$; Fig. 7.2 (B)). Amplitudes remained consistent between the first and last trials for both groups ($p > 0.3$), with the exception of a small reduction of 0.23° in Fast movement trials for STR (adj. $p = 0.001$, $r = 0.41$).

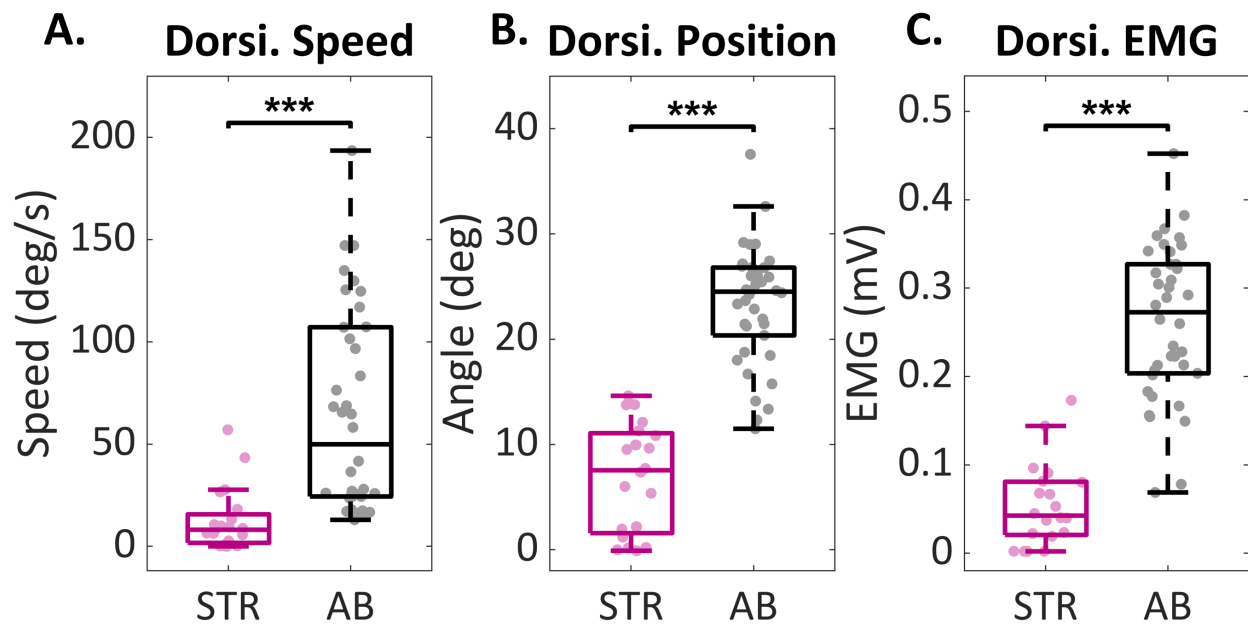


Figure 7.2: Comparison of A. Dorsiflexion Speed, B. Dorsiflexion Position, and C. EMG. The cascade of deficit for the Dynamic Task follows from the median EMG (84.25%), to the median Position (68.98%), and the median Speed (83.77%) drop of the STR group from the AB group.

Table 7.3: Dynamic Movement Results

Dynamic Test Features	Able-Bodied			Stroke		
	Slow	Fast	Combined	Slow	Fast	Combined
Dorsiflexion Speed (°/s, median [IQR])	24.4 [17.2 - 26.2]	107.2 [70.7 - 128.7]	49.9 [24.4 - 107.2]	6.9 [0.7 - 9.5]	11.6 [2.7 - 27.7]	8.1 [1.7 - 15.7]
Dorsiflexion Amplitude (°, median [IQR])	25.4 [20.6 - 27.4]	24.3 [19.2 - 25.6]	24.5 [20.4 - 26.8]	8.5 [1.2 - 11.3]	6.5, [2.0 - 10.8]	7.6 [1.6 - 11.1]
EMG Amplitude (mV, median [IQR])	0.228 [0.189 - 0.336]	0.281 [0.206 - 0.327]	0.273 [0.204 - 0.327]	0.042 [0.019 - 0.080]	0.053 [0.022 - 0.081]	0.043 [0.021 - 0.081]
Movement-Related ERD (%, median [IQR])	-33.7 [-43.2 - -18.7]	-42.8 [-54.2 - -34.9]	-41.716 [-51.6 - -27.6]	-55.5, [-62.4 - -43.9]	-47.9 [-58.4 - -37.2]	-54.9 [-60.0 - -42.2]
Post-Movement ERS (%, median [IQR])	87.4 [51.8 - 158.4]1	109.6 [58.7 - 157.8]	102.9 [53.3 - 158.4]	39.3 [29.0 - 99.6]	1.9 [10.3 - 115.1]	41.0 [19.6 - 105.1]
Idle ERS (%, median [IQR])	n/a	n/a	-1.2 [-5.2 - 5.9]	n/a	n/a	9.2 [-2.6 - 35.8]

7.3.2 Dynamic EMG: Reduced activation and contralateral mirroring in STR group

The AB group produced substantially stronger TA EMG than the STR group overall (adj. $p < 0.001$, $r = 0.78$; Fig. 7.2(C)). EMG did not differ significantly between Slow and Fast movements overall (adj. $p = 0.260$, $r = 0.29$), though STR showed a trend toward higher activation during Fast movements (adj. $p = 0.073$, $r = 0.71$). STR participants also exhibited significantly higher contralateral ankle EMG than AB participants (STR: 0.011 [0.006–0.016] mV; AB: 0.002 [0.002–0.005] mV; adj. $p < 0.001$, $r = 0.58$), indicative of movement mirroring.

7.3.3 EEG Features: STR group shows beta-dominant ERD with Cz-centered source localization

ERD frequency band classifications differed significantly between groups (χ^2 , $p = 0.043$), with the AB group showing a more even split between μ - and β -dominant bands (μ : $n = 8$, β : $n = 8$, mixed: $n = 3$), while STR participants were predominantly β -dominant (μ : $n = 1$, β : $n = 9$, mixed: $n = 0$). ERS band classifications did not differ significantly between groups (χ^2 , $p = 0.130$), with β -dominant bands prevailing in both the AB group ($n = 19$) and the

STR group ($n = 10$). Source channel distributions did not differ significantly between groups (ERD: $p = 0.220$; ERS: $p = 0.495$). For the STR group, both ERD and ERS source channels were centered at Cz. In AB, ERD source channels were more broadly distributed across CPz, Fz, and Cz, with CPz being the most common, while ERS was consistently localized at Cz.

7.3.4 Movement-related EEG: STR group shows prominent ERD but reduced ERS relative to AB group

Movement-related cortical dynamics revealed opposing group differences in ERD and ERS. ERD was significantly stronger in the STR group than AB group (adj. $p = 0.027$, $r = 0.30$; Fig. 7.3(A)), a finding that was consistent across multiple alternate ERD estimation methods and within the range of approximately -20% to -80% reported in the literature [76, 65, 52]. In contrast, post-movement ERS was substantially stronger in the AB group than the STR group (adj. $p = 0.014$, $r = 0.34$; Fig. 7.3(B)), while idle-period ERS did not differ between groups (adj. $p = 0.124$, $r = 0.29$; Fig. 7.3(C)), confirming that the group difference was specific to movement-related activity. Speed-dependent differences were also observed: the AB group showed stronger ERD and ERS during and after faster movements (ERD: adj. $p = 0.005$, $r = 0.82$; ERS: adj. $p = 0.014$, $r = 0.71$), whereas the STR group showed weaker ERD at faster speeds and no significant speed-dependent modulation in ERS (ERD: adj. $p = 0.027$, $r = 0.78$; ERS: adj. $p = 0.492$, $r = 0.27$).

7.3.5 Modeling Coupling Parameters: Gain is highly reduced in the STR group while weight parameters remain comparable to the AB group

The EEG–EMG relationship was modeled using a two-parameter exponential function, yielding a weight parameter w_E , representing the strength of cortical-to-motor neuron transfor-

Table 7.4: Personalized frequency bands and source channel selection

Participant (Group Num)	ERD Band			ERS Band		
	Optimized Channel	Start	Stop	Optimized Channel	Start	Stop
STR 1	'Cz'	8	21.5	'Cz'	15	30
STR 2	'C1'	15	26	'Cz'	8.5	17.5
STR 3	'Cz'	12.5	30	'CPz'	8.5	14
STR 4	'CPz'	8	23	'FCz'	8	30
STR 5	'C2'	8	11	'C1'	24.5	27.5
STR 6	'C2'	8	21.5	'Cz'	27	30
STR 7	'C2'	21.5	30	'CPz'	10	30
STR 8	'Cz'	18.5	28.5	'Cz'	8	23.5
STR 9	'Cz'	22	28	'Cz'	18	21
STR 10	'CPz'	12.5	30	'Cz'	17	30
AB 1	'CPz'	8	15.5	'Cz'	15.5	30
AB 2	'Cz'	16	29	'Cz'	10	30
AB 3	'FCz'	8	12	'C2'	22	26.5
AB 4	'C1'	8	11	'CPz'	20	26
AB 5	'CPz'	9	15.5	'Cz'	8	30
AB 6	'C2'	11	29.5	'Cz'	13.5	26.5
AB 7	'Cz'	16.5	30	'Cz'	12	29.5
AB 8	'CPz'	8.5	11.5	'Cz'	10.5	29
AB 9	'CPz'	8.5	12	'Cz'	12	28.5
AB 10	'CPz'	8.5	17	'Cz'	23.5	30
AB 11	'C2'	9	14	'Cz'	19	28.5
AB 12	'CPz'	8	12	'Cz'	12.5	30
AB 13	'CPz'	8	30	'Cz'	11.5	29.5
AB 14	'FCz'	27	30	'Cz'	10	30
AB 15	'Cz'	10.5	30	'C1'	17.5	25
AB 16	'FCz'	9.5	12	'Cz'	23	30
AB 17	'FCz'	21.5	25.5	'Cz'	20.5	30
AB 18	'Cz'	8	30	'Cz'	19.5	30
AB 19	'FCz'	10	12.5	'CPz'	12.5	30

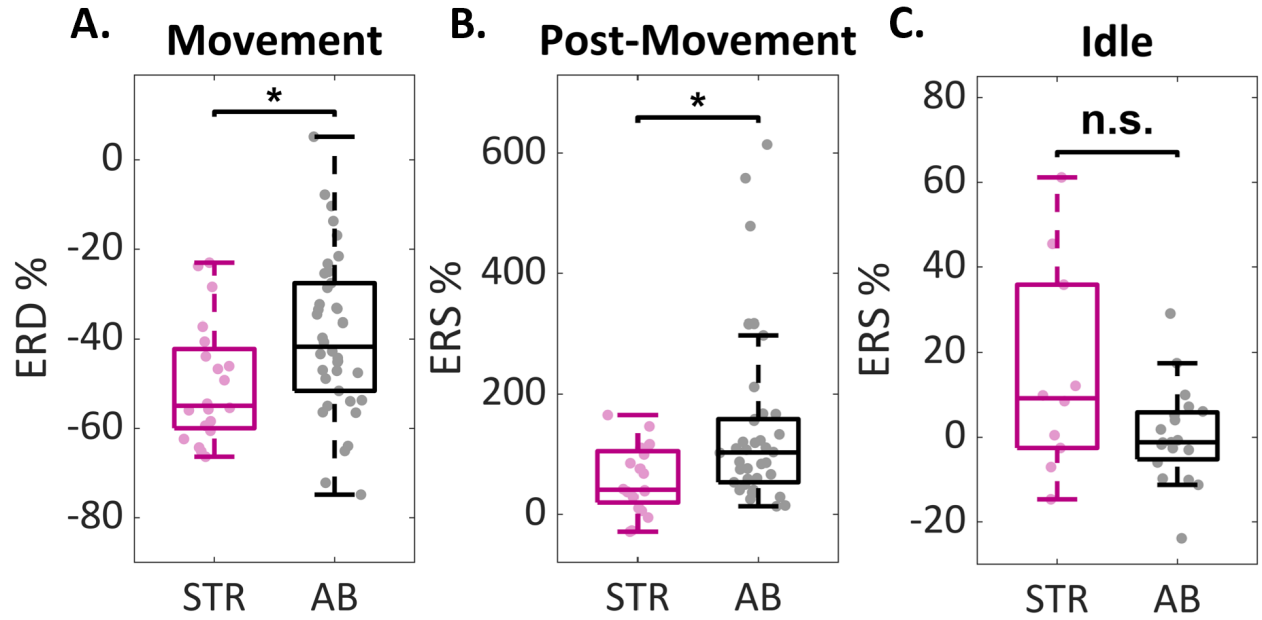


Figure 7.3: Comparison of A. Movement-Related ERD, B. Post-Movement ERS, and C. Idling ERS. While significant differences are found between groups, the general values are comparable.

mation, and a gain parameter g_m , reflecting corticospinal integrity and downstream motor unit recruitment (shown in Fig. 7.4). A parallel model applied to EEG and dorsiflexion position features yielded analogous parameters w and g .

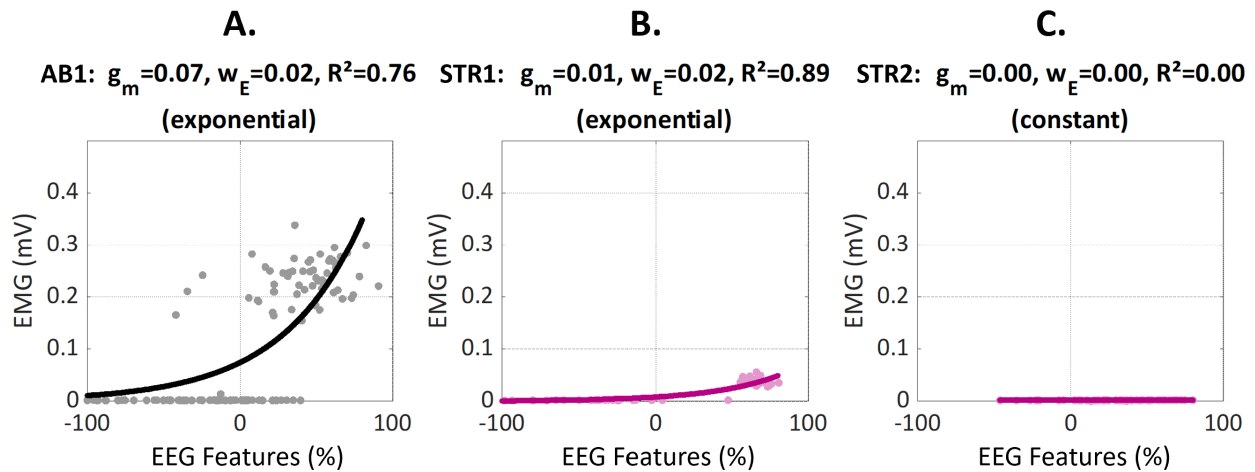


Figure 7.4: Representative model selection and fit for one AB participant: A. AB1, and two STR participants: B. STR1, and C. STR2. Model selection criteria selected the exponential model for AB1 and STR1, and the constant model for STR2.

