



# Development of a Multiparametric Postural Control Signature: BioVRSea paradigm

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Dissertation submitted to the Department of Engineering at Reykjavík  
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BioVRSea paradigm**

submitted by **Lorena Guerrini** in partial fulfillment of the requirements for  
the degree of **Doctor of Philosophy (Ph.D.) in Engineering**

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## **Abstract**

**Intro:** The proposed thesis builds on an extensive investigation into the complex motor and sensory neural mechanisms underlying human balance in response to visuomotor stimulation. It employs a multi-modal approach, combining neurophysiological and biomechanical measurements within a purpose-built virtual reality environment, the BioVRSea.

**Results:** The thesis demonstrates how identifying sensitive biomarkers can contribute to the development of a multi-parametric profile of postural control in healthy individuals. This profile enables the detection of subtle changes associated with aging, medical conditions or experiences such as long-term training in unstable environments. The findings also highlight the potential of this approach to support the diagnosis of Parkinson's disease in its early stages and persistent post-concussion symptoms.

**Conclusion:** The identification of biomarkers from non-invasive bio-signals, combined with the novel methodologies proposed in this study, can lead to the development of innovative tools for clinical assessment, monitoring and support in evaluating postural control deficits and neurodegenerative diseases

**Keywords:** Postural control, motor visual task, Parkinson's disease, post concussion disability, electroencephalography (EEG), electromyography (EMG), center of pressure (CoP), BioVRSea

## Ágrip

Inngangur: Ritgerðin byggir á umfangsmikilli rannsókn á flóknum hreyfi- og taugakerfisferlum sem liggja að baki jafnvægi manna við sjón-hreyfi ertingu. Hún nýtir fjölþætta nálgun að vandamálinu og sameinar taugaeðlisfræði- og verkfræðilegar líftækni mælingar innan sérhannaðs sýndarveruleika umhverfis.

Niðurstaða: Ritgerðin sýnir hvernig greining á næmum lífmerkjum getur stuðlað að þróun fjölþætta mælikerfis yfir stöðugleikastjórn hjá heilbrigðum einstaklingum. Þetta mælikerfi gerir kleift að greina smávægilegar breytingar sem tengjast sjúkdómum eins og afleiðingum heilaáverka, öldrun og flóknum taugahrönnunarsjúkdómum. Sérstaklega ber að hafa í huga möguleika þessarar nálgunar til að styðja við snemmkomna greiningu á Parkinsons-sjúkdómi.

Samantekt: Greining lífmerkja með mælingum án áverka, ásamt nýstárlegum mæliaðferðum sem lagðar eru til í þessari rannsókn, geta leitt til þróunar nýrra verkfæra fyrir klínískar greiningar og eftirlit á afleiðingum áverka á heila, öldrun og taugahrönnunarsjúkdómum sem samanlagt hafa áhrif á stöðu- gleikastjórnun.

**Leitarorð:** Stöðugleikastjórnun, sýndarveruleiki (VR), taugahrönnun, heilahristingur, heilarafritun (EEG), vöðvarafritun (EMG), fótaspors þrýstingur (CoP), BioVRSea

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# List of Abbreviations

| Abbreviation | Meaning                        |
|--------------|--------------------------------|
| PC           | Postural Control               |
| VR           | Virtual Reality                |
| CoP          | Center of Pressure             |
| CoM          | Center of Mass                 |
| EEG          | Electroencephalography         |
| EMG          | Electromyography               |
| ECG          | Electrocardiography            |
| HRV          | Heart Rate Variability         |
| HR           | Heart Rate                     |
| FP           | Force Platform                 |
| AP           | Anterior-posterior             |
| ML           | Medio-lateral                  |
| PD           | Parkinson's Disease            |
| FFT          | Fast Fourier Transform         |
| BH           | Benjamini–Hochberg             |
| FDR          | False Discovery Rate           |
| IMU          | Inertial Measurement Unit      |
| BMI          | Body Mass Index                |
| CI           | Complexity Index               |
| wMNW         | Weighted Minimum Norm Estimate |
| PLV          | Phase-Locking Value            |
| BEM          | Boundary Element Method        |
| FEM          | Finite Element Method          |



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# Chapter 1

## Introduction

### 1.1 Postural Control (PC)

Postural control (PC) is a fundamental aspect of human motor function, referring to the complex ability to achieve, maintain, or restore balance during both static and dynamic postures. Despite being essential for daily activities, PC represents a highly complex mechanism that is challenging to fully understand, study, and evaluate. Although the majority of individuals maintain effective postural control, a considerable proportion of the global population experiences balance impairments, which can significantly affect mobility and quality of life. PC plays a crucial role in functional movement and in the effective response to external perturbations encountered in daily life [1]. The term itself is derived from two components: “postural,” which pertains to the spatial orientation and alignment of the body, and “control,” which encompasses the regulatory mechanisms that coordinate sensory inputs and motor outputs to maintain stability. This definition emphasizes PC as an integrative process, reflecting the interplay between neural, musculoskeletal (motor), and sensory systems required for adaptive and precise postural regulation, as shown in Figure 1.1. PC can be categorized into static and reactive components. Static stability involves maintaining the body’s center of mass (CoM) within its base of support, whereas reactive control governs compensatory responses to unexpected perturbations. Multisensory integration is essential for effective postural regulation, as the central nervous system (CNS) dynamically combines and weights afferent inputs from the somatosensory, vestibular, and visual systems to generate an optimal internal estimate of body dynamics across varying postural configurations and environmental contexts.

#### 1.1.1 Physiology behind PC

##### **Motor Strategies and Biomechanics of Postural Control**

From a biomechanical perspective, PC relies on the coordinated recruitment of primary strategies, including the ankle, knee, hip, and stepping strategies [3].

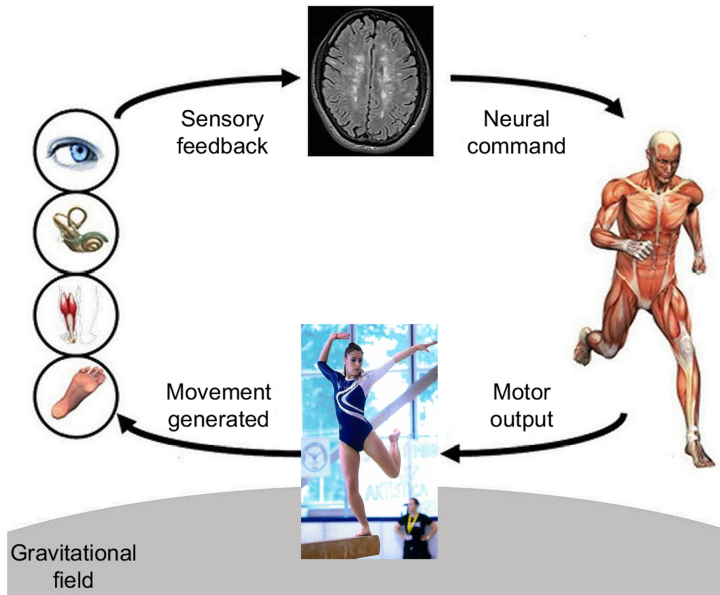


Figure 1.1: Postural and motor control [2]. Sensory inputs (visual, vestibular, and somatosensory) are integrated by the central nervous system to generate neural commands that produce motor and postural outputs. The resulting movement or balance continuously updates sensory feedback within a closed-loop system under the influence of gravity

These strategies are employed to maintain balance by generating appropriate joint torques and body segment movements in response to variations in the CoM and external perturbations. The ankle strategy is employed to regulate small, slow postural sway during standing. It involves the initial activation of the ankle dorsiflexor or plantarflexor muscles, followed by the engagement of hip and trunk musculature, resulting in the upper and lower body moving synchronously as a single inverted pendulum over the ankle joints. When the CoM moves rapidly or when the support surface is narrow, the hip strategy is recruited. This strategy is characterized by the initial activation of large hip and trunk muscles, including the hip abductors, followed by engagement of ankle musculature, causing the upper and lower body to move in opposite directions to restore balance. For larger or faster perturbations, or when the limits of stability are exceeded, the stepping strategy is employed, involving a compensatory step to prevent a fall. Effective execution of this strategy relies on rapid central processing and timely initiation of movement. Anticipatory postural adjustments (APAs) are feedforward mechanisms that activate muscles in advance of voluntary movements to counteract self-induced destabilization. [4]. APAs are centrally programmed and occur prior to movement initiation, typically 40–150 ms before the action. Reactive postural responses (RPRs) are feedback mechanisms triggered by unexpected external perturbations and

involve rapid, automatic activation of muscle synergies to restore equilibrium. RPRs are scalable to the magnitude of the disturbance and are refined by experience.

The selection and modulation of postural strategies are dependent on both the specific task and the environmental context. Synergistic muscle groups act in a coordinated manner to control joint movements and restore the body to a stable position. Effective balance maintenance requires motor responses that are precisely timed and appropriately scaled, with muscles activating in a well-organized sequential pattern.

### **Neural Mechanisms Underlying Postural Control**

PC is the result of different parts of the nervous system working together to keep the body balanced and stable. This control happens at multiple levels, from the spinal cord up to the brain [5]. At the spinal level, reflex circuits and neuronal networks regulate muscle activation and coordinate agonist and antagonist muscles. These mechanisms allow for fast, automatic responses to disturbances. The brainstem acts as a central hub, integrating sensory information from the body and environment to adjust muscle tone and automatic postural reactions, ensuring balanced muscle activity. The cerebellum plays a key role in comparing incoming sensory information with motor commands. It helps correct postural errors, fine-tune movements, and adapt posture to different tasks. The basal ganglia contribute to the selection and initiation of appropriate postural responses, suppress unnecessary movements, and support automatic postural strategies. Higher brain areas, such as the cerebral cortex, are involved when PC requires attention, planning, or adaptation to new or complex situations. Cognitive functions like attention and executive control therefore influence postural stability. Finally, the nervous system continuously integrates sensory input from the visual, vestibular, and somatosensory systems. Depending on the environment and the task, the brain dynamically adjusts the weight given to each sensory source to maintain balance.

#### **1.1.2 Across Lifespan and in Neurological Disorders**

PC undergoes a developmental progression, maturing from the head to the trunk and finally to the lower limbs, with early postural regulation relying predominantly on feedback mechanisms and anticipatory control emerging later [6]. Sensory integration also evolves during childhood, with vision dominating in infancy and gradual shifts toward somatosensory and vestibular contributions, leading to mature multisensory postural control typically achieved between 7 and 10 years of age. This developmental foundation underlies stable and adaptive balance throughout adulthood.

With advancing age, PC gradually declines due to reductions in muscle strength, flexibility, and reaction speed, coupled with age-related deterioration of visual, vestibular, and somatosensory systems. These changes compromise the detection of and response to postural perturbations, while slower central

processing and decreased proprioceptive sensitivity, particularly in the lower limbs, further elevate the risk of falls. Neurological conditions, including Parkinson's disease, stroke, multiple sclerosis, and vestibular disorders, can profoundly impair PC by disrupting sensory integration, motor coordination, and the neural networks responsible for balance [7]. In Parkinson's disease, for example, dopaminergic deficits, rigidity, and impaired automatic postural reflexes contribute to increased body sway and risk of falls.

Given the dynamic interplay between developmental maturation, aging, and pathological influences on PC, its assessment is critical in clinical practice. Accurate evaluation enables clinicians to identify deficits, monitor disease progression, guide individualized rehabilitation, and implement fall-prevention strategies. Postural control can be assessed through direct observation of movement patterns, standardized clinical scales such as the Berg Balance Scale or the Functional Reach Test, and instrumented measurements that provide objective, quantitative insights into body sway, CoM displacement, and postural responses. Comprehensive assessment is therefore essential for understanding functional balance, optimizing interventions, and mitigating the risk of falls across the lifespan.

### 1.1.3 State of Art in Clinical Evaluation

Clinical assessment of PC includes a range of tests that typically evaluate postural sway during quiet stance under eyes-open and eyes-closed conditions. Among these, the Romberg test is one of the most widely used clinical assessments and has been employed in practice for over 150 years [8]. It is particularly useful for identifying sensory ataxia, a gait and balance disorder resulting from impaired proprioceptive input related to joint position and movement, commonly associated with degeneration of the dorsal columns of the spinal cord, as observed in conditions such as vitamin B12 deficiency. The test is performed by asking the patient to stand with feet together, arms alongside the body or crossed in front of the chest, first with eyes open and then with eyes closed, attempting to maintain balance. Performance is typically quantified by measuring the duration for which the patient can maintain the standing position with eyes closed, and the test is considered positive when the patient demonstrates excessive sway, compensatory steps, or a fall (Figure 1.2a). Despite its long clinical use, the Romberg test remains largely qualitative and provides limited insight into the underlying mechanisms of PC. To complement such evaluations, more structured clinical tools, including the Berg Balance Scale (BBS) and the Functional Reach Test (FRT), are frequently employed. The BBS consists of 14 tasks of increasing difficulty that assess balance during daily activities such as standing, reaching, turning, and transferring, with each task scored from 0 to 4 (maximum total score of 56); lower scores indicate higher fall risk. The FRT measures the maximal forward reach without stepping or losing balance, providing an index of anterior-posterior stability and dynamic trunk control. Both assessments are simple to administer, validated in clinical populations, and useful for evaluating balance impairments and predicting fall risk. While the Romberg,

BBS, and FRT provide valuable information about postural performance, more structured protocols such as the Clinical Test of Sensory Interaction on Balance (CTSIB) systematically manipulate sensory inputs to assess sensory integration [9]. The CTSIB evaluates how individuals integrate visual, somatosensory, and vestibular information to maintain postural stability across different conditions, and performance can now be quantified using instrumented implementations with force plates, inertial sensors, or motion capture systems [10]. These tools allow precise measurement of center-of-pressure displacement, sway velocity, and non-linear metrics, providing sensitive and objective characterization of PC. Similarly, instrumented assessments such as the Sensory Organization Test (SOT) use dynamic force plates, visual surrounds, or virtual reality to manipulate sensory inputs and quantify postural responses. Performance is evaluated through equilibrium scores, sensory analysis ratios, and sway characteristics, enabling the detection of subtle impairments, differentiation of sensory deficits, and monitoring of rehabilitation outcomes [11].

In addition, Inertial Measurement Unit (IMU) devices, including accelerometers and gyroscopes, are increasingly used to quantify PC during sitting, standing, and walking. These sensors are typically placed on the trunk, pelvis, or lower limbs to capture three-dimensional linear accelerations and angular velocities. By analyzing these signals, researchers can extract quantitative measures such as sway amplitude, sway velocity, trunk tilt, step variability, and postural transitions, providing insight into dynamic balance strategies, segmental coordination, and compensatory movements. IMU-based assessments are particularly valuable for evaluating PC in different environments, such as daily life activities, where laboratory-based force plates are impractical.

Beyond biomechanical and clinical evaluations, neuroimaging and electrophysiological techniques have been increasingly applied to investigate the neural mechanisms underlying balance. Electroencephalography (EEG), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI) have all contributed to elucidating the cortical and subcortical networks involved in postural control. Research applying these techniques to PC began in the 1990s, when EEG studies first revealed cortical involvement in anticipatory and reactive postural adjustments. PET studies during upright stance demonstrated activation in cerebellar and visual cortical areas, highlighting the critical role of sensory integration in maintaining balance. With the development of fMRI, researchers have increasingly explored functional networks engaged during postural tasks, despite technical challenges related to imaging posture.

Today, EEG provides high temporal resolution to investigate rapid neural dynamics and cortical oscillations during balance tasks, PET and fMRI provide spatially precise maps of brain regions involved, and combining these methods allows researchers to link behavioral measures of balance with underlying neural activity. These approaches have advanced our understanding of the cortical and subcortical networks responsible for sensory integration and motor coordination [5].

Neurorehabilitation strategies to improve PC target both sensory integration and motor function in individuals with balance impairments. Virtual reality

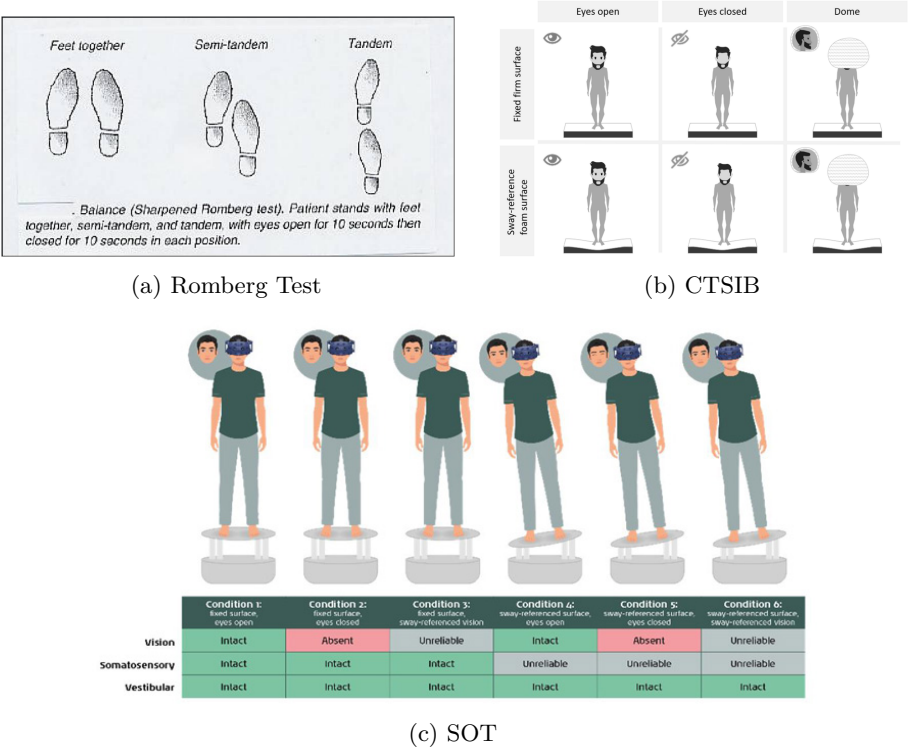


Figure 1.2: Conventional clinical assessment tests

(VR) offers immersive, interactive environments that challenge balance under controlled and progressively varied conditions, providing real-time visual and proprioceptive feedback that facilitates motor learning and enhances postural responses [12]. Assisted gait training, including treadmill-based or robotic-supported systems, promotes repetitive, task-specific practice of walking and postural adjustments, reinforcing neural circuits involved in locomotion and balance. Non-invasive brain stimulation techniques, such as transcranial direct current stimulation (tDCS), can be combined with physical rehabilitation to enhance neural plasticity, modulate cortical excitability, and potentially accelerate the acquisition of PC skills. In addition, cognitive-motor dual-task training challenges individuals to maintain balance while simultaneously performing attention-demanding tasks in real-world environments.

1.1.4 New Directions for PC Evaluation

Recent approaches to PC assessment are shifting from traditional clinical tests toward quantitative and multimodal methods, although most evaluations are still conducted in static laboratory settings. Instrumented tools, such as force plates and wearable IMUs, can be integrated with virtual or augmented reality

environments to provide controlled sensory perturbations and real-time feedback. The addition of neuroimaging techniques, including EEG, allows investigation of the neural mechanisms underlying balance, while computational analyses and machine learning (ML) enhance the detection of subtle impairments and enable prediction of fall risk. Furthermore, dual-task and functional assessments performed in real-life scenarios provide insight into the integration of cognitive and motor functions required for daily activities. Integrative approaches that combine force, motion, neuroimaging, and physiological signals are increasingly used to study the interplay between motor, sensory, and cognitive components of PC. These multimodal assessments allow researchers to examine how factors such as attention, fatigue, or stress influence balance in real time, offering opportunities for targeted rehabilitation strategies. Advances in tele-monitoring and home-based evaluations now enable continuous tracking of postural stability in real-world environments, facilitating early detection of subtle impairments and supporting proactive interventions before functional decline occurs. Collectively, these innovations represent a paradigm shift in PC assessment, from isolated, largely static laboratory tests to integrated, adaptive, and predictive systems that reflect the complexity and variability of everyday balance. This approach not only improves diagnostic precision and fall prevention but also supports the personalization of rehabilitation strategies across diverse populations, including hidden disability after brain concussion and individuals, especially adults, with all the complicated expressions of neurological disorders.

### 1.1.5 The Effectiveness of Early-Stage Detection in Neurological Diseases

Given that PC is susceptible to age-related decline and neurological disorders, and that its assessment is non-invasive, quantitative evaluation of balance can provide valuable early indicators of dysfunction. Detecting subtle changes in postural stability may facilitate timely diagnosis. Early detection is particularly important in neurodegenerative diseases, as minor impairments in balance and PC often precede overt clinical symptoms and may remain undetected with conventional assessments. Objective methods, including center of pressure (CoP) analysis and wearable sensor technologies, have shown promise in identifying these early deficits. In particular, spectral and nonlinear features extracted from postural sway data can reveal alterations in sensory integration, motor planning, and adaptive postural responses before significant mobility limitations emerge. The clinical relevance of early detection lies in its ability to inform interventions aimed at slowing disease progression, reducing fall risk, and improving quality of life. By integrating quantitative postural metrics with standard clinical evaluations, clinicians can more accurately stratify patient risk, monitor disease evolution longitudinally, and tailor rehabilitation strategies to individual needs. Moreover, identifying impairments at an early stage facilitates research into therapies, allowing interventions during periods when neural circuits retain considerable plasticity. Assessment of PC in the early stages of neurodegenerative disease thus provides a critical window into the functional

integrity of the nervous system, offering both diagnostic and prognostic insights with substantial implications for patient management and clinical research.

## 1.2 Objectives of the Thesis

The primary objective of this thesis is to investigate PC mechanisms using an immersive and multimodal experimental framework based on the BioVRSea paradigm. By integrating neural (EEG), biomechanical (CoP and EMG), and autonomic (HRV) measures, the aim is to characterize and quantify the processes underlying PC. A key objective is to identify sensitive and objective biomarkers of PC capable of capturing changes in postural strategies and neurophysiological responses across healthy individuals and multiple cohorts, including age-stratified populations, individuals with concussion, and sailors.

The second objective is to identify early and subtle neural and balance related alterations associated with early-stage Parkinson's disease by highlighting changes observed during the BioVRSea paradigm, with the aim of detecting early signs of the disease before they become evident in standard clinical assessments.

Overall, this thesis aims to demonstrate the potential of immersive, multimodal paradigms as advanced tools for personalized assessment, early diagnosis, and monitoring of balance impairments, with implications for both research and clinical applications.

## Chapter 2

# The BioVRSea

### 2.1 Background

Visual and motor stimulation play a crucial role in PC, as it relies on the integration of sensory and motor information. Visual input provides spatial orientation and external references for stability, while motor perturbations challenge the postural system and elicit both anticipatory and compensatory postural adjustments. Therefore, visual and motor stimuli are fundamental components in the assessment of PC strategies. To address this, we developed a novel system capable of providing both visual and motor stimulation, either separately or simultaneously. This approach enabled the exploration of two dimensions of postural learning: adaptation, defined as transient improvements in motor responses to upright balance perturbations, and habituation, defined as a gradual decrease in response to repeated perturbations. In a previous study, Barollo et al. [13] demonstrated that postural adaptation and habituation to proprioceptive vibratory stimulation applied to the calf muscles are associated with progressive improvements in postural stability. Specifically, a progressive reduction in the normalized sway path length was observed, indicating improved postural performance as stimulation progressed. These behavioral changes were accompanied by distinct patterns of cortical activity measured using high-density EEG. During adaptation, visual feedback strongly modulated neural dynamics. With eyes closed, adaptation was associated with significant shifts in spectral power toward higher frequencies and increased theta-band activity in frontocentral regions. With eyes open, increases in theta and beta power were mainly observed in parietal areas, suggesting enhanced sensory integration. During habituation, no major spectral power changes were observed in the eyes-closed condition, whereas with eyes open, additional increases in alpha and beta band power emerged, indicating sustained neural processing supported by visual input. Furthermore, functional connectivity analyses revealed dynamic reorganization of cortical networks during PC, with increased local connectivity in the theta band, potentially reflecting the planning of corrective movements and balance-related control demands. Changes in alpha-band connectivity

suggested a reduced processing of repeated perturbations, consistent with habituation mechanisms. These findings support the view that PC is not purely reflexive but depends on flexible, vision-dependent cortical networks that reorganize during balance learning. Overall, these features make the developed BioVRSea protocol an innovative tool for evaluating novel biomarkers and the strategies underlying PC.

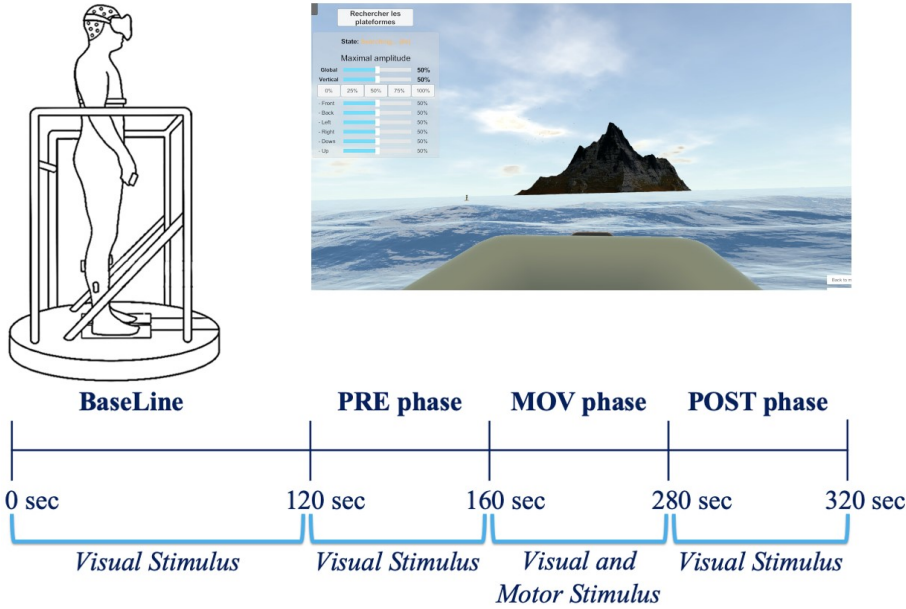


Figure 2.1: BioVRSea protocol characterized by different simulation phases, each defined by distinct types of stimulation, including visual and motor stimuli

## 2.2 Experimental Protocol

The BioVRSea setup combines VR technology with a synchronized moving platform, as shown in Figure 2.1. The system is designed to study PC by providing a challenging balance environment that engages body movements, activates the lower limb muscles, and relies on the nervous system to integrate multisensory information from the immersive environment. The VR goggles provide continuous visual stimulation throughout the experiment, simulating a sea environment in which the subject is positioned on a small virtual boat. Motor stimulation is introduced through the movement of the platform, which becomes particularly pronounced towards the end of the experiment. The perception of waves is generated both by the visual VR simulation and by the platform movements.

The experimental protocol is divided into four main phases, as detailed in Figure 2.2. It begins with the baseline phase (BASE), during which the

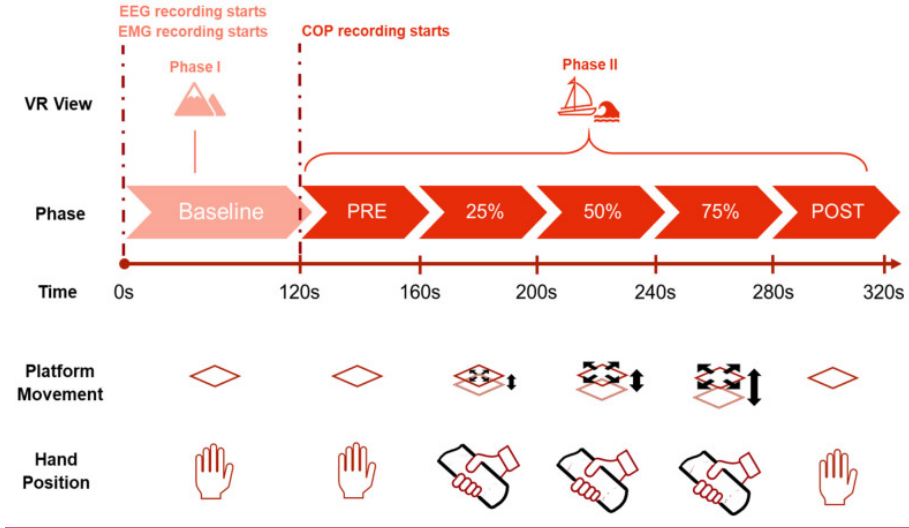


Figure 2.2: Timing of the BioVRSea protocol phases: the baseline phase (0–120 s), characterized by a dark mountain view with no motor stimulation; the PRE phase (120–160 s), involving the visual simulation of the boat; the MOV phase (160–280 s), combining visual and motor stimulation with the platform moving at different amplitudes; and the POST phase (280–320 s), in which only visual stimulation remains after the platform stops moving. For each signal, the onset of data acquisition is indicated, as well as whether the subject was holding the bar or not

participant stands on a platform with their arms relaxed at their sides for two minutes after the start of the acquisition. During this phase, the VR environment displays a mountainous landscape to activate all sensors and prepare the system for the upcoming experiment. This is followed by the pre-motor stimulus phase (PRE), during which visual stimuli simulating ocean waves are presented through the VR goggles. Then, the platform begins to move, initiating the movement-stimulus phase (MOV), during which participants are asked to grasp a bar. The platform executes synchronized movements of varying amplitudes, integrating motor and visual stimuli. The experiment concludes with the post-motor stimulus phase (POST), during which the movement of the platform is suddenly stopped while the VR sea simulation continues. In this phase, participants are required to maintain their balance without holding the bar again, as only visual stimuli are presented. This phase introduces the additional challenge of residual instability from the earlier platform movements. The previously listed phases (PRE, MOV, and POST) each last 40 seconds, bringing the total experiment duration to approximately five minutes. BioVRSea is designed to evaluate the distinct responses across the different experimental phases, each defined by the type of stimulation applied. In certain studies, particular emphasis is placed on the latency between the PRE and POST phases,

as both involve the same visual stimulation, with the POST phase occurring after movement induction.

Data acquisition during the experiment is systematically carried out through the integration of multiple measurement systems, including EEG, electromyography (EMG), heart rate variability (HRV), and force platform (FP) recordings. These data are combined to enable a comprehensive comparison across individuals.

This integrative approach allows for the investigation of neurophysiological responses elicited by the BioVRSea simulation, providing valuable insights into the mechanisms underlying complex PC tasks, particularly under conditions of sensory conflict.

### 2.2.1 Questionnaire

Before the experiment, each participant completes a questionnaire designed to gather information about their physical condition, neural status, lifestyle, and family history. The Lifestyle Index is calculated based on responses regarding Body Mass Index (BMI), physical activity, and consumption of nicotine, caffeine, and alcohol, all of which can affect overall health. Further, two more indices are established: the Physiological/Vegetative (PHY) and Neurological/Muscle Strain (NEURO) indices [14]. Both indices are calculated based on the difference in symptoms before and after the experiment. The PHY index is based on responses regarding general discomfort, increased salivation, sweating, and nausea, while the NEURO index focuses on general discomfort, fatigue, headache, blurred vision, and dizziness. These indices are crucial for evaluating the effects of the VR simulation on the PC of the participants. Additionally, participants complete questions adapted from Golding's Motion Sickness Susceptibility Questionnaire (MSSQ) [15] to assess prior experiences of motion sickness (MS). Symptoms such as general discomfort, headache, increased salivation, sweating, and dizziness are used to calculate the BioVRSea Effect Index (also called BVSEI), which quantifies changes in symptoms before and after the VR simulation. This index classifies individuals into two groups: those who experience one or more symptom changes following the simulation, and those who experience no changes [14]. Understanding these symptom changes is particularly relevant for individuals with neurodegenerative conditions, as such disorders can impair postural stability and exacerbate symptoms during balance-demanding tasks. Another relevant metric is the Proness Index, which quantifies an individual's history of motion sickness (i.e., how frequently they have felt sick in the past). While motion sickness-related indices will not be the primary focus of this thesis, they have been applied in studies using the BioVRSea system and will be referenced in certain chapters.

## 2.3 Measured Biosignals

### 2.3.1 Center of Pressure (CoP)

PC can be quantitatively assessed by analyzing the time series of the center of pressure (CoP) [16]. The CoP represents the point of application of the resultant ground reaction force that compensates for body sway through the PC system [17]. As the body moves, the CoP coordinates change and can be recorded using a FP. The CoPx and CoPy components correspond to the orthogonal X and Y axes of the coordinate system, respectively, reflecting Medio-Lateral (ML) and Antero-Posterior (AP) sway. The CoP trajectory reflects the movement of the CoM and the torque applied at the support surface to control body-mass acceleration. The CoM is a theoretical point representing the average location of the body's mass distribution. Maintaining stability requires alignment between the CoP and CoM, deviations in this alignment trigger postural adjustments to preserve balance. The time-series of CoP movements, called a stabilogram, is widely used to assess stability during balance tasks and for the early detection of balance deterioration to prevent falls. The stabilogram provides temporal variations of CoP, with the X and Y components corresponding to ML and AP oscillations, respectively. From these coordinates, features such as average velocity, sway area, and CoP Sample Entropy can be computed to quantitatively assess PC. In 1981, the International Society of Posturography recommended mean velocity and root mean square distance of the CoP as standardized measures for postural steadiness. More broadly, CoP analysis can be classified into linear and non-linear approaches. Linear metrics describe the magnitude and variability of CoP displacements (e.g., sway range, velocity, ellipse area), whereas non-linear metrics capture the temporal structure of CoP variations over time [18]. For example, CoP Sample Entropy quantifies the unpredictability of postural sway, while ellipse area estimates the spatial extent of sway and overall balance stability. CoP excursion is also commonly used to measure stability and related pathological mechanisms [17]. CoP-based measures vary with age [19] and medical conditions [20]. During dual-task performance, changes in CoP behavior are more pronounced in older adults, who exhibit higher sway area and velocity compared to younger individuals [21]. In PD, individuals show reduced sway and impaired coordination of agonist and antagonist muscles, leading to greater difficulty in maintaining stability. Limb rigidity in PD further reduces sway area [22]. Force platforms provide high-precision measurements of the forces applied to the ground. Typically fixed to a stable surface to minimize vibrations, these systems capture rapid CoP fluctuations at high sampling rates. They are valuable for assessing balance in conditions such as vestibular disorders, neurological diseases, neuromuscular lesions, or age-related postural deficits, enabling precise quantification of postural sway. Although balance control is often evaluated during static upright standing, various protocols exist, including different test conditions (e.g., eyes open, eyes closed, head rotation), typically assessing spontaneous PC without external perturbations.

In our studies, we used a force plate (Virtualis, Clapiers, France) with four

sensors located under each foot platform (Figure 2.3). The sensors provided CoM information along the AP and ML axes with a sampling frequency of 90 Hz.

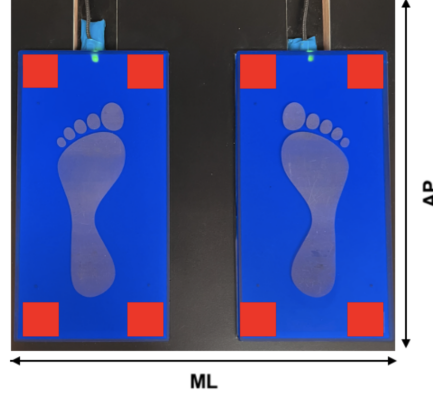


Figure 2.3: FP of the BioVRSea protocol

### 2.3.1.1 Processing

All recordings were sampled at 90 Hz and segmented into the time windows: PRE (5–35 s), MOV (45–155 s), and POST (165–195 s). To minimize transitional artifacts, the first and last 5 seconds of each phase were excluded. For each subject, ML and AP components were calculated from FP sensors. Signals were smoothed using a Savitzky-Golay filter (polynomial of order 2, and frame length of 7) and converted to physical units (cm) according to the dimensions of the platform. The AP displacement is calculated using the formula:

$$AP\_Displacement \text{ (cm)} = Y \text{ (cm)} \cdot \frac{StaticVR\_AP}{2} \quad (2.1)$$

where StaticVR\_AP is the percentage of the vertical size of the board between -1 and 1. The ML displacement is calculated using the formula:

$$ML\_Displacement \text{ (cm)} = X \text{ (cm)} \cdot \frac{StaticVR\_ML}{2} \quad (2.2)$$

where StaticVR\_ML is the percentage of the horizontal size of the board between -1 and 1.

After centering the ML and AP time series by subtracting the mean, features were computed for each phase and for each subject in both directions. The principal features are described below and can be grouped into:

- **Spatiotemporal Measures** Total excursion on the support plane (TOTEX, in cm), which represents the overall length of the CoP path and

reflects the cumulative displacement of the center of pressure during a trial; the 95% confidence ellipse (in  $\text{cm}^2$ ), fitted to the CoP trajectory using Principal Component Analysis (PCA), which provides the area encompassing the majority of sway and quantifies the spatial dispersion of postural adjustments; and the root mean square (RMS, in cm) distance of the CoP, representing the average magnitude of deviations from the mean position and providing an estimate of postural variability.

- **Non-linear Features** Sample entropy (SampEn, in nats) and fractal dimension (computed using Higuchi's method [23]) are widely used to quantify the complexity of CoP trajectories. SampEn measures the unpredictability or irregularity of a time series, with higher values indicating more complex and less predictable sway patterns, while lower values correspond to more regular, controlled postural behavior. The fractal dimension captures the self-similarity and scaling properties of the CoP trajectory, reflecting how fine-scale fluctuations contribute to overall postural dynamics. The optimal number of reconstructed data sets for fractal dimension estimation was determined by plotting the curve length on a log-log scale against the corresponding  $k$  values. Together, these measures provide complementary information about the dynamical characteristics, helping to distinguish between sway patterns that are tightly regulated and stable versus those exhibiting higher irregularity, variability, and potential instability.
- **Spectral Features** Power spectral density (PSD) of the centered CoP signals is analyzed to quantify the distribution of postural sway across different frequencies. Key spectral metrics include Total Power [ $\text{cm}^2$ ], which reflects the overall magnitude of sway; Mean and Median Frequency [Hz], indicating the dominant oscillation rates; Spectral Variance [ $\text{Hz}^2$ ], representing the variability of sway across frequencies; and Peak Frequency [Hz], identifying the frequency with maximum power. The CoP time series was divided into seven overlapping segments (25% overlap), with each segment detrended and windowed using a Hanning window to minimize spectral leakage. PSD is estimated via Fast Fourier Transform (FFT) with a frequency resolution of 0.02 Hz, using  $\text{nfft} = \text{fs}/0.02$  [24]. The resulting PSD, normalized by the sampling frequency and window energy, yielded power per Hz in units of  $\text{cm}^2/\text{Hz}$ , providing a measure of the spectral energy associated with body sway. These spectral measures offer insights into the dynamical characteristics of PC, helping to distinguish between slow, controlled sway and faster, potentially less stable oscillations.

The data were centered and normalized following the procedure described in [25]. For centralization, the CoP data were mean-centered by subtracting the mean from each value, producing variations relative to the subject's average position. This ensures that the data reflect displacements from the individual mean, minimizing the effect of an uncentered initial position. For normalization, the data were either scaled to a range of 0 to 1 or standardized using the

mean and standard deviation, enabling meaningful comparisons across different subjects. All analyses were performed using Matlab 2023a. CoP features are summarized in Table 2.1, and the corresponding formulas are provided in the appendices. Figure 2.4 illustrates an example of a raw CoP signal projected onto the support plane. The CoP trajectory is represented by the blue line, corresponding to the sequence of coordinates recorded by the FP throughout the experiment.

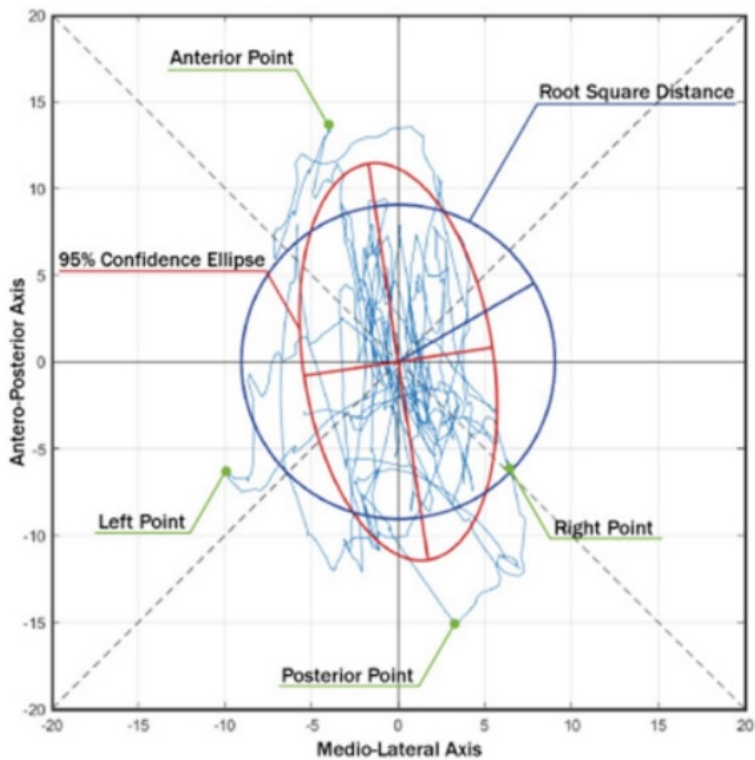


Figure 2.4: Example of the raw CoP signal in horizontal-plane coordinates, with the Root Mean Square Distance, 95% Confidence Ellipse, Left and Right points, and AP points displayed

Table 2.1: CoP features

| Name                        | Definition                                              | Reference |
|-----------------------------|---------------------------------------------------------|-----------|
| <b>TIME PARAMETERS</b>      |                                                         |           |
| AAC                         | Average Amplitude Change                                | 7.63      |
| AE                          | Average Energy                                          | 7.64      |
| ASM                         | Absolute Value of the Summation of the Exponential Root | 7.65      |
| ASS                         | Absolute Value of the Summation of the Square Root      | 7.67      |
| CV                          | Coefficient of Variation                                | 7.68      |
| DAMV                        | Difference Absolute Mean Value                          | 7.69      |
| DASDV                       | Difference Absolute Standard Deviation Value            | 7.70      |
| DVARV                       | Difference Absolute Standard Deviation Value            | 7.71      |
| EMAV                        | Enhanced Mean Absolute Value                            | 7.72      |
| EWL                         | Enhanced Wavelength                                     | 7.74      |
| FZC                         | New Zero Crossing                                       | 7.77      |
| KURT                        | Kurtosis                                                | 7.79      |
| IEMG                        | Integrated EMG                                          | 7.80      |
| IQR                         | Interquartile Range                                     | 7.81      |
| LCV                         | Log Coefficient of Variation                            | 7.82      |
| LD                          | Log Detector                                            |           |
| LDAMV                       | Log Difference Absolute Mean Value                      | 7.83      |
| LDASDV                      | Log Difference Absolute Standard Deviation              | 7.84      |
| L-Moments                   | L-mean: Mean of the sorted signal                       | 7.85      |
|                             | L-scale: Scale or dispersion of the data                | 7.86      |
|                             | L-skewness: Asymmetry via linear combinations           | 7.87      |
|                             | L-kurtosis: Peakedness or flatness of distribution      | 7.88      |
| LTKEO                       | Log Teager Kaiser Energy Operator                       | 7.89      |
| MAD                         | Mean Absolute Deviation                                 | 7.90      |
| MAV                         | Mean Absolute Value                                     | 7.91      |
| MFL                         | Maximum Fractal Length                                  | 7.92      |
| MN                          | Mean                                                    |           |
| MD                          | Median                                                  |           |
| MMAV                        | Modified Mean Absolute Value                            | 7.93      |
| MMAV2                       | Modified Mean Absolute Value 2                          | 7.95      |
| MSR                         | Mean Value of the Square Root                           | 7.97      |
| Poincaré                    | S1: Short-term variability from Poincaré Plot           | 7.98      |
|                             | S2: Long-term variability from Poincaré Plot            | 7.99      |
|                             | RatioSD Ratio variability                               | 7.100     |
| RMS                         | Root Mean Square                                        | 7.101     |
| SD                          | Standard Deviation                                      | 7.102     |
| SKEW                        | Skewness                                                | 7.103     |
| SSI                         | Single Square Integral                                  | 7.104     |
| TM                          | Temporal Moment                                         | 7.105     |
| VAR                         | Variance                                                | 7.106     |
| VARE                        | Variance of EMG                                         | 7.107     |
| VO                          | V-Order                                                 | 7.108     |
| WL                          | Waveform Length                                         | 7.109     |
| WL                          | Waveform Length                                         | 7.109     |
| <b>FREQUENCY PARAMETERS</b> |                                                         |           |
| PT                          | Total Power                                             | 7.113     |
| Pmax                        | Maximum Power                                           | 7.115     |
| Fmax                        | Maximum Frequency                                       | 7.116     |
| FMD                         | Median Frequency                                        | 7.112     |
| FMN                         | Mean Frequency                                          | 7.111     |
| Fkurt                       | Frequency Kurtosis                                      | 7.117     |
| Fskew                       | Frequency Skewness                                      | 7.118     |

### 2.3.2 Electromyography (EMG)

Electromyography (EMG) records the electrical activity generated by muscle fibers during contraction, providing a direct measure of muscle activation. EMG is closely linked to PC, as maintaining balance requires precise coordination of muscle activity. By measuring the timing and amplitude of muscle activation, EMG sensors provide insight into the temporal and force characteristics of postural adjustments. The onset of EMG activity indicates when a muscle is recruited in response to a postural challenge, revealing the timing of corrective actions, while the amplitude reflects the intensity of the response needed to maintain or recover balance. By analyzing these patterns across muscles and over time, it is possible to infer how the nervous system coordinates multiple muscles to control posture. Analyzing EMG signals from lower limb and trunk muscles allows investigation of how sensory inputs are translated into coordinated motor responses, revealing strategies used to maintain or recover balance. This makes EMG a fundamental tool for studying neuromuscular contributions to PC in both healthy and clinical populations. The typical amplitude of surface EMG signals varies depending on the muscle state, ranging from low microvolt levels at rest to several millivolts during maximal voluntary contraction.

In the BioVRSea experiment, muscle activity of the lower limbs was recorded using six wireless EMG sensors (Kiso ehf, Reykjavik, Iceland) placed on the Tibialis Anterior (TA), Gastrocnemius (GL), and Soleus (S) muscles of both legs. The suffix (R) denotes the right leg and (L) the left leg (e.g., TAL refers to the left Tibialis Anterior). Sensor placement on the body is illustrated in Figure 2.5. Signals were acquired at a sampling frequency of 1600 Hz and processed using MATLAB R2021b with the built-in Signal Processing Toolbox.



(a) Tibialis Anterior (TA)

(b) Gastrocnemius Lateralis (GL) and Soleus (S)

Figure 2.5: Placement of EMG sensors on the lower limbs

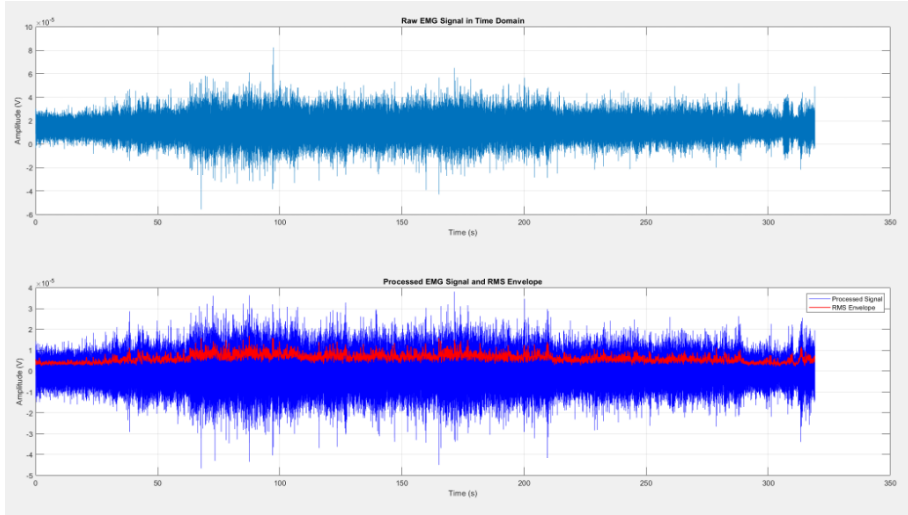


Figure 2.6: Example of the raw EMG signal in the time domain, with the processed EMG signal and its RMS envelope shown below

### 2.3.2.1 Processing

Figure 2.6 illustrates a representative EMG signal, which served as the basis for subsequent processing and quantitative feature extraction. The EMG signals were segmented into four distinct phases: BASE, PRE, MOV, and POST, based on predefined time intervals. After removing the transition periods between phases, each segment corresponded to 20 s of data. A fourth-order Butterworth bandpass filter (20–500 Hz) was applied to retain the relevant neuromuscular frequency components, while power line interference and its harmonics at 50 Hz were attenuated using notch filters. This filter was selected due to its widely recognized use in EMG signal processing and its maximally flat magnitude response within the passband, which avoids amplitude ripple. Extreme amplitude values were identified and removed through thresholding, and missing segments were reconstructed using spline interpolation. The processed signals were then rectified, and a 100-ms moving window was applied to compute the root mean square (RMS) envelope. Normalization was performed by scaling both the filtered and enveloped signals to the maximum peak amplitude observed across all phases for each subject and muscle, ensuring comparability between phases while preserving within-subject variability.

Also in this case, after preprocessing the EMG signals, features were computed for each phase and for each subject for all recorded muscles. The principal features are described below and can be grouped into:

- **Time-domain Features** These include Root Mean Square (RMS), reflecting the overall amplitude and intensity of muscle activation; Mean Absolute Value (MAV), providing an estimate of average muscle activity;

Integrated EMG (iEMG), indicating total muscle activation over time; and Waveform Length (WL), capturing both amplitude and frequency changes. Additional features, such as Coefficient of Variation (CV), Mean Absolute Deviation (MAD), Zero Crossing (ZC / FZC), Kurtosis (KURT), Skewness (SKEW), and Poincaré parameters (S1, S2, RatioSD), were also extracted to quantify the variability, asymmetry, and complexity of muscle activation patterns.

- **Frequency-domain Features** Extracted from the PSD of the EMG signals, these include Total Power (PT), representing the overall energy of muscle activity; Maximum Power (Pmax) and Maximum Frequency (Fmax), indicating the dominant firing rates of motor units; Mean Frequency (FMN) and Median Frequency (FMD), describing the spectral centroid and the frequency dividing the power spectrum in half; and Frequency Skewness (Fskew) and Frequency Kurtosis (Fkurt), reflecting the asymmetry and peakedness of the spectral distribution. Together with time-domain features, these measures provide a comprehensive characterization of muscle activation, enabling investigation of both the intensity and temporal dynamics of postural adjustments.

All the computed features are summarized in Table 2.2, and the corresponding formulas are provided in the appendices.

Table 2.2: EMG features

| Name                        | Definition                                              | Reference |
|-----------------------------|---------------------------------------------------------|-----------|
| <b>TIME PARAMETERS</b>      |                                                         |           |
| AAC                         | Average Amplitude Change                                | 7.63      |
| AE                          | Average Energy                                          | 7.64      |
| ASM                         | Absolute Value of the Summation of the Exponential Root | 7.65      |
| ASS                         | Absolute Value of the Summation of the Square Root      | 7.67      |
| CV                          | Coefficient of Variation                                | 7.68      |
| DAMV                        | Difference Absolute Mean Value                          | 7.69      |
| DASDV                       | Difference Absolute Standard Deviation Value            | 7.70      |
| DVARV                       | Difference Absolute Standard Deviation Value            | 7.71      |
| EMAV                        | Enhanced Mean Absolute Value                            | 7.72      |
| EWL                         | Enhanced Wavelength                                     | 7.74      |
| FZC                         | New Zero Crossing                                       | 7.77      |
| KURT                        | Kurtosis                                                | 7.79      |
| IEMG                        | Integrated EMG                                          | 7.80      |
| IQR                         | Interquartile Range                                     | 7.81      |
| LCV                         | Log Coefficient of Variation                            | 7.82      |
| LD                          | Log Detector                                            |           |
| LDAMV                       | Log Difference Absolute Mean Value                      | 7.83      |
| LDASDV                      | Log Difference Absolute Standard Deviation              | 7.84      |
| L-Moments                   | L-mean: Mean of the sorted signal                       | 7.85      |
|                             | L-scale: Scale or dispersion of the data                | 7.86      |
|                             | L-skewness: Asymmetry via linear combinations           | 7.87      |
|                             | L-kurtosis: Peakedness or flatness of distribution      | 7.88      |
| LTKEO                       | Log Teager Kaiser Energy Operator                       | 7.89      |
| MAD                         | Mean Absolute Deviation                                 | 7.90      |
| MAV                         | Mean Absolute Value                                     | 7.91      |
| MFL                         | Maximum Fractal Length                                  | 7.92      |
| MN                          | Mean                                                    |           |
| MD                          | Median                                                  |           |
| MMAV                        | Modified Mean Absolute Value                            | 7.93      |
| MMAV2                       | Modified Mean Absolute Value 2                          | 7.95      |
| MSR                         | Mean Value of the Square Root                           | 7.97      |
| Poincaré                    | S1: Short-term variability from Poincaré Plot           | 7.98      |
|                             | S2: Long-term variability from Poincaré Plot            | 7.99      |
|                             | RatioSD Ratio variability                               | 7.100     |
| RMS                         | Root Mean Square                                        | 7.101     |
| SD                          | Standard Deviation                                      | 7.102     |
| SKEW                        | Skewness                                                | 7.103     |
| SSI                         | Single Square Integral                                  | 7.104     |
| TM                          | Temporal Moment                                         | 7.105     |
| VAR                         | Variance                                                | 7.106     |
| VARE                        | Variance of EMG                                         | 7.107     |
| VO                          | V-Order                                                 | 7.108     |
| WL                          | Waveform Length                                         | 7.109     |
| WL                          | Waveform Length                                         | 7.109     |
| <b>FREQUENCY PARAMETERS</b> |                                                         |           |
| PT                          | Total Power                                             | 7.113     |
| Pmax                        | Maximum Power                                           | 7.115     |
| Fmax                        | Maximum Frequency                                       | 7.116     |
| FMD                         | Median Frequency                                        | 7.112     |
| FMN                         | Mean Frequency                                          | 7.111     |
| Fkurt                       | Frequency Kurtosis                                      | 7.117     |
| Fskew                       | Frequency Skewness                                      | 7.118     |

### 2.3.3 Electrocardiography (ECG)

ECG measures the electrical activity of the heart, capturing the depolarization and repolarization of atrial and ventricular muscle fibers during each cardiac cycle. ECG represents a critical tool for the study of PC, as HRV serve as indirect markers of autonomic nervous system activity, which is closely involved in the regulation of balance and postural responses. Continuous ECG recording allows the characterization of cardiovascular adjustments to postural perturbations and provides insight into the dynamic interaction between autonomic and musculoskeletal systems. Typical surface ECG signals range from 0.5 to 5 mV with a frequency content between 0.05 and 150 Hz, depending on the recording setup and subject.

For ECG recordings in the BioVRSea protocol, we employed the BioSignalsPlux Explorer Kit, which comprises a wireless 4-channel BioSignalsPlux HUB, professional sensors, a PLUX-certified Bluetooth dongle, electrodes, and a medical-grade charger. The ECG sensors are connected to the wireless 4-channel BioSignalsPlux HUB to acquire the data throughout all the experiment (Figure ??). The ECG electrodes are positioned on the subject from the Right Arm (RA) to the Left Foot (LF), as illustrated in Figure ??). They are positioned following the Einthoven triangle configuration to ensure accurate and reliable ECG measurements; for practical reasons, the left foot electrode was positioned on the highest point of the left leg, which does not significantly affect signal accuracy.



(a) Body positions of the ECG electrodes



(b) Wireless 4-channel HUB and sensor cables

Figure 2.7: BiosignalsPlux Explorer Kit

### 2.3.3.1 Processing

Figure 2.8 illustrates a representative ECG signal, in which some of the characteristic peaks, such as the P wave, QRS complex and T wave, are clearly visible.

From the ECG recordings, features were computed for each phase and for each subject, and they can be grouped into:

- **Time-domain Features** Include Heart Rate (HR), representing the average beats per minute; RR intervals, capturing the time between consecutive R peaks; SDNN (standard deviation of NN intervals) and RMSSD (root mean square of successive differences), reflecting overall and parasympathetic HRV; and pNN50/pNN20, indicating the percentage of successive RR intervals differing by more than 50 ms (or 20 ms).
- **Frequency-domain features** Derived from power spectral analysis of RR intervals, included Low Frequency (LF, 0.04–0.15 Hz) and High Frequency (HF, 0.15–0.4 Hz) components, the LF/HF ratio, and total spectral power, providing information on sympathetic–parasympathetic balance and overall autonomic modulation.
- **Nonlinear and complexity features** Include Sample Entropy (SampEn) to assess the irregularity of HR dynamics, Poincaré plot parameters (SD1, SD2) for short and long term variability, and fractal measures such as the detrended fluctuation analysis exponent (DFA 1) to capture self-similarity and scaling properties of the RR time series.

ECG processing was conducted using the OpenSignals (r)evolution software (<https://www.pluxbiosignals.com>) designed for processing ECG sensor data, providing real-time visualization and recording. It enables the extraction of Beat-to-Beat interval series, from which various temporal, spectral, and nonlinear HRV parameters are computed. All the implemented algorithms adhere to the established standards [26]. A total of 31 features, listed and described in Table 2.3, are obtained for each of the four phases of the experiment (BASE, PRE, MOV, and POST), resulting in a total of 124 features per subject.