Across both models, the STR group exhibited significantly lower gain values than AB, while weight parameters remained comparable between groups. For the EEG–EMG model, g_m was significantly lower in the STR group than the AB group (adj. $p < 0.001$, $r = 0.75$), while w_E did not differ significantly (adj. $p = 0.191$, $r = 0.24$; Fig. 7.5). The EEG–Dorsiflexion Position model followed the same pattern: g was significantly lower in the STR group than the AB group (adj. $p < 0.001$, $r = 0.77$), while w did not differ significantly (adj. $p = 0.450$, $r = 0.14$; Fig. 7.6). These findings suggest that the gain parameters are more sensitive to group differences in neuromuscular coupling than the weight parameters.

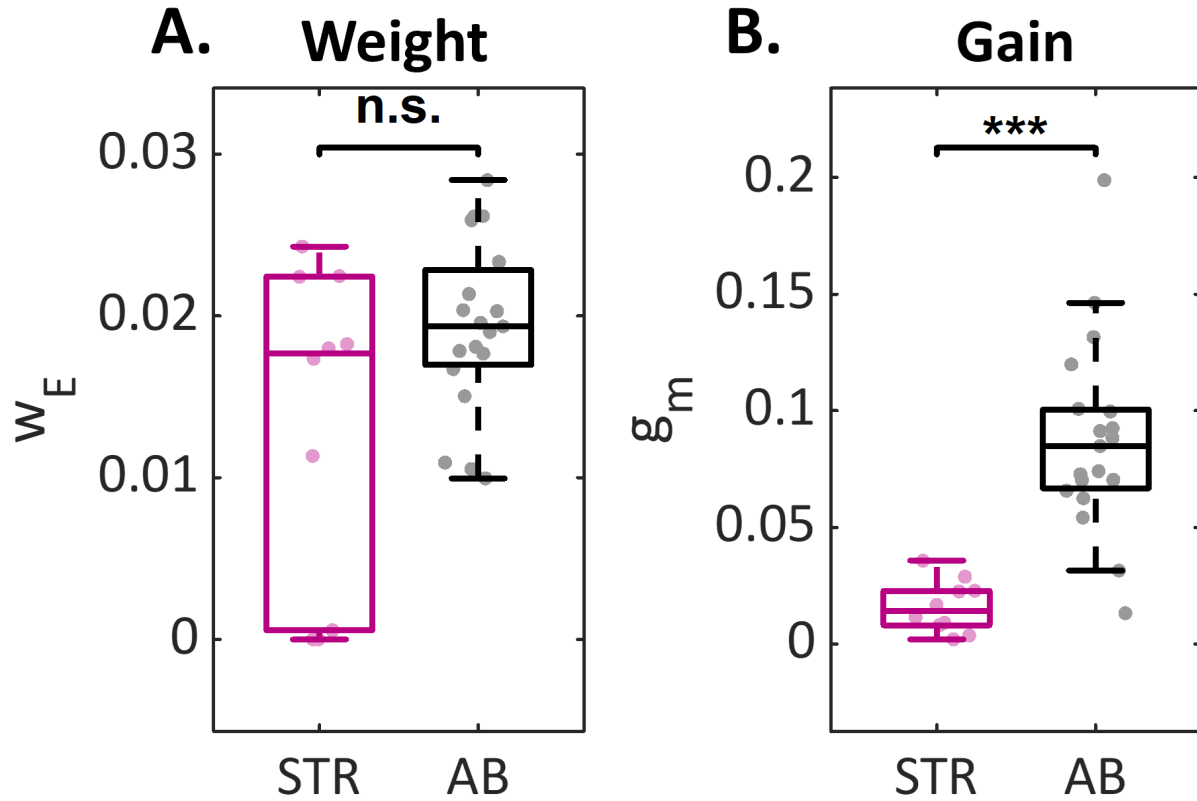


Figure 7.5: Boxplot comparison of EEG–EMG model parameters between the AB and STR groups derived from individual participant modeling. The left panel shows the weight parameter w_E (STR: 0.018 [IQR: 0.001–0.022]; AB: 0.019 [IQR: 0.017–0.023]; adj. $p = 0.191$, $r = 0.24$), and the right panel shows the gain parameter g_m (STR: 0.014 [IQR: 0.008–0.023]; AB: 0.085 [IQR: 0.067–0.101]; adj. $p < 0.001$, $r = 0.75$). The STR group exhibited significantly lower g_m values, while w_E remained comparable between groups.

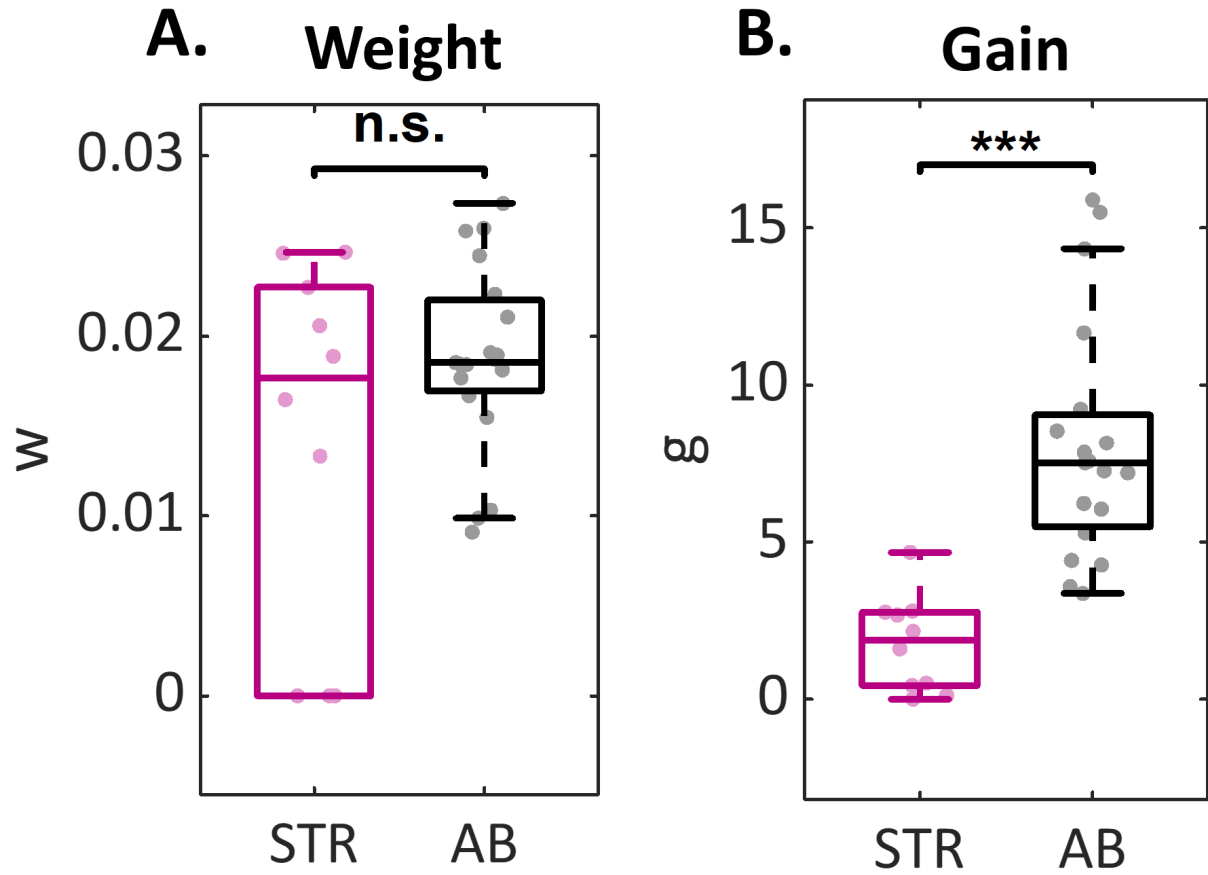


Figure 7.6: Boxplot comparison of EEG-Dorsiflexion Position model parameters between AB and STR groups derived from individual participant modeling. The left panel shows the weight parameter w (STR: 0.018 [IQR: 0.000–0.023]; AB: 0.019 [IQR: 0.017–0.022]; adj. $p = 0.450$, $r = 0.14$), and the right panel shows the gain parameter g (STR: 1.878 [IQR: 0.437–2.764]; AB: 7.511 [IQR: 5.472–9.058]; adj. $p < 0.001$, $r = 0.77$). The STR group exhibited significantly lower g values, while w remained comparable between groups.

The two models were also highly consistent with each other. The weight parameters w_E and w showed a near-perfect linear correspondence (slope = 0.96, $R^2 = 0.92$, $p < 0.001$), indicating an approximately 1:1 mapping between the two models. The gain parameters g_m and g also showed a strong linear relationship (slope = 78.99, $R^2 = 0.76$, $p < 0.001$), reflecting a consistent scalar relationship between muscle and ankle output (see Fig. 7.7).

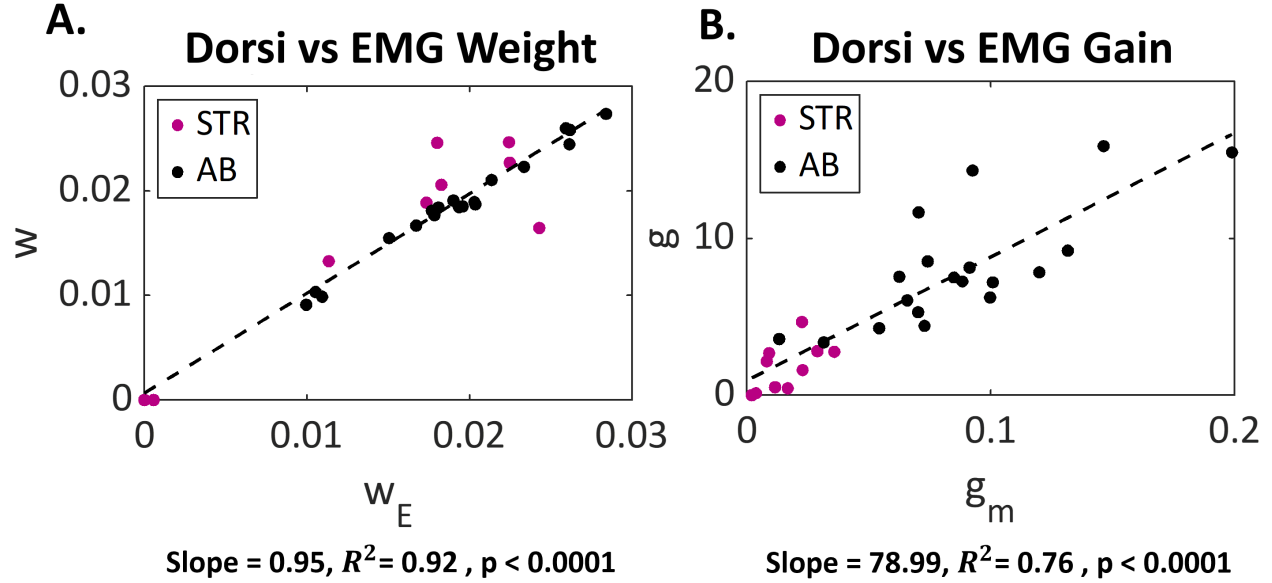


Figure 7.7: Linear Regression between w_E and g_m values with corresponding w and g values revealed strong linear relationships validating the cascade originating from the brain and descending from muscle (EMG) to ankle output

Coupling Parameters: Strong predictors of biomechanical ability than weight parameters

All four coupling parameters (w_E , g_m , w , g) demonstrated significant positive associations with at least one biomechanical measure across AB and STR participants, with gain parameters consistently explaining more variance than weight parameters (as shown in Fig. 7.8).

Both gain parameters significantly predicted both maximum dorsiflexion position and MVC torque, though the relative predictive strength differed. For dorsiflexion position, g was the stronger predictor ($R^2 = 0.533$, $p < 0.001$), followed by g_m ($R^2 = 0.395$, $p < 0.001$).

This order was reversed for MVC torque, where g_m explained more variance ($R^2 = 0.505$, $p < 0.001$) than g ($R^2 = 0.439$, $p < 0.001$).

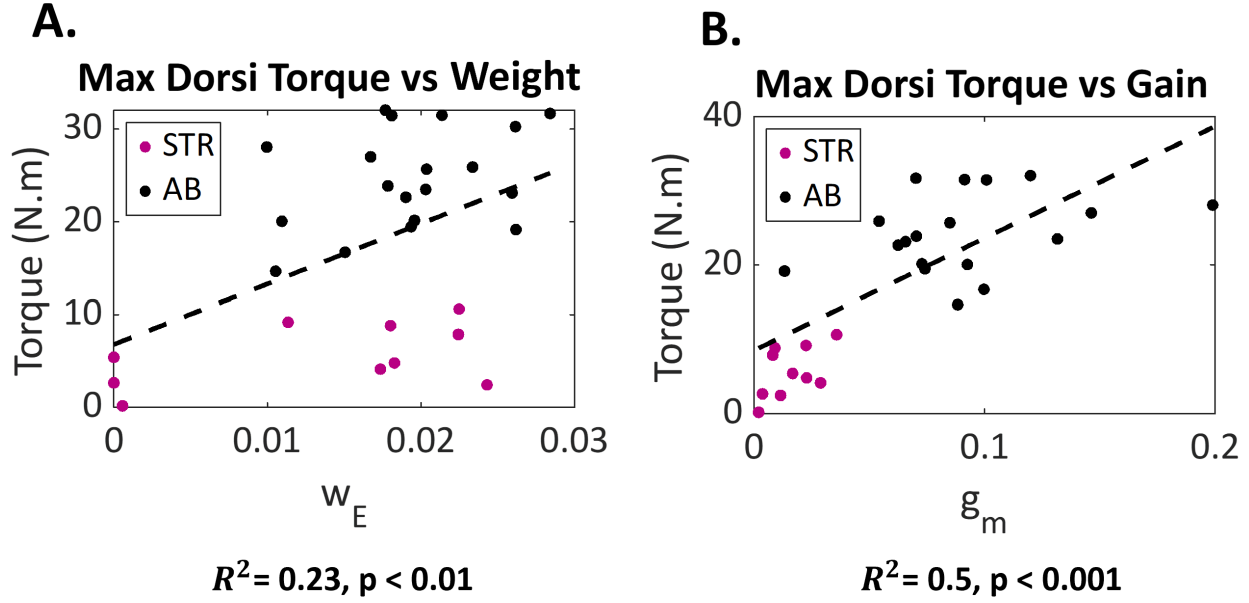


Figure 7.8: Linear regression between EEG–EMG coupling parameters (w_E , g_m) against maximum dorsiflexion torque across STR and AB participants.