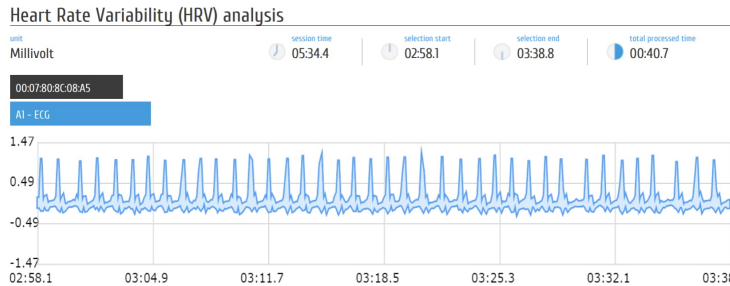


Figure 2.8: Example of an ECG signal with its characteristic peaks

Table 2.3: ECG features

| Name                                 | Definition                                                                                                         |
|--------------------------------------|--------------------------------------------------------------------------------------------------------------------|
| <b>TIME PARAMETERS</b>               |                                                                                                                    |
| MIN NN (ms)                          | Minimum value of NN intervals                                                                                      |
| MAX NN (ms)                          | Maximum value of NN intervals                                                                                      |
| AVG NN (ms)                          | Mean value of NN intervals                                                                                         |
| SD NN (ms)                           | Standard deviation of the NN series                                                                                |
| RMSSD NN                             | Square root of the mean-squared differences between successive RR intervals                                        |
| NN20                                 | Number of successive intervals differing more than 20 ms                                                           |
| pNN20%                               | Percentage of successive RR intervals differing more than 20 ms (NN20 divided by the total number of RR intervals) |
| NN50                                 | Number of successive intervals differing more than 50 ms                                                           |
| pNN50%                               | Percentage of successive RR intervals differing more than 50 ms (NN50 divided by the total number of RR intervals) |
| AVG IHR (bpm)                        | Mean value of the heart rate                                                                                       |
| SD IHR (bpm)                         | Standard deviation of the heart rate                                                                               |
| SD NN Index                          | Mean of the st dev of all the NN intervals for each 5 min segment of a 24-h HRV record                             |
| SD RR (ms)                           | St dev of the RR series                                                                                            |
| SDANN (ms)                           | St dev of the 5 min average NN intervals                                                                           |
| AVG RR (ms)                          | Mean value of the RR series                                                                                        |
| rMSSD RR                             | Root-mean-squared of the RR series                                                                                 |
| Max RR (ms)                          | Maximum value of the RR series                                                                                     |
| Min RR (ms)                          | Mainimum value of the RR series                                                                                    |
| Max HR (bpm)                         | Maximum Heart Rate (beats for minutes)                                                                             |
| <b>FREQUENCY PARAMETERS</b>          |                                                                                                                    |
| VLF FREQ (%)                         | VLF frequency                                                                                                      |
| VLF peak                             | Frequency corresponding to the maximum power within the frequency band                                             |
| VLF POWER ( $ms^2$ )                 | Spectral power of the VLF component (0–0.04 Hz) presented in absolute units                                        |
| VLF POWER (%)                        | Spectral power of the VLF component as percentage of total power                                                   |
| LF Freq                              | Low-Frequency power: frequency activity in the 0.04–0.15 Hz range                                                  |
| LF PEAK                              | LF Peak frequency                                                                                                  |
| LF Power ( $ms^2$ )                  | Spectral power of the LF component (0.04–0.15 Hz) presented in absolute units                                      |
| LF POWER (%)<br>or $P_{VLF}/P_{Tot}$ | LF percentage with respect to the total power                                                                      |
| LF Power (nu)                        | Spectral power of the LF component in normalized units                                                             |
| HF freq                              | High-Frequency power: frequency activity in the 0.15–0.40 Hz range                                                 |
| HF PEAK                              | HF Peak frequency                                                                                                  |
| HF POWER ( $ms^2$ )                  | Spectral power of the HF component (0.15–0.4 Hz) presented in absolute units                                       |
| HF POWER (%)<br>or $P_{HF}/P_{Tot}$  | HF percentage with respect to the total power                                                                      |
| HF POWER (nu)                        | Spectral power of the HF component in normalized units                                                             |
| LF/HF                                | Ratio between absolute power in the LF band and absolute power in the HF band                                      |
| <b>NON LINEAR PARAMETERS</b>         |                                                                                                                    |
| SD1                                  | Standard deviation along the minor axis                                                                            |
| SD2                                  | Standard deviation along the major axis                                                                            |
| SD1/SD2                              | Ratio between SD1 and SD2                                                                                          |
| AREA                                 | Area of the ellipse                                                                                                |

### 2.3.4 Electroencephalography (EEG)

Electroencephalography (EEG) records the electrical activity generated by cortical neurons, providing a direct measure of brain signals associated with sensory processing, motor control, and postural regulation. EEG signals reflect the summed postsynaptic potentials of cortical neurons and are typically recorded in the range of 0.1–100  $\mu\text{V}$ . The signals are highly sensitive to both ongoing brain activity and transient responses to stimuli, providing insights into cortical processing at millisecond resolution. EEG allows investigation of cortical activity underlying balance and postural adjustments. By recording brain signals during visual and motor perturbations, it is possible to study how the nervous system integrates sensory information and generates motor responses to maintain or recover posture. This enables the identification of cortical networks involved in anticipatory and compensatory postural strategies.

Within the BioVRSea protocol, cortical electrical activity was recorded using two types of 64-channel EEG caps, both manufactured by ANT Neuro (Hengelo, The Netherlands) and connected to a dedicated amplifier (Figures 2.9a, 2.9c). Signals were acquired at a sampling frequency of 4096 Hz for both the CA-208 and NA-261 gel caps. Electrode impedance values below 40  $\text{k}\Omega$  were considered acceptable. The NA-261 cap was introduced for its faster and more efficient immersion in saline solution for at least 20 minutes prior to acquisition, allowing good impedance values and quicker placement on the head.

#### 2.3.4.1 Processing

Across all EEG studies, we systematically developed and optimized preprocessing strategies to preserve meaningful neural signals while effectively removing artifacts and spurious noise. Signal preprocessing was conducted using the EEGLAB Matlab toolbox to eliminate artifacts such as eye blinks and line noise. Each EEG recording was manually inspected to customize the preprocessing pipeline for each subject. The signals were downsampled from the original acquisition rate to 1024 Hz. A dual-filter approach was applied, consisting of a low-pass filter at 1 Hz and a high-pass filter at 45 Hz, to enhance signal clarity and reduce noise interference. Channels displaying flat signals or a correlation coefficient below 60% with neighboring channels were excluded as noisy channels. Artifact removal began with the Artifact Subspace Reconstruction (ASR) method [27]. Next, Independent Component Analysis (ICA) was performed using the probabilistic ICA for reliable data (PICARD) method [28], which is particularly effective for dynamic recordings. Non-brain components identified in this step were rejected. Subsequently, previously excluded and flat channels were interpolated. Mastoid electrodes (M1 and M2) and PO5/PO6 electrodes, which primarily capture neck activity, were excluded from further analysis. Finally, the remaining channels (excluding EOG) were interpolated back to 61 channels and re-referenced to the average. Figure 2.10 illustrates an example of the final cleaned EEG signal.

After preprocessing, EEG signals were analyzed in both the time domain, to

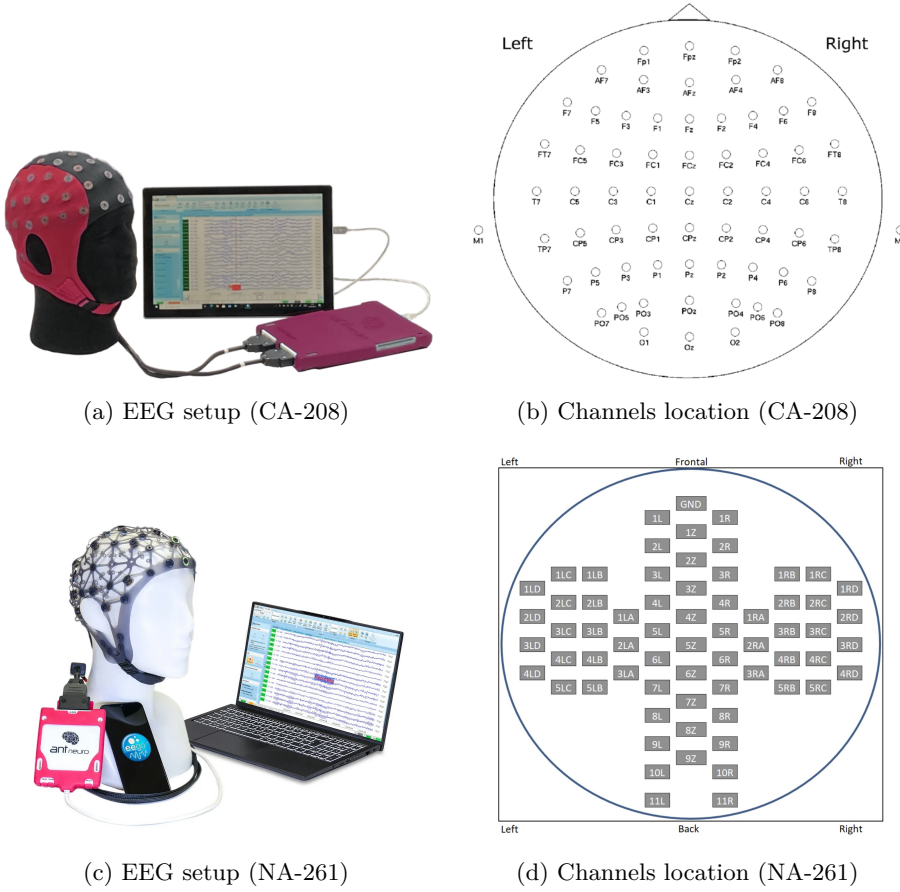


Figure 2.9: Comparison of the two high-density EEG setups used in the BioVRSea protocol. (a) and (b) show the CA-208 cap and electrode layout; (c) and (d) show the NA-261 cap and electrode layout

assess temporal patterns such as amplitude, variability, and microstate dynamics, and the frequency domain, to examine spectral content across standard EEG bands (delta, theta, alpha, beta, and gamma). Analyses were performed both at the level of individual electrodes and by grouping electrodes into functionally defined cortical regions. Table 2.4 summarizes the functional significance of the EEG frequency bands and cortical regions. Each frequency band reflects distinct oscillatory brain activity associated with specific physiological or cognitive states: delta (deep sleep and profound relaxation), theta (REM sleep, emotional processing, and certain cognitive processes), alpha (relaxed wakefulness and calmness), beta (active thinking and focused attention), and low gamma (integration of multiple sensory inputs). The cortical regions represent major functional areas of the brain: frontal (higher-order cognitive functions such

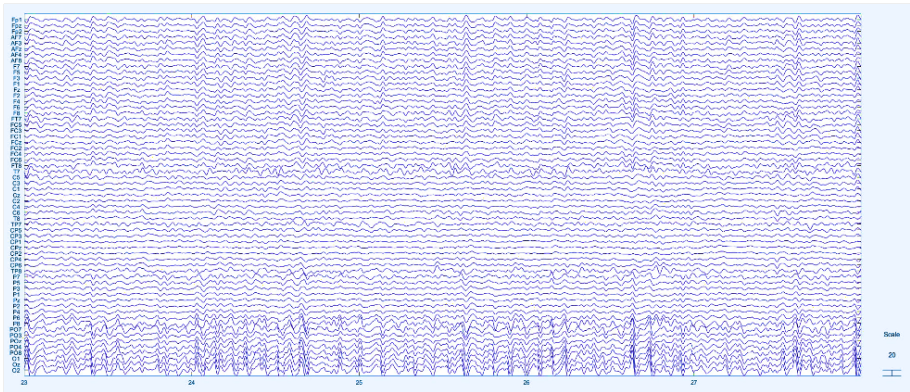


Figure 2.10: Example of the cleaned EEG signal in the time domain

as planning, concentration, judgment, emotional regulation, and creativity), temporal (associative functions including short-term memory, balance, and emotion), parietal (primary processing of somatosensory input from muscles and skin), and occipital (visual and somatosensory association for object recognition, evaluating weight, texture, and temperature).

Table 2.4: Functional roles associated with EEG frequency bands and cortical regions

| Name         | Significance                                                                                             |
|--------------|----------------------------------------------------------------------------------------------------------|
| BANDS        |                                                                                                          |
| ALPHA        | Drowsy state, Relaxation, Calmness                                                                       |
| BETA         | Conscious state, Thought process                                                                         |
| DELTA        | Deep Sleep, Deepest level of Relaxation                                                                  |
| LOWGAMMA     | Elaboration of two different senses at same time                                                         |
| THETA        | REM Sleep, Deep and Raw Emotions, Cognitive processing                                                   |
| REGIONS      |                                                                                                          |
| FRONTAL      | Higher Mental Functions: Concentration, planning, judgment, emotional expression, creativity, inhibition |
| TEMPORAL R&L | Association Area: Short-term memory, equilibrium, emotion                                                |
| PARIETAL     | Sensory Area: Sensation from muscles and skin                                                            |
| OCCIPITAL    | Somatosensory Association Area: Evaluation of weight, texture, temperature, etc. for object recognition  |

## 2.4 Overview of Studies

The following chapters present a series of studies based on the data acquired through the BioVRSea paradigm, designed to explore PC using the biosignals previously described. These studies aim to provide a detailed analysis of the neural, biomechanical, and autonomic components involved in PC under complex sensory stimulation. Particular attention is given to how individual characteristics such as age, gender, and physiological or pathological status may influence postural responses and adaptive capacity.

By integrating EEG, CoP measurements, EMG activity, and HRV parameters, this chapter examines how individuals respond to visually and mechanically induced perturbations in immersive VR environments. This multimodal approach highlights the potential of the BioVRSea paradigm as a sensitive and versatile tool for investigating PC. The studies presented here are organized around distinct experimental questions, each focused on a specific biosignal or population group.

The first study on PC considers the influence of age and gender on cortical activity during a PC task based on high-density EEG recordings. Participants were stratified by gender and divided into two age groups (under 40 and over 40), and were exposed to the BioVRSea protocol. Spectral power density was analyzed both across the different phases of the experiment and through direct comparisons between groups. Initial trends suggest that age may be associated with specific shifts in cortical dynamics during balance regulation.

The second study focuses on biomechanical aspects of PC by analyzing CoP trajectories across the different stages of the VR task. Spatiotemporal, spectral, and nonlinear features of CoP were extracted, enabling a characterization of balance strategies. The results point toward age-related patterns in postural performance, with older adults showing indications of reduced stability and slower recovery following perturbations.

The third study investigates the role of the autonomic nervous system in PC using HRV analysis during the BioVRSea protocol. HRV features in the time, frequency, and nonlinear domains were examined in relation to age, gender, and concussion history. Preliminary findings reveal distinct autonomic responses to complex postural challenges, with some modulation patterns reflecting the interplay between sensory processing, cognitive load, and emotional engagement in immersive environments.

In addition to these studies, the BioVRSea paradigm was applied to two contrasting populations: individuals with a history of concussion and experienced sailors. These studies allowed us to examine how PC may be affected either by transient neurological disruption or by long-term adaptation to unstable environments. Participants with a history of concussion exhibited signs of altered postural strategies even in the absence of acute symptoms, whereas expert sailors demonstrated features consistent with enhanced postural efficiency and sensorimotor resilience. Together, these contrasting cases highlight the capacity of the BioVRSea paradigm to capture both maladaptive and adaptive mechanisms of PC in response to different experiential or clinical conditions.

Chapters 4 and 5 explore Parkinson’s disease (PD), with the aim of detecting subtle alterations in postural and neural activity that are often not captured by standard clinical assessments, particularly during the early stages of the disease.

The study of Chapter 4 on PD highlights measurable differences in EMG and CoP parameters, along with significant changes in cortical activity recorded through EEG. These preliminary findings point to early indicators of impaired sensory integration and postural adaptation, observed for the first time in a dynamic setting such as the BioVRSea paradigm. Notably, this represents a novel approach to analyzing PD-related neural dynamics outside of resting-state conditions.

The study of Chapter 5 on PD builds on this work with a more advanced analysis of functional brain connectivity. The focus is on identifying specific neural signatures and large-scale network alterations associated with PD. By examining the temporal dynamics and reconfiguration of brain networks during complex postural tasks, this study contributes to the characterization of early neurophysiological disruptions in PD and provides insights with potential relevance for early detection and personalized rehabilitation strategies.

Together, the studies presented in the following chapters demonstrate the versatility of the BioVRSea paradigm in assessing PC across a range of populations and conditions. These chapters also provide detailed statistical findings, offering insights and interpretations relevant to the physiological mechanisms underlying PC.

## 2.5 Ethical Approval and Consent

This thesis is based on data collected from individuals recruited between 2021 and 2025. Sincere thanks are extended to all participants who contributed to the study by taking part in the experimental sessions, including friends, volunteers, and patients who attended the laboratory.

All participants received detailed written information about the study and provided written informed consent prior to participation.

The research was conducted in accordance with the principles of the Declaration of Helsinki and in compliance with Icelandic statutory requirements. The study protocol was approved by the Icelandic National Bioethics Committee (No. VSN-20-101) and was subsequently amended to include the Parkinson’s disease cohort (Amendment No. VSN-20-101-V2).

Financial support from RANNIS, the Icelandic Research Fund (Grant of Excellence No. 239612-051), and the Research Fund of Landspítali University Hospital is gratefully acknowledged.



## Chapter 3

# Studies on BioVRSea for Postural Control Assessment

### 3.1 Power Spectral Analysis during the BioVRSea

This work was presented at the IEEE International Conference on Metrology for eXtended Reality, Artificial Intelligence and Neural Engineering (MetroXRINE 2025) and published in the official conference proceedings.

#### 3.1.1 Introduction

Aging is a major factor influencing PC, leading to a progressive decline in stability. Older adults typically exhibit greater postural sway and decreased ability to adapt to balance perturbations compared to younger individuals. These changes are driven by age-related alterations in both neural and musculoskeletal systems, including declines in sensorimotor integration, proprioceptive function, and cortical processing. EEG provides a window into cortical activity underlying balance regulation [29, 30]. By analyzing the PSD across different frequency bands, researchers can examine how aging affects the engagement of specific brain regions during postural tasks. For instance, theta and alpha power in frontal and central areas reflects attentional and sensorimotor processing, while beta activity in parietal regions is associated with motor planning and execution [31]. This study specifically investigates how age influences cortical and postural responses to complex balance challenges. Using the BioVRSea paradigm, which systematically modulate visual and motion stimuli, we compare EEG and PC responses across younger and older adults. Differentiating participants by age allows us to identify age-dependent adaptation and habituation strategies, and to understand how aging interacts with neural and musculoskeletal mechanisms to affect overall postural stability. In addition, questionnaire-based indices capturing neurological, physical, and experimental factors are analyzed to complement EEG recordings, providing a comprehensive view of how aging shapes individual PC strategies and cortical dynamics during complex postural tasks.

3.1.2 Materials and Methods

Participants

A total of 289 healthy individuals with normal balance were recruited for this study. Participants were first divided into cohorts based on sex (female and male), followed by a secondary grouping based on age (Under40 and Over40) for further analysis. The exclusion criterion was the presence of any neurological or orthopedic condition that could affect balance. Their demographic and anthropometric information is detailed in Table 3.1. A Mahalanobis distance analysis was conducted to assess group separation. The results revealed no significant differences based on sex or BMI, suggesting that these variables did not influence group division.

Table 3.1: Participants stratified by sex and age group. Data are reported as Mean and Standard Deviation (SD) for age, height, and weight

| Feature     | Female (n=171) |       | Male (n=118) |       | Under40 (n=209) |       | Over40 (n=80) |       |
|-------------|----------------|-------|--------------|-------|-----------------|-------|---------------|-------|
|             | Mean           | SD    | Mean         | SD    | Mean            | SD    | Mean          | SD    |
| Age (years) | 31.92          | 13.74 | 34.62        | 15.51 | 24.83           | 4.34  | 54.40         | 8.69  |
| Height (cm) | 168.05         | 6.61  | 181.50       | 7.14  | 173.36          | 9.68  | 174.06        | 9.18  |
| Weight (kg) | 68.99          | 13.35 | 83.14        | 14.70 | 70.93           | 13.08 | 84.88         | 16.88 |

Table 3.2: Percentage distribution of participants for the Proness, BioVRSea, Phy, and Neuro indices, stratified by sex (top) and by age group (bottom)

| Indices (%) | Proness Index |      | BioVRSea Index |      | Phy Index |      | Neuro Index |      |
|-------------|---------------|------|----------------|------|-----------|------|-------------|------|
|             | 0             | 1    | 0              | 1    | 0         | 1    | 0           | 1    |
| Female      | 60.9          | 39.1 | 30.0           | 70.0 | 49.6      | 50.4 | 50.8        | 49.2 |
| Male        | 86.0          | 14.0 | 45.3           | 54.7 | 64.0      | 36.0 | 64.0        | 36.0 |
| Under40     | 71.4          | 28.6 | 31.4           | 68.6 | 52.4      | 47.6 | 51.4        | 48.6 |
| Over40      | 68.8          | 31.2 | 47.5           | 52.5 | 63.8      | 36.2 | 70.0        | 30.0 |

Data Acquisition

The participants completed the BioVRSea experiment while wearing a 64-channel CA-208 wet EEG cap (ANT Neuro, Hengelo, the Netherlands), with a sampling rate of 4096 Hz, following the international 10–20 system for electrode placement (Table 3.3).

Relative PSD values were computed for each subject across the five canonical frequency bands: delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12-30 Hz), and low gamma (30-45 Hz) for each experimental phase. The topographic

scalp maps of the PSD for the two groups are shown in Figure 3.1, highlighting group differences across frequency bands and phases. Color maps represent the mean PSD values for each electrode ( $\mu\text{V}^2/\text{Hz}$ ).

Table 3.3: Electrode placement across different brain lobes for the CA-208 waveguard cap

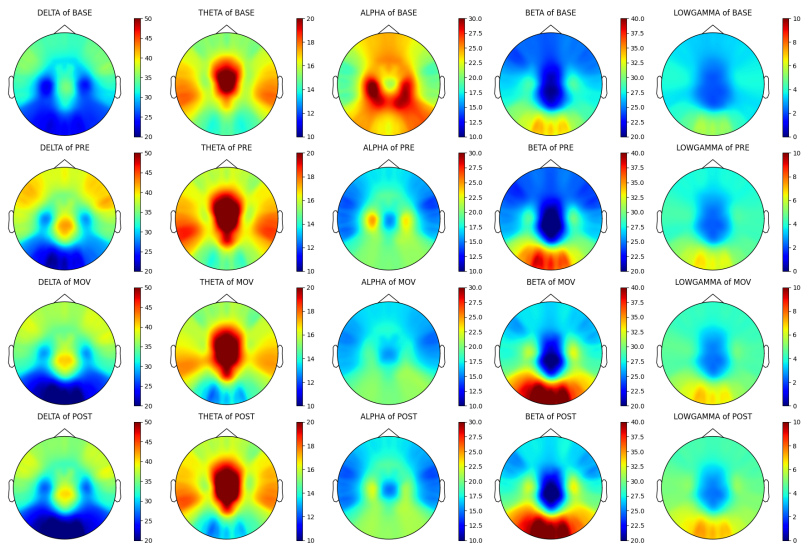
| Lobes          | Electrode names                                                                                                         |
|----------------|-------------------------------------------------------------------------------------------------------------------------|
| Frontal        | FP1, FPz, FP2, AF7, AF3, AFz, AF4, AF8, F7, F5, F3, F1, Fz, F2, F4, F6, F8, FC3, FC1, FCz, FC2, FC4, C3, C1, Cz, C2, C4 |
| Temporal Left  | FT7, FC5, T7, C5, TP7, CP5                                                                                              |
| Temporal Right | FC6, FT8, C6, T8, CP6, TP8                                                                                              |
| Parietal       | CP3, CP1, CPz, CP2, CP4, P7, P5, P3, P1, Pz, P2, P4, P6, P8                                                             |
| Occipital      | PO7, PO3, POz, PO4, PO8, O1, Oz, O2                                                                                     |

### Statistical analysis

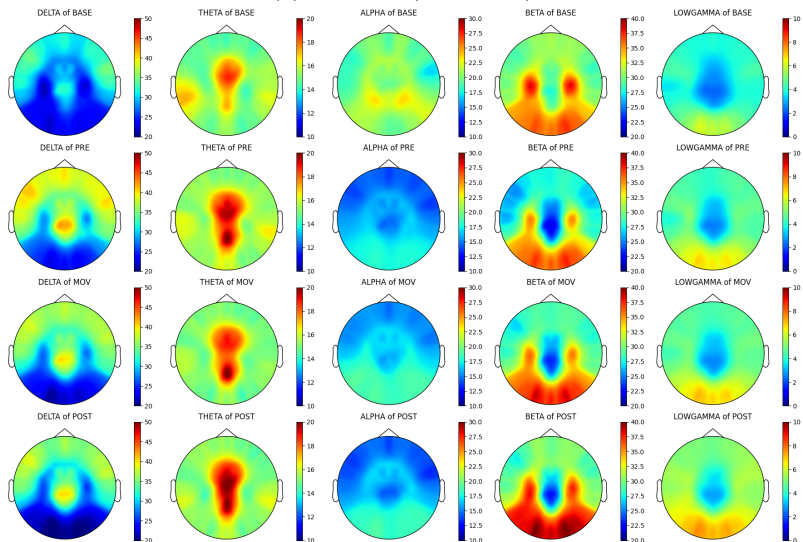
The statistical analysis was performed to compare the Under40 group with the Over40 group during each task. For each electrode and frequency band, non-parametric group comparisons were conducted using the Mann–Whitney U test, assessing whether PSD distributions significantly differed between the two age groups. To correct for multiple comparisons across electrodes, False Discovery Rate (FDR) correction was applied to the p-values using the Benjamini–Hochberg procedure ( $q = 0.05$ ). Electrodes passing FDR correction were considered statistically significant. For each frequency band and task, scalp topographies were computed by calculating the mean PSD difference between the two groups at each electrode. Only electrodes showing statistically significant differences after FDR correction were visualized. In Figure 3.2, black crosses indicate electrodes significant at  $p < 0.05$  (uncorrected), and a green circle indicates electrodes significant after FDR correction.

### 3.1.3 Results

The distribution of questionnaire-based indices was analyzed across sex and age groups, as shown in Table 3.2. It presents the percentage distribution of participants across the four indices (Proneness, BioVRSea, Phy, and Neuro), stratified by sex and age group. Focusing on the age-based stratification, the BioVRSea Index showed a higher proportion of positive responses (index = 1) in the Under40 group (68.6%) compared to the Over40 group (52.5%), suggesting a stronger effect of the experimental paradigm in the younger cohort. Conversely, both the Phy and Neuro indices had a lower percentage of positive responses in the Over40 group (36.2% and 30.0%, respectively) compared to the Under40 group (47.6% and 48.6%), indicating age-related differences in physical and neurocognitive aspects.



(a) Under40 (<40 years)



(b) Over40 ( $\geq 40$  years)

Figure 3.1: Topographical plots of PSD distribution across brain regions for each frequency band and phase ( $\mu V^2/Hz$ ). Each column corresponds to a specific frequency band, while each row represents a different experimental phase. The color scale indicates relative PSD values, with warm colors (red/yellow) representing higher power and cool colors (blue) indicating lower power

Regarding EEG-derived cortical activity, the comparison between age groups

revealed distinct patterns in PSD, as illustrated in Figure 3.1. The figure displays PSD distributions across frequency bands and experimental phases for both the Under40 and Over40 groups. To facilitate direct comparisons, the color scale was kept consistent across phases within each frequency band. The overall topographical patterns are similar but exhibit age-related differences in power distribution and regional activation. Notably, variations in the Alpha and Beta bands suggest potential age-related changes in neural oscillatory activity in all the phases. Moreover, the results highlight distinct responses in the groups across phases, reflecting phase-dependent neural activity. From a statistical perspective (see Figure 3.2), delta band differences were minimal, indicating limited age sensitivity. Theta power was significantly higher in younger participants, particularly in central and temporal regions, with electrodes showing significant differences after FDR correction. Similarly, alpha power was higher in younger participants across all phases except MOV, where most electrodes demonstrated significant differences after FDR correction. In contrast, beta power was consistently higher in the Over40 group across all conditions, suggesting an age-related increase in beta activity. Low-gamma power was slightly higher in older participants during the BASE, PRE, and POST phases, with most electrodes showing significant differences. During the MOV phase, significant group differences persisted only for the theta and beta bands, while alpha and low-gamma showed no statistical differences.

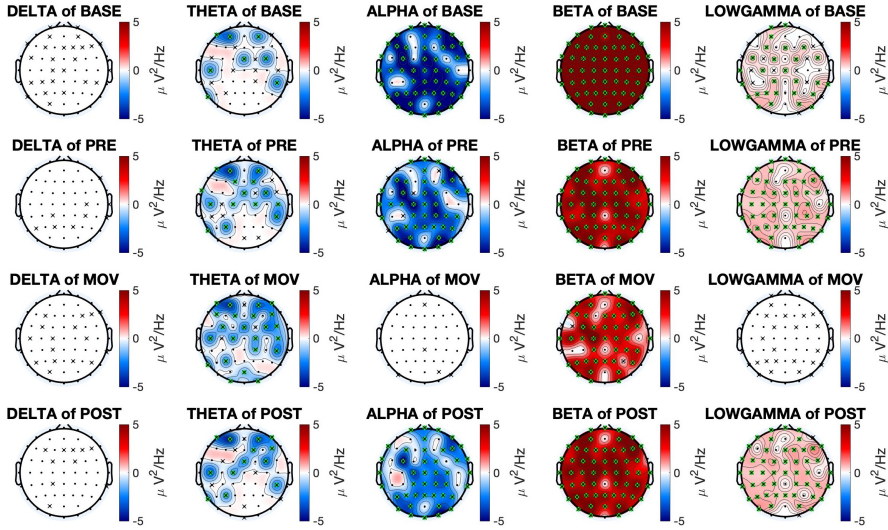


Figure 3.2: Statistical differences between the two groups, Under40 (blue) and Over40 (red), in the relative PSD for each frequency band and phase. Black crosses indicate electrodes significant at  $p < 0.05$  (uncorrected), and green circles indicate electrodes significant after FDR correction

## 3.2 Center of Pressure Dynamics during the BioVRSea

This work was presented at the IEEE International Conference on Metrology for eXtended Reality, Artificial Intelligence and Neural Engineering (MetroXRaine 2025) and published in the official conference proceedings.

### 3.2.1 Introduction

Balance is a complex and essential aspect of human movement, supported by the coordinated activation of multiple strategies that underlie PC and its integration with the central nervous system. Both gender and age are known to influence PC: women often demonstrate superior balance performance across tasks [32], whereas aging is associated with a progressive decline in stability [33, 34]. Older adults typically exhibit greater postural sway, reduced efficiency in sensorimotor integration, muscle weakening, and increased cognitive demands to maintain balance. Muscle strength declines by roughly 10% per decade, with noticeable reductions beginning around 40–50 years of age [35]. The measurement of the CoP via a force platform provides a quantitative and sensitive method to capture these age- and gender-related differences in PC. CoP analysis enables the assessment of postural stability, adaptive responses, and subtle alterations in balance control that may not be detectable through observational methods. By investigating CoP metrics across the lifespan, researchers can reveal how aging impacts postural strategies differently in men and women, supporting early detection of balance impairments, guiding personalized interventions, and informing strategies to promote healthy and independent living [17, 36]. Despite its widespread use, traditional CoP analysis has largely focused on simple metrics under static conditions. There is growing interest in extending its application to dynamic tasks, nonlinear analyses, and individualized evaluations to enhance clinical relevance. Advanced CoP metrics have been successfully applied to differentiate pathological populations, demonstrating the potential of sophisticated CoP quantification for clinical use [37]. While conventional PC assessments provide valuable insights, they often fail to simulate complex real-world conditions. This study employs the BioVRSea system, analyzing CoP data by gender (Females vs. Males) and age group (Under 40 vs. Over 40) using a multidimensional approach. Spectral, nonlinear (entropy and fractal dimension), and geometric features were examined in both the anterior-posterior (AP) and medial-lateral (ML) planes to explore postural strategies under complex stimulation. The current work aims to investigate how sensory stimuli affect PC across gender and age groups and to identify potential biomarkers for early detection of balance impairments in aging. The results may contribute to the development of personalized balance rehabilitation programs and more effective interventions that account for individual variability in PC across the lifespan.

3.2.2 Materials and Methods

Participants

The study included 304 healthy individuals, all of whom were screened to exclude any neurological or orthopedic conditions that could affect balance. As part of the inclusion criteria, volunteers were selected to represent a wide age range (18 to 69 years). Participants were first classified by gender (male or female) and then stratified into two age groups: Under40 and Over40. Table 3.4 reports the mean and standard deviation of participant age, height, and weight by group, providing an overview of the population distribution.

Table 3.4: Participants stratified by gender and age group. Data are reported as Mean and Standard Deviation (SD) for age, height, and weight. Minimum and maximum ages are reported separately

| Feature         | Female (n=151) |       | Male (n=153) |       | Under40 (n=221) |       | Over40 (n=83) |       |
|-----------------|----------------|-------|--------------|-------|-----------------|-------|---------------|-------|
|                 | Mean           | SD    | Mean         | SD    | Mean            | SD    | Mean          | SD    |
| Age (years)     | 31.93          | 14.64 | 33.58        | 14.68 | 24.43           | 4.14  | 54.93         | 8.26  |
| Height (cm)     | 166.99         | 6.60  | 181.18       | 9.42  | 174.00          | 8.99  | 174.48        | 9.20  |
| Weight (kg)     | 66.53          | 12.70 | 84.06        | 14.53 | 71.95           | 15.96 | 84.40         | 16.95 |
| Min Age (years) | 18             | –     | 18           | –     | 18              | –     | 40            | –     |
| Max Age (years) | 69             | –     | 69           | –     | 39              | –     | 69            | –     |

Data acquisition and analysis

Raw CoP signals were recorded from the force platform throughout the entire BioVRSea experiment and underwent the same processing and feature extraction procedures.

Statistical Analysis

Before statistical analysis, outliers were identified using the interquartile range (IQR) method, flagging values below Q1 minus 1.5×IQR or above Q3 plus 1.5×IQR. Participants with outliers in more than 40% of features were excluded, resulting in the removal of 28 subjects. The IQR method was selected for its robustness against non-normal data, and excluding these participants helped reduce noise and improve data reliability for group comparisons. The final sample included 143 females, 133 males, 65 Over40, and 211 Under40. Statistical analyses within each experimental phase evaluated differences in PC responses by age and gender using independent t-tests or Mann–Whitney U tests ( $\alpha<0.001$ ), depending on data normality assessed with Shapiro–Wilk test. To evaluate differences across the three experimental phases, the Friedman test was applied. Post hoc comparisons were conducted using the Wilcoxon signed-rank test to

assess phase-related differences within each age and gender group. P-values were adjusted for multiple comparisons using the Bonferroni correction.

### 3.2.3 Results

Table 3.5: Age-related statistically significant features ( $p < 0.001$ ) within each experimental phase, assessed using Mann–Whitney or t-tests with Bonferroni correction. Values in bold indicate statistical significance

| Feature                                 | PRE             | MOV   | POST            |
|-----------------------------------------|-----------------|-------|-----------------|
| TOTEX (cm)                              | <b>2.62E-06</b> | 0.429 | <b>4.50E-05</b> |
| TOTEX ML (cm)                           | <b>7.00E-05</b> | 0.780 | <b>2.46E-05</b> |
| TOTEX AP (cm)                           | <b>2.62E-06</b> | 0.486 | <b>1.27E-04</b> |
| Ellipse Area (cm <sup>2</sup> )         | <b>1.73E-06</b> | 0.428 | <b>1.08E-05</b> |
| RMS AP (cm)                             | <b>5.03E-06</b> | 0.543 | <b>6.58E-04</b> |
| RMS ML (cm)                             | <b>4.37E-06</b> | 0.707 | <b>5.55E-06</b> |
| Total Power ML (cm <sup>2</sup> )       | <b>9.74E-05</b> | 0.399 | 0.003           |
| Mean freq. ML (Hz)                      | 2.17E-03        | 0.319 | 0.005           |
| Spectral variance ML (Hz <sup>2</sup> ) | <b>6.02E-06</b> | 0.289 | <b>5.44E-04</b> |
| Total Power AP (cm <sup>2</sup> )       | <b>5.62E-05</b> | 0.583 | <b>6.88E-04</b> |

The results of the statistical analysis within the phases revealed no statistically significant differences based on gender, while age-related comparisons are presented in Table 3.5. In particular, age-related differences emerged mainly during the PRE and POST phases, when participants were exposed to visual stimuli alone. No significant differences were observed during the MOV phase when the platform was in motion, and the participant could grasp the bar. The geometrical features of PC, particularly the area of the stabilogram, indicated greater oscillations and reduced stability in the Over40 group in both the ML and the AP directions.

Following the Friedman test, post hoc Wilcoxon comparisons across the phases revealed significant changes ( $p < 0.001$ ) in several CoP features. Both age groups exhibited a marked and statistically significant increase in TOTEX and ellipse area during the MOV phase compared to PRE, reflecting a greater postural demand during platform movement. However, in the Over40 group, some measures, such as TOTEX\_AP and the ellipse area, did not differ significantly between MOV and POST ( $p < 0.05$ ), indicating sustained instability after perturbation. RMS values showed a significant rise in both directions, particularly in the ML direction ( $p < 0.001$ ), for both groups between the MOV and PRE phases (Figure 3.3).

Additionally, a continued elevation in RMS values was observed in the AP direction from MOV to POST, suggesting front-to-back instability following the perturbation. This effect is directly linked to platform motion and the transition to a more challenging balance condition without mechanical support.

Spectral analysis revealed that Total Power in the AP direction significantly increased from the PRE to the MOV phase, followed by a significant decrease in the POST phase, for both groups. In contrast, Total Power in the ML direction

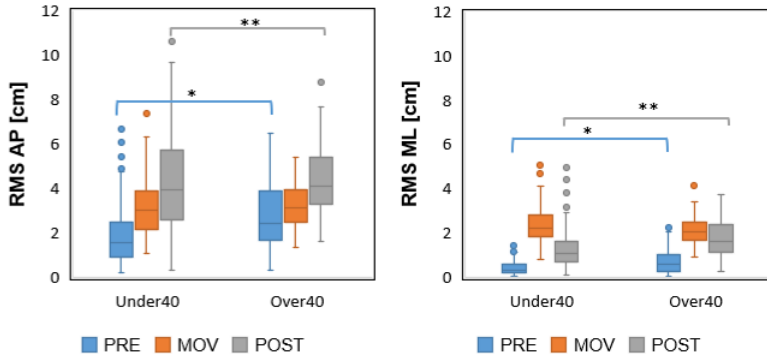


Figure 3.3: RMS in AP and ML directions for Under40 and Over40 across experimental phases. Dots represent outliers

showed a consistent and significant increase across all phases, also for both groups. The Total Power of the CoP signal reflects the overall energy and is indicative of the amount of postural sway. In both directions, the Over40 group exhibited significantly higher values than the Under40, except during the MOV phase, where no significant difference was found. These differences between age groups were confirmed through statistical analysis, as shown in Figure 7.113.

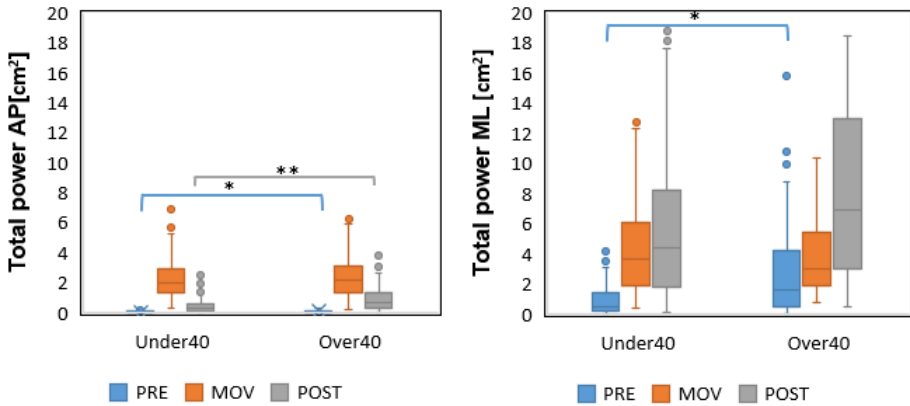


Figure 3.4: Total Power in AP and ML direction for Under40 and Over40 across experimental phases. Dots represent outliers

Moreover, Mean and Median frequencies increased significantly in MOV across all participants ( $p < 0.001$ ), suggesting increased neuromuscular engagement during perturbation. Spectral Variance also increased across the phases, indicating broader frequency dispersion and reduced control precision. Although

these values decreased slightly in POST, they remained significantly higher than in PRE ( $p < 0.001$ ), suggesting residual instability. The analysis within phases (Table 3.5) revealed that Over40 participants exhibited significantly higher Spectral Variance in both the PRE and POST phases, as well as a higher Mean frequency in the ML direction during the PRE phase, compared to Under40 participants ( $p < 0.001$ ), as shown in Figure 3.5, reflecting less focused and more variable postural strategies.

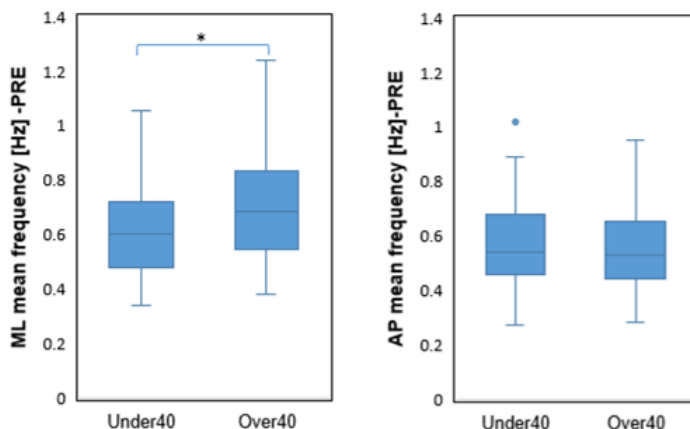


Figure 3.5: Mean frequency in AP direction for Under40 and Over40 in the PRE phase, where the dots represent outliers

Although within-phase comparisons did not reveal significant differences in SampEn, a significant decrease was observed during the MOV phase in both directions and across both cohorts, particularly in the ML direction, as illustrated in Figure 3.6. This effect can also be related to the platform motion. Changes in SampEn are likely driven by the perturbation and, more specifically, by the experimental protocol. During the MOV phase, participants actively hold the support bar, providing external mechanical stabilization that likely constrains the complexity of the PC system and alters signal regularity. In contrast, during phases in which participants progressively release the support, PC relies more strongly on internal feedback mechanisms. This shift may increase signal complexity and variability, as reflected by SampEn in both the AP and ML directions.

For the fractal dimension within the phases, the analysis did not reveal statistically significant differences. However, post hoc comparisons after the Friedman test across phases indicated higher values during the MOV phase for both groups, with slightly elevated mean values also observed in the PRE and POST phases in the AP direction.

Regarding gender differences between phases, although the Friedman test showed significant results, post hoc Wilcoxon analyzes conducted within gen-

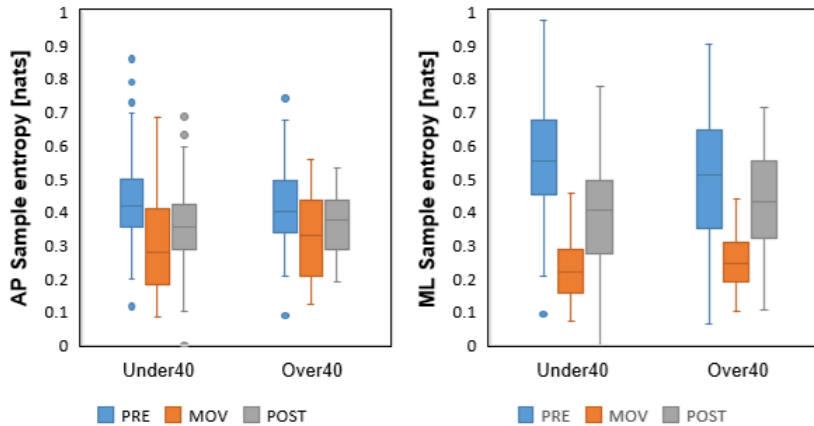


Figure 3.6: Sample Entropy in AP and ML direction for Under40 and Over40 across the experimental phases. Dots represent outliers identified

der subgroups did not reveal substantial differences, indicating that postural responses to visual and motor stimuli were consistent between men and women. Both groups showed comparable increases in postural sway during the perturbation (MOV) phase, followed by similar partial recovery trajectories.

### 3.3 Heart Rate Variability during the BioVRSea

This work brings together two contributions: one presented at the 2nd edition of the IEEE International Conference on Metrology for eXtended Reality, Artificial Intelligence and Neural Engineering (MetroXRINE 2023), and a second contribution presented at the 2025 edition and published in the official conference proceedings.

#### 3.3.1 Introduction

The regulation of cardiac function plays a crucial role in maintaining physiological homeostasis in response to external stimuli such as movement and visual changes [38]. HRV, defined as the variation in time intervals between consecutive heartbeats, is widely used as a non-invasive marker of autonomic nervous system activity. Reduced HRV is commonly associated with impaired health conditions and autonomic dysfunction [39]. Beyond time-domain measures, HRV can be analyzed in the frequency domain, focusing on oscillations at specific frequency bands that reflect sympathetic and parasympathetic modulation. In particular, spectral analysis typically considers low-frequency (0.04–0.15 Hz) and high-frequency (0.15–0.5 Hz) components to characterize autonomic regulation of cardiac activity [40]. HRV is influenced by several individual and physiological factors, including age, sex, physical fitness, health status, and lifestyle habits such as alcohol and tobacco consumption [41–43]. Additional modulators include circadian rhythms, body position, breathing patterns, emotional and cognitive processes, psychosocial stress, movement, and pathological conditions [39, 44, 45]. Consequently, individual-related information must be carefully considered when interpreting HRV changes. During movement and postural transitions, cardiac output is partly regulated by vestibulo-sympathetic mechanisms [46]. Postural challenge tests represent an effective approach for investigating cardiac biosignal modulation and its relationship with PC strategies, commonly assessed through EMG activity and CoP displacement [47, 48].

With the increasing use of VR in both entertainment and medical applications, several studies have reported significant alterations in HR and autonomic regulation during immersive simulations [49]. VR has been employed to investigate cardiac autonomic responses in different populations, including athletes and individuals with spinal cord injuries, and to reproduce controlled realistic conditions that may challenge physiological regulation [49]. Exposure to VR environments has been shown to elicit changes in sympathetic and parasympathetic activity, sometimes accompanied by motion sickness (MS) symptoms [50]. Previous studies have explored HR and HRV responses to VR-induced stress, cognitive load, and simulated driving tasks, highlighting distinct autonomic patterns in individuals prone to MS [51, 52]. Conversely, certain immersive VR scenarios, particularly nature-based environments, have been associated with stress reduction and decreased HR [53].

In this context, subjective questionnaires represent a valuable complementary tool for assessing physiological and perceptual changes before and after specific

experimental conditions in relation to HRV. The BioVRSea platform has been applied in studies investigating lifestyle factors and susceptibility to MS [14, 54]. The BioVRSea induces MS in subjects through complex PC tasks. HR is measured, and a specific MS Susceptibility Questionnaire (MSSQ) is used to assess and quantify MS symptoms [14]. Since HRV is influenced by several factors as previously mentioned, the questionnaire can be one of the promising tools for comparing changes before and after a given condition. In an initial BioVRSea study [14], HR was recorded using a chest-mounted sensor providing average HR and standard deviation measures (Polar Electro, Kempele, Finland; sampling frequency 1000 Hz).

In the present study, ECG acquisition was enhanced using the BioSignal-Plus system, enabling more precise signal recording and the extraction of detailed HRV and ECG features. The primary objective is to evaluate ECG-derived measures in healthy subjects during the complex BioVRSea task, with a particular focus on age and gender related differences in HRV. The second part focuses on applying machine learning models to identify the HRV features most relevant for classifying individuals who experienced MS symptoms during the task.

### 3.3.2 Materials and Methods

#### Cohort

A total of 112 participants were included in the study, 35 of whom had a history of concussion. To investigate age-related differences in HRV, a threshold of 40 years was adopted, as HRV changes are known to become more pronounced across distinct age decades. The cohort exhibited a markedly unbalanced age distribution, with 103 participants younger than 40 years (mean age:  $24.21 \pm 3.67$  years; 61 female, 40 male, and 2 not specified) and only 9 participants aged 40 years or older (mean age:  $53.44 \pm 7.65$  years; 4 female and 5 male). To enable fair age-group comparisons, 100 random subsets of 9 younger participants were generated to match the size of the older group.

For sex-based comparisons, the 2 participants who did not specify their sex were excluded, resulting in a final cohort of 65 female (mean age:  $25.48 \pm 8.09$  years) and 45 male participants (mean age:  $28.04 \pm 10.15$  years).

For comparisons between concussed and healthy individuals, each concussed participant was matched to a control participant based on exact age and sex. When multiple matches were available, one was randomly selected. In cases where no exact age match was possible, matching was performed based on sex and the closest available age. This procedure yielded 15 concussed participants (mean age:  $29.33 \pm 11.68$  years; 11 female, 3 male, and 1 not specified) and 15 matched healthy controls (mean age:  $29.40 \pm 10.19$  years; 11 female, 3 male, and 1 not specified).

### Acquisition Protocol

The group performed the BioVRSea acquisition protocol with the BioSignalsPlus device positioned at the chest level. Before and after the experiment, participants complete the questionnaire. In this study, 25 %, 50 %, 75 % phases are analyzed as a unique phase labeled MOV. For the concussion subject cohort, SCAT5 was used evaluate the symptoms resulting from a concussion injury.

Signal acquisition and processing were performed using the OpenSignals software, which automatically extracted a set of meaningful features over the entire acquisition period.

In accordance with the protocol, each participant also completed the MSSQ to assess self-perceived MS symptoms, including nausea, dizziness, vertigo, and fatigue. Participants rated symptom severity on a scale from 0 to 2, both before and after the BioVRSea protocol. The Binary BioVRSea Effect Index (BVSEI) was used to differentiate individuals who reported a change in one or more symptoms between pre- and post-experiment assessments (BVSEI = 1,  $n = 50$ ) from those who did not report any symptoms (BVSEI = 0,  $n = 20$ ).

### Data Analysis

HRV is extracted from ECG signals and analyzed in three domains: time, frequency, and non-linear. The analysis was performed with custom-developed code. R-peak detection was carried out using the Pan-Tompkins QRS detection algorithm [55]. To enhance accuracy, the RR interval series underwent outlier removal process using the quartile method. For spectral analysis, the time series was linearly interpolated at 1000 Hz to ensure equally spaced samples and then down sampled to 4 Hz using a spline method, as recommended by [56]. The HR series, expressed in beats per minute (bpm), was subsequently derived from the RR intervals. Welch's method was applied after detrending the RR series. Nonlinear features were computed using a lag of 10. HRV parameters were analyzed across the PRE, MOV, and POST phases, as well as over the entire recording, with particular emphasis on the concussion group.

### Statistical Analysis

The analysis comprised three primary group comparisons: male versus female, healthy versus concussed, and participants over-40 versus under-40. All subsequent statistical tests were conducted with reference to these groupings. To evaluate age-related differences, comparisons between the under-40 and over-40 groups were repeated across 100 random subsets of under-40 participants, each matched in size to the over-40 cohort. Age and gender analyses were performed on features extracted from the entire acquired signal, whereas comparisons between healthy and concussed participants were additionally carried out for each experimental phase.

Additionally, age was treated as a continuous variable to investigate potential linear relationships between age and the extracted cardiac features. Correlation analyses were performed both on the entire dataset and separately within female

and male subgroups. The strength of these associations was quantified using Pearson’s correlation coefficient. For each feature, the distribution of values within the relevant groups was first assessed. Normality was evaluated using the Shapiro–Wilk test. When both groups exhibited Gaussian distributions, between-group differences were analyzed using a parametric t-test. In cases where the assumption of normality was violated, a nonparametric test for independent samples was applied using the MATLAB rank sum function. If either group included fewer than 10 observations, or if the total sample size was less than 20, exact p-values were computed using the Mann–Whitney U test; otherwise, p-values were estimated based on the corresponding z-statistic. In all analyses, statistical significance was assessed at an alpha level of 0.05. To account for the large number of comparisons, the Benjamini–Hochberg (BH) procedure was applied to control the false discovery rate, thereby limiting the proportion of false-positive findings.

### Machine Learning Model

A comprehensive dataset was constructed, including all features extracted across the different phases of the BioVRSea experiment. The machine learning analysis aimed to perform binary classification of subjects based on BVSEI using 124 HR features (31 features  $\times$  4 phases). The first stage involved feature selection using wrapper methods, specifically Forward Selection (FS) and Backward Elimination (BE) [57]. FS starts from an empty feature set and iteratively adds the most relevant features until no further improvement in model performance is achieved. In contrast, BE begins with the full feature set and progressively removes the least informative features until performance no longer improves. These procedures were applied to identify the most discriminative features and the experimental phases in which they provide the greatest contribution. Both FS and BE were implemented using Linear Regression (LR) and Random Forest (RF), yielding four groups of 25 features each. Classification was then performed using Decision Tree (DT), RF, and LR models [58]. The four feature groups were used as model inputs, and hyperparameters were optimized for each algorithm using 10-fold cross-validation. Model performance was evaluated using accuracy, precision, recall, and F1-score [59]. The best-performing models were selected for subsequent analysis. Feature importance analysis was conducted on the top-performing models. As discussed in the following sections, RF and DT achieved the highest performance across all evaluation metrics and were therefore used to assess feature relevance. In addition, a Logistic Regression model with Random Search hyperparameter optimization was implemented to examine the contribution of individual features to motion sickness (class 1) and non-motion sickness (class 0). In this framework, positive coefficients indicate features associated with class 1, whereas negative coefficients indicate features associated with class 0. All machine learning analyses were performed using Python (scikit-learn) and KNIME software.

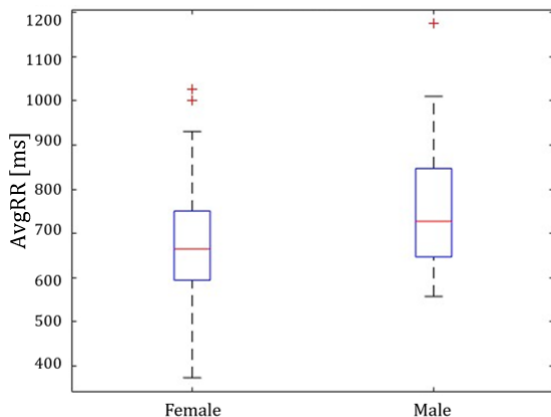


Figure 3.7: Distribution of AvgRR in female and male participants

### 3.3.3 Results

#### Statistical Analysis

##### A. Age differences

Regarding age differences, several discriminative features emerged: participants over-40 showed lower Min HR ( $p=0.0465$ ), and a lower  $P_{VLF}/P_{TOT}(\%)$ , ( $p=0.0066$ ), while younger individuals had lower  $P_{LF}/P_{TOT}(\%)$  ( $p=0.0230$ ). After applying the BH correction, the number of statistically significant comparisons decreased, while the mentioned features remained unchanged.

##### B. Gender differences

Statistical analyses revealed significant differences only in the time domain using uncorrected  $p$ -values (Table 3.6), particularly in Avg RR, Max RR. RR series features tended to be lower in females, as shown in Figure 3.7 for Avg RR.

 Table 3.6: HRV features by gender showing statistically significant differences (mean  $\pm$  standard deviation)

| Parameter   | Females             | Males               | $p$ -value    |
|-------------|---------------------|---------------------|---------------|
| AVG RR (ms) | 673.11 $\pm$ 129.56 | 753.05 $\pm$ 136.06 | <b>0.0033</b> |
| Max RR (ms) | 812.08 $\pm$ 166.10 | 906.96 $\pm$ 183.27 | <b>0.0057</b> |

##### C. Correlation analysis

Results of the correlation analysis are listed in Table 3.7. Correlation analysis showed age-related effects: Min RR and  $P_{VLF}/P_{TOT}$  positively correlated with age of the whole cohort participants, while Max HR,  $P_{LF}/P_{TOT}$ , and SD1/SD2 (lag  $j = 10$ ) were negatively correlated. In females, only SD1/SD2 showed

a significant negative correlation. In males, Min RR and  $P_{VLF}/P_{TOT}$  were positively correlated with age, while Max HR and  $P_{LF}/P_{TOT}$  were negatively correlated.

Table 3.7: Correlation analysis between cardiac features and age. Pearson’s correlation coefficient ( $r$ ) quantifies the strength and direction of the linear relationship between each cardiac feature and age. Results are reported for the overall cohort and separately for female and male participants. Statistically significant correlations ( $p < 0.05$ ) are highlighted in bold

| Parameter             | Overall        |               | Females        |               | Males          |               |
|-----------------------|----------------|---------------|----------------|---------------|----------------|---------------|
|                       | $r$            | $p$ -value    | $r$            | $p$ -value    | $r$            | $p$ -value    |
| Min RR (ms)           | <b>0.2498</b>  | <b>0.0079</b> | 0.0800         | 0.5259        | <b>0.3758</b>  | <b>0.0110</b> |
| Max HR (bpm)          | <b>-0.2202</b> | <b>0.0196</b> | 0.0959         | 0.4484        | <b>-0.3458</b> | <b>0.0200</b> |
| $P_{VLF}/P_{TOT}$ (%) | <b>0.2402</b>  | <b>0.0107</b> | 0.2071         | 0.0978        | <b>0.3148</b>  | <b>0.0352</b> |
| $P_{LF}/P_{TOT}$ (%)  | <b>-0.2193</b> | <b>0.0210</b> | 0.1673         | 0.2662        | <b>-0.3640</b> | <b>0.0140</b> |
| SD1/SD2 ( $j = 10$ )  | <b>-0.2131</b> | <b>0.0240</b> | <b>-0.2482</b> | <b>0.0462</b> | 0.2040         | 0.1788        |

#### D. Concussion

Statistical analyses performed on the entire experimental recording did not reveal any significant differences between concussed and healthy participants. However,  $P_{LF}$  ( $p=0.0564$ ) had an average value of  $1.28 \cdot 10^3 \pm 757.64 \text{ ms}^2$  for the healthy group, and an average value of  $1.07 \cdot 10^3 \pm 607.44 \text{ ms}^2$  for the one composed of concussed participants. Differences emerged when the parameters were calculated separately in the experimental phases of interest, as shown in Table 3.8. As illustrated in Figure 3.8,  $P_{LF}$  exhibited differences in both the MOV and POST phases.