Both w_E and w were also significant positive predictors of MVC torque (w_E : $R^2 = 0.227$, $p = 0.009$; w : $R^2 = 0.189$, $p = 0.018$), but neither significantly predicted dorsiflexion position (w_E : $R^2 = 0.109$, $p = 0.080$; w : $R^2 = 0.100$, $p = 0.095$). The gain parameters demonstrated stronger associations with biomechanical capacity than the weight parameters.

7.4 Isometric and dynamic CMC

Isometric CMC was estimated from an isometric contraction task (30% and 60% MVC) in AB participants ($n = 18$), while dynamic CMC was estimated from the neurophysiological task in both AB ($n = 19$) and STR ($n = 10$) participants. We first compared dynamic CMC against the established isometric approach within AB participants, then compared dynamic CMC between groups.

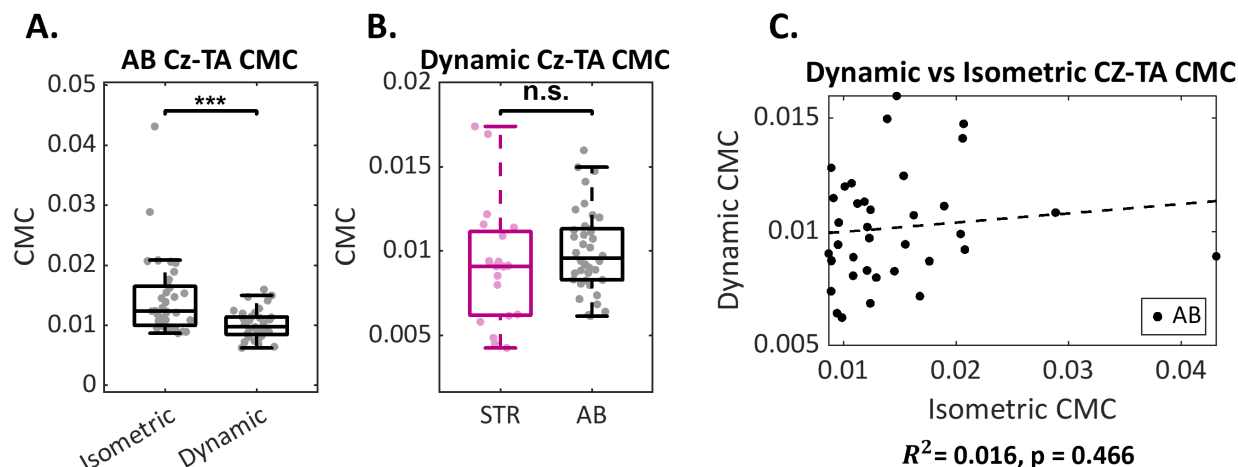


Figure 7.9: Comparison of mean Cz-TA CMC in the μ - β band (8-30Hz) A. Isometric vs Dynamic CMC for AB group ($n = 18$, both conditions combined, paired testing between high and low effort), B. Dynamic CMC for AB ($n = 19$) vs STR ($n = 10$) groups, C. Linear regression between Isometric and Dynamic Cz-TA CMC for AB group.

Dynamic CMC in AB participants was significantly lower than isometric CMC (see Fig. 7.9 (A)) (isometric: median = 0.012 [IQR: 0.010–0.017]; dynamic: median = 0.010 [IQR: 0.009–0.011]; Wilcoxon signed-rank, $p < 0.001$, $r = 0.75$), indicating that the two estimation approaches do not yield equivalent CMC magnitudes, with the dynamic task producing systematically lower values. Dynamic CMC did not significantly differ between STR and AB participants, as shown in Fig. 7.9 (B), though STR values were numerically lower (STR: median = 0.009 [IQR: 0.006–0.011]; AB: median = 0.010 [IQR: 0.008–0.011]; Mann-Whitney U, $p = 0.263$, $r = 0.147$).

Furthermore, there was no linear relationship between the isometric and dynamic CMC values in AB participants (see Fig. 7.9 (C): $R^2 = 0.016$, $p = 0.466$), indicating that these metrics may be independent and not represent similar aspects of the corticomuscular relationship.

The topoplots for all participants combined, as shown in Fig. 7.10, revealed a physiologically relevant signature for the isometric CMC in AB participants with high values centered

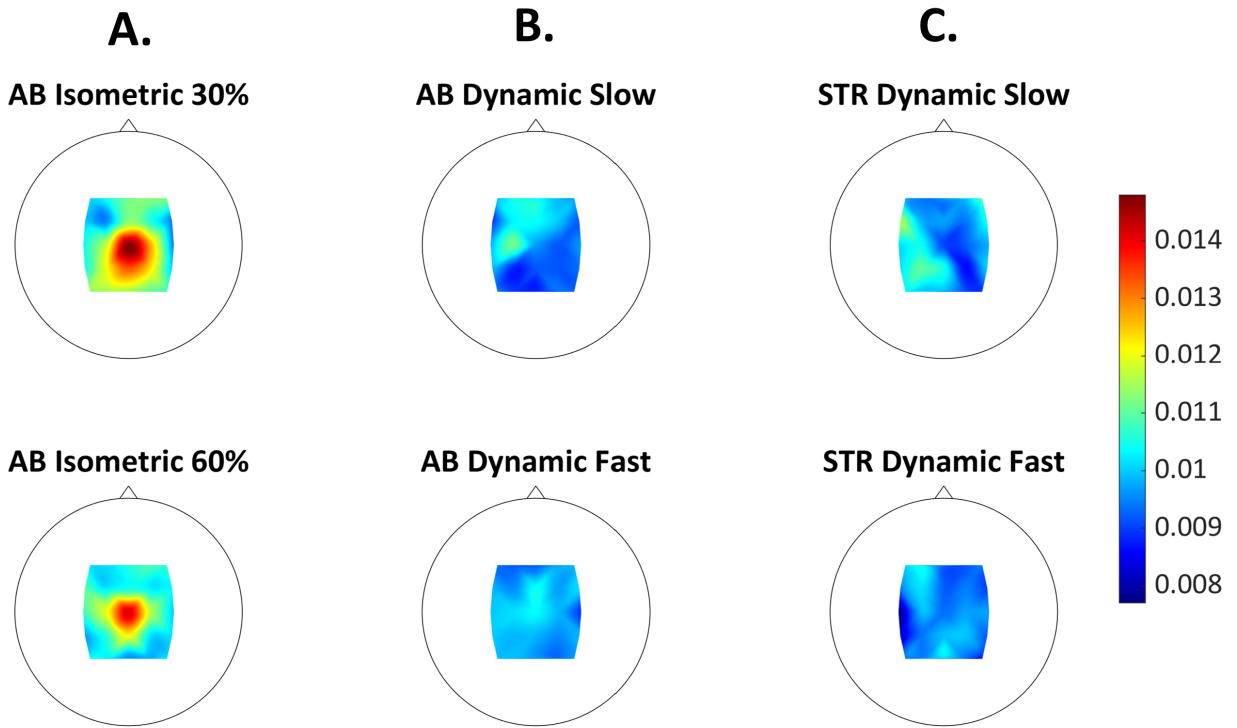


Figure 7.10: Topoplots representing physiological trend of μ - β CMC for all participants in a cohort. A. Isometric CMC for the AB group ($n = 18$): 30% (top), 60% (bottom), B. Dynamic CMC for the AB group ($n = 19$): Slow (top), Fast (bottom), C. Dynamic CMC for the STR group ($n = 10$): Slow (top), Fast (bottom). All are scaled to the same scale bar as represented on the right side.

at the Cz electrode. This signature was not prominently observed in the Dynamic CMC calculations.

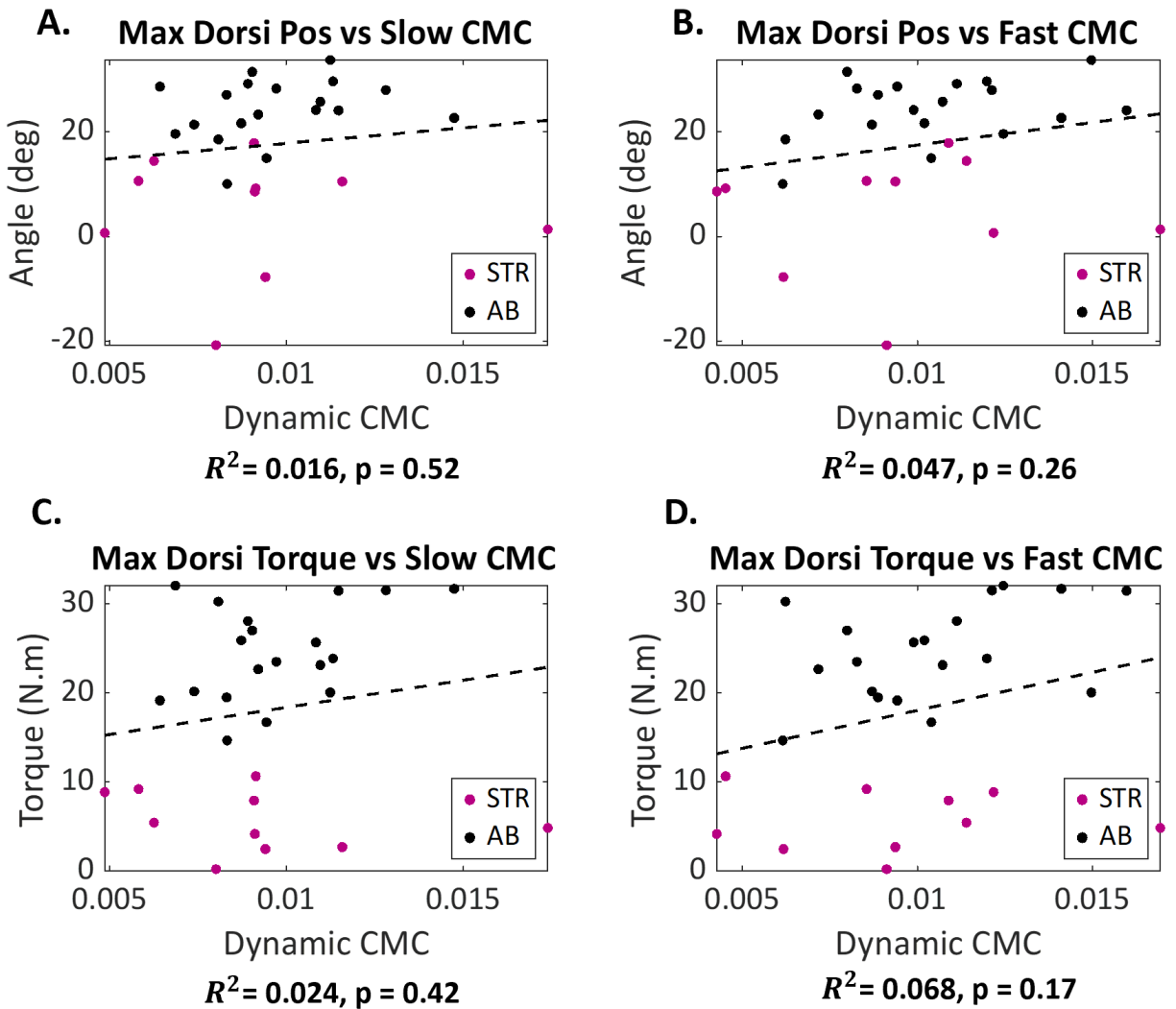


Figure 7.11: Linear Regression between Dynamic CMC values for AB and STR groups with corresponding biomechanical assessment results. A. Maximum Dorsiflexion Position (AROM) and Dynamic CMC (Slow), B. Maximum Dorsiflexion Position and Dynamic CMC (Fast), C. Maximum Dorsiflexion Torque (MVC) and Dynamic CMC (Slow), D. Maximum Dorsiflexion Torque and Dynamic CMC (Fast).

Dynamic CMC: No relationship with biomechanical ability

Dynamic corticomuscular coherence (CMC) did not significantly predict maximum dorsiflexion position or MVC torque at either movement speed across AB and STR participants (as

shown in Fig. 7.11). For dorsiflexion position, neither slow nor fast CMC reached significance (slow: $R^2 = 0.016$, $p = 0.520$; fast: $R^2 = 0.047$, $p = 0.260$), and the same held for MVC torque (slow: $R^2 = 0.024$, $p = 0.420$; fast: $R^2 = 0.068$, $p = 0.172$). This stands in contrast to the gain parameters, which consistently explained substantial variance in both biomechanical measures, suggesting that dynamic CMC does not capture the same neuromuscular information reflected in biomechanical capacity.

7.5 Discussion

We designed an experimental and computational methodology to study neurophysiological biomarkers of chronic stroke injury in individuals with FD and compared them to the AB group. Computational modeling guided our choice of using an exponential model to quantify the relationships between EEG, EMG, and kinematics during a dynamic task as a measure of corticomuscular integrity. Standard impairment assessment methods, including active range of motion (AROM) and maximum voluntary contraction (MVC), were also conducted to contextualize the neurophysiological findings. The main results of this study were, first, biomechanical assessments (AROM and MVC) reflected significant impairments in the injured side of the STR group when compared to the AB group. The dorsiflexion position for the uninjured side remained unaffected, but torque was reduced.

7.5.1 AROM, MVC, and related EMG captured the post-stroke deficits on the maximum potential of movement

The large reductions in dorsiflexion range of motion (Maximum Dorsiflexion and Plantarflexion Positions) and strength (Maximum Dorsiflexion Torque) observed in the STR group relative to the AB group, and relative to their own uninjured limb, were expected, given that our recruitment criteria specifically targeted individuals with foot drop, a condition characterized by the inability to adequately dorsiflex the ankle. These findings are consistent with

those reported in literature [36, 6, 136], including the observation that the uninjured limb of stroke participants exhibited dorsiflexion range of motion comparable to the AB group, though strength remained lower, suggesting a systemic effect of stroke on neuromuscular capacity beyond the directly affected limb.