Table 3.8: Summary of statistically significant differences between healthy and concussed participants across experimental phases. Reported are the parameters showing significant effects and their corresponding uncorrected p-values

| Phase | Parameter                       | $p$ -value    |
|-------|---------------------------------|---------------|
| MOV   | $P_{LF} \text{ (ms}^2\text{)}$  | <b>0.0344</b> |
|       | $P_{HF} \text{ (ms}^2\text{)}$  | <b>0.0161</b> |
|       | $P_{TOT} \text{ (ms}^2\text{)}$ | <b>0.0161</b> |
|       | SD1 (ms)                        | <b>0.0202</b> |
| POST  | SD RR (ms)                      | <b>0.0310</b> |
|       | $P_{LF} \text{ (ms}^2\text{)}$  | <b>0.0421</b> |
|       | SD1 (ms)                        | <b>0.0251</b> |

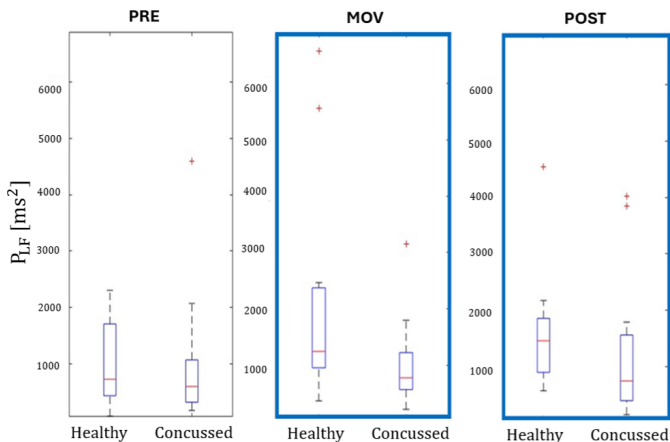


Figure 3.8: Distribution of  $P_{LF}$  and its evolution across PRE, MOV, and POST phases. Statistically significant differences between healthy and concussed participants are observed in the MOV and POST phases

## Machine Learning

Regarding the application of machine learning to identify features capable of discriminating MS during the BioVRSea task, the most accurate models were obtained using features from FS and BE in combination with random forest (RF) and decision tree (DT) classifiers. Among the three algorithms tested, the maximum time required to train and evaluate the models using 10-fold cross-validation was observed with DT, amounting to 8.386 ms.

Table 3.9 displays the classification metrics, where the RF algorithm combined with FS feature selection achieved the highest accuracy (0.742) and F1 score (0.834). The other two top-performing models also utilized the RF algorithm in combination with the BE feature selection. The LR algorithm proved to be efficient when used with the latter. Among the three approaches, DT was the least effective algorithm. Additionally, conducting feature importance analysis for the two best machine learning models revealed that the most important features were largely shared in the RF model implemented with both FR and BR. These features included VLF Power % MID, SD IHR MID, SD2 MID, and Area PRE, as highlighted by the colors in Table 3.10. Notably, VLF Power% MID contributed to the classification by more than 8% of the total values in both cases. Similarly, in the LR model, the same features were deemed important. Specifically, SD IHR (BPM) MID and SD2 (ms) MID were relevant in predicting class 1, while VLF Power % MID was predictive of class 0 [60]. This significance was evident in both FR and BR cases, as depicted in Figure 3.9. By integrating machine learning and statistical analysis, two features were identified as both relevant and statistically significant: VLF POWER% MID and Area in the PRE phase. Figure ?? presents their distribution, highlighting

the disparities between individuals with and without symptoms caused by the BioVRSea experiment.

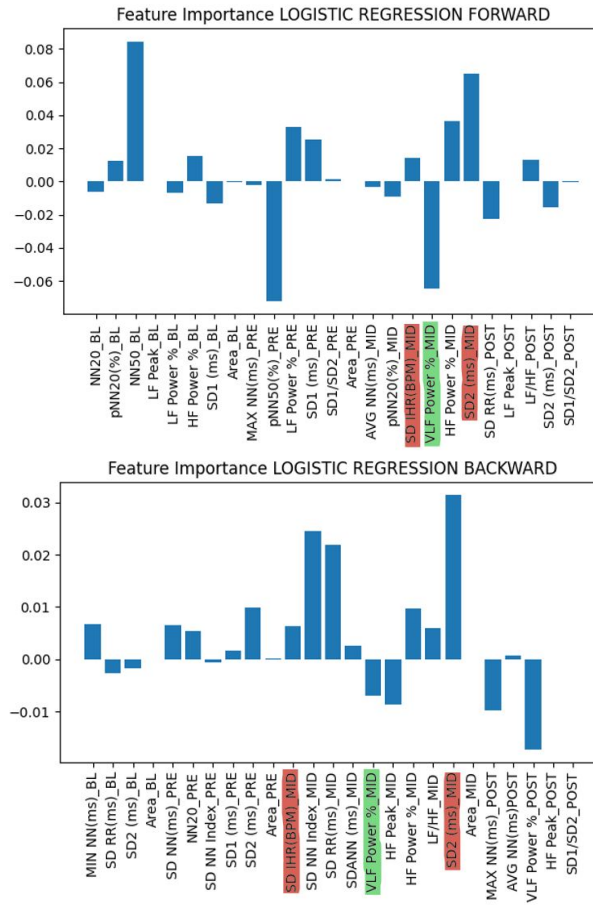


Figure 3.9: Feature importance with Logistic Regression machine learning model: positive features are predicting class BVSEI=1 while the negative ones are predicting BVSEI=0. Features highlighted in red predict class 1 and are shared between FS and BE while the ones in green predict class 0

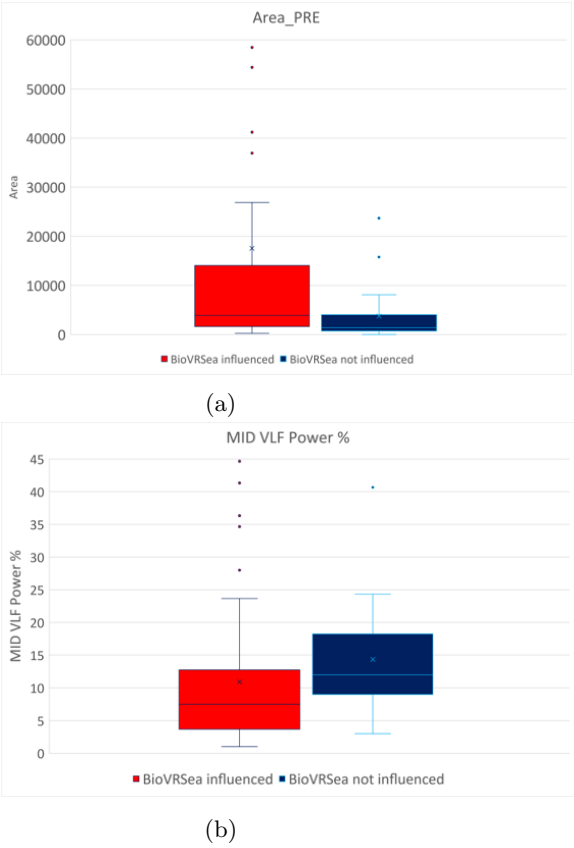


Figure 3.10: Box plot describing the distribution of the most important features comparing subjects influenced (red) and not influenced (blue) by BioVRSea

Table 3.9: Classification metrics for machine learning models using FS and BE with RF

| MODELS | ACCURACY | PRECISION | RECALL | F1 SCORE |
|--------|----------|-----------|--------|----------|
| RF FS  | 0.742    | 0.611     | 0.649  | 0.834    |
| RF BE  | 0.728    | 0.502     | 0.609  | 0.829    |
| DT FS  | 0.614    | 0.502     | 0.521  | 0.719    |
| DT BE  | 0.700    | 0.640     | 0.699  | 0.765    |
| LR FS  | 0.700    | 0.575     | 0.584  | 0.791    |
| LR BE  | 0.728    | 0.638     | 0.673  | 0.810    |

Table 3.10: Most important features for RF classification model, where features are in order of importance. The features shared by both selection methods are highlighted with colors

| RF FR            | %     |  | RF BR            | %     |
|------------------|-------|--|------------------|-------|
| VLF Power% MID   | 8.737 |  | VLF Power% MID   | 8.204 |
| SD IHR (BPM) MID | 8.616 |  | SD2(ms) PRE      | 6.481 |
| SD2 (ms) MID     | 7.367 |  | SD IHR (BPM) MID | 6.086 |
| Area PRE         | 6.854 |  | SD NN Index MID  | 5.901 |
| NN50 BL          | 5.755 |  | Area MID         | 5.429 |
| Area VL          | 5.656 |  | SD2 (ms) MID     | 5.267 |
| pNN20(%) BL      | 4.986 |  | Area PRE         | 5.013 |

### 3.4 Postural Control Alterations Following Sport-related Concussion

This study was presented at the CMBBE 2024 Symposium, the 19th International Symposium on Computer Methods in Biomechanics and Biomedical Engineering (Vancouver, Canada).

#### 3.4.1 Introduction

A concussion, or mild traumatic brain injury (mTBI), is a transient neurological impairment caused by a blow or forces transmitted to the head [61].

Sports participation, especially in high-impact disciplines, increases the risk of sustaining concussions. Acute symptoms include headache, emotional disturbances, loss of consciousness, amnesia, sleep–wake alterations, and cognitive deficits, with balance and gait impairments being particularly prevalent and reflecting PC alterations [62, 63]. Although most concussions resolve spontaneously, some individuals experience persistent physical, cognitive, and psychological symptoms, often with prolonged recovery [64]. PC deficits may persist beyond the acute phase, interfering with daily activities. Currently, no objective diagnostic marker exists, and clinical diagnosis relies on symptom-based tools. Conventional assessments often fail to detect subtle deficits, highlighting the need for objective measures of PC. Concussion evaluation is commonly performed using standardized questionnaires. The Sport Concussion Assessment Tool, fifth edition (SCAT5), is widely employed to assess symptom severity shortly after injury and to monitor recovery. While SCAT5 includes balance-related components and is easily administered, it should not be used in isolation for diagnostic purposes. However, reliance on self-reported symptoms, clinical interviews, and medical records frequently considered the gold standard in concussion research may result in reduced diagnostic accuracy, as many individuals with concussion do not seek medical attention. This limitation underscores the need for more objective and sensitive measures to better characterize concussion-related impairments and recovery dynamics.

Table 3.11: Population distribution, divided into concussion group and healthy group. Age is reported as mean  $\pm$  standard deviation

|            | Number of subjects | Female | Male | Age            |
|------------|--------------------|--------|------|----------------|
| Concussion | 23                 | 23     | 0    | 28.6 $\pm$ 5.7 |
| Healthy    | 23                 | 23     | 0    | 30.3 $\pm$ 8.4 |

Quantitative PC assessment, including CoP measures, provides a sensitive indicator of balance dysfunction and have been proposed as potential indicators of concussive injury. In fact, some studies revealed that individuals with a history of concussion exhibit larger, slower, and more irregular CoP oscillations and seem to persist for up to one year [33, 65].

Although not routinely adopted in clinical practice, EEG, EMG, HR measures, and VR environments represent complementary tools for investigating PC deficits following concussion. EEG provides a non-invasive measure of brain activity, revealing functional alterations and disrupted neural networks underlying sensorimotor integration, which can be linked to impaired PC [66, 67]. EMG offers direct insight into the neuromuscular mechanisms supporting balance, with abnormal patterns correlating with injury severity, particularly when recorded from muscles crucial for stability, such as the TA muscle [68–70]. HR and HRV provide additional information on autonomic function and recovery trajectories, though their interpretation should account for factors such as sex and age [71, 72]. VR environments allow for controlled, immersive assessment of PC under challenging visual and physical conditions, often combined with EMG, CoP, and accelerometry, revealing subtle balance deficits not detectable with standard clinical tests [73, 74]. Together, these multi-modal techniques enable a comprehensive evaluation of sensorimotor, neuromuscular, and autonomic mechanisms, supporting a more complete understanding of concussion-related postural instability.

### 3.4.2 Material and Methods

#### Participants

A total of 46 participants were included in this study, as summarized in Table 3.11. Among them, 23 female athletes reported a history of concussion (mean age: 28.6  $\pm$  5.7 years), while 23 young females without a history of concussion were included as a healthy control group (mean age: 30.3  $\pm$  8.4 years), also reported in Table 3.11. All participants completed the BioVRSea paradigm, during which all biosignals were recorded.

#### Data Processing

In this study, the primary focus was on EMG and CoP signals, reflecting the aim of investigating biomechanical responses in isolation. The integration of these findings with neurophysiological data, such as EEG, was planned as a

future step. Following data acquisition, pre-processing procedures were applied to facilitate signal analysis and remove noise components while preserving the integrity of the information.

### Statistical Analysis

A statistical analysis was performed to assess significant differences between the concussion group and the healthy control, within all the phases of the experiment. For both EMG and CoP data, statistical analysis was performed using the same methodology across all four experimental phases. Specifically, all features related to each muscle were included in the analysis. An initial assessment of normality was performed using the Shapiro-Wilk test to evaluate the distribution of all features extracted from both the EMG and CoP datasets. Given the prevalence of non-normal distributions in both EMG and CoP features, p-values were computed using the Mann-Whitney U test. The results were subsequently validated using the Kolmogorov-Smirnov test. The significance level ( $\alpha$ ) was set at 0.05, with p-values below this threshold considered statistically significant. To account for multiple comparisons and enhance the robustness of the results, the Bonferroni correction was applied, as the Mann-Whitney U test was performed multiple times ( $n = 43$  for EMG, and  $n = 36$  for CoP features).

### 3.4.3 Results

#### A. EMG

The activation of the TA, S, and GL muscles in both the right and left legs was analyzed across all 43 EMG-derived features throughout the experimental phases. The Mann-Whitney U test revealed that significant differences ( $p < 0.05$ ) were mainly observed during the PRE and POST phases, when participants were exposed solely to visual stimuli. Notably, a greater number of features reached significance in the POST phase, whereas only two features were significant in the MOV phase across all muscles considered (Pmax of GLL and CV of GLR). During the PRE phase, significant differences were primarily observed in the TA and S muscles during the balancing task, including Kurtosis and Fskew in TAR, skewness in TAL, and FMD and FMN in SR and SL. The most pronounced effects emerged in the POST phase, where the tibialis anterior showed greater engagement relative to the other recorded muscles. Specifically, five features were significant in the left TA (TAL) and 25 features in the right TA (TAR), as shown in Table 3.12. The features that consistently exhibited significant differences in both TAL and TAR were ASM, KURT, MMAV, and MMAV2. It is important to note that none of these results remained statistically significant after applying the Bonferroni correction for multiple comparisons ( $\alpha = 0.05/43 \approx 0.00116$ ).

Table 3.12: Example of TAR values across the experimental phases of PRE and POST only for the comparison of the two cohorts. Statistically significant values are highlighted in bold

| TAR          | PRE          | POST         |
|--------------|--------------|--------------|
| <b>PT</b>    | 0.323        | <b>0.046</b> |
| Pmax         | 0.913        | 0.053        |
| Fmax         | 0.156        | 0.235        |
| FMD          | 0.546        | 0.429        |
| FMN          | 0.913        | 0.709        |
| <b>Fkurt</b> | <b>0.021</b> | 0.965        |
| <b>Fskew</b> | <b>0.046</b> | 0.826        |
| <b>AAC</b>   | 0.312        | <b>0.021</b> |
| <b>AE</b>    | 0.323        | <b>0.046</b> |
| <b>ASM</b>   | 0.468        | <b>0.011</b> |
| <b>ASS</b>   | 0.645        | <b>0.012</b> |
| CV           | 0.253        | 0.323        |
| <b>DAMV</b>  | 0.312        | <b>0.021</b> |
| DASDV        | 0.323        | 0.068        |
| DVARV        | 0.323        | 0.068        |
| <b>EMAV</b>  | 0.709        | <b>0.022</b> |
| <b>EWL</b>   | 0.482        | <b>0.020</b> |
| FZC          | 0.135        | 0.637        |
| <b>KURT</b>  | 0.468        | <b>0.031</b> |
| <b>IEMG</b>  | 0.429        | <b>0.021</b> |
| <b>IQR</b>   | 0.843        | <b>0.011</b> |
| LCV          | 0.368        | 0.416        |
| <b>LD</b>    | 0.693        | <b>0.012</b> |
| <b>LDAMV</b> | 0.312        | <b>0.021</b> |
| LDASDV       | 0.323        | 0.068        |
| LTKEO        | 0.312        | 0.059        |
| <b>MAD</b>   | 0.429        | <b>0.020</b> |
| <b>MAV</b>   | 0.429        | <b>0.020</b> |
| MFL          | 0.323        | 0.068        |
| MN           | 0.292        | 0.334        |
| MD           | 0.895        | 0.982        |
| <b>MMAV</b>  | 0.380        | <b>0.024</b> |
| <b>MMAV2</b> | 0.496        | <b>0.024</b> |
| <b>MSR</b>   | 0.660        | <b>0.007</b> |
| <b>RMS</b>   | 0.323        | <b>0.046</b> |
| <b>SD</b>    | 0.323        | <b>0.046</b> |
| SKEW         | 0.109        | 0.553        |
| <b>SSI</b>   | 0.323        | <b>0.046</b> |
| TM           | 0.380        | 0.091        |
| <b>VAR</b>   | 0.323        | <b>0.046</b> |
| <b>VARE</b>  | 0.323        | <b>0.046</b> |
| <b>VO</b>    | 0.323        | <b>0.046</b> |
| <b>WL</b>    | 0.312        | <b>0.021</b> |

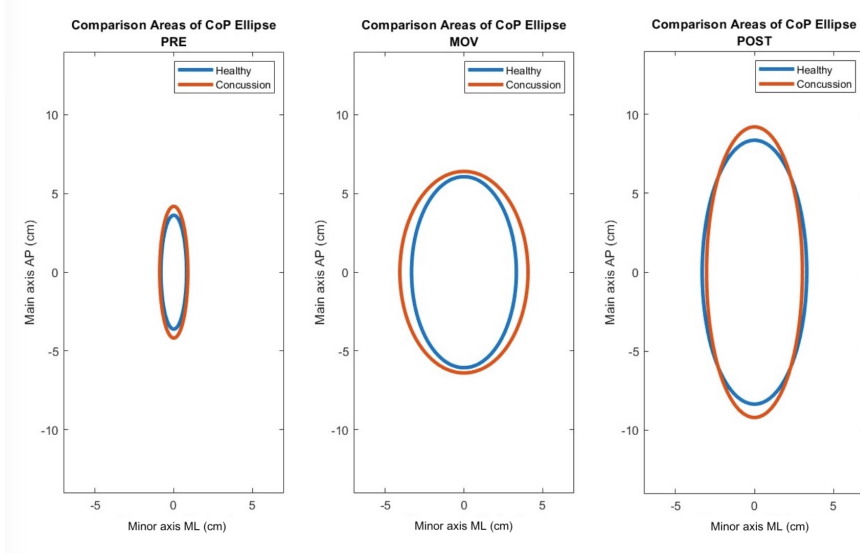


Figure 3.11: Comparison of Ellipse Areas among concussion group (solid orange line) and healthy controls (solid blue line) across the PRE, MOV, and POST phases

## B. CoP

The CoP data were analyzed across all the segments of the experiment. The ellipse that best represents each group behavior during the experiment phases is shown in Figure 3.11. Ellipse Areas resulted comparable between groups, showing instead a differentiation between phases. In fact, after conducting the Mann-Whitney U test between groups, it was found that none of the ellipse features exhibited statistical significance ( $p\text{-value} < 0.05$ ) in all three phases among groups (as in Figure 3.12). Instead, a clear distinction exists between the PRE and MOV phases when compared to the POST phase. This is attributed to the limited number of significant features in the initial two segments, where only one is observed during the visual stimuli (PRE) and two during the moving platform phase (MOV). Conversely, during the POST phase, in which the movement of the patient is induced by the memory of the previous segment of the experiment, six features show a significant difference between groups. Especially, the Total Excursion feature and the Mean Velocity feature allow to give a good explanation in this differentiation, as shown in the respective boxplots in Figure 3.13.

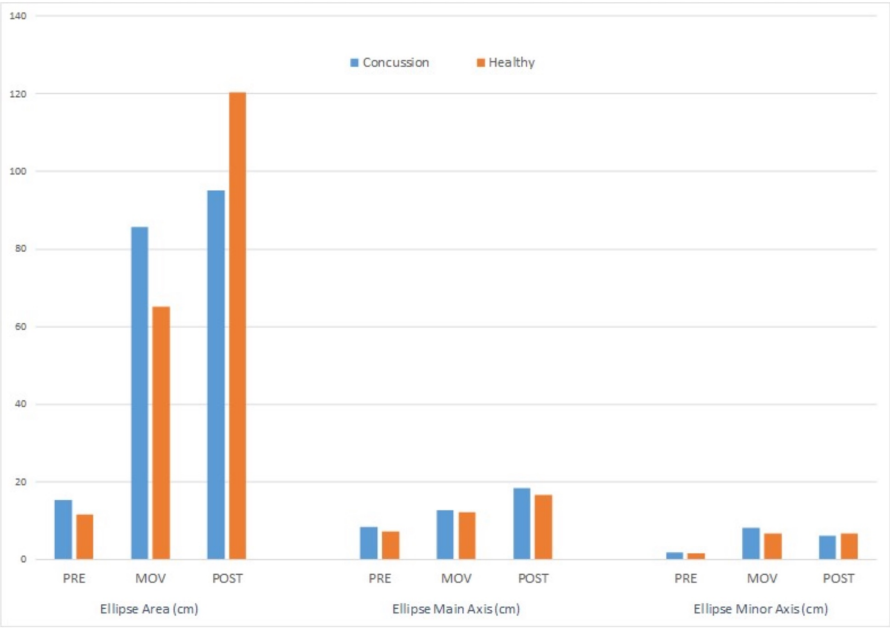


Figure 3.12: Comparison of some of Ellipse features values among the concussion group (orange) and healthy controls (blue) during PRE, MOV, and POST phases

Table 3.13: Statistical analysis of ellipse features showing significant differences between groups in the PRE and POST phases after the Mann-Whitney U test. Statistically significant p-values ( $p < 0.05$ ) are highlighted in bold

| Ellipse Feature    | PRE phase p-value | POST phase p-value |
|--------------------|-------------------|--------------------|
| Ellipse Area       | <b>0.01452</b>    | <b>0.00047</b>     |
| Ellipse Main Axis  | <b>0.00745</b>    | <b>0.00043</b>     |
| Ellipse Minor Axis | <b>0.03211</b>    | <b>0.00345</b>     |

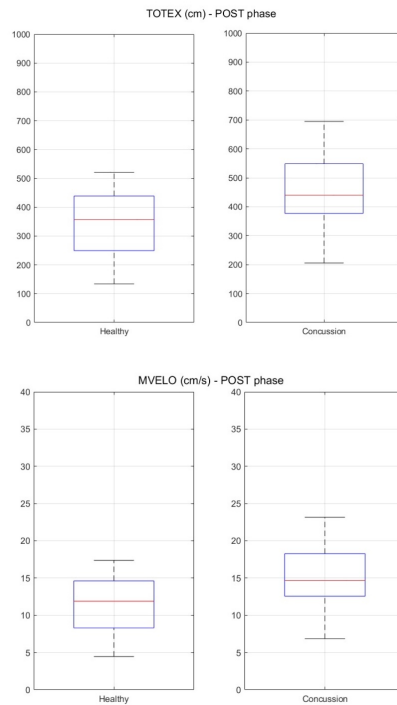


Figure 3.13: Statistically significant features, Total Excursion and Mean Velocity, in POST phase (p-value = 0.016636)

### 3.5 Adaptive Postural Strategies in Experienced Maritime Subjects

This study was presented at the CMBBE 2024 Symposium, the 19th International Symposium on Computer Methods in Biomechanics and Biomedical Engineering, and was later expanded and published in the proceedings of the IEEE MetroXRaine 2025 conference.

#### 3.5.1 Introduction

Extant research has characterized PC as a fundamental 'learned' motor skill, whose function and efficiency can be systematically enhanced through routine postural tasks or targeted training [75, 76]. From these studies, two dimensions of postural learning have been proposed: adaptation, defined as transient improvements in motor responses to upright balance perturbations [77], and habituation, characterized by a gradual reduction in response to repeated perturbations [78]. Both adaptation and habituation processes are critical in shaping effective PC [13]. Investigating PC responses in individuals exposed to prolonged unbalanced conditions, such as maritime environments, may reveal distinctive strategies of adaptation and habituation. Accordingly, this study compares the PC responses of sailors recently subjected to extended maritime conditions with those of a control group of healthy individuals, with particular emphasis on differences in adaptation and habituation mechanisms.



Figure 3.14: One of the participants from Akureyri who took part in the study on sailors after spending at least two weeks ashore

### 3.5.2 Material and Methods

#### Participants

This study initially involved two cohorts: 21 male sailors and 114 healthy male controls. The control group was drawn from a larger dataset of 550 participants of both sexes and was refined by selecting only males within the age range of the sailor group. To capture the effects of recent sea exposure, the sailors had spent three weeks at sea and were tested immediately upon returning to shore. Figure 3.14 shows a sailor during data acquisition conducted in Akureyri. All participants had no history of balance disorders or neurological conditions. To ensure group comparability, we applied a statistical selection method based on the Mahalanobis distance. This technique considered height, weight, and body mass index (BMI) to identify the 21 most similar healthy individuals from the larger control group, reducing potential biases related to anthropometric differences. Descriptive statistics for age, height, and weight before and after cohort selection are reported in Table 3.14 and 3.15.

Table 3.14: Mean and standard deviations of age, height, weight before and after control cohort selection using Mahalanobis distance matching

| Feature | Sailors (n=21) |       | Controls (n=114) |       | Controls (n=21) |       |
|---------|----------------|-------|------------------|-------|-----------------|-------|
|         | Mean           | SD    | Mean             | SD    | Mean            | SD    |
| Age     | 41.71          | 11.99 | 31.90            | 13.71 | 38.05           | 10.42 |
| Height  | 182.33         | 6.34  | 181.39           | 10.19 | 182.05          | 3.87  |
| Weight  | 93.62          | 13.42 | 84.21            | 14.01 | 89.57           | 8.83  |

Table 3.15: p-values before and after cohort selection (t-test)

| Feature | p-value (Controls n=114) | p-value (Controls n=21) |
|---------|--------------------------|-------------------------|
| Age     | <0.01                    | 0.29                    |
| Height  | 0.68                     | 0.86                    |
| Weight  | 0.01                     | 0.25                    |

All participants completed the BioVRSea experiment, during which biosignals were recorded. For the present analysis, we focus on EMG data collected via the Kinelive sensors and on CoP measurements obtained from the FP.

#### Statistical Analysis

To determine the appropriate statistical test for each feature, the Shapiro–Wilk test was used to assess the normality of data distributions. Features exhibiting normal distributions were analyzed using two-sample t-tests, while non-normally distributed features were evaluated using the Mann–Whitney U test. To account for multiple comparisons, Bonferroni correction was implemented to the p-values

obtained from both t-tests and Mann–Whitney U tests, adjusting the significance threshold based on the total number of tests conducted within each dataset. Additionally, to control the false discovery rate and minimize type I errors, FDR correction using the Benjamini–Hochberg procedure was applied to the combined set of p-values, yielding corresponding q-values for each feature.

3.5.3 Results

A. EMG

A trend toward significance was observed for several features in all muscles and phases before correction; however, only SKEW for the SR during the adaptation phase remained statistically significant after Bonferroni correction, as detailed in Figure 3.15 and Table 3.16.

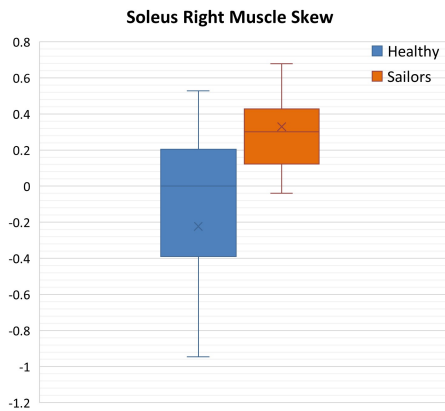


Figure 3.15: Comparison of SKEW between sailors and healthy control participants during the adaptation phase (MOV), showing higher SKEW values in the sailor group

Table 3.16: Corrected and uncorrected p-values, q-values, and group statistics for SKEW in the adaptation phase

| Feature          | p-value               | p-value corrected | q-value |
|------------------|-----------------------|-------------------|---------|
| SKEW             | $6.23 \times 10^{-4}$ | 0.037             | 0.037   |
| Healthy Controls |                       |                   |         |
| Mean $\pm$ SD    | $-0.223 \pm 0.692$    |                   |         |
| Sailors          |                       |                   |         |
| Mean $\pm$ SD    | $0.329 \pm 0.302$     |                   |         |

### B. CoP

An initial analysis was conducted to investigate potential differences in sway behavior between the two cohorts, focusing on the AP and ML directions, as in Figure 3.16. During the adaptation phase, the TOTEX AP, MVELO AP, Magnitude Entropy, and Multivariate CI features violated the normality assumption and were therefore analyzed using the Mann–Whitney U test. In contrast, the ML SampEn, ML CI, and Direction Entropy features were normally distributed and analyzed using two-sample t-tests. All of these features exhibited statistically significant group differences, which remained significant after Bonferroni correction, as detailed in Table 3.17. During the habituation phase, the AP CI feature was normally distributed and was the only feature to show a statistically significant difference between groups (Table 3.17).