The proportional reduction in tibialis anterior EMG during MVC, found to be comparable to the reductions observed in maximum dorsiflexion torque and position, suggests a largely linear loss of neuromuscular function across these measures. This parallel decline indicates that the observed functional deficits may not be attributable to deficits in the ankle biomechanics, but rather to the muscle’s inability to generate the required activation and torque. While disuse-related muscle atrophy and spasticity [124, 51] may have contributed to the further reduction in the maximum dorsiflexion position, the presence of residual muscle activity, as evidenced by responsiveness to FES (part of our inclusion criteria for STR), suggests that the primary cause of impairment lies upstream of the muscle itself, within the corticospinal pathway. This points to a disruption in descending motor drive rather than a peripheral or purely muscular deficit.

These results all highlight the major impact of stroke on the capabilities and potential for producing ankle movement that also transfers to the uninjured side despite not directly being impacted.

7.5.2 Neurophysiological features of dynamic movement reflect post-stroke deficits in realization of maximum potential

Ankle Kinematics of Dynamic Movement

The repetitive ankle dorsiflexion protocol captured neurophysiological features of continuous and self-paced volitional movement in the STR and AB groups. The two movement speeds captured characteristics of the distinct movement types: deliberate and controlled

slow movements and ballistic fast movements that reflected each participant’s maximum attainable speed.

Despite the variation in movement speed across conditions, the consistent EMG amplitude and dorsiflexion kinematics indicated that participants maintained their ankle movement patterns throughout the trials as instructed. The absence of significant changes in movement features between the first and last trials, as well as within individual trials, suggests that the number of repetitions was appropriately calibrated and that fatigue did not influence the results.

Interestingly, the cascade of functional loss observed during the dynamic task differed from that seen during the biomechanical assessments that required maximum effort. This dissociation could reflect a difference between a participant’s maximum capacity and the consequent utilization of that capacity during a self-paced dynamic task. Additionally, the reduction in EMG production being compensated by 13% at the ankle position level was interesting as it suggests that the deficits in the ankle biomechanics were less prominent during the task. The proportional drop from EMG was instead reflected in the production of speed. This distinction highlights the value of dynamic task paradigms in capturing aspects of motor behavior that “maximum effort” assessments alone may not fully reflect.

Comparison of EEG Features in STR and AB groups

The personalization of frequency bands and source electrodes revealed that the STR group was able to produce movement-related cortical output measured by the ERD and ERS Features of EEG. While AB participants produced ERD that was in the spread between the μ (8-13Hz) to β (13-30Hz) regions, the STR groups ERD was more prominent exclusively in the Beta ranges. There are no formal studies that have reported such frequency-specific changes post stroke. While this could be a result of the small cohort size of STR participants, future studies should explore the possibility of frequency band changes in ERD post stroke.

As found in literature, topographical patterns reflect a more widespread ERD phenomenon and a highly localized ERS pattern, with ERS being much stronger in magnitude than ERD [128, 86].

The stronger motor-related ERD observed in the STR group compared to AB group was initially surprising, as prior studies have reported attenuated ERD in stroke populations relative to able-bodied individuals [15, 20]. However, the observed group difference remained robust across other ERD calculation methods and was not solely a product of our analytical approach.

Examining the broader literature revealed supporting evidence for our observed comparable and enhanced ERD magnitude in stroke. Studies that specifically explored the relationship between lesion location and ERD found that when the lesion does not directly involve the motor cortex, motor-related ERD may be preserved or even enhanced due to compensatory mechanisms [101, 94, 41, 52]. All the participants in our cohort had subcortical strokes, and hence the observed results are consistent with the findings in the literature. Specifically, lesions in the basal ganglia have been reported to produce enhanced ERD [89]. Additionally, some studies reported age-related increases in ERD magnitude [33, 22, 126, 102], which may have contributed, given the older age profile of our stroke participants. It is also worth noting that ERD in the lower extremities remains comparatively underexplored relative to the upper limb, with the majority of existing literature focused on hand and arm movements, making direct comparisons more challenging. The proximity of the contralesional and ipsilesional locations makes it difficult to distinguish the compensatory activity from the intentional activity using non-invasive methods.

Corticomuscular coherence (CMC) was also considered as a possible measure of corticomuscular integrity for this study [147, 120]. We found that the isometric CMC was stronger than dynamic for AB and followed the appropriate physiological signature centered around Cz. The dynamic CMC did not follow this physiological signature, and the values for AB

and STR were comparable. This could indicate that the dynamic CMC did not accurately capture the corticomuscular integrity and was unsuitable for this estimation. Literature has also shown CMC to fail for dynamic movement conditions, revealing inherent neurophysiological differences between dynamic and static/sustained movement production [115, 24]. Additionally, Mima et al [70] found CMC to be non-significant for the affected limb in stroke populations, limiting its utility as a sensitive biomarker in this context. In contrast, the subject-specific modeling framework adopted here enabled a method to characterize the EEG-EMG and EEG-kinematics relationships during dynamic movement at an individual level.

The preservation of the weight parameter values across both groups suggests that the transformation of cortical activity that excites lower motor neurons remained relatively intact following stroke. The brain continues to send organized motor commands, and the pattern of that signaling may not be fundamentally disrupted within our cohort of participants, especially with subcortical lesions. In contrast, the significantly reduced gain parameters in the STR group point to a breakdown in how effectively those signals are converted into functional motor output. This likely reflects some combination of weakened corticospinal tract integrity, reduced motor unit recruitment, and downstream muscle atrophy, all of which are well-documented consequences of stroke [25, 104, 71, 54]. Hence, our results suggest that post-stroke foot drop following a subcortical stroke may primarily be a deficit in signal execution rather than signal generation.

The consistency between the two modeling frameworks (EMG and Dorsiflexion Position) further validates these interpretations. The near 1:1 correspondence between weight parameters across both models suggests that the weight is a shared physiological property, regardless of whether motor output is measured as muscle activity or joint position. Similarly, the consistent scalar relationship between the gain parameters reflects the biomechanical

transformation from muscle activation to joint movement, suggesting that the models are capturing meaningful physiology rather than artifacts.

Additionally, the linear relationships observed between the estimated weight and gain parameters from neurophysiological data, and MVC torque and AROM measures provide evidence that these neurophysiological biomarkers meaningfully reflect residual motor function. Specifically, the gain parameters (g_m and g), which we hypothesize to reflect the integrity of the corticospinal pathway and its influence on motor unit recruitment and muscle firing capacity, consistently demonstrated strong associations with both functional measures. The weight parameters, while showing marginal associations with MVC torque, were not significantly associated with range of motion, suggesting they may capture a distinct and potentially more upstream aspect of communication.

While the factorization of the exponential model into separate weight and gain parameters was intended to isolate distinct physiological contributions, we acknowledge that both w_E and g_m likely reflect upper motor neuron (UMN) dysfunction to a greater degree than they reflect purely downstream impairments. Additionally, the ability to produce FES-elicited dorsiflexion further confirmed that the downstream pathway for the α MN to TA muscle recruitment was not completely severed and excitable. This suggests that the variance captured by both parameters is more attributable to UMN pathology than to peripheral changes. In this light, the slope at $x=0$, represented by the product of the two parameters, may serve as a more clinically meaningful summary of the combined neuromuscular weakness, capturing the overall degradation in the cortex-to-output pathway without requiring factorization of its components. Future work could investigate whether this composite metric offers stronger sensitivity or clinical interpretability than either parameter alone.

These findings support the utility of exponential EEG-EMG and EEG-kinematics modeling as a framework for deriving individualized, physiologically interpretable biomarkers of corticomuscular integrity in chronic stroke. From a clinical standpoint, the combination of the

weight and gain parameters may offer an interpretable measure of residual neuromuscular capacity, with potential utility as a biomarker for tracking rehabilitation progress over time.

Chapter 8

Study of Stroke Rehabilitation via Biomechanical and Neurophysiological Assessments

8.1 Overview

Ten participants with chronic stroke-related foot drop (STR group) were recruited to undergo 4 weeks of BCI-based FES or robot intervention. One participant withdrew after the BL visit ($n = 9$), and two participants each missed one follow-up visit (1M and 3M, respectively). Clinical and novel dynamic neurophysiological assessments were conducted at Baseline (BL), Post-Therapy (PT), 1-Month Follow-up (1M), and 3-Month Follow-up (3M).

8.2 Gait speed assessment

Group-level gait speed increased from 0.22 m/s at BL to 0.24 m/s at PT, remained stable at 1M, and declined to 0.19 m/s at 3M. S4 demonstrated the largest individual improvement,

Table 8.1: Demographic Data for STR (I: Ischemic, H: hemorrhagic, L: left, R: right, AFO: Ankle Foot Orthosis)

Subject	Age/Sex	Time Since Stroke (mo)	Stroke Type	Stroke Location	Impaired Side	Gait Speed			
						BL	PT	1M	3M
STR1	F/77	70	I	R MCA territory	L	0.16	0.16	0.14	0.15
STR2	M/65	60	H	L basal ganglia	R	0.54 (AFO)	0.52 (AFO)	0.53 (AFO)	0.43 (AFO)
STR3	F/47	166	H	R basal ganglia, Wallerian degeneration	L	0.27	0.28	0.33	0.36
STR4	F/44	60	H	L cerebral peduncle, L thalamus	R	0.5	0.68	0.74	No Visit
STR5	F/69	35	I + H	L basal ganglia hemorrhage, pons	R	0.16	0.16	0.16	0.17
STR6	M/69	82	H	L basal ganglia, parietal, frontal lobes	R	0.18 (AFO)	0.19 (AFO)	0.17 (AFO)	0.20 (AFO)
STR7	F/48	81	I	Bilateral corona radiata	L	0.54	0.51	0.52	0.59
STR8	M/74	74	H	L basal ganglia	R	0.22	No Visit	No Visit	No Visit
STR9	F/50	49	H	R basal ganglia	L	0.14	0.17	No Visit	0.19 (AFO)
STR10	M/64	38	I	Uncal herniation, R midbrain, L temporal-occipital	L	0.22	0.22	0.31 (AFO)	0.26

with gait speed increasing from 0.50 m/s at BL to 0.74 m/s at 1M (48% improvement), but was absent at 3M. Two participants (S2, S6) used AFOs at all time points, and two additional participants required AFO support at later visits (S10 at 1M; S9 at 3M). S9 also had missing data at 1M.

8.3 Biomechanical assessments

8.3.1 AROM: maximum dorsiflexion position

Maximum dorsiflexion position showed a directional trend of improvement across the study period, with the most pronounced effect observed at 1M. Although no time point reached statistical significance (PT: $p = 0.149$, $d_z = 0.53$; 1M: $p = 0.073$, $d_z = 0.74$; 3M: $p = 0.719$, $d_z = 0.16$; Fig. 8.1), the medium-to-large effect sizes at PT and 1M suggest a meaningful improvement that the study was likely underpowered to confirm statistically. This is further supported by the responder-level data where six of nine participants demonstrated a clinically meaningful increase exceeding 2.5° at PT, with 4 maintaining this improvement at 1M and 3 at 3M.

8.3.2 MVC: Maximum Dorsiflexion Torque

Maximum dorsiflexion torque followed an improvement trajectory across the study period with a peak at 1M. The change at PT was not statistically significant ($p = 0.097$, $d_z = 0.627$). However, a statistically significant increase was confirmed at 1M ($p = 0.029$, $d_z = 1.075$), and both represented large effect sizes (see Fig. 8.1(B)). Although this was not maintained at 3M ($p = 0.519$, $d_z = 0.283$), the overall trajectory from BL through 1M suggests a meaningful and progressive strengthening response to the intervention. The transition from a medium effect at PT to a large, significant effect at 1M suggests delayed neuromuscular gains, where the total improvement in strength may require additional time beyond the immediate post-therapy period. The same responder subgroup that demonstrated clinically

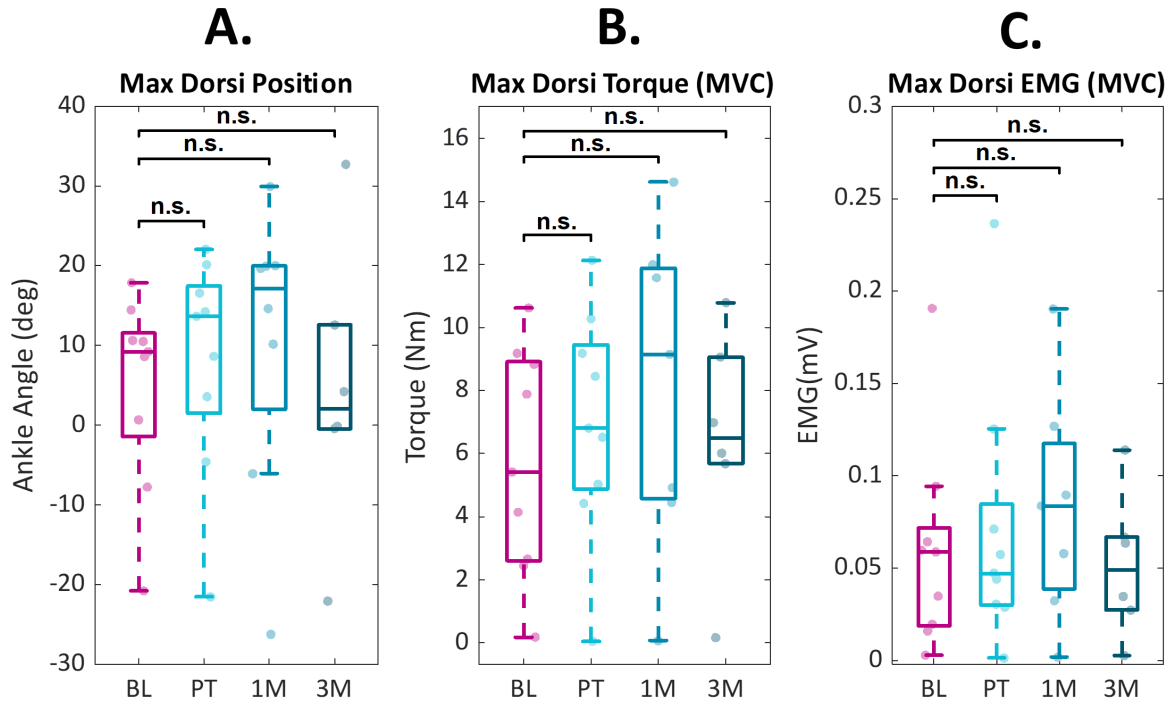


Figure 8.1: Population-wise comparison of Biomechanical Assessment measures before (BL: $n = 9$) and after 4 weeks of rehabilitation (PT $n = 9$) and follow-up visits (1M: $n = 8$, 3M: $n = 8$). A. Maximum Dorsiflexion Position (AROM), B. Maximum Dorsiflexion Torque (MVC), C. Maximum Dorsiflexion EMG (MVC). Paired statistical comparisons show no significant differences between the time points, but a post-rehabilitation increasing trend is observed with a peak at 1M.

meaningful increases in dorsiflexion position also exhibited $> 10\%$ increases in maximum dorsiflexion torque across all follow-up time points.