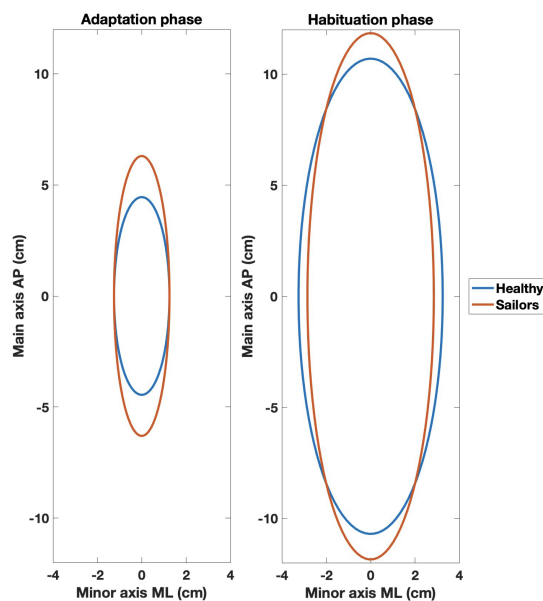


Figure 3.16: Mean CoP ellipses for healthy individuals and sailors. The major axis represents AP sway, while the minor axis represents ML sway

Table 3.17: Significant CoP features during the adaptation and habituation phases, along with their corresponding p-values and q-values

| Feature           | p-value               | corrected p-value     | q-value               |
|-------------------|-----------------------|-----------------------|-----------------------|
| Adaptation        |                       |                       |                       |
| TOTEX AP          | $1.40 \times 10^{-3}$ | $4.90 \times 10^{-2}$ | $7.00 \times 10^{-3}$ |
| MVELO AP          | $1.40 \times 10^{-3}$ | $4.90 \times 10^{-2}$ | $7.00 \times 10^{-3}$ |
| ML SampEn         | $2.31 \times 10^{-6}$ | $8.08 \times 10^{-5}$ | $5.62 \times 10^{-5}$ |
| ML CI             | $3.21 \times 10^{-6}$ | $1.12 \times 10^{-4}$ | $5.62 \times 10^{-5}$ |
| Magnitude Entropy | $2.17 \times 10^{-4}$ | $7.61 \times 10^{-3}$ | $1.90 \times 10^{-3}$ |
| Direction Entropy | $1.01 \times 10^{-4}$ | $3.54 \times 10^{-3}$ | $1.18 \times 10^{-3}$ |
| Multivariate CI   | $3.22 \times 10^{-4}$ | $1.13 \times 10^{-2}$ | $2.25 \times 10^{-3}$ |
| Habituation       |                       |                       |                       |
| AP CI             | $1.41 \times 10^{-3}$ | $4.95 \times 10^{-2}$ | $2.67 \times 10^{-2}$ |

## Chapter 4

# Postural and Neural Signatures in Early-Stage Parkinson's Disease

### 4.1 Introduction of the study

The following material is extracted from a publication in the journal *Frontiers* (2023), entitled “Adaptation strategies and neurophysiological responses in early-stage Parkinson’s disease: the BioVRSea approach,” and has been adapted for the present thesis. This work represents the first study on Parkinson’s disease (PD) conducted using data obtained with the BioVRSea system.

### 4.2 Parkinson’s Disease

PD is a progressive disorder of the nervous system characterized by muscle tremors, muscle rigidity, decreased mobility (bradykinesia), stooped posture, slow voluntary movements, and a mask-like facial expression. It may take time to diagnose because some of its symptoms are associated with the natural process of aging [79]. Globally, disability and death in PD are increasing faster than any other neurological disorder. The World Health Organization (WHO) reports that the prevalence of PD has doubled in the past 25 years and world estimates count over 8.5 million individuals with PD in 2019. In people with early-onset PD, the initial symptoms can arise between the ages of 21 and 40 years, while the first symptoms in juvenile-onset disease occurs before the age of 20 years.

Nowadays, establishing a standardized criterion for the evaluation of this disorder, as with many others, remains a central objective for clinicians. Determining the progression of the disease is essential for selecting the most appropriate treatments. The classification of PD relies not only on the observation of clinical signs and symptoms, but also on the results of various diagnostic tests. Over the years, diagnostic protocols have evolved to integrate both qualitative assessments, including clinical observation and patient-reported outcomes, and quantitative measures, such as motor performance parameters

or neurophysiological recordings. This comprehensive approach has improved the accuracy of disease evaluation and enhanced clinicians' ability to identify relevant patterns of progression. Nevertheless, detecting individuals in the earliest stages of PD, when symptoms are subtle or even absent, remains a significant clinical challenge, highlighting the need for more sensitive diagnostic strategies.

#### 4.2.1 Stages of the Disease

Traditionally, PD stages have been identified based on clinical observations. According to the Hoehn-Yahr staging system, stages are based primarily on motor symptoms [80]. The progression of this neurodegenerative disease can be divided into several stages. In the pre-clinical stage, individuals do not exhibit any signs or symptoms, although genetic testing and counselling may allow identification of risk factors and opportunities for early intervention. The prodromal stage follows, during which the first symptoms begin to appear, reflecting underlying neurodegenerative changes in the nervous system. These early symptoms are often nonspecific, but this stage provides a potential window for early therapeutic approaches. During the early stage, mild motor symptoms emerge, including subtle tremors and slight difficulties in walking, typically affecting only one side of the body. Facial expressiveness may be reduced, yet these manifestations generally do not interfere significantly with daily activities and may be easily overlooked. As the disease progresses to the middle stage, balance and coordination become increasingly impaired, and the disability reaches a moderate-to-severe level, impacting everyday life. In the later stage, patients experience advanced disease with severe disability, often requiring assistance to stand or walk.

Figure 4.1 provides a visual summary of these stages, highlighting the progression of key motor and functional symptoms throughout the course of the disease.

### 4.3 Clinical Assessment

A preliminary analysis can be performed by clinicians through a careful evaluation of both the qualitative and quantitative aspects of the disease, considering the range and severity of motor symptoms but also their evolution and progression over time. Such a comprehensive assessment provides an initial overview of disease impact, supports the identification of relevant clinical patterns, and informs decisions regarding further diagnostic investigations and potential management strategies. Figure 4.2 illustrates some these qualitative and quantitative factors integrated into the clinical evaluation process.

#### Assessment Scales

Before discussing the various methods used for the clinical assessment of PD, it is important to introduce key assessment scales. The Hoehn and Yahr scale is a

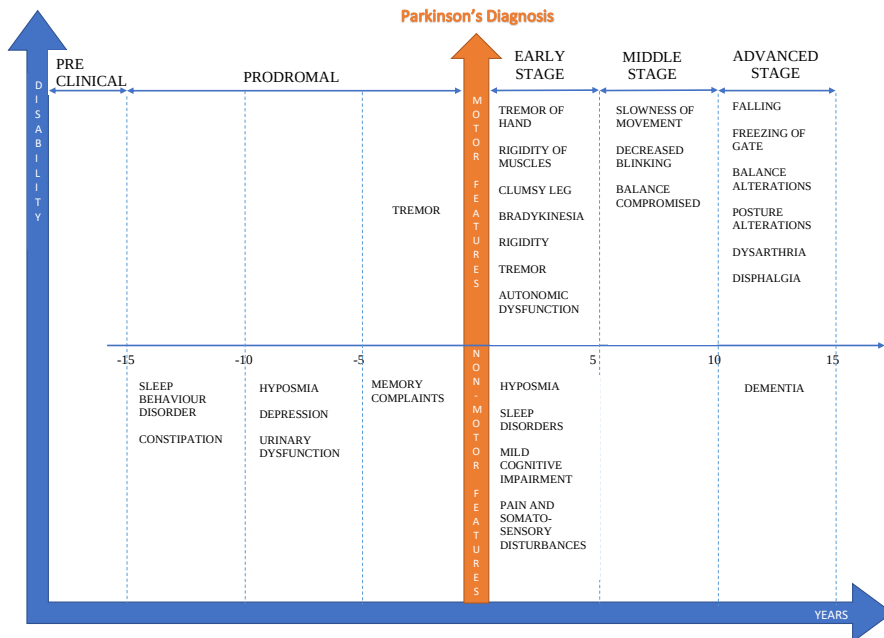


Figure 4.1: Evolution of symptoms and their relationship with the various classification stages in PD

widely used clinical rating scale for staging the progression of PD. It provides a standardized framework to classify the severity of motor symptoms, ranging from mild, unilateral manifestations to severe, bilateral impairments with postural instability. Understanding the Hoehn and Yahr stages is essential for interpreting clinical assessments, comparing patient populations, and evaluating the effectiveness of therapeutic interventions. However, it should be noted that this scale is not commonly used in Iceland, where clinicians rely primarily on the Montreal Cognitive Assessment (MoCA).

The MoCA is a cognitive screening scale designed to detect mild cognitive impairment in PD patients. It evaluates domains such as attention, executive function, memory, language, visuospatial abilities, and orientation. Compared to traditional tools, the MoCA is more sensitive in identifying early cognitive deficits, which can appear alongside or even before prominent motor symptoms. In Iceland, the MoCA is more widely used than the Hoehn and Yahr scale, highlighting differences in clinical practice and emphasizing the importance of considering alternative assessment approaches.

### Gait and Mobility

Mobility and gait impairment evolve with the progression of the disease. Therefore, they can be considered as valuable parameters for clinical evaluation.

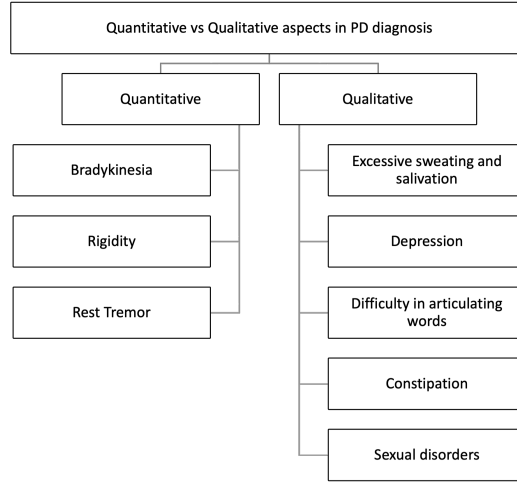


Figure 4.2: Quantitative and qualitative aspects in PD diagnosis [81]

Common gait-related difficulties include problems with gait initiation, freezing episodes, reduced balance, and overall impairments in PC. Quantifying these motor changes provides insight into disease severity and functional limitations, supporting both diagnosis and monitoring of progression [82]. An overview of the main assessment methods, their associated tests, and specific objectives is presented in Table 4.3.

### Molecular Profiling

Beyond traditional clinical observation, innovative approaches such as molecular profiling through blood tests are under investigation. Preliminary studies have identified potential biomarkers capable of defining early-stage PD, though these findings remain experimental and are not yet implemented in routine clinical practice [83].

### Brain Imaging

In recent years, non-invasive neuroimaging techniques for the detection and monitoring of PD have become increasingly accurate, allowing researchers and clinicians to identify both structural and functional alterations in the brain. Several studies have reported significant differences in brain morphology and activity between healthy individuals and PD patients [84]. Among them, EEG offers a direct measure of neurophysiological activity, providing insights into the integrity and activation of brain networks under different stimuli and conditions. In Parkinson's individuals, EEG analyses have revealed altered cortico-cortical and cortico-thalamic connectivity, particularly in the anterior cingulate and temporal lobes, as well as excessive beta-band coherence, reflecting disruptions

| ASSESSMENTS | TESTS                                                                                                                                                                                                                                                | GOALS                                                                                                                                                                                                  |
|-------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Balance     | Timed Up and Go Test<br>Tinetti Balance and Gait Test<br>Retropulsion Test<br>One-leg Stance<br>Åstrand-Rhyming protocol during Graded Exercise Test<br>Balance Evaluation System Test<br>Mini Balance Evaluation Systems Test<br>Berg Balance Scale | Functional mobility<br>Static and dynamic balance<br>Postural stability<br>Static balance<br>Dynamic balance<br>Balance Systems<br>Dynamical balance<br>Static and dynamic balance                     |
| Endurance   | 2-min Walk Test<br>6-min Walk Test<br>Two-minute Step test<br>Modified Bruce Protocol during Graded exercise test<br>Åstrand-Rhyming protocol during Graded exercise test<br>Borg Ratio Scale                                                        | Functional capacity, walking ability<br>Physical capacity and gait<br>Aerobic capacity<br>Cardiac functional capacity<br>Maximal functional capacity<br>Physical capacity                              |
| Resistance  | Handgrip Strength Test<br>Isokinetic Strength Test<br>Manual Muscle Test<br>Arm Curl Test<br>Chair Stand Test<br>Five Time Sit to Stand Test<br>One Repetition Maximum Test                                                                          | Upper limb strength<br>Upper/lower limb strength<br>Individual or grouped muscle strength<br>Upper limb strength<br>Lower limb strength<br>Lower limb strength<br>Maximum lower or upper limb isotonic |
| Flexibility | Goniometer<br>Inclinator<br>Leighton flexometer<br>Sit and Reach Test<br>Back Scratch Test                                                                                                                                                           | General Joint Flexibility<br>Angles of slope measurement<br>Joint flexibility<br>Lower back and hamstring muscles tightness<br>Shoulder range of motion                                                |

Figure 4.3: Gold standard for gait assessments

in neural communication associated with motor and cognitive symptoms [85]. Other imaging modalities provide complementary structural and functional information. Magnetic resonance imaging (MRI) can detect subtle tissue changes, even in early-onset PD, offering early markers of disease before clinical symptoms manifest. Positron emission tomography (PET) allows the assessment of regional brain metabolism and can support clinical diagnosis and monitoring of disease progression. Using radiotracers such as 18F-DOPA and 18F-FDG, PET provides detailed maps of affected brain regions and functional activity [86]. Similarly, single-photon emission computed tomography (SPECT) enables the evaluation of cerebral blood flow and dopamine transporter (DAT) availability, with DAT-SPECT scans highlighting degeneration in the basal ganglia, a key region controlling movement. Transcranial sonography (TCS) has emerged as a valuable supplementary tool, particularly for detecting hypo echogenicity in the mesencephalic brainstem, which correlates with increased iron accumulation—a potential early indicator of PD pathogenesis [87]. Collectively, these neuro imaging approaches provide a multi-dimensional understanding of PD, linking structural, functional, and biochemical changes to clinical manifestations and disease progression.

## 4.4 EEG Band-Specific Differences

Map structure and functions of the brain are obtained measuring the signals produced by neural activity. Each region can have a particular influence according to the disease and the activation of an area can be considered important in the understanding of the progression of the disease. Although cortical EEG coherence can serve as a reliable measure of disease severity, the use of EEG to study PD has not been fully investigated. Neurophysiological signals provide instantaneous information and can aid in improving the accuracy of the diagnosis.

EEG signals have different specific frequency bands. Features in sub-bands are particularly important to characterize different brain states. The standard frequency bands of interest are  $\delta$ -band (0–4 Hz),  $\theta$ -band (4–8 Hz),  $\alpha$ -band (8–13 Hz), and  $\beta$ -band (13–30 Hz). Moreover, the quantification of EEG rhythms could provide an important biomarker for different neuropsychiatric disorders, such as schizophrenia, Alzheimer's disease, epilepsy, and PD [88], [89], [90]. The combination of new analysis methods and EEG signal processing can contribute to the detection of early stage of PD. EEG reveals more important information underlying brain dysfunctions, which would be lost if analysis were restricted to traditional methods. Nowadays, many novel methods are suggested for EEG signal processing.

A recent study analyzed the EEG signals from 15 early-stage PD patients and 15 age-matched healthy controls during eyes-closed resting state [91]. Most EEG electrodes showed an increase in  $\theta$ -band relative power for PD patients, while several other electrodes decreased, such as in the frontal and occipital cortex (Fp1, Fp2, F7, F3, Fz, Oz). Moreover, an increase in  $\delta$ -band relative powers were reported, and a decrease in  $\alpha$ -band and  $\beta$ -band relative powers for PD patients compared with healthy patients. Other studies present higher spectral power in the low frequency domain of EEG, compared with controls. Also in these cases, subjects were in the resting awake condition with the eyes closed [92], [93].

## 4.5 Object of the Study

Neurological disorders arise from disruptions or alterations in the central nervous system, which is crucial for maintaining balance and adapting to external challenges. Despite its fundamental role, the analysis of postural kinematics in individuals with movement disorders has not yet been fully explored, highlighting a critical gap in current research. The clinical evaluation of PD remains challenging, primarily because reliable markers beyond overt motor deficits are still lacking. Although reduced stability in PD is well documented, it is not yet clear whether these deficits emerge progressively during the disease or could serve as early indicators of postural instability.

In this context, the comprehensive analysis of biosignals recorded by the proposed paradigm offers a novel, non-invasive approach to study how PC

| EEG in resting state (No Visual & No movement stimulations) | Statistical Tools     | $\delta$ -band (0–4 Hz)              | $\theta$ -band (4–8 Hz) | $\alpha$ -band (8–13 Hz)             | $\beta$ -band (13–30 Hz) |                                                                   |
|-------------------------------------------------------------|-----------------------|--------------------------------------|-------------------------|--------------------------------------|--------------------------|-------------------------------------------------------------------|
| Eyes Closed                                                 | AR Burg method        | ↑                                    | ↑                       | ↓                                    | ↓                        | Electrodes activity decreased in the frontal and occipital cortex |
|                                                             | Bonferroni correction |                                      |                         |                                      |                          |                                                                   |
| Eyes Closed                                                 |                       | —                                    | ↑<br>Frontal channels   | —                                    | ↓<br>Posterior channels  | Power in central and parietal channels decreased                  |
| Eyes Closed but kept awake<br>Seated comfortably            | CNN T-test            | ↑ in 3.5-4.5Hz<br>Right frontal lobe | —                       | ↓ in 7.5-11Hz<br>Left occipital lobe | —                        |                                                                   |
| Eyes Opened<br>Eyes Close                                   | ANOVA                 | ↑                                    | ↑                       | ↓                                    | —                        |                                                                   |
| Awake patients to minimize eye and body movement            | ANOVA                 | ↑                                    | ↑↑                      | ↑ in 8-10Hz<br>↓ in 10-13Hz          | ↓                        |                                                                   |

Figure 4.4: PSD Bands Analysis in different studies [91], [94], [95], [96] [97]

differs between individuals with PD and healthy participants. In particular, EEG measurements can be used to identify distinct cortical activity patterns in response to various postural perturbations, providing valuable insights into the neural mechanisms underlying balance deficits [13, 98]. Moreover, this approach may allow the identification of distinctive biomarkers associated with PD, contributing to earlier and more precise characterization of the disease.

The aims of this study are: (i) to investigate the postural strategies adopted by individuals with PD compared to healthy subjects, and (ii) to describe adaptation and how the brain adapts to the induced movement of the platform and a visual stimulus using VR.

## 4.6 Study of PC with EEG

Although PC has not been extensively studied in individuals with neurological disorders, it has been widely investigated in both healthy and blind populations, given the crucial role of vision in maintaining balance. In a recent study [13], postural kinematics were recorded using high-density EEG (HD-EEG) during postural perturbations applied to the calf muscles. The main cortical changes were observed in Absolute Spectral Power (ASP) across four frequency bands.

During postural adaptation, increases in the  $\theta$  band were observed in the frontal-central regions for eyes-closed trials, whereas increases in both the  $\theta$  and  $\beta$  bands were reported in the parietal regions for eyes-open trials. During the habituation phase, no significant changes in ASP were observed in eyes-closed trials, while eyes-open trials showed increases in the  $\theta$ ,  $\alpha$ , and  $\beta$  bands [99]. Overall, eyes-open conditions generally yielded a greater number of significant differences across all frequency bands during both adaptation and habituation, suggesting that cortical activity during postural perturbation is strongly modulated by visual feedback. These findings demonstrate a clear correspondence between cortical activity and postural kinematics and suggest potential applications for assessing pathological PC. Similar results have been reported in other studies on healthy subjects, indicating that cortical activity primarily changes in the frontal-central and frontal-parietal regions during balance perturbations, particularly in the  $\alpha$  and  $\theta$  frequency bands [30, 100]. In addition, increases in ASP in the central region have been observed during high-demand postural corrections, such as maintaining balance without allowing corrective foot placement [13]. In this context, elevated  $\theta$  activity in the frontal-central regions reflects the processing of postural stability and the planning of corrective steps, while changes in the  $\alpha$  band are associated with the inhibition of error detection in the cingulate cortex due to habituation. Studies on blind individuals, both congenitally and acquired, further emphasize the role of sensory input in PC. Congenitally blind subjects exhibit greater AP and ML sway compared to sighted individuals, yet they rely on more efficient strategies, such as increased joint stiffness, to maintain balance. These findings highlight how motor coordination, localization, and perception of body segments can be compensated by enhanced proprioceptive and vestibular inputs in visually impaired individuals [101]. Building on this background, our novel BioVRSea setup introduces a unique multi-biometric system that combines VR with a moving platform to evaluate PC responses. The system simulates the sensation of being at sea on a small boat, requiring the implementation of diverse balancing strategies. During the experiment, participants undergo six alternating phases in which various biosignals are measured, including EMG, CoP, and EEG. Participants are exposed to different types of stimuli: visual (PRE phase), motor (MOV phase), and balance control (POST phase). Recent studies have demonstrated the potential of the BioVRSea paradigm for differentiating cohorts and assessing pathological conditions [14, 31]. In the present work, individuals with early-stage PD are subjected to this complex visuomotor task, enabling the investigation of altered postural strategies and cortical adaptations in response to controlled perturbations.

## 4.7 Materials and Methods

### 4.7.1 Participants

A total of 9 early-stage PD participants (6 male, 3 females, aged 56–76 years) and 29 healthy subjects (17 male, 12 female, aged 50–73 years) took part in the BioVRSea experiment. PD participants exhibited mild symptoms, such as slight

tremors, and were all under Levodopa medication, while healthy participants showed no signs of the disease.

#### 4.7.2 Data acquisition

Each participant in this study completed the BioVRSea protocol using the full experimental setup to collect neurophysiological data, which were then compared with those of an age-matched cohort of healthy individuals. As previously stated, our hypothesis is that the responses to the BioVRSea paradigm will differ between the PD and healthy groups across all phases of the experiment. Participants completed a single trial in accordance with the experimental protocol. The collected data were subsequently post-processed in MATLAB, and analyses were performed for each phase of the experiment.

#### 4.7.3 HRV analysis

In this study, heart rate was measured using a chest heart sensor (Polar Electro, Kempele, Finland, sampling frequency 1 Hz). Average and standard deviation for the HR for each section of the experiment were calculated.

#### 4.7.4 EMG analysis

Muscle electrical activities from the lower limbs were acquired using the six wireless EMG sensors placed on the lower limbs, as in the standard BioVRSea protocol. The computed features are listed in Table 4.2.

Pearson correlation coefficients were computed among the extracted features for each muscle.

The Shapiro-Wilk test along with visual inspection of the distribution of each variable were used to test the normality of the data. Statistical comparisons between the healthy and PD groups in both the PRE and POST phases were carried out using the t-test with Welch's correction for the normally distributed variables and the Mann-Whitney U-test for the non-normally distributed variables, with a significance value of  $p < 0.05$ . Effect sizes were calculated through the non-parametric Cliff's delta using the R package "effsize". Cliff's delta ranges from +1 if all observations in the first group are larger than all observations in the second group, to -1 if all observations in the first group are smaller than all observations in the second group.

#### 4.7.5 CoP analysis

CoP measurements were made using 4 sensors located under each foot platform. Included in the CoP analysis were several multi-scale entropy measurements, which have been shown to have great importance in the analysis of CoP data in discriminating between pathological subjects. Multiscale entropy measurements include features such as complexity index (CI), which indicate the complexity of the CoP signal as calculated using multi-scale entropy methods. We extract

several parameters from the stabilogram for evaluating the PC response of the subject during the experiment. The list of features extracted from the CoP is outlined in Table 4.3.

Normality was checked through the Shapiro-Wilk test and visual inspection of the variables, and comparisons were made between the healthy and PD groups for all features in the PRE and POST phases using the t-test with Welch's correction and the Mann-Whitney U-test with significance level  $p < 0.05$ . Effect sizes were calculated using Cliff's delta. Sway profiles were also outlined using 95% confidence ellipses in PRE and POST, as seen in Figure 4.8.

#### 4.7.6 EEG analysis

In this study, we used the CA-204-64 wet electrode cap to measure brain electrical activity with 64 electrodes. EEG data underwent the pre-processing protocol over the entire duration of the recording for each participant. Subsequently, the signals were segmented according to the different phases of the experimental protocol, and PSD was computed for each segment.

PSD values were compared between the PD and healthy groups for each experimental phase and across the delta, theta, alpha, and beta frequency bands. A Mann-Whitney U-test with significance level ( $\alpha = 0.05$ ) was used to determine significance. False detection rate (FDR) correction was applied to each electrode.

### 4.8 Results

The following results are reported for the analysis of the PRE and POST phases of the experiment with the aim of distinguishing between the PD and healthy groups based on their biosignal responses before and after the simulation. Our experiment was able to identify changes in many of the analyzed domains.

#### 4.8.1 HRV

The results of the heart rate analysis are shown in Table 4.1. An increase in beats per minute (bpm) was measured in PD subjects, although not statistically significant. No statistically significant differences were found between groups.

Table 4.1: Average and standard deviation for Heart Rates inside cohorts in PRE and POST phases

| Beats per minute (BPM) | Parkinson's       | Controls          |
|------------------------|-------------------|-------------------|
| PRE phase              | $88.76 \pm 18.09$ | $82.48 \pm 14.63$ |
| POST phase             | $94.19 \pm 20.97$ | $82.54 \pm 14.35$ |

### 4.8.2 EMG

The right TA muscle showed a number of statistically significant features in the POST phase, with a p value ( $p < 0.05$ ) and the corresponding effect sizes for each variable shown in bold in Table 4.2. The right side could be considered the dominant leg in the prevalence of the group. Significant changes were found also in the left soleus (MN mean,  $p = 0.003$ , cliff delta = -0.64) in the POST phase and the soleus right which had one significant feature (MD median,  $p = 0.007$ , cliff delta = -0.586) in the PRE phase. Moreover, Figures 4.5 and 4.6 illustrate the correlation matrices for each muscle, showing distinct group-dependent patterns (red for the PD group and green for the healthy group) for the SR and TAR muscles across all features. Both muscles enable clear differentiation between the two cohorts.

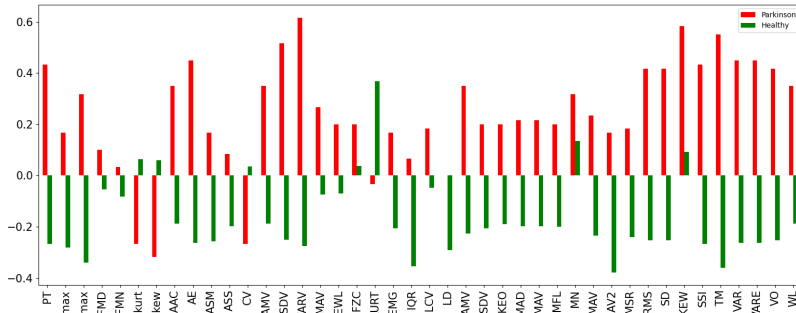


Figure 4.5: Features for the SR muscle showing differences between PD and healthy cohorts

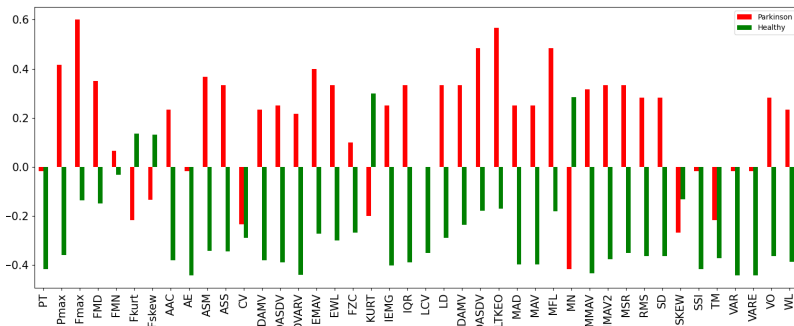


Figure 4.6: Features for the TAR muscle showing differences between PD and healthy cohorts

Table 4.2: EMG features. In bold the features that were significantly different between PD and healthy groups in the TAR muscle in the POST phase

| Feature                                                     | PRE p-value | POST p-value | Cliff delta |
|-------------------------------------------------------------|-------------|--------------|-------------|
| Total Power (PT)                                            | -           | -            | 0.425       |
| <b>Maximum Power (Pmax)</b>                                 | -           | 0.0394       | 0.464       |
| Maximum frequency (Fmax)                                    | -           | -            | 0.141       |
| Median Frequency (FMD)                                      | -           | -            | 0.153       |
| Mean frequency(FMN)                                         | -           | -            | 0.191       |
| Frequency Kurtosis (Fkurt)                                  | -           | -            | 0.073       |
| Frequency skewness (Fskew)                                  | -           | -            | 0.08        |
| <b>Average amplitude change (AAC)</b>                       | -           | 0.0256       | 0.502       |
| Average energy (AE)                                         | -           | -            | 0.425       |
| <b>Absolute value of the exponential root sum (ASM)</b>     | -           | 0.0195       | 0.524       |
| <b>Absolute value of the square root sum (ASS)</b>          | -           | 0.0234       | 0.0509      |
| Coefficient of variation (CV)                               | -           | -            | -0.172      |
| <b>Difference absolute mean value (DAMV)</b>                | -           | 0.0256       | 0.502       |
| <b>Difference absolute standard deviation value (DASDV)</b> | -           | 0.0362       | 0.471       |
| <b>Difference variance value (DVARV)</b>                    | -           | 0.0362       | 0.471       |
| <b>Enhanced mean absolute value (EMAV)</b>                  | -           | 0.0234       | 0.51        |
| <b>Enhanced wavelength (EWL)</b>                            | -           | 0.0162       | 0.0.540     |
| New zero crossing (FZC)                                     | -           | -            | 0.333       |
| <b>Kurtosis (KURT)</b>                                      | -           | 0.0162       | -0.54       |
| <b>Integrated EMG (IEMG)</b>                                | -           | 0.0214       | 0.517       |
| <b>Inter-quartile range (IQR)</b>                           | -           | 0.0394       | 0.463       |
| Log CV (LCV)                                                | -           | -            | -           |
| <b>Log Detector (LD)</b>                                    | -           | 0.0428       | -0.02       |
| <b>Log DAMV (LDAMV)</b>                                     | -           | 0.0256       | 0.502       |
| <b>Log DASDV (LDASDV)</b>                                   | -           | 0.0362       | 0.417       |
| <b>Log Teager Kaiser energy operator (LTKEO)</b>            | -           | 0.0394       | 0.464       |
| Mean absolute deviation (MAD)                               | -           | 0.0256       | 0.502       |
| <b>Mean absolute value (MAV)</b>                            | -           | 0.0256       | 0.502       |
| <b>Maximum fractal length (MFL)</b>                         | -           | 0.0362       | 0.471       |
| Mean (MN)                                                   | -           | -            | 0.21        |
| Median (MD)                                                 | -           | -            | -0.241      |
| <b>Modified mean absolute value (MMAV)</b>                  | -           | 0.0234       | 0.51        |
| <b>Modified mean absolute value 2 (MMAV2)</b>               | -           | 0.0428       | 0.455       |
| <b>Mean value of the square root (MSR)</b>                  | -           | 0.0195       | 0.524       |
| Root mean square (RMS)                                      | -           | -            | -           |
| Standard deviation (SD)                                     | -           | -            | 0.425       |
| Skewness (SKEW)                                             | -           | -            | 0.333       |
| Single square integral (SSI)                                | -           | -            | 0.425       |
| Absolute value of temporal moment (TM)                      | -           | -            | 0.433       |
| Variance (VAR)                                              | -           | -            | 0.425       |
| Variance of EMG (VARE)                                      | -           | -            | 0.425       |
| Variance order (VO)                                         | -           | -            | 0.425       |
| <b>Waveform length (WL)</b>                                 | -           | 0.0256       | 0.502       |

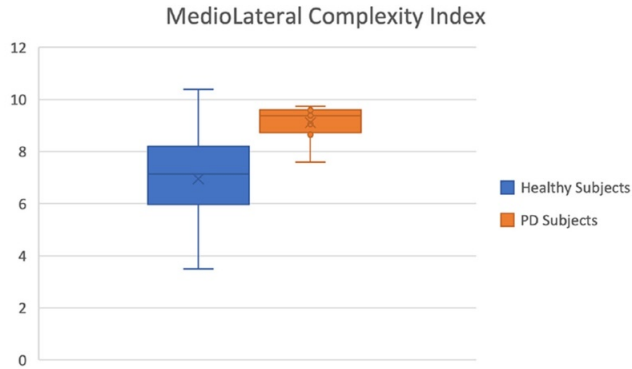


Figure 4.7: MedioLateral Complexity Index of healthy (blue) and PD (orange) groups

### 4.8.3 CoP

Platform-derived CoP data allow the computation of several parameters indicative of different postural sway strategies between cohorts. Among these, the sway ellipse was extracted as a representative descriptor of balance point displacement during unstable movement. Figure 4.8 compares the main ellipse characteristics (area and axis length) between PD and healthy cohorts. In the healthy group, the ellipse area increases in the POST phase, indicating greater sway, whereas PD participants exhibit a reduced ellipse area in the POST phase, reflecting a diminished ability to maintain postural stability. Regarding statistical analysis, the only significant CoP feature in the PRE phase is Direction Entropy (Nats) ( $p < 0.05$ ), while the statistically significant features in the POST phase are reported in Table 4.3, together with their corresponding p-values and Cliff's delta values.