8.3.3 MVC: Maximum dorsiflexion EMG

Maximum tibialis anterior EMG activity during MVC showed a consistent increasing trend across the study period, though it did not reach statistical significance at any time point relative to BL (PT: $p = 0.359$, $r = 0.49$; 1M: $p = 0.219$, $r = 0.78$; 3M: $p = 0.438$, $r = 0.78$; Fig. 8.1). The large-to-very-large effect sizes at 1M and 3M ($r = 0.78$ at both time points) suggest a substantial directional trend toward increased muscle activation that the study was likely underpowered to confirm statistically. This pattern mirrors the trajectory observed in dorsiflexion position and torque, with the most pronounced trend emerging at 1M. Five of the six participants in the previously identified responder subgroup produced $> 20\%$ increases in EMG amplitude at PT, with this improvement sustained through 1M and 3M.

8.4 Neurophysiological assessments

8.4.1 Dorsiflexion speed during dynamic task

Dorsiflexion speed increased following the intervention, with the most pronounced effect observed at 1M. At the trial level, speeds were significantly higher than BL at all follow-up time points (Wilcoxon signed-rank; PT: $p < 0.001$, $r = 0.46$; 1M: $p < 0.001$, $r = 0.82$; 3M: $p < 0.001$, $r = 0.54$). When trials were averaged, this improvement was not significant at PT ($p = 0.407$, $r = 0.23$), but reached significance with a large effect at 1M, and later attenuated at 3M ($p = 0.007$, $r = 0.76$ and $p = 0.179$, $r = 0.38$ respectively; Fig. 8.2).

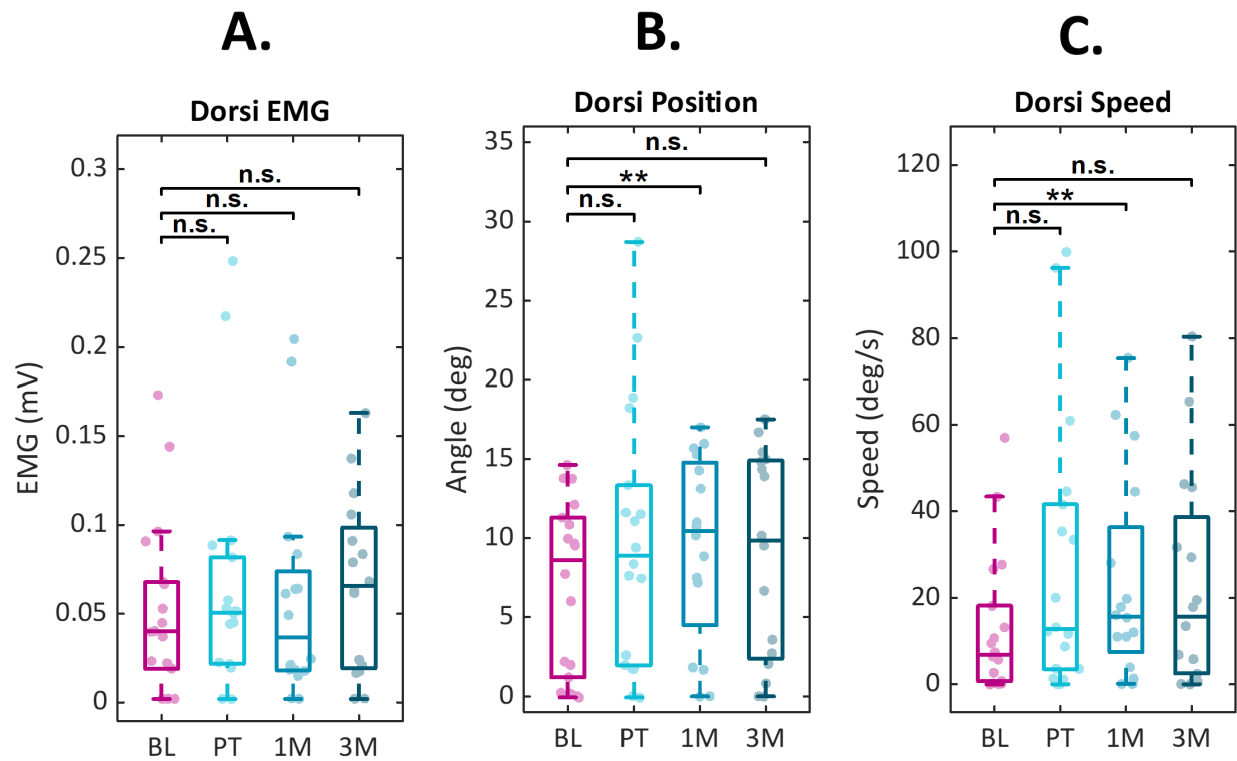


Figure 8.2: Group-level comparison of dynamic assessment measures at BL ($n = 9$), PT ($n = 9$), 1M ($n = 8$), and 3M ($n = 8$) following 4 weeks of rehabilitation. (A) Dorsiflexion EMG, (B) dorsiflexion position, (C) dorsiflexion speed. Paired statistical comparisons indicate significant increases in dorsiflexion position and speed at 1M, with a general improving trend observed across the post-rehabilitation period.

8.4.2 Dorsiflexion position during dynamic task

Peak dorsiflexion positions showed the greatest improvement at 1M, with the effect attenuating at 3M. At the trial level, a near-significant increase was present at PT ($p = 0.068$, $r = 0.32$), which reached significance at 1M ($p < 0.001$, $r = 0.87$) and 3M ($p < 0.001$, $r = 0.49$) with a very large effect. On averaging the trials, while no significant change was observed at PT ($p = 0.687$, $r = 0.11$), the significant improvement with a large effect size was retained at 1M ($p = 0.004$, $r = 0.82$; Fig. 7.2). The significance was not sustained at 3M ($p = 0.215$, $r = 0.35$), but the moderate effect size indicates that the improvement was still preserved.

8.4.3 Dorsiflexion EMG during dynamic task

Dorsiflexion EMG activity increased consistently from BL across the entire follow-up period. At the trial level, the increase was significant at all time points (PT: $p = 0.001$, $r = 0.29$; 1M: $p = 0.010$, $r = 0.46$; 3M: $p = 0.001$, $r = 0.31$), with effect sizes peaking at 1M before slightly attenuating at 3M. When averaged across trials per participant, values did not reach significance at any time point (PT: $p = 0.248$, $r = 0.31$; 1M: $p = 0.469$, $r = 0.21$; 3M: $p = 0.301$, $r = 0.29$), though the directional trend of increased activation was consistently present (Fig. 8.2).

8.4.4 Movement related desynchronization

ERD magnitude remained unchanged from BL at PT ($p = 0.170$, $r = 0.37$) or 1M ($p = 0.877$, $r = 0.04$), with the near-zero effect at 1M suggesting the cortical motor activation pattern was stable in the early post-therapy period. A significant reduction in ERD magnitude emerged at 3M ($p = 0.013$, $r = 0.71$), representing a large effect (Fig. 8.3).

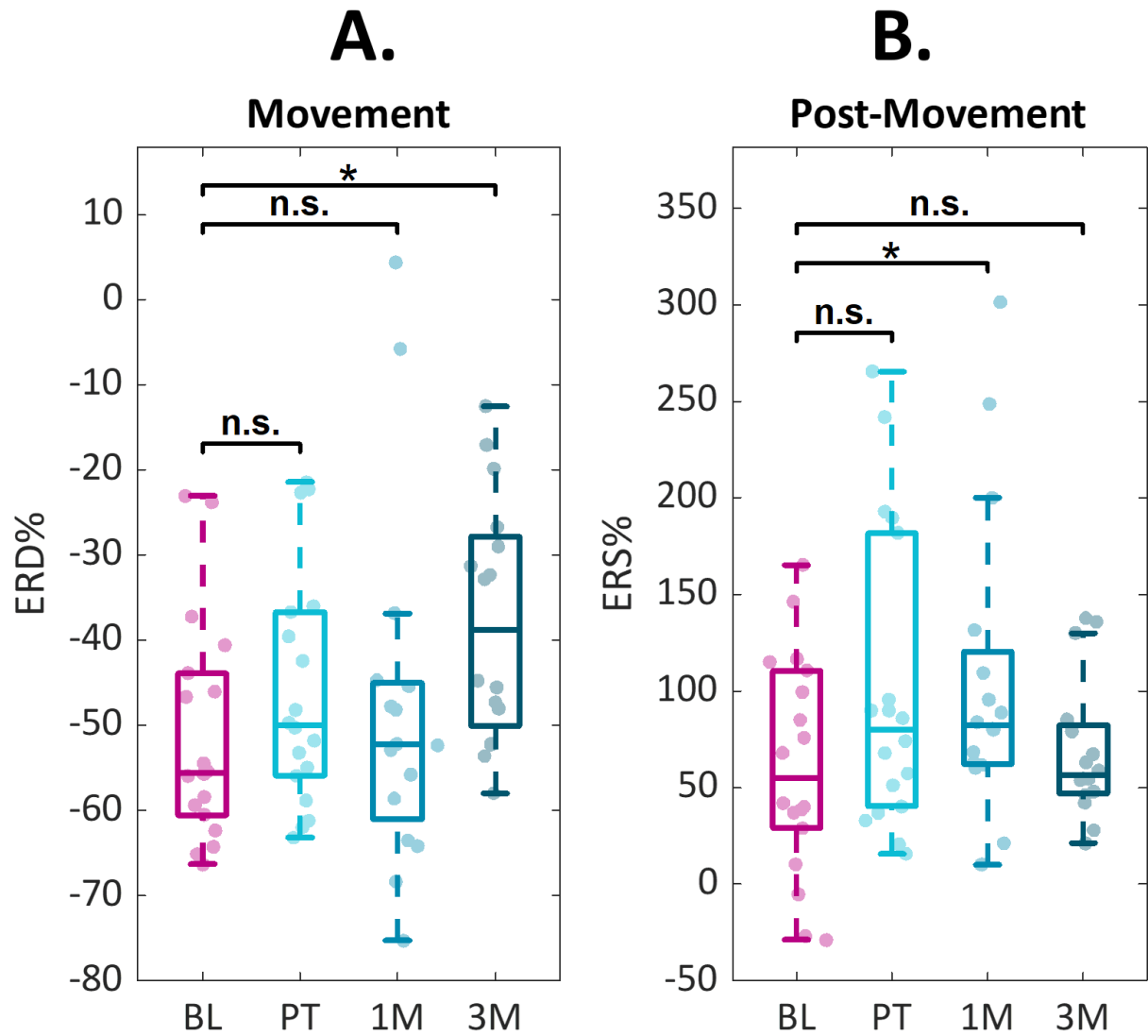


Figure 8.3: Population-wise comparison of ERD and ERS measures before (BL: $n = 9$) and after 4 weeks of rehabilitation (PT $n = 9$) and follow-up visits (1M: $n = 8$, 3M: $n = 8$). A. Dorsiflexion Movement related ERD, B. Post-Movement related ERS. Paired significance tests show a reduction in ERD at 3M and an increase in ERS at 1M.

8.4.5 Post-Movement resynchronization

ERS magnitude also remained comparable to BL at PT ($p = 0.170$, $r = 0.37$), though the moderate effect size suggests a directional trend emerging. A significant increase with a large effect size was observed at 1M ($p = 0.039$, $r = 0.59$), coinciding with the period of peak functional improvement across biomechanical and dynamic neurophysiological measures (Fig. 7.2). While this was not sustained at 3M ($p = 0.163$, $r = 0.40$), the moderate effect size again points to a directional trend of enhanced post-movement rebound persisted, even in the absence of statistical significance.

8.4.6 Modeling and estimating coupling coefficients

The exponential model parameters derived from both the EEG-EMG and EEG-Dorsiflexion Position relationships were examined across all time points to assess changes in weight and gain following BCI-based intervention.

The EEG-EMG gain parameter g_m did not show statistically significant changes from BL at any follow-up time point (PT: adj. $p = 0.910$, $r = 0.13$, 1M: adj. $p = 0.820$, $r = 0.53$, 3M: adj. $p = 0.820$, $r = 0.53$; Fig. 8.4). The median g_m showed a consistent directional trend toward increasing values across the study period, rising from 0.0091 [IQR: 0.0066–0.0242] at BL to 0.0142 [IQR: 0.0068–0.0222] at PT, 0.0114 [IQR: 0.0065–0.0189] at 1M, and 0.0183 [IQR: 0.0077–0.0276] at 3M. The effect size grew from small at PT ($r = 0.13$) to large at 1M and 3M ($r = 0.53$ at both time points), suggesting an increasingly consistent directional shift in the gain parameter over time.