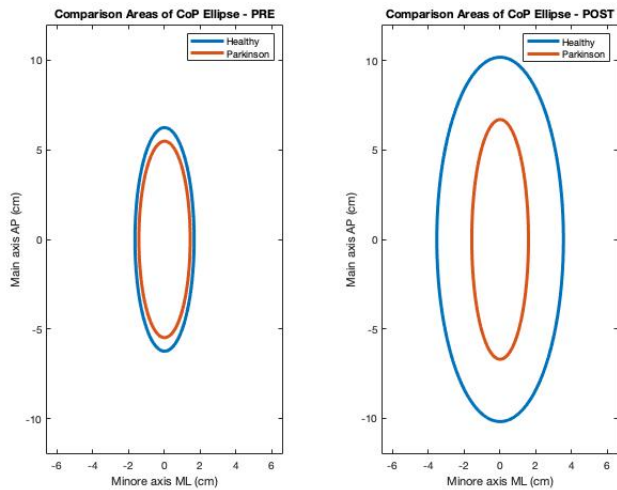


Figure 4.8: Ellipse areas comparison between PD and Healthy subjects in PRE and POST phases

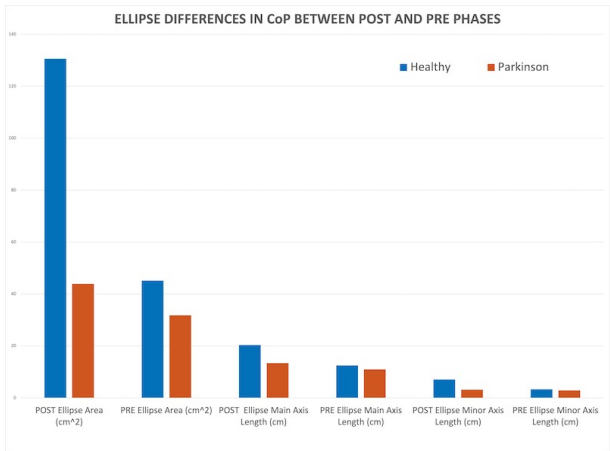


Figure 4.9: Changes in ellipse features from PRE to POST phases in PD versus healthy participants

Table 4.3: CoP features. In bold the features that were significantly different in the POST phase of the experiment when comparing the PD and healthy group

| Feature                                                        | PRE p-value | POST p-value | Cliff delta |
|----------------------------------------------------------------|-------------|--------------|-------------|
| Consecutive movement samples on the support plane (TOTEX)      | -           | -            | 0.379       |
| Consecutive movement samples on ML plane(TOTEX-ML)             | -           | -            | 0.402       |
| Consecutive movement samples on AP plane(TOTEX-AP)             | -           | -            | 0.371       |
| Square root distance between a point and the plane origin (RD) | -           | 0.017        | 0.494       |
| <b>Mean distance in ML direction (MDIST-ML)</b>                | -           | 0.034        | 0.494       |
| <b>Mean distance in AP direction (MDIST-AP)</b>                | -           | 0.017        | 0.494       |
| Mean velocity on support plane (MVELO)                         | -           | -            | 0.379       |
| Mean velocity on ML plane (MVELO-ML)                           | -           | -            | 0.402       |
| Mean velocity on AP plane (MVELO-AP)                           | -           | -            | 0.371       |
| <b>Root mean square distance respect to origin (RDIST)</b>     | -           | 0.012        | 0.540       |
| <b>Root mean square distance in ML direction (RDIST-ML)</b>    | -           | 0.026        | 0.517       |
| <b>Root mean square distance in AP direction (RDIST-AP)</b>    | -           | 0.012        | 0.533       |
| ML sample entropy (ML-SampEn)                                  | -           | 0.000        | -0.709      |
| AP Sample Entropy (AP-SampEn)                                  | -           | -            | -0.333      |
| <b>ML complexity index (ML-CI)</b>                             | -           | 0.001        | -0.793      |
| AP Complexity Index (AP-CI)                                    | -           | -            | -0.325      |
| <b>Ellipse area</b>                                            | -           | 0.008        | 0.571       |
| <b>Ellipse angle</b>                                           | -           | -            | 0.057       |
| <b>Ellipse main axis length</b>                                | -           | 0.007        | 0.571       |
| <b>Ellipse minor axis length</b>                               | -           | 0.013        | 0.571       |
| <b>Standard deviation in AP direction (SD AP)</b>              | -           | 0.012        | 0.532       |
| <b>Standard deviation in ML direction (SD ML)</b>              | -           | 0.026        | 0.517       |
| <b>SD magnitude</b>                                            | -           | 0.007        | 0.563       |
| SD direction                                                   | 0.013       | -            | -0.256      |
| <b>Magnitude entropy</b>                                       | -           | -            | -0.510      |
| <b>Direction entropy</b>                                       | -           | -            | -0.249      |
| <b>Multivariate complexity index (multivariate CI)</b>         | -           | 0.013        | -0.639      |
| Antero magnitude                                               | -           | -            | 0.379       |
| Antero angle                                                   | -           | -            | 0.019       |
| <b>Postero magnitude</b>                                       | -           | 0.014        | 0.548       |
| <b>Postero angle</b>                                           | -           | -            | 0.065       |
| Left magnitude maximum                                         | -           | 0.041        | 0.417       |
| Left angle                                                     | -           | -            | -0.065      |
| <b>Right magnitude maximum</b>                                 | -           | 0.028        | 0.448       |
| <b>Right angle</b>                                             | -           | -            | -0.494      |

#### 4.8.4 EEG

The topological plots were computed for all frequency bands during the phases of the acquisition. Each plot depicts the differences in PSD between the PD and healthy groups for statistically significant electrodes only ( $p \leq 0.05$ , represented by a green point in the figure).

Significant electrodes were identified in the theta and alpha frequency bands in multiple brain regions. In theta band, significant electrodes are found mostly in the temporal lobe (T7, T8, C6, FT7), one in the frontal lobe (AF3) and one in the occipital (PO6). In alpha band, significant electrodes are found mostly in the temporal lobe (FC5, T7, T8, FT8), one in the parietal lobe (P4) and one in the occipital (PO6).

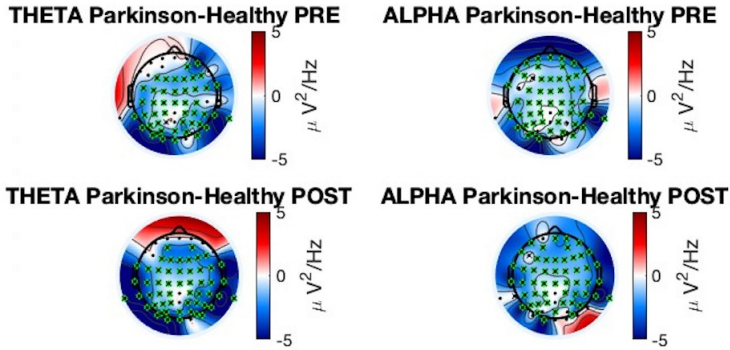


Figure 4.10: Absolute PSD Bands Analysis in PD vs Healthy cohort for theta and alpha frequency bands

Table 4.4: Electrodes for theta band with corresponding p-values comparing the two cohorts in POST and PRE phases. In bold when they were significantly different in the POST phase of the experiment

| Electrodes | PRE phase | POST phase    |
|------------|-----------|---------------|
| M1         | 0.124     | <b>0.0326</b> |
| T7         | 0.07040   | <b>0.0169</b> |
| T8         | 0.139     | <b>0.0215</b> |
| AF3        | 0.0947    | <b>0.0383</b> |
| C6         | 0.0784    | <b>0.0247</b> |
| PO6        | 0.0983    | <b>0.0409</b> |
| FT7        | 0.112     | <b>0.0476</b> |

Table 4.5: Electrodes for alpha band with corresponding p-values comparing the two cohorts in POST and PRE phases. In bold when they were significantly different in the POST phase of the experiment

| Electrodes | PRE phase | POST phase    |
|------------|-----------|---------------|
| FC5        | 0.0597    | <b>0.0247</b> |
| T7         | 0.122     | <b>0.0187</b> |
| T8         | 0.0703    | <b>0.0247</b> |
| P4         | 0.0596    | <b>0.0391</b> |
| PO6        | 0.276     | <b>0.0247</b> |
| FT8        | 0.0674    | <b>0.0165</b> |

## Chapter 5

# Altered Brain Network Dynamics in Parkinson's Disease during the BioVRSea

This work has successfully undergone peer review and is scheduled for publication in Brain Topography in 2026 under the title “Exploring dynamic alpha band connectivity in Parkinson's disease: A novel approach to postural control assessment using the BioVRSea paradigm.” It has been adapted for inclusion in the present thesis.

### 5.1 Introduction of the study

EEG is increasingly being recognized for its role in assessing PC in neurological disorders, due to its high temporal resolution and sensitivity to functional brain alterations [102, 103]. In PD, the progressive degeneration of dopaminergic neurons compromises the neural mechanisms underlying balance regulation, leading to postural instability and a markedly increased risk of falls [104, 105]. EEG studies have consistently reported altered brain oscillatory activity in PD during PC tasks, reflecting impairments in sensory integration, motor planning, and attentional control. In particular, alpha-band activity has been widely associated with postural stability and balance regulation [106–108]. Increased alpha power has been linked to improved postural stability and efficient sensorimotor processing [109, 110], whereas alpha desynchronization has been interpreted as reflecting increased attentional demands or postural instability [111, 112]. Moreover, alpha-band coherence between cortical regions plays a key role in sensory processing and motor planning, both of which are essential for maintaining balance [30, 113]. In PD, EEG analyses have revealed disrupted functional connectivity and reduced synchronization within sensorimotor and parietal networks, further contributing to impaired PC [114].

Despite these advances, most EEG studies in PD have focused on resting-state conditions or static postural tasks, leaving a critical gap in understanding

the neural mechanisms underlying PC during dynamic and ecologically relevant balance challenges. Traditional PC assessment tools, such as gait analysis or force-platform-based measures, primarily capture behavioral or kinematic outcomes and are often more sensitive to later stages of motor dysfunction. As a result, subtle neural alterations associated with early-stage PD may remain undetected.

Within this context, the BioVRSea paradigm represents a novel and complementary approach for PC assessment during a dynamic balance task. Notably, recent work using this paradigm has reported significant differences in theta and alpha power between early-stage PD patients and healthy controls, highlighting its sensitivity to PD-related neural dysfunctions even in the absence of overt motor symptoms [115]. Compared to conventional PC assessments, BioVRSea allows for a more integrative and neurophysiological evaluation of postural deficits by capturing subtle adaptations to combined visual and motor perturbations.

Recent advances in EEG analysis have further enabled the characterization of brain network states (BNSs), defined as dynamic patterns of functional connectivity that reconfigure in response to task demands [116, 117]. In the context of PC, effective balance control requires the coordinated interaction of sensory, motor, and cognitive networks. Altered BNSs have been identified in PD using both fMRI and EEG, revealing disruptions in sensorimotor, attentional, and executive networks, as well as in cortico-striatal circuits involved in motor planning [118]. These network-level alterations provide promising biomarkers for disease characterization and progression monitoring. Building on these findings, the present study adopts a dynamic EEG approach to investigate functional brain connectivity during a complex postural task using the BioVRSea paradigm. By focusing on alpha-band connectivity and BNS dynamics during visually and motorically demanding balance conditions, this work aims to identify early neurophysiological markers of PD. Although exploratory in nature, this approach addresses a critical gap in the literature by examining brain network dynamics during a visuomotor PC task, offering new insights into the neural mechanisms underlying postural instability in PD and supporting the potential of BioVRSea as a sensitive tool for early-stage assessment.

## 5.2 Materials and methods

### 5.2.1 Participants

Participants were recruited between 18/01/2022 and 03/10/2023. The study involved 42 participants: 20 PD patients (54–82 years old, mean age=65.35) and 22 age-matched healthy control (CTR) individuals (55–72 years old, mean age=62.78). Table 5.1 demonstrates that neither the t-test for age nor the chi-squared test for gender revealed any significant differences, indicating homogeneity in the population characteristics between the two groups. Participants in the PD group had a diagnosis of early-stage PD, and they were under levodopa medication. The Hoehn and Yahr (H/Y) scale [119] was used to classify

Parkinson’s patients, with stages ranging from 1 to 3. After a medical review, 11 patients showed no signs of cognitive decline, while the remaining patients were classified as having mild cognitive impairment (MCI). None were diagnosed with Parkinson’s dementia, and none exhibited obvious motor symptoms. According to both the medical screening performed before participation and our direct observations during data acquisition, none of the patients exhibited visible tremor, dyskinesia, or other involuntary movements throughout the BioVRSea experiment. Every participant successfully completed the full experiment and responded to both a pre-experiment and a post-experiment questionnaire. From these responses, we did not register any cognitive issues or impairments.

Table 5.1: Age and gender distribution in PD and CTR groups. No significant differences were found (t-test for age, chi-squared test for gender)

|                   | PD (n=20)       | CTR (n=22)      | P value |
|-------------------|-----------------|-----------------|---------|
| <b>Age</b>        |                 |                 | 0.182   |
| Mean $\pm$ SD     | 65.4 $\pm$ 4.50 | 62.8 $\pm$ 4.27 |         |
| Min-Max           | 54-82           | 55-72           |         |
| <b>Gender (%)</b> |                 |                 | 0.817   |
| Female            | 8 (40%)         | 12 (54.5%)      |         |
| Male              | 12 (60%)        | 10 (45.5%)      |         |

### 5.2.2 Data Acquisition

EEG data were recorded using a 64-electrode CA-208 wet cap. Each electrode can be associated with a region of interest (frontal, temporal, parietal, or occipital), and their assignments are shown in Table 5.2. The signals were preprocessed as described previously.

Table 5.2: EEG cap. Electrode placement across different brain lobes for the CA-208 waveguard cap

| Lobes          | Electrode names                                                                                                         |
|----------------|-------------------------------------------------------------------------------------------------------------------------|
| Frontal        | FP1, FPz, FP2, AF7, AF3, AFz, AF4, AF8, F7, F5, F3, F1, Fz, F2, F4, F6, F8, FC3, FC1, FCz, FC2, FC4, C3, C1, Cz, C2, C4 |
| Temporal Left  | FT7, FC5, T7, C5, TP7, CP5                                                                                              |
| Temporal Right | FC6, FT8, C6, T8, CP6, TP8                                                                                              |
| Parietal       | CP3, CP1, CPz, CP2, CP4, P7, P5, P3, P1, PZ, P2, P4, P6, P8                                                             |
| Occipital      | PO7, PO3, POz, PO4, PO8, O1, Oz, O2                                                                                     |

### 5.2.3 Data Processing

#### Connectivity to dynamic network computation

Several preliminary steps were required before computing the dynamic brain networks, as described in Fig. 5.1. EEG source connectivity is a valuable method for identifying brain networks linked to specific cognitive functions, as demonstrated by Hassan et al. [120].

The first step was the reconstruction of brain sources from the signals recorded on the scalp. In fact, estimating connectivity directly from the sensor level is limited by low spatial resolution and the effects of volume conduction. These issues can cause false correlations in connectivity measurements, as signals from different electrodes may originate from the same neural source. As a result, connectivity at the sensor level does not accurately reflect functional interactions between brain areas. To address this, we used EEG source localization techniques to reconstruct cortical activity, which involves solving the complex EEG inverse problem. The neural sources for artifact-free EEG data were estimated using the following equation.

$$S = GD + N \quad (5.1)$$

where  $S(t)$  represented the EEG signals recorded at  $M$  electrodes,  $G$  is the lead

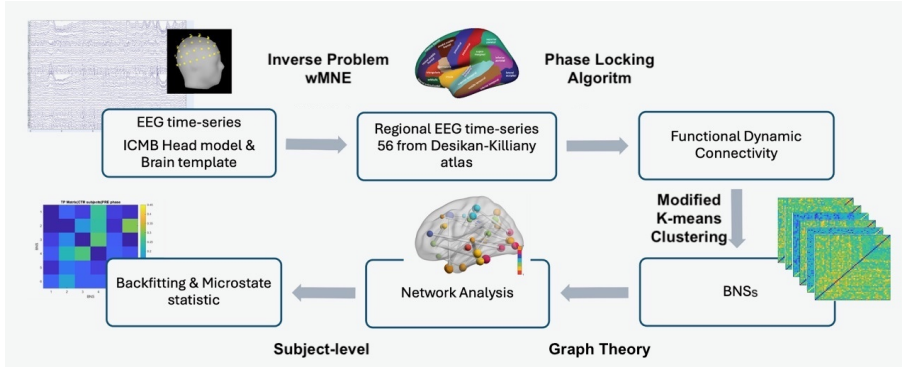


Figure 5.1: Workflow description. EEGs were recorded using 64 electrodes during the BioVRSea experiment. The cortical sources were reconstructed by solving the inverse problem using the wMNE method. After reconstructing the signals based on brain sources, they were reorganized according to 68 brain ROIs of the Desikan-Killiany atlas. Some areas were aggregated to achieve 56 ROIs, aiming for fewer than the 64 total channels. Functional connectivity matrices were computed between the 56 regional time series using the PLV method across six frequency bands: Delta, Theta, Alpha, Beta, and Gamma. Connectivity matrices were first obtained separately for the PD and CTR groups, then concatenated before being input into the k-means++ clustering algorithm. This clustering process identified distinct BNSs, followed by network analysis at the subject level to compute metrics for group comparisons

field matrix that models how sources contribute to the scalp potentials,  $D(t)$  denotes the unknown brain activity at  $P$  source locations, and  $N(t)$  accounts for noise and modeling errors. To solve the inverse problem, we used the *Weighted Minimum Norm Estimate (wMNE)*, given by the formula:

$$D_{wMNE} = (G^T W G + \lambda I)^{-1} G^T W S \quad (5.2)$$

where  $G$  is the lead field matrix,  $W$  is a depth-weighting matrix,  $\lambda$  is a regularization parameter, and  $S$  represents the EEG signals.

We used the ICBM MRI template with three-layer segmentation (scalp, outer skull, and inner skull) from the OpenMEEG plugin within the Brainstorm toolbox. The Boundary Element Method (BEM) was employed to model the head volume conductor, validated by prior research [121–123]. The initial 45 seconds of the EEG were used to construct the noise covariance matrix, while the remaining 273 seconds were allocated for source reconstruction. The signals were then divided into the 68 brain regions of interest (ROIs) based on the Desikan-Killiany atlas [124]. Some ROIs were aggregated (aiming at a lower number of ROIs than the number of channels), resulting in a final set of 56 ROIs (Appendix ROI-Node-RSN Mapping).

Functional connectivity between the EEG time series of the 56 ROIs was calculated across multiple frequency bands (Delta: 1-4 Hz, Theta: 4-8 Hz, Alpha: 8-13 Hz, Beta: 13-30 Hz, Gamma: 30-45 Hz) using the Phase Locking Value (PLV) algorithm with a sliding window approach (50% overlap and window size of six cycles) [125]. The combination of wMNE and PLV demonstrated optimal performance in capturing meaningful brain network dynamics in the alpha band during complex PC tasks [120, 126].

The PLV computation produced 56x56 square dynamic matrices for each band. The number  $N$ , representing the total number of computed connectivity matrices, is detailed in Appendix Phase-Locking Value (PLV) Calculation. Specifically, for the alpha band, 953 matrices were created. Each matrix element  $A_{i,j}$  represented the strength of the connections from node  $i$  to node  $j$ , referred to as an *edge* in graph theory-based analysis (Table 5.3).

BNS segmentation was performed on this dataset using a clustering algorithm to identify stable periods over time. The analysis was based on functions from the EEGLab Microstate toolbox, originally designed for EEG voltage topography. We adapted the microstate analysis pipeline described by Poulsen et al. to extract BNSs from functional connectivity data [127]. The optimal number of classes was determined based on goodness-of-fit metrics, including Global Explained Variance (GEV) criterion [127, 128].

For the clustering process, we transformed the symmetric connectivity matrices into vectors of size  $(n \times (n - 1)/2) = 1540$  by extracting the upper triangular elements, excluding the diagonal. Each vector was then concatenated across all time points, resulting in a subject-specific matrix of dimensions  $1540 \times 953$ , where each column represents a time window, and each row corresponds to a specific connection within the network. These matrices were concatenated among subjects and served as input for the Modified K-means (k-means++)

Table 5.3: Dynamic Connectivity Variables: A list of the number of matrices ( $N$ ) calculated for each frequency band. The dimension ( $n$ ) of each matrix is based on the number of ROIs, with each element ( $A_{i,j}$ ) representing the connectivity between the respective regions

| Variable  | Description                                | Band  | Value |
|-----------|--------------------------------------------|-------|-------|
| N         | Number of dynamic connectivity matrices    | Alpha | 953   |
|           |                                            | Beta  | 1953  |
|           |                                            | Delta | 226   |
|           |                                            | Gamma | 3407  |
|           |                                            | Theta | 544   |
| n         | Dimension of dynamic connectivity matrices | 56×56 |       |
| $A_{i,j}$ | Element of one connectivity matrix         | –     |       |

clustering algorithm [129], which has been successfully used in other previous studies on the dynamic functional connectivity of EEG and fMRI [130, 131]. Clustering was performed with the following parameters: the number of clusters varied from 2 to 10 (K\_range), the number of random initializations (rep) was set to 100, and the maximum number of iterations (iter) was 1000, with a default convergence threshold of  $10^{-6}$ .

A meta-criterion was applied to obtain the optimal number of clusters [130, 132, 133], which was determined to be six. Specifically, the meta-criterion was implemented using the CVIK Toolbox [134], a MATLAB framework that integrates 28 Cluster Validity Indices (e.g., Silhouette, Davies–Bouldin, Dunn, PBM, S\_Dbw) and multiple proximity measures to automatically determine the optimal number of clusters based on index consensus.

Each identified cluster was defined as a BNS, representing the temporal evolution of brain connectivity. K-means++ was run multiple times with different parameters to ensure the robustness of the clustering results. The BNSs obtained from each clustering iteration were then compared using Pearson correlation analysis to assess the consistency of the identified patterns. A strong correlation indicated high similarity between BNSs across different clustering runs, validating the reliability of the extracted states (Table 5.4).

The topological visualization of the six BNSs was conducted, and they were labeled based on the most prevalent RSNs, as detailed in Subsection Association of BNSs with RSNs. Each BNS was characterized by distinct spatial distributions and temporal dynamics that correspond to specific cognitive and functional processes. This allowed for a more intuitive interpretation of the BNSs in relation to established RSNs, facilitating comparisons between the two groups in our study.

As a final step, we computed the back-fitting at the subject level using Global Map Dissimilarity (GMD) to identify the best-fitting BNSs throughout the experiment. The smoothing process involved rejection based on small-segment criteria of five matrices [126–128]. For the identified BNSs, we calculated

Table 5.4: Pearson correlation of the six Brain Network States (BNSs) across different clustering runs. The optimal number of clusters ( $K = 6$ ) was determined using the meta-criterion based on multiple internal Cluster Validity Indices (CVIs). Modified k-means clustering was then repeated four times with different parameter configurations. Cluster #1, defined by the parameters  $K_{\text{range}} = 2:10$ ,  $\text{rep} = 100$ ,  $\text{ite} = 1000$ , was used as the reference for comparison. We therefore computed the Pearson correlation between the corresponding cluster maps obtained in different runs to evaluate the similarity and stability of the clustering results

| Clusters   | Parameters                                                        | Pearson correlation |      |      |      |      |      |
|------------|-------------------------------------------------------------------|---------------------|------|------|------|------|------|
|            |                                                                   | BNS1                | BNS2 | BNS3 | BNS4 | BNS5 | BNS6 |
| Cluster #2 | $K_{\text{range}}=2:10$ ;<br>$\text{rep}=100$ ; $\text{ite}=1000$ | 1                   | 1    | 1    | 1    | 1    | 1    |
| Cluster #3 | $K_{\text{range}}=3:7$ ;<br>$\text{rep}=100$ ; $\text{ite}=1000$  | -1                  | 1    | 0.99 | 0.99 | 0.99 | 1    |
| Cluster #4 | $K_{\text{range}}=3:7$ ;<br>$\text{rep}=200$ ; $\text{ite}=1000$  | 1                   | 1    | 1    | 0.99 | 0.99 | 1    |

several common metrics used in microstate analysis, including Global Field Power (GFP), occurrence per second (occurrence), average duration (duration), percentage of time occupied (coverage), global explained variance (GEV), and the transition probabilities (TP). These metrics were subjected to statistical analysis between the two groups. A comprehensive description of these metrics is provided in Appendix Computational Methods for BNS Metrics.

### Association of BNSs with RSNs

Each obtained BNS was computed from a vector to form a  $56 \times 56$  symmetric matrix, that represented the associated functional network. Based on some studies [135, 136], each of the 56 nodes was assigned to one of seven RSNs: Default Mode Network (DMN), Dorsal Attention Network (DAN), Salience Network (SAN), Motor Network (MOT), Auditory Network (AUD), Visual Network (VIS), and Other. The node-RSN affiliations are detailed in Appendix (ROI-Node-RSN Mapping). Using the Brain Connectivity Toolbox [137], the strength of each node was calculated, representing the sum of the weights of all links connected to that node. Subsequently, we determined the strength of each RSN by summing the values of nodes associated with the specific RSN and normalizing this sum by dividing it by the number of nodes within the RSN. To identify the dominant RSN for each BNS, we considered those with a value exceeding the sum of the average and standard deviation of the strengths of the seven RSNs. We utilized BrainNet Viewer [138] for visualization, where each ROI was represented by a color corresponding to its specific RSN. Each network was displayed with a sparsity of 0.01.

#### 5.2.4 Correlations between questionnaire scores and brain state metrics

The study examined the relationships between coverage, duration, and occurrence variables derived from the BNS analysis of the PRE and POST phases, and the two indices PHY and NEURO. Spearman correlation analysis was conducted to evaluate these relationships. Data were analyzed iteratively for each BNS and subject. Significant correlations ( $p < 0.05$ ) indicated both linear and monotonic relationships across the data subsets.