Similarly, the EEG-Dorsiflexion Position gain parameter g showed a statistically significant increase from BL at 1M (adj. $p = 0.047$, $r = 0.96$), representing a very large effect, while no statistically significant changes were observed at PT (adj. $p = 0.461$, $r = 0.45$) or 3M (adj. $p = 0.461$, $r = 0.56$; Fig. 8.5). The median g values showed a consistent directional trend toward increasing values across all time points, rising from 2.157 [IQR: 0.179–2.773] at BL

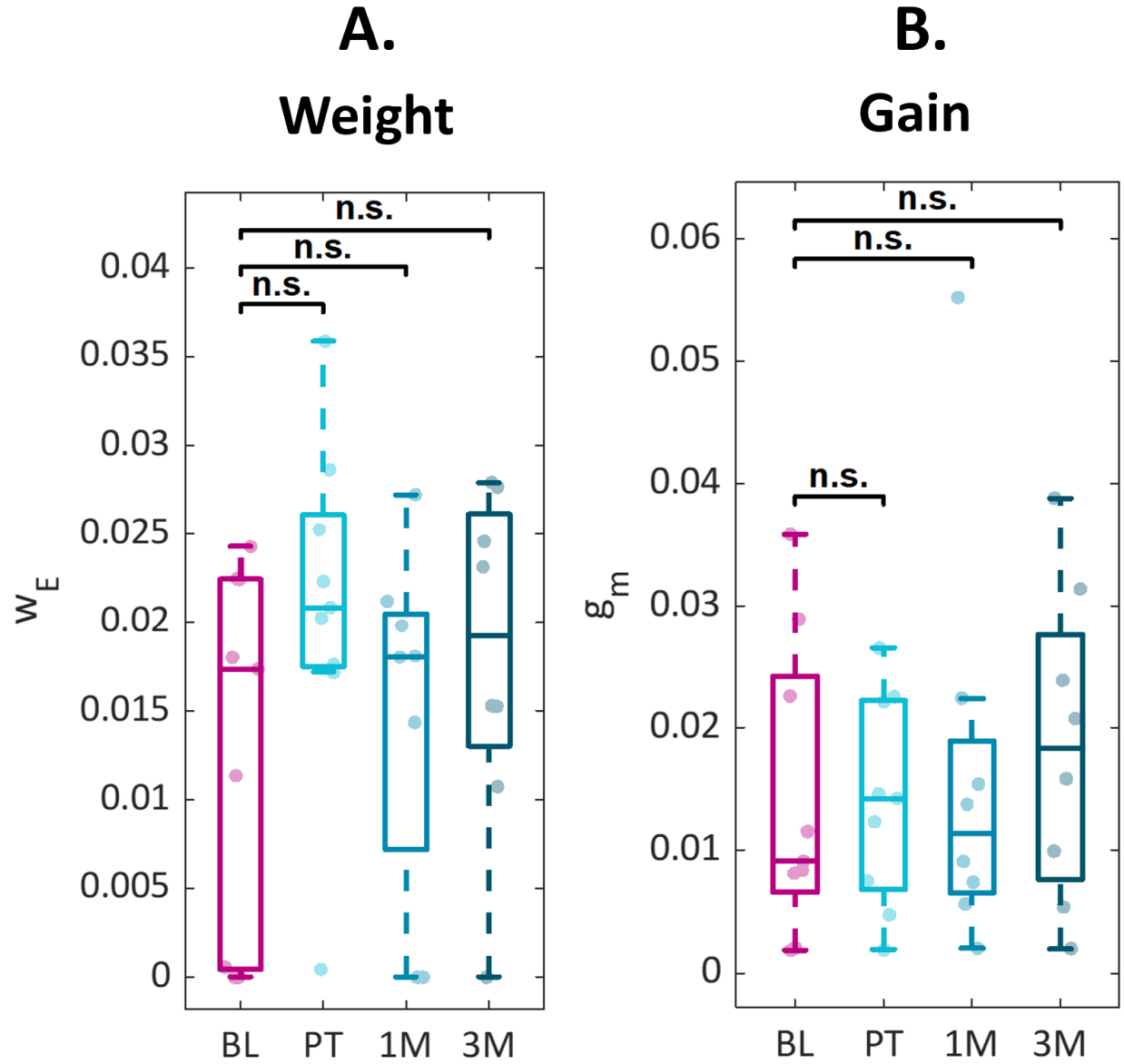


Figure 8.4: EEG-EMG weight and gain parameters over Time Points: (BL: $n = 9$, PT $n = 9$, 1M: $n = 8$, 3M: $n = 8$). No significant differences were found when comparing post-rehabilitation time points to baseline. A transient increase was observed in the weight parameter, and a sustained increase was observed in the gain parameter.

to 2.510 [IQR: 0.650–3.403] at PT, 2.831 [IQR: 1.159–3.260] at 1M, and 2.698 [IQR: 0.505–4.259] at 3M. The effect sizes grew progressively from PT ($r = 0.45$) to 1M ($r = 0.96$) before attenuating slightly at 3M ($r = 0.56$), remaining moderate and directionally consistent with improvement. The weight parameters from both models followed a broadly similar pattern of non-significant but directionally positive trends.

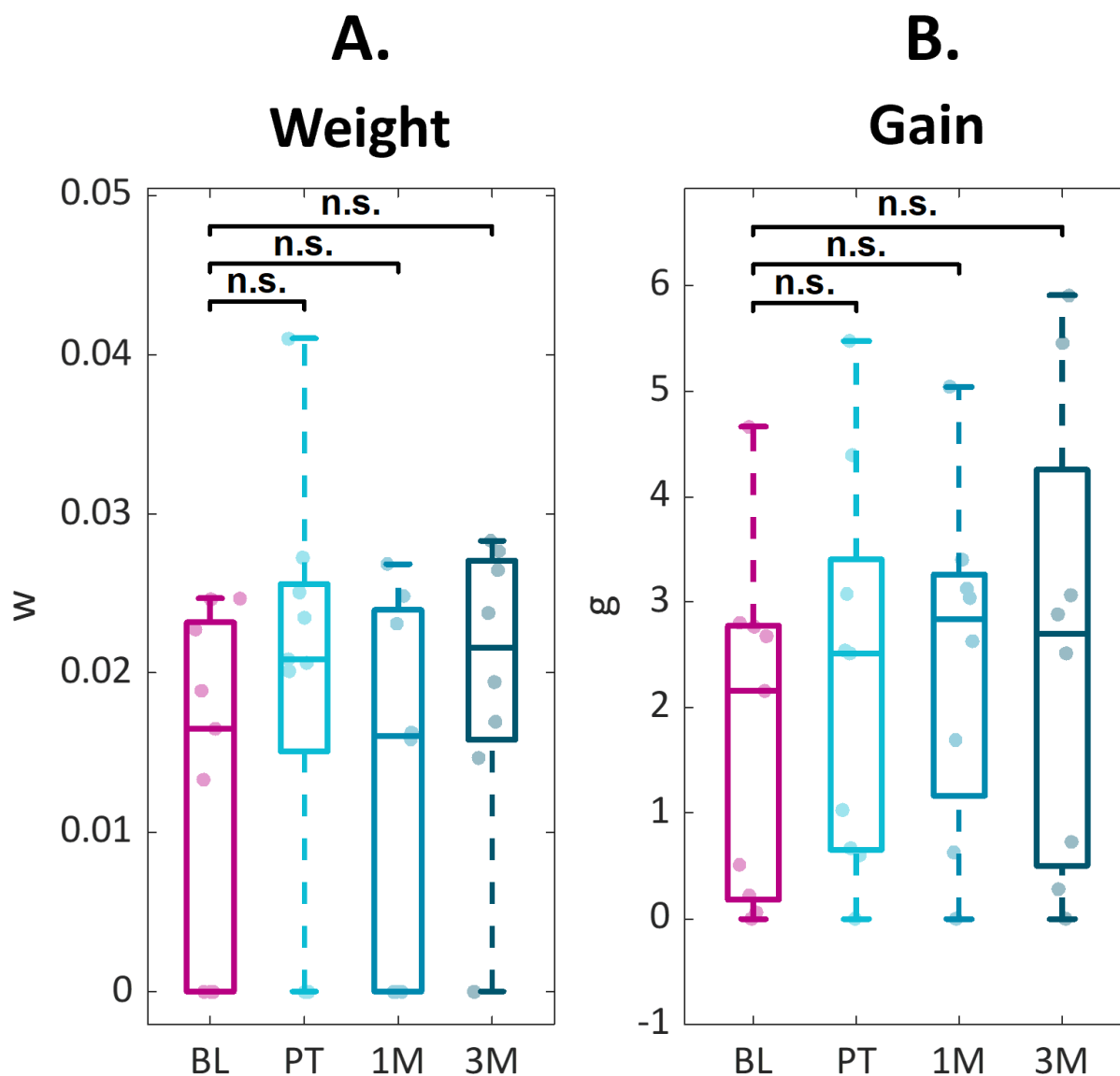


Figure 8.5: EEG-Dorsiflexion Position weight and gain parameters over Time Points: (BL: $n = 9$, PT $n = 9$, 1M: $n = 8$, 3M: $n = 8$). Similar to the EEG-EMG weight, no significant differences were found when comparing post-rehabilitation time points to baseline, with a transient increase in the weight parameter and a sustained increase in the gain parameter.

The EEG-EMG weight parameter w_E did not show statistically significant changes from BL at any time point (PT: adj. $p = 0.383$, $r = 0.60$, 1M: adj. $p = 0.383$, $r = 0.11$, 3M: adj. $p = 0.383$, $r = 0.60$; Fig. 8.4). The median w_E increased from 0.0173 [IQR: 0.0004–0.0224] at BL to 0.0208 [IQR: 0.0175–0.0261] at PT, 0.0180 [IQR: 0.0072–0.0205] at 1M, and 0.0192 [IQR: 0.0130–0.0261] at 3M. The effect sizes were large at PT ($r = 0.60$) and 3M ($r = 0.60$), with a smaller effect observed at 1M ($r = 0.11$).

Similarly, the EEG-Dorsiflexion Position weight parameter w did not reach statistical significance at any time point: (PT: adj. $p = 0.328$, $r = 0.69$, 1M: adj. $p = 0.563$, $r = 0.22$, or 3M: adj. $p = 0.328$, $r = 0.73$; Fig. 8.5). The median w values increased from 0.0165 [IQR: 0.0000–0.0232] at BL to 0.0209 [IQR: 0.0151–0.0256] at PT and 0.0216 [IQR: 0.0158–0.0270] at 3M, while remaining largely comparable to BL at 1M (0.0160 [IQR: 0.0000–0.0239]). The effect sizes were large at PT ($r = 0.69$) and 3M ($r = 0.73$), with a smaller effect observed at 1M ($r = 0.22$).

Across both model types, the gain parameters (g_m and g) and weight parameters (w_E and w) demonstrated consistent directional trends toward improvement following BCI-based intervention. The gain parameter g from the EEG-Dorsiflexion Position model reached statistical significance, showing a very large and significant increase at 1M (adj. $p = 0.047$, $r = 0.96$), coinciding with the broader pattern of peak functional improvement observed at this time point across the biomechanical and neurophysiological assessments.

The weight and gain parameters derived from the EEG-EMG and EEG-Dorsiflexion Position models were compared across all time points to assess their relationship. The EEG-EMG weight w_E was significantly correlated with the EEG-Dorsiflexion Position weight parameter w (slope = 0.962, SE = 0.105, $p < 0.001$), explaining a large proportion of the variance in w ($R^2 = 0.724$; Fig. 8.6). The near-unity slope and near-zero intercept further suggest a strong linear correspondence between the two weight parameters across time points. The

correspondence between the two gain parameters was moderate, with a significant positive linear relationship between g_m and g (slope = 91.323, SE = 20.074, $p < 0.001$, $R^2 = 0.393$).

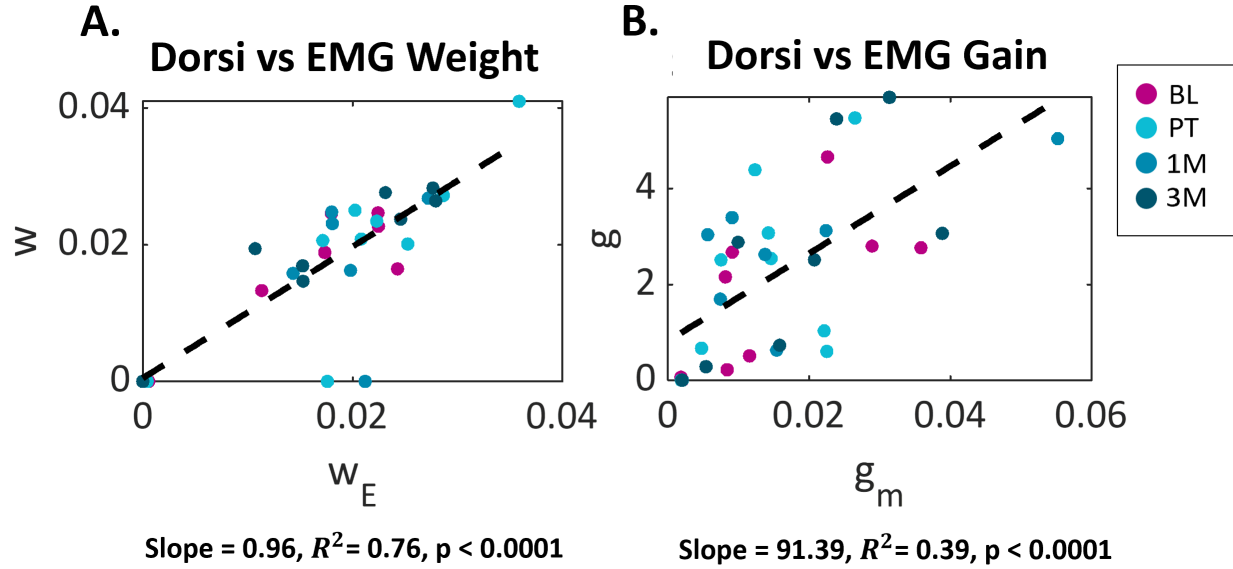


Figure 8.6: Correspondence between weight and gain parameters derived from EEG-EMG and EEG-Dorsiflexion Position

8.4.7 Association of model parameters with biomechanical assessments and gait Speed

All four model parameters demonstrated significant positive associations with both maximum dorsiflexion position and MVC torque across all time points, with gain parameters consistently explaining more variance than weight parameters (see Fig. 8.7). For maximum dorsiflexion position, g explained the greatest proportion of variance ($R^2 = 0.483$, adj. $p < 0.001$), followed by g_m ($R^2 = 0.252$, adj. $p = 0.003$), w_E ($R^2 = 0.186$, adj. $p = 0.014$), and w ($R^2 = 0.159$, adj. $p = 0.024$). The same ordering was broadly preserved for MVC torque, with g again explaining the greatest variance ($R^2 = 0.358$, adj. $p < 0.001$), followed by g_m ($R^2 = 0.287$, adj. $p = 0.002$), w_E ($R^2 = 0.235$, adj. $p = 0.006$), and w ($R^2 = 0.209$, adj. $p = 0.010$).