#### 5.2.5 Statistical Analysis

The statistical analysis was conducted to investigate the effects of the BNSs and subject group on occurrence, duration, and coverage across different phases of the experimental protocol. The study utilized a linear mixed-effects modeling approach (LMM) to account for the hierarchical structure of the data, where repeated measures within subjects were nested within the levels of the BNSs factor. The primary objective was to ascertain any significant main effects and interactions between the subject group (PD vs. CTR) and the BNSs. Model fit was assessed by examining model summary statistics, including coefficients, standard errors, and p-values derived from likelihood ratio tests. Additionally, an analysis of variance (ANOVA) was performed to assess the overall significance of the fixed effects in the model. To further elucidate significant effects identified by the primary analysis, post-hoc pairwise comparisons were conducted using estimated marginal means. These comparisons aimed to delineate differences in the specific metrics between specific levels of the BNSs factor within each subject group across different experiment phases. To mitigate the risk of Type I errors arising from multiple pairwise comparisons, p-values were adjusted using the Benjamini-Hochberg method. This method controls the False Discovery Rate (FDR) and helps maintain the overall integrity of statistical inference. Results were visually represented through empirical cumulative distribution functions and pairs plots to illustrate the distributional properties of the data and highlight significant differences between experimental conditions.

### 5.3 Results

#### 5.3.1 BNSs presence

Following the back-fitting process, we initially identified distinct patterns in the presence of BNSs between individuals with PD and CTR subjects across the experimental phases (Fig. 5.2). All BNSs appeared in each phase for both cohorts, but their relative frequencies varied. Specifically, BNS1 was slightly more frequent in the PD group, except during the POST phase, where it was higher in the CTR group. The trend of BNS1 in the PD group remained consistent across all phases except for the POST phase, whereas in the CTR group, it differed in the PRE phase. BNS2 was consistently less frequent in

the PD group across all phases. Conversely, BNS3 and BNS5 were consistently more prominent in the PD group. BNS4 was more frequent in the PD group except during the PRE phase, while BNS6 showed a higher presence in the CTR group except during the PRE phase.

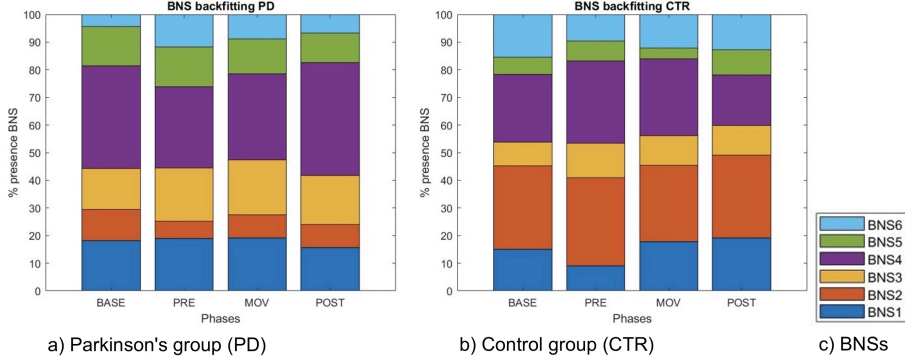


Figure 5.2: Distribution of BNSs as a percentage across different experimental time phases for (a) PD patients and (b) CTR group. Each bar represents the frequency of a specific BNS during the respective phase, illustrating how often each state was engaged throughout the experiment. (c) Lists the identified BNSs

### 5.3.2 Correlations between questionnaire scores and brain state metrics

The correlation analysis between questionnaire indices and BNS metrics uncovered several significant relationships specific to BNS3. For the CTR group, a notable Spearman correlation was found between the occurrence metric and the NEURO index ( $\rho = 0.27$ ,  $p < 0.01$ ). Both groups showed significant correlations between NEURO scores and the metrics of coverage and duration within BNS3. In the CTR group, the correlation of duration with NEURO was  $\rho = 0.24$  ( $p < 0.02$ ), and for coverage,  $\rho = 0.26$  ( $p < 0.01$ ). Similarly, in the PD group, the duration-NEURO correlation was  $\rho = 0.21$  ( $p < 0.05$ ), and the coverage-NEURO correlation was  $\rho = 0.22$  ( $p < 0.05$ ). These findings indicated that both groups demonstrated significant associations between the NEURO index and the metrics of duration and coverage. However, the occurrence metric exhibited a unique correlation pattern that appeared only within the CTR group.

### 5.3.3 Statistical analysis of BNSs

We investigated the following parameters of the BNSs: occurrence, duration, coverage, and TP. Statistical analysis revealed significant variations in BNS2 coverage during the PRE ( $p = 0.019$ ) and MOV ( $p = 0.036$ ) phases following

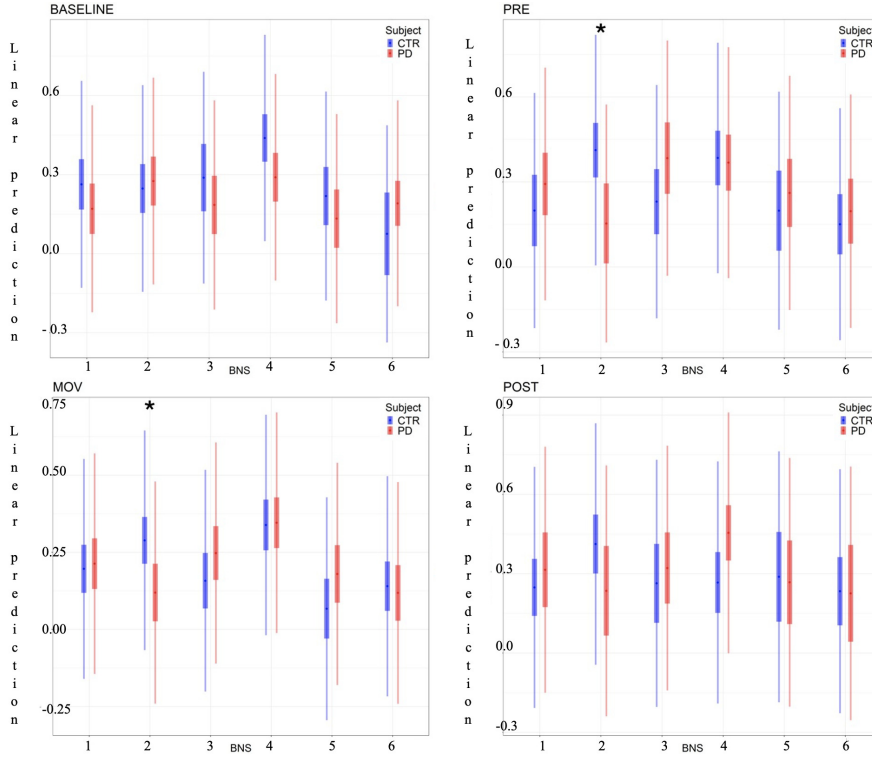


Figure 5.3: LMM analysis. Coverage for each BNS across all experimental phases in PD patients and CTR. Coverage refers to the proportion of total activity distributed across the six identified BNSs, indicating how dominant each BNS was relative to the others during each phase. Significant differences between groups, corrected using the False Discovery Rate (FDR) method, are highlighted: \*  $p < 0.05$

FDR correction with  $\alpha < 0.05$  (Fig. 5.3), consistent with an initial trend observed in these phases. For BNS4, a similar trend was observed in the BL and POST phases, although it did not remain significant after correction (Appendix Statistical Result of Coverage).

No statistically significant results were observed for occurrence; however, a trend was evident in BNS2 during the PRE and MOV phases (Appendix Statistical Result of Occurrence). For duration, no statistically significant results were found; however, a trend was noted in BNS5 during the BL phase and in BNS4 during the POST phase. TP analysis indicated that, in individuals with PD, transitions from BNS1 to BNS4 and from BNS4 to BNS1 consistently exhibited significantly higher probabilities compared to the CTR group. Conversely, transitions from BNS4 to BNS1 and BNS3 to BNS4 in CTR subjects displayed higher probabilities than those in the PD group starting from the PRE phase. In PD, activation within the same BNSs occurred later during the POST phase

(Fig. 5.4, Appendix Statistical Result of Duration).

The statistical results findings are summarized in Table 5.5, which provides an overview of the main statistical outcomes for each BNS metric and experimental phase.

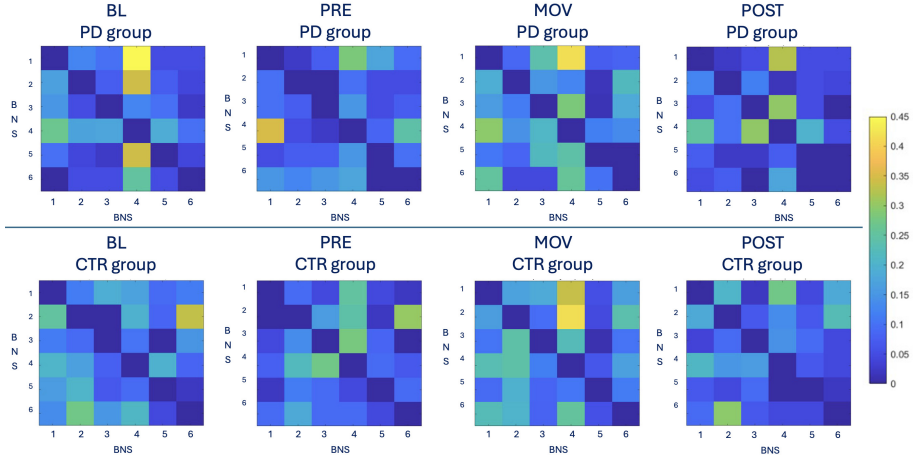


Figure 5.4: Transition Probability matrices. PD and CTR subjects across BL, PRE, MOV, and POST phases. Each heatmap represents the likelihood of transitioning between different BNSs within each phase, with lighter colors indicating higher transition probabilities. These matrices highlight the patterns of state transitions and the differences between groups in terms of network dynamics

Table 5.5: Summary of main statistical outcomes for each BNS metric and experimental phase. Linear Mixed Model (LMM) analysis with False Discovery Rate (FDR) correction ( $\alpha < 0.05$ ). Significant results are highlighted in bold, while non-significant trends are also reported for clarity

| Metric     | Phase | BNS  | Group difference (PD vs. CTR) | p-value (FDR) |
|------------|-------|------|-------------------------------|---------------|
| Coverage   | PRE   | BNS2 | PD < CTR                      | <b>0.019</b>  |
| Coverage   | MOV   | BNS2 | PD < CTR                      | <b>0.036</b>  |
| Coverage   | BL    | BNS4 | PD > CTR                      | n.s.          |
| Coverage   | POST  | BNS4 | PD > CTR                      | n.s.          |
| Occurrence | PRE   | BNS2 | CTR > PD                      | n.s.          |
| Occurrence | MOV   | BNS2 | CTR > PD                      | n.s.          |
| Duration   | BL    | BNS5 | PD > CTR                      | n.s.          |
| Duration   | POST  | BNS4 | CTR > PD                      | n.s.          |

#### 5.3.4 Association between BNSs and RSNs

In Fig. 5.5, only the nodes were displayed, where the size of each node represented its strength, corresponding to the overall connectivity at that node.

For visualization purposes, a sparsity threshold of 0.01 was applied, displaying only the strongest connections. This approach highlighted the most significant interactions, using color-coding to distinguish different RSNs. In BNS1, the VIS predominated, with nodes concentrated in the left hemisphere, particularly in the parietal and occipital lobes. The SAN was also prominent, with nodes distributed across the frontal and right parietal lobes. In the remaining five BNSs, the DAN was the dominant RSN. BNS2 featured the DAN primarily in the parietal lobe, with nodes of similar sizes spread across the interhemispheric fissure, followed by the SAN in the frontal lobe. BNS3 included the DMN in the frontal lobe, with balanced node strength between the left and right hemispheres, and the AUD in the parietal lobe. BNS4 comprised the DMN, with node strength balanced across the interhemispheric fissure in the parietal lobe, while being exclusively present in the right hemisphere in the frontal lobe. Additionally, the VIS network was mainly localized in the left occipital lobe for the BNS4. BNS5 was similar to BNS4, with larger node sizes across the interhemispheric fissure and in the frontal lobe for the DAN, whereas the SAN was present in both hemispheres across the interhemispheric fissure. Finally, BNS6 involved both the DMN and the SAN, similar to BNS5, but with the DMN absent in the right hemisphere of the parietal lobe.

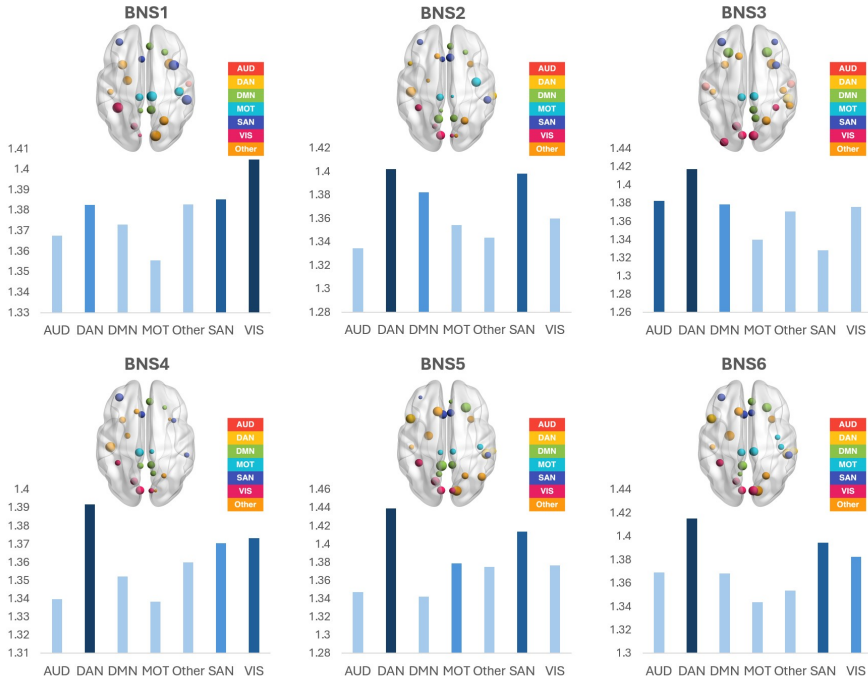


Figure 5.5: Prevalence of RSNs in each BNS. Calculated as the sum of the node strength values for each ROI associated with the specific RSN. Each BNS is visualized with nodes sized proportionally to their strength (the sum of connections at each node), and edges are shown based on their connectivity, with a sparsity threshold of 0.01 applied to filter weak connections. Different colors represent distinct RSNs, facilitating clear visual differentiation of the dominant networks in each BNS. This visualization highlights the key RSNs contributing to the overall network dynamics across experimental phases



## Chapter 6

# Discussion

The studies presented in this thesis offer a comparative analysis of postural and physiological responses across healthy, expert, and clinical populations, with the goal of identifying both shared and condition-specific alterations during the BioVRSea paradigm. This work supports the validation of BioVRSea as a sensitive and versatile tool for capturing PC strategies and emphasizes its potential in quantitatively identifying physiological markers of balance regulation.

Immersive VR has emerged as a valuable tool for balance assessment, enabling multisensory perturbations that can uncover impairments often missed by conventional testing. In this context, BioVRSea offers a realistic and dynamic platform for challenging PC, while simultaneously capturing neural, muscular, and autonomic responses. Although some evidence suggests that VR environments can themselves modulate PC mechanisms [139], structured and supervised VR interventions have also been shown to enhance balance, mobility, and confidence, particularly in older or vulnerable individuals [140]. This dual role of VR underscores the importance of precise, multimodal analysis to interpret its effects across different contexts and populations.

The following discussion integrates the results of each study, comparing them with existing literature and examining how BioVRSea captures complex postural challenges.

### 6.1 Influence of Age, Gender, and Concussion History in the BioVRSea Paradigm

In Chapter 3, three studies investigated how age and gender influence PC using the multimodal BioVRSea paradigm. Across EEG, CoP, and HRV analyses, age consistently emerged as the most influential factor, while gender differences were negligible.

The first study analyzed cortical activity using EEG PSD to evaluate age and gender differences in neural processing during the BioVRSea task. Although overall topographic distributions were comparable across age groups,

frequency-specific patterns diverged significantly. Younger participants (Under40 years) exhibited increased theta and alpha power in frontal and central regions, indicating more efficient attentional regulation and sensorimotor integration. In contrast, older participants (Over40 years) showed elevated beta and reduced alpha power across most phases, consistent with compensatory cortical recruitment and reduced flexibility, as previously reported in the aging brain [141–143]. These spectral shifts suggest fundamentally different neural strategies for postural control: while younger adults engage fast, efficient oscillatory activity, older adults rely more on higher cortical effort to maintain stability.

The second study investigated age and gender effects on PC by analyzing CoP metrics across three experimental phases. Age-related differences were most prominent during the PRE and POST phases, where participants balanced without holding the support bar. The Over40 group exhibited greater sway amplitude (TOTEX, RMS), larger ellipse area, and higher sway velocity, especially in the ML direction. Spectral features showed broader frequency distributions in older adults, suggesting reduced lateral stability and increased reliance on compensatory mechanisms. Non-linear measures, such as sample entropy, confirmed that older individuals adopted more rigid and predictable postural strategies under perturbation. In contrast, younger participants maintained lower-frequency, more stable sway and exhibited higher postural complexity. Gender did not significantly influence any postural variables, reinforcing age as the dominant factor in determining postural behavior under immersive conditions. Importantly, the evolution of CoP signal across directions and experimental phases appears to be closely linked to the characteristics of the platform motion. During the MOV phase, participants actively interact with the moving platform while holding the support, whereas in the POST phase they release it and are required to maintain balance relying solely on visual input. Accordingly, the observed differences in CoP features across phases and age groups are best interpreted as adaptive responses to changes in task constraints and sensorimotor demands induced by the platform motion.

The third study focused on HRV as an indicator of autonomic responses to the BioVRSea task. Age-related changes were consistent with existing literature: older adults exhibited longer RR intervals and lower HR, reflecting reduced autonomic flexibility [144–146]. Gender-related differences were minimal, with females showing slightly shorter RR intervals, in line with known anatomical factors. In participants with a history of concussion, HRV alterations were detected during the MOV and POST phases, particularly in frequency-domain features. These changes pointed to autonomic dysregulation and altered sympathetic-parasympathetic balance, consistent with earlier studies on post-concussion physiology [147].

Machine learning analysis further identified discriminative HRV features, especially during visually and physically demanding phases. The most informative parameters included VLF power, SD of instantaneous heart rate (SD IHR) during movement, and the Poincaré plot area during PRE. These features reflect both rapid and slow components of autonomic regulation and may serve as

biomarkers for stress response, motion sickness susceptibility, or post-concussion alterations.

Together, these three studies demonstrate that age has a significant impact on cortical dynamics, biomechanical balance strategies, and autonomic responses. The BioVRSea paradigm, through its integration of EEG, CoP, and HRV data, offers a robust platform for detecting physiological differences that may not be apparent through traditional clinical tools. Its potential application in the assessment of age-related decline, concussion recovery, and autonomic function supports its utility in both research and clinical contexts.

## 6.2 Postural Control Alterations Following Sport-related Concussion

A separate study in Chapter 3 examined neuromuscular and postural adaptations in individuals with a history of concussion, based on EMG and CoP data recorded during the BioVRSea protocol. Although participants were young, physically active, and clinically recovered, differences emerged during specific phases of the experiment.

EMG analysis revealed that the TA muscle, particularly on the right side, displayed significantly altered activation patterns in the concussion group during both the PRE and POST phases. Over twenty features, including RMS, MMAV, skewness, kurtosis, and frequency-based metrics (Fmax, Fskew), differed between groups, with the most consistent differences observed during the POST phase. These results highlight the TA critical role in balance recovery and its sensitivity to neurological alterations, aligning with its established function as a primary dorsiflexor during postural adjustments [148, 149]. No relevant EMG differences were found during the MOV phase, when participants held a support bar, likely reducing lower-limb demands and masking underlying neuromuscular differences. In unsupported conditions, the concussion group demonstrated more variable and asymmetrical TA activity, potentially reflecting compensatory strategies or instability in motor control during sensory conflict. Limb dominance is an important consideration in PC analysis, particularly when interpreting asymmetries between sides. However, feature differences between leg muscles cannot be solely explained by dominance. Instead, muscle activation should be interpreted within the functional context of each limb, accounting for the coordinated role of muscles within the same limb rather than relying exclusively on inter-limb comparisons.

Analysis of CoP features further supported these observations. While global measures such as ellipse area remained similar across groups, significant differences emerged in dynamic features during the POST phase. Specifically, Total Excursion (TOTEX) and Mean Velocity (MVELO) were significantly higher in the concussion group, suggesting increased sway amplitude and speed following the perturbation. These patterns may reflect a need for greater postural effort or reorganization of motor strategies to maintain stability after dynamic challenges. The POST phase proved particularly informative, as it

required participants to maintain balance without support, relying solely on internal feedback after multisensory perturbation. This condition appears to unmask residual deficits not evident during other tasks.

These findings suggest that concussion-related neuromuscular adaptations persist beyond clinical symptom resolution and can be detected using objective physiological measures. EMG activity in the TA and CoP dynamics during recovery provide robust indicators of PC changes in this population. While not intended as a replacement for established clinical protocols such as the SCAT5, the BioVRSea paradigm offers a complementary perspective by providing objective and physiological evidence of post-concussive alterations. The integration of SCAT5 with BioVRSea may enhance diagnostic confidence and support more comprehensive assessments of postural function following concussion.

### 6.3 Adaptive Postural Strategies in Experienced Maritime Subjects

The final study presented in Chapter 3 examined PC strategies in a cohort of experienced sailors with prolonged exposure to maritime environment. EMG and CoP analyses obtained through the BioVRSea protocol were used to explore how long-term sensorimotor experience influences neuromuscular coordination under challenging conditions.

EMG features revealed significant differences in muscle activation patterns between sailors and matched controls, particularly in the soleus muscle. The most relevant discriminator was the skewness (SKEW) of right soleus (SR) activity during the MOV phase, which remained significant after correction for multiple comparisons. While control participants showed near-symmetrical or slightly negative SKEW, indicating balanced low and high intensity muscle activations, sailors exhibited a significantly more positive skewness, suggesting a predominance of low-intensity activation with occasional high-intensity bursts. This pattern likely reflects an adaptive control strategy, developed through repeated exposure to unstable environments, in which the muscle maintains a low-level background activity with rapid, targeted responses to perturbations [150, 151].

Analysis of CoP dynamics further supported these neuromuscular differences. During the adaptation (MOV) phase, sailors showed significantly higher total excursion (TOTEX) and mean velocity (MVELO) in the AP direction, indicating faster and broader postural adjustments. Despite this increased sway, no balance loss or instability was observed, suggesting that these features reflect an efficient and responsive postural strategy rather than instability. Sailors appeared to anticipate motion and correct posture more dynamically than controls, consistent with previous studies on motor learning and balance adaptation [152, 153]. Entropy-based features provided further insight. Sailors exhibited significantly higher magnitude entropy, direction entropy, and multivariate complexity index (CI), particularly in the AP direction. These findings indicate a more variable and multidirectional control strategy, characterized by greater

complexity and adaptability in sway dynamics. Higher entropy reflects increased use of diverse postural strategies and more refined sensorimotor integration in response to complex stimuli. The increased CI observed in the habituation phase also suggests enhanced coordination and temporal precision in sway modulation. These results align with the hypothesis that prolonged exposure to balance-challenging environments, such as those experienced at sea, leads to specialized motor strategies and neuromuscular plasticity. Sailors demonstrated more dynamic and flexible postural control, marked by increased sway variability and anticipatory muscle engagement that likely optimize stability under unpredictable conditions.

Overall, the BioVRSea platform effectively captured these adaptive patterns through EMG and CoP analysis, demonstrating high sensitivity in distinguishing expert motor behavior. These findings underscore its potential as a valuable tool for investigating motor learning, postural expertise, and adaptation to environmental demands in both experimental and applied settings.

## 6.4 Postural and Neural Signatures in Early-Stage Parkinson's Disease

Chapter 5 presented the first study conducted on early-stage PD using data acquired through the BioVRSea protocol. The investigation focused on identifying early physiological alterations using EMG, CoP, EEG, and brain network connectivity measures. All participants were in the early stages of diagnosis, with minimal clinical motor impairments, allowing the detection of dysfunctions and compensatory mechanisms that may not be captured by standard clinical assessments.

Muscle activation patterns, particularly from the tibialis anterior (TA) and soleus (S) muscles, revealed consistent differences between PD and control groups. The right TA (TAR) was the most discriminative, with several time- and frequency-domain features—such as RMS, MMAV, Fmax, and skewness—showing significant alterations during the POST phase. PD participants exhibited higher-frequency components and more asymmetrical muscle activity, likely reflecting impaired coordination and increased effort to maintain stability after perturbation. These findings support previous reports of reduced adaptability and delayed modulation of muscle activation in PD during postural adjustments [154, 155].

CoP analysis confirmed reduced sway variability and rigidity in the PD group. While overall sway area was comparable, measures such as Total Excursion and Mean Velocity in the POST phase were diminished, indicating a more constrained and cautious postural strategy. Interestingly, CI values in the ML direction were higher in PD participants, suggesting disorganized or maladaptive sway patterns. This contrasts with typical age-related decline in postural complexity and may represent early compensatory overactivation of motor control systems. The use of unassisted stance during the POST phase appears to effectively reveal these alterations.

EEG spectral analysis identified significant group differences in the alpha and theta bands. Healthy participants exhibited stronger alpha activity across the scalp, particularly during visually demanding phases, indicating better attentional and cognitive processing during postural tasks. In contrast, PD participants showed reduced alpha power and weaker task-related modulation. Theta band differences were also pronounced in frontal regions, where controls displayed elevated activity linked to motor prediction and executive control. These spectral alterations align with known disruptions in sensorimotor and attentional networks in PD, even at early stages [31, 156].

## 6.5 Altered Brain Network Dynamics in Parkinson's Disease during the BioVRSea

The second study in Chapter 5 investigated large-scale brain network reorganization in early-stage Parkinson's disease by applying the novel methodology from dynamic EEG connectivity data recorded during the BioVRSea paradigm. This approach captures dynamic patterns of functional connectivity, offering insights into network flexibility, transitions, and compensatory mechanisms in early-stage Parkinson's disease (PD) under the complex PC task.

Six recurring BNSs were identified across the experimental task phases. Each BNS represented a quasi-stable configuration of synchronized activity between brain regions, linked to well-established resting-state networks (RSNs) such as the dorsal attention network (DAN), salience network (SAN), visual network (VIS), and auditory network (AUD). These BNSs reflected transient but functionally meaningful neural configurations supporting cognitive and sensorimotor demands during the immersive postural task. PD and control participants expressed all six BNSs, but with distinct patterns. BNS2, characterized by strong engagement of the DAN and SAN, showed significantly lower coverage in PD across the PRE and MOV phases. These networks are involved in top-down attention, salience detection, and the integration of sensory cues with goal-directed functions that are frequently disrupted in PD. The reduced presence of BNS2 in the PD group suggests impaired allocation of attention and diminished responsiveness to task-relevant stimuli, especially during visually and physically demanding stages of the task. In contrast, BNS3 associated with the AUD and DAN was more prevalent in PD participants. This network may reflect compensatory reliance on alternative sensory integration pathways, particularly auditory feedback, to support postural regulation in the presence of impaired visual-motor coupling. The increased occurrence of BNS3 suggests that PD patients may shift their neural resources toward more stable or familiar sensory modalities under dynamic conditions.

Transition probability analysis further revealed that PD participants exhibited less diverse switching between BNSs, tending instead to rely on narrower sets of recurring configurations. This reduced network flexibility is consistent with previous research showing constrained functional connectivity in neurodegenerative disorders and may reflect difficulties in dynamically reconfiguring

brain states in response to changing task demands. These patterns were further reflected in BNS coverage metrics, which showed that control participants engaged a broader range of network states, whereas PD subjects tended to rely on limited configurations. Correlation analysis with questionnaire-based neurological scores indicated that greater BNS3 coverage was associated with higher subjective neurophysiological burden in PD, suggesting that altered network dynamics may correspond with perceived dysfunction.

These findings provide evidence of early neural reorganization in PD, even in the absence of overt motor impairments. The BNS approach complements classical PSD and behavioral metrics by capturing the temporal structure and functional relevance of large-scale brain dynamics during postural tasks. Within the BioVRSea framework, BNS analysis offers a novel, task-specific window into attentional, sensory, and integrative processes affected by PD, supporting its use for early-stage evaluation and longitudinal monitoring.

The selection of the methodological approach was carefully considered and extensively discussed. The literature provides a wide range of methods for estimating brain connectivity, and there is no universally optimal pipeline; rather, the most appropriate combination depends on several interacting factors. In particular, as highlighted by [120], the estimation of functional brain networks from EEG data is strongly influenced by three main components: (i) the solution of the inverse problem, (ii) the choice of functional connectivity metric, and (iii) the frequency bands and temporal parameters used in the analysis. Importantly, these elements do not act independently, and their combination can significantly affect the resulting network topology and interpretation. First, the choice of the head model and inverse solution plays a critical role in reconstructing cortical sources. More realistic head models, such as multi-tissue FEM models can improve the modeling of volume conduction and potentially enhance source localization accuracy. However, the three-layer BEM head model (scalp, outer skull, inner skull) represents a well-established compromise between anatomical realism and computational efficiency. Within the EEG source connectivity framework, solving the inverse problem is inherently ill-posed and requires the introduction of anatomical and mathematical constraints. In this context, BEM-based forward models combined with distributed inverse solutions (e.g., minimum norm approaches) have been widely validated and are commonly used in the literature, particularly when subject-specific conductivity information is unavailable. Therefore, the use of a three-layer BEM model in this study ensures methodological robustness, reduces dependence on complex tissue segmentation, and facilitates comparability with a large body of previous EEG source connectivity studies. While FEM-based approaches may offer increased anatomical accuracy, they