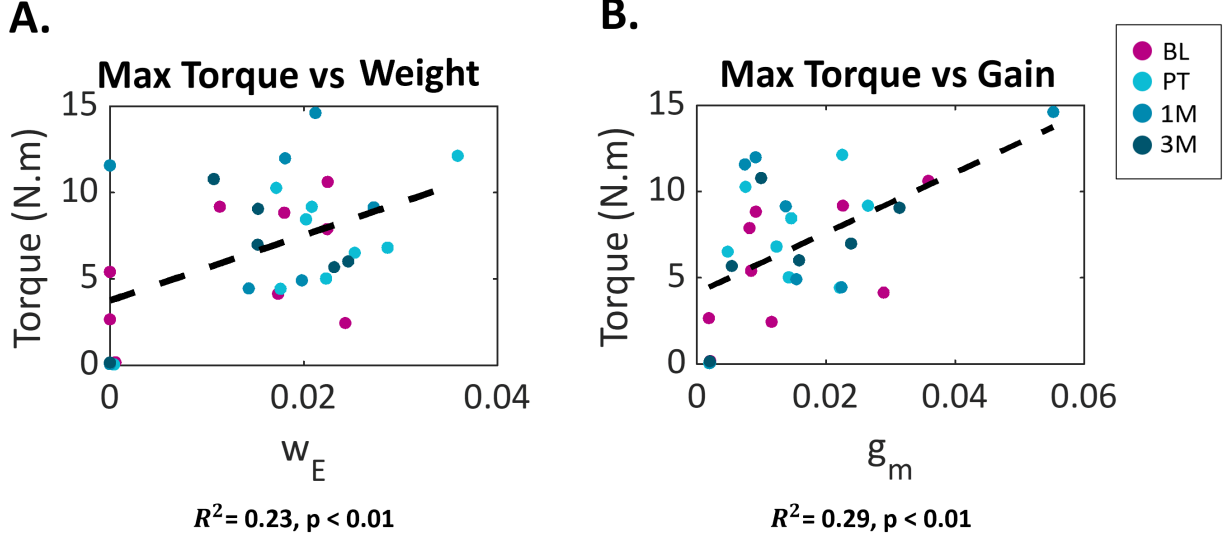


Figure 8.7: Relationship between Biomechanical measures and Neurophysiologically derived weight and gain

Neither w_E ($R^2 = 0.016$, adj. $p = 0.505$) nor g_m ($R^2 = 0.015$, adj. $p = 0.510$) was a significant predictor of gait speed across all time points. However, when examining the change of parameters from BL to PT, the change in w_E was a significant positive predictor of the change in gait speed over the same interval ($R^2 = 0.508$, adj. $p = 0.031$), Fig. 8.8.

8.5 Discussion

In this study, we observed a consistent pattern of neuromuscular improvement following BCI-based intervention across biomechanical, neurophysiological, and functional assessments, with effects peaking at the 1M follow-up. The convergence of medium-to-large effect sizes across maximum dorsiflexion position, torque, and tibialis anterior EMG activity at 1M, despite the absence of statistical significance in most comparisons, is a recurring trend that likely reflects the study being underpowered rather than a true absence of effect. This interpretation is consistent with the broader BCI rehabilitation literature, where small chronic stroke samples are common, and effect sizes are often used as the primary indicator of clinical relevance [138, 23]. The delayed gains from PT to 1M observed across multiple outcome

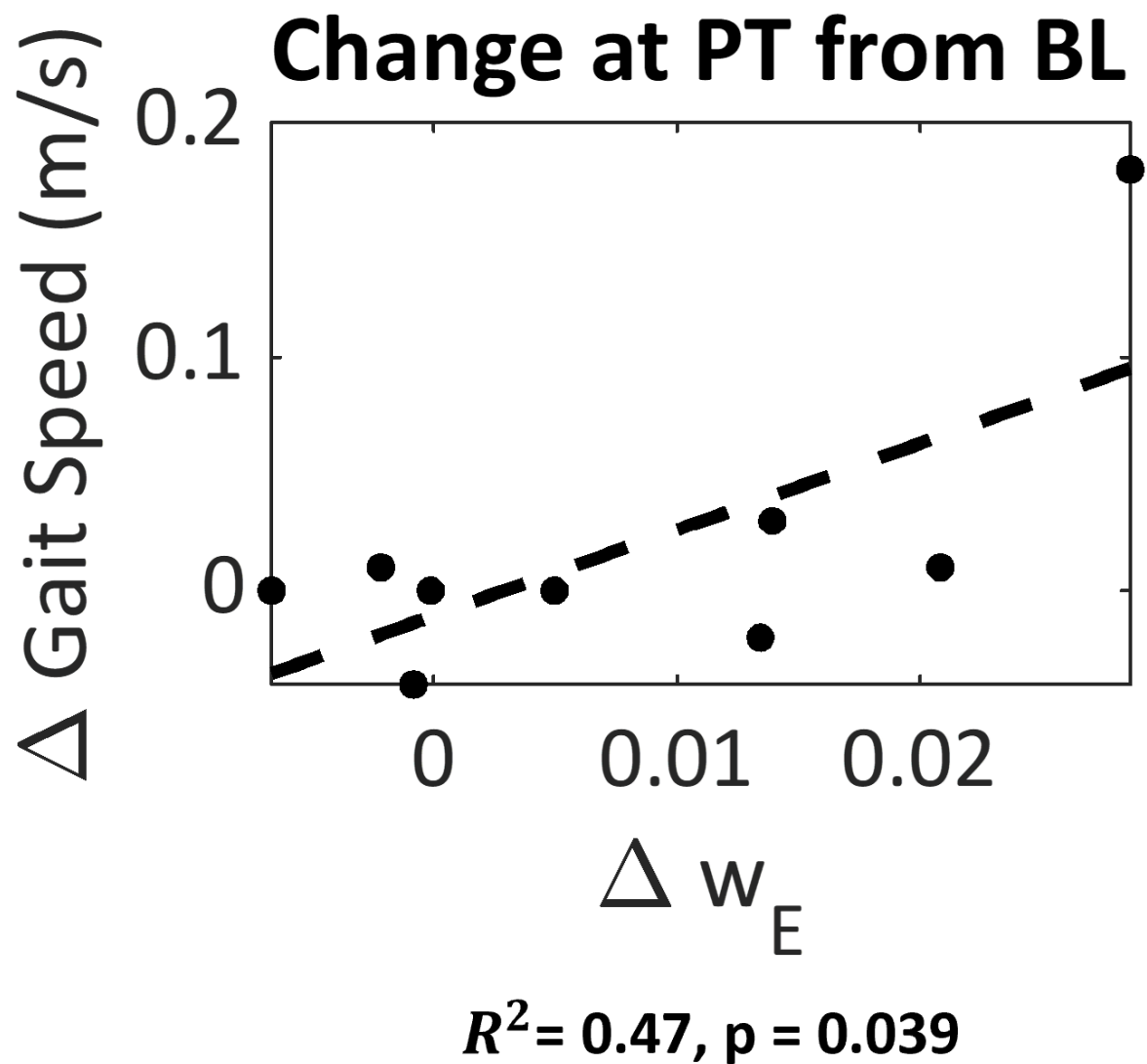


Figure 8.8: Change in weight (Δw_E) from BL to PT had a statistically significant linear relationship with observed change in gait speed

measures may suggest that the neuroplastic processes initiated by BCI-based rehabilitation continue to evolve and enable improvements beyond the immediate post-intervention period.

While the gait speed findings were limited by missed participant visits and AFO usage at later time points, a clinically meaningful improvement was observed at PT for one subject and a second subject at 1M, again reflecting a delay in producing the functional change. The dynamic task findings also reflect this trend of improvement following BCI-based intervention, with the most robust and consistent effects similarly at the 1M time point. The significant improvements in dorsiflexion speed, maximum dorsiflexion position, and tibialis anterior EMG activity during the dynamic task at 1M, with very large effect sizes, suggest that the intervention led to meaningful gains in the active neuromuscular control of ankle dorsiflexion. The trial-level analyses were used to amplify the significant improvements that were not significant in the participant-averaged analyses. These were also more sensitive to within-participant changes and may have captured the actual magnitude of improvement in the small heterogeneous group. The persistent significance at the trial level alongside the non-significant but directionally consistent participant-averaged results again points to high inter-individual variability as the primary limiting factor, rather than an absence of a true treatment effect.

From the EEG features, the statistically significant reduction in ERD magnitude at 3M was a surprising result. While this was unexpected, this result mirrored our observation with the AB group in Chapter 7, suggesting a trend toward the behavior observed in the AB population. Additionally, this could reflect a couple of factors: potential less engagement with the task at 3M [50], either because of the nature of follow-up visits and lowered incentive.

The significant increase in post-movement ERS at 1M is similarly noteworthy, as enhanced post-movement rebound has been associated with more effective inhibitory gating of the sensorimotor cortex following voluntary movement, which could suggest improvement following BCI-driven Hebbian plasticity [60, 97]. The peak ERS enhancement at 1M, coinciding with

peak functional improvements across biomechanical and dynamic task measures, further supports the interpretation that the 1M time point represents a critical window of consolidated neuroplastic change following BCI-based intervention.

The exponential modeling framework offers a novel approach to quantifying corticomuscular integrity in the context of BCI-based rehabilitation, and the results provide some important insights. The consistent directional trends observed across all four model parameters (w_E , w , g_m , and g) toward higher values following intervention, even in the absence of statistical significance in most cases, suggest that the model is sensitive to the underlying neuromuscular changes induced by BCI training.

The gain parameter, which scales the overall output of the neuromuscular mapping, may be particularly sensitive to changes in the descending corticospinal drive to the tibialis anterior, as increased cortical input following BCI-driven Hebbian plasticity would be expected to manifest as a proportional scaling of muscle output based on our computational modeling insights (Chapter 3).

The strong linear correspondence between the EEG-EMG and EEG-Dorsiflexion Position weight parameters, with a near-unity slope, followed the results from our baseline study (Chapter 7), with the near-unity slope suggesting that the weight dynamics captured by the EEG-EMG model are largely preserved when the output is replaced with a kinematic measure. This indicates that the model parameters reflect a generalizable property of the corticomuscular pathway rather than being specific to the EMG signal itself. The moderate correspondence between the two gain parameters is expected, given the inherently different scales and units of EMG and kinematic outputs, and the significant positive relationship nonetheless supports the interpretation that both parameters index a common underlying construct of neuromuscular gain.

The significant associations of all four model parameters with both maximum dorsiflexion position and MVC torque across all time points further validate the relevance of the model parameters with clinical outcomes. The consistently stronger associations observed for the gain parameters compared to the weight parameters across both biomechanical measures again suggest that the gain parameter may be a more sensitive index of neuromuscular capacity, potentially reflecting the degree to which cortical signals are effectively translated into muscle force and joint displacement.

The finding that the change in w_E from BL to PT was a significant predictor of the change in gait speed over the same interval ($R^2 = 0.508$) suggests that early shifts in weight parameters may serve as a meaningful neural biomarker of functional locomotor recovery following BCI intervention. This finding is particularly interesting, considering that gait speed is a highly complex process involving several joints [132, 45], and the experimental setup for this study involved a seated position and isolation of the ankle movement. This explains why such a relationship cannot be observed with the gain, considering the gain is shown to have a stronger relationship to the specific joint movement production. Despite a good explanation of the variability, the robustness of this result should be taken with caution, given the study power.

The results of this study demonstrate a consistent pattern of directional improvement across multiple levels of assessment following BCI-based intervention. Biomechanical assessments revealed significant gains in maximum dorsiflexion position and MVC torque, and the exponential model parameters corroborated these findings, with the gain parameter g reaching statistical significance at 1M and all parameters demonstrating consistent positive associations with biomechanical outcomes. Gait speed, though not significantly predicted by model parameters across all time points, showed a significant association with the change in w_E from BL to PT, suggesting that early shifts in weight may be relevant to functional locomotor recovery. The 1M time point consistently stood out as a period of peak improvement across

functional, biomechanical, and neurophysiological measures, a pattern also observed in our previous work, suggesting that neuroplastic gains may continue developing beyond the immediate post-intervention period. Finally, these findings support the potential of BCI-based rehabilitation to drive meaningful and lasting neuromuscular recovery in chronic stroke, and highlight the use of the novel dynamic assessment framework as a comprehensive method of tracking therapeutic outcomes and neurophysiological changes beyond static measures.

Chapter 9

Conclusions and Future Directions

The progress of BCI as a stroke rehabilitation intervention has been consistently demonstrated in the literature, large clinical trials have not yet been established. For quantifiable functional gains, interventions require longer treatment doses of over 8 weeks, and current clinical assessments are primarily limited to functional outcomes under static conditions or with external stimulation. These limitations motivated the development of a series of novel contributions presented in this dissertation.

We first developed a computational framework based on human motor control theory that models the sensorimotor control loop governing ankle dorsiflexion (Chapter 2). The model incorporated both feedforward motor commands and sensory feedback pathways, allowing simulation of different sites of neurological injury leading to foot drop after stroke. Using this framework, we identified which specific pathway disruptions could have the most impact on clinically observed impairment patterns, isolated potential therapeutic targets, and generated predictions about how BCI-based intervention may affect these pathways. These simulations informed the design of the neurophysiological assessment and guided the hypotheses tested in subsequent chapters.

Guided by these computational insights, we then described the design of the Ankle Measuring Proprioception Device (AMPD), a custom robotic platform built to facilitate simultaneous collection of kinematic, EEG, and EMG data during dynamic ankle movement tasks (Chapter 3). AMPD was designed to support both biomechanical assessments, including active range of motion and MVC torque, and the neurophysiological assessment protocol, providing a controlled and repeatable dynamic movement paradigm suitable for deployment in a clinical trial setting.

We also developed a novel signal processing framework for quantifying EEG movement-related features, personalizing the estimation of ERD and ERS frequency bands, and channel selection (Chapter 6, Appendix A). Rather than applying fixed frequency bands, a custom algorithm using robust statistical methods identified the most informative EEG channels and frequency bands for each participant, improving the sensitivity of feature extraction. This approach was validated against standard fixed-band methods, with results remaining consistent across both.

Building on this infrastructure, we implemented and validated the novel non-invasive neurophysiological assessment in able-bodied and chronic stroke participants (Chapters 4 and 7). The assessment combined EEG, EMG, and kinematic measures during active repeated ankle dorsiflexion at self-paced slow and fast speeds. An exponential modeling framework was applied to quantify the trial-wise mapping between cortical activity and both EMG and dorsiflexion position, yielding weight and gain parameters. The gain parameters were significantly lower in the stroke group than in able-bodied participants (adj. $p < 0.001$), while the weight parameters were comparable across groups, suggesting that the gain reflects corticospinal integrity while the weight captures a more preserved aspect of corticomuscular organization.

Finally, we applied this assessment longitudinally in chronic stroke participants undergoing BCI-based rehabilitation (Chapters 5 and 8). The model parameters demonstrated consistent

directional improvement across all time points, with the gain parameter g reaching statistical significance at 1M, and all four parameters showing significant positive associations with maximum dorsiflexion position and MVC torque. The change in weight parameter w_E from baseline to post-treatment was a significant predictor of the change in gait speed, further supporting the clinical relevance of the proposed framework. Future work should focus on higher-density acquisition, richer movement protocols, characterization of the afferent pathway, and validation in larger cohorts undergoing longer interventions combined with complementary neuroplasticity measures.

9.1 Future work

Three primary future directions are identified from this work. Each builds on the contributions described above and begins with dataset and clinical considerations before moving toward deeper questions of a principled, mechanistic understanding of movement and how it can be restored.

9.1.1 1: Data collection upgrades and larger cohorts

While the data collection paradigm implemented in this work utilized 25 of the available 64 EEG channels, EMG was recorded using a single channel placed on the TA muscle. Expanding coverage to utilize all 64 channels would provide a more complete picture of cortical activity, enabling investigation of whether the changes observed in the motor cortex are accompanied by concurrent activity in other regions, such as the frontal and prefrontal areas involved in motor planning and executive function. Single-channel EMG recordings are sensitive to electrode placement [148], which can impact both signal quality and repeatability across sessions. Transitioning to high-density EMG arrays could not only provide greater spatial resolution of neuromuscular activity but also enable the simultaneous study of multiple muscles, offering deeper insight into how different muscle groups coordinate to

produce movement. Additionally, incorporating an fNIRS system could provide complementary hemodynamic information, offering a means to quantify changes such as muscle fatigue and cortical hemodynamic shifts that may emerge following stroke and across the course of rehabilitation.

Upgrading the experimental protocol would also strengthen the model’s sensitivity and generalizability. Testing in larger cohorts undergoing longer interventions of greater than 8 weeks, ideally combined with structured physical therapy, would help maximize functional outcome improvements and provide greater statistical power for biomarker validation. Expanding movement protocol variability by systematically controlling amplitude and EMG output generation, in addition to the established velocity conditions, would enable a more thorough parametric investigation of the model’s response to kinematic and neuromuscular parameters. Integrating complementary neuroplasticity measures such as corticomuscular coherence, motor evoked potentials, and diffusion tensor imaging would further validate the distinct contribution of the proposed biomarkers to rehabilitation assessment. Extending this approach to other rehabilitation interventions in larger cohorts with lesion-specific subgroup analyses would also allow for direct comparisons across methods and enable hypothesis testing grounded in the computational modeling framework developed in this dissertation.

Finally, the movement paradigm itself also presents several meaningful opportunities. First, we plan to repeat the current ankle dorsiflexion protocol on the stronger, uninjured side within the stroke population. The current work focuses exclusively on the injured side, and including the contralateral limb would provide a within-subject reference for direct comparison of the corticospinal drive between the two sides. This could help characterize the degree of motor asymmetry present and how it evolves over the course of rehabilitation. Additionally, walking is a fundamentally complex, multi-joint process [150]. While dorsiflexion impairment is a central feature of foot drop post stroke, plantarflexion is also affected and plays a critical role in push-off mechanics during gait [44]. The coordinated relationship

between agonist and antagonist muscle groups at the ankle, along with contributions from the hip and proximal limb musculature, is integral to functional ambulation.

Extending the paradigm to capture EEG across the phases of the gait cycle, paired with high-density EMG arrays recording from multiple lower limb muscle groups simultaneously, would allow for an even more comprehensive characterization of the neural and neuromuscular dynamics underlying walking post stroke. This would shift the framework from isolated joint-level analysis toward a more functionally meaningful assessment directly relating to walking abilities.

Implementing this study on upper extremity movement would also be meaningful. The neural control of the upper limb introduces additional complexity relative to the lower extremity, especially relating to hand or finger functionality [56, 110]. Applying this paradigm to upper extremity tasks would broaden the clinical applicability of the framework and also allow us to examine hemispheric differences in motor generation that are much more apparent due to the clearer separation of sides in the motor cortex representation of the upper extremities. The bilateral nature of upper limb movement, combined with the broader EEG coverage discussed earlier, would provide additional insight into how motor drive differs between the affected and unaffected sides and how these differences evolve across rehabilitation.

9.1.2 2: Investigating other pathways within the sensorimotor control loop

The focus of this work was primarily on modeling and quantifying the efferent pathway from cortex to muscle. However, the original control model of dorsiflexion identified additional pathways contributing to the total sensorimotor output, including sensory and cortico-cortical interactions. The afferent pathway in particular should be investigated further, as sensory integrity has been shown to predict rehabilitation outcomes in stroke, and several rehabilitation interventions specifically target its restoration.

Somatosensory deficits are often accompanied by motor deficits post-stroke, yet the clinical tools currently available for quantifying these deficits remain limited in their sensitivity and scope. Commonly used assessments such as the Nottingham Sensory Assessment [53], tuning fork testing, two-point discrimination [142], and joint position reproduction [11] offer valuable but largely static and subjective characterizations of sensory function. More recently, novel assessments have been developed on the 2AMPD robotic platform, including the Criss Cross and Move and Match (a dynamic form of joint position reproduction) paradigms [36]. These provide a more nuanced and quantitative characterization of sensory function, particularly under dynamic conditions that more closely reflect real-world movement. Incorporating EEG recordings alongside these assessments would add a measure of the cortical response to sensory input, enabling a more objective and comprehensive characterization of sensory pathway integrity in stroke. This combination has the potential to serve as a robust multi-modal sensory assessment tool that bridges behavioral and neurophysiological measurement in a way that current clinical tools cannot.

To begin exploring this direction, a passive movement paradigm was implemented with participants from both study groups (AB and STR). EEG, EMG, and trajectory data were collected as 2AMPD passively moved participants' ankles through a repeated dorsiflexion paradigm analogous to the active protocol described in this work. Preliminary analyses revealed that in a subset of participants, passive movement triggered an ERD followed by a post-movement ERS, often accompanied by a distinct ERD-ERS pattern from individual dorsiflexion-plantarflexion movements. The ERD during passive movement may reflect sensory-driven desynchronization of the sensorimotor cortex in response to proprioceptive input, while the subsequent ERS may reflect cortical idling or inhibition following movement cessation. These signatures may therefore be physiologically meaningful markers of afferent proprioceptive pathway integrity.

This preliminary study should be further explored in a large cohort by stratifying the stroke participants by degree of sensory impairment and examining whether these passive movement EEG signatures differ meaningfully across subgroups. Not all stroke survivors experience equivalent sensory deficits, and this variability could contribute to differences in rehabilitation trajectory and outcome. Correlating the model parameters of the EEG-passive movement trajectory relationship with both established clinical sensory assessments and the novel 2AMPD-based proprioception measures described above would help validate these neurophysiological signatures as objective indicators of afferent pathway integrity.

Building further on this, cortico-cortical coherence analyses [118, 115], incorporating directionality, could be implemented to capture interactions between different brain regions, such as sensory to motor and motor to premotor areas. This would extend the modeling framework beyond the corticospinal pathway examined here and provide a more complete characterization of the broader sensorimotor network. However, such analyses may benefit from higher electrode density for EEG than currently employed, and in some cases, more spatially precise recordings, such as electrocorticography (ECoG), may be better suited for resolving cortico-cortical connectivity for proximal regions. Therefore, expanding the framework to include the afferent pathway alongside the efferent mechanisms already characterized would move this work toward a more complete account of the sensorimotor loop underlying voluntary movement and its disruption following stroke.

9.1.3 3: Developing a mechanistic understanding of movement

The focus of the previous two directions is on enriching the dataset and broadening the clinical applicability of the framework, building the foundation for understanding the mechanisms underlying both movement and rehabilitation. While examining these movements and abilities individually offers meaningful insight, there may be greater value in adopting a skill-based view of learning rather than treating each in isolation. Wolpaw’s recent work

on heksors [143] focuses directly on this, particularly in the context of BCIs. The central argument is that functional recovery may be most effectively achieved not by developing BCI-based or muscle-based skills independently, but by their joint development, framing the co-acquisition of neural and muscular skill as a unified, bidirectional learning process. This aligns with the co-adaptation framework, where both the user’s nervous system and the BCI system continuously adapt to one another over time, much as the sensorimotor system refines itself through ongoing efferent and afferent interaction. With this in mind, the computational framework developed here can be extended to study how these two classes of skill interact and develop longitudinally over the course of rehabilitation. Characterizing this joint trajectory could help identify which patients are most likely to benefit from BCI-assisted approaches and at what stage of recovery, ultimately informing the design of more targeted and responsive rehabilitation interventions.

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Appendix A

Estimation of trial-wise ERD and ERS from EEG Data

A.1 Extracting epochs from trajectory Data

To extract the ERD and ERS for the trials, the data were divided into 1-second-long epochs. First, the reference was defined as the 2 sec to 7 sec period at the beginning of each trial in the Relax trial-state. The idle was defined as 8 sec to 13 sec period in the same trial state. Each 5 sec period was then separated into the 1 sec epochs (30 trials would result in 150 reference epochs and 150 idle epochs).

Next, a 1 sec period was extracted from the start of each discrete dorsiflexion movement for both slow and fast trial states from the filtered trajectory data. For this, peaks and troughs of movement were detected using a threshold-based algorithm, where peaks that exceeded the mean signal amplitude and were separated by a minimum inter-peak distance of 0.5 sec to prevent detection of spurious oscillations within a single tap. The same procedure was applied to the inverted signal to identify troughs. To ensure physiologically valid peak-

trough pairings, an iterative cleaning procedure was applied to enforce strict alternation between consecutive peaks and troughs. If no movement was detected, the entire trial state, defined by the visual cues, was divided into non overlapping 1 sec epochs. All slow and fast movement epochs together were the “move” epochs.

Finally, post movement was defined as the first 3 sec period right after movement cessation for both slow and fast, defined as reaching 1% of maximum peak movement, further divided into 1 sec epochs, and when combined for post-slow and post-fast referred to as “post-move” epochs. The corresponding synchronized EEG data epochs were used to estimate the Power Spectral Density (PSD).

A.2 Choosing source channel and personalizing frequency bands

PSD was estimated for each 1 sec epoch with equal-length Hamming windows and no overlap with frequency bins of 0.5Hz. To choose the optimum source channel and personalized frequency bands, the maximum statistically significant event-related activity was calculated. A Wilcoxon rank-sum test ($\alpha = 0.05$) was used to determine which frequencies in the PSD were significantly desynchronized for move epochs and resynchronized for post-move epochs when compared to reference conditions. μ measure, a measure of statistical distance between two populations [74], was calculated for each frequency bin within the μ - β (8Hz - 13Hz) range. The source electrode was selected from a subset of 5 electrodes over the M1 foot area: Fz, C1, Cz, C2, and CPz to account for cap-mounting differences. The electrode corresponding to the highest Mu measure within the significant frequency ranges was used to choose the source electrode. If statistical significance was not achieved, the default electrode was set to Cz.

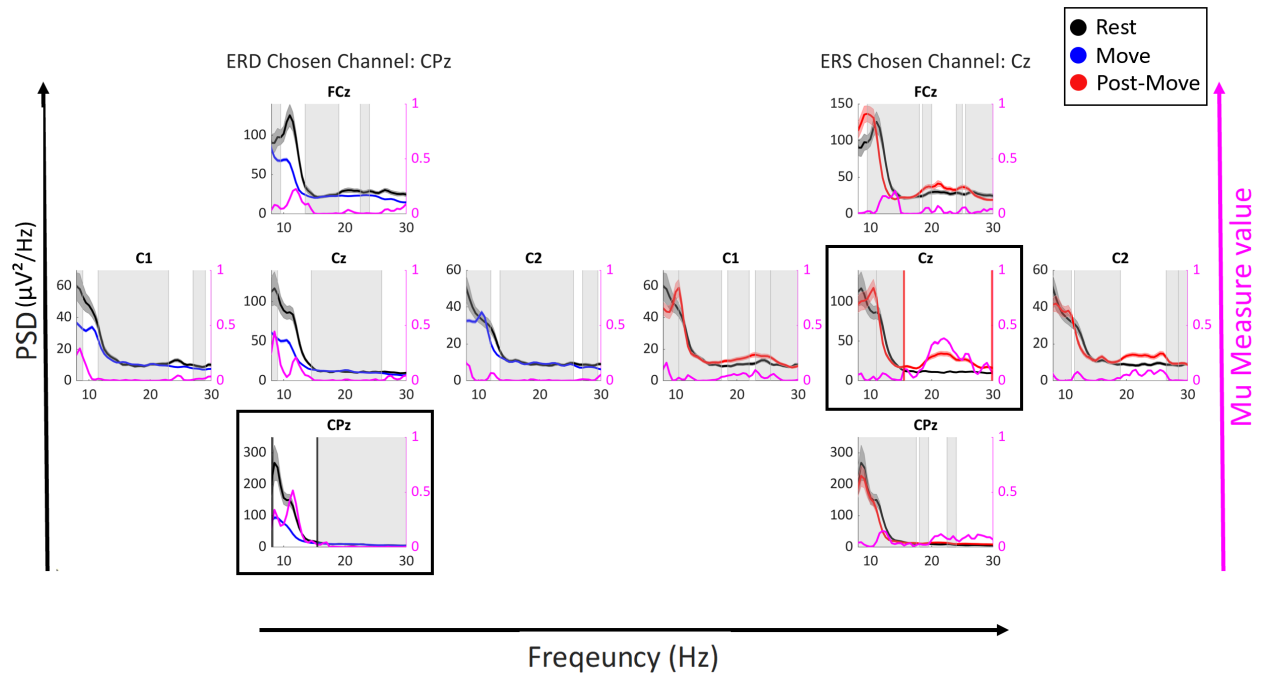


Figure A.1: Source channel and personalized frequency band selection. The set of panels on the left shows the ERD, and the right shows the ERS in topographically closest channels surrounding C_Z . The left y-axis represents the PSD values, and the right y-axis represents the μ measure value used to measure effect size. The channels chosen as source channels are highlighted by boxes with the chosen personalized and significant frequency bands.

The personalized frequency band was determined as the largest band of significant frequencies containing the maximum μ measure. Any gaps smaller than or equal to 2Hz were bridged when searching for the contiguous frequency band. If no significant frequency band was found, the entire μ - β range was used as the default. Signal power was re-computed for the chosen electrode and personalized frequency band for each epoch and averaged over epochs for each trial in each trial state. Trial-wise ERD and ERS features were quantified as the percentage change of average signal power for slow, fast, post-slow, and post-fast epochs from reference epochs for each trial. The overall ERD and ERS features were the average of these trial-wise features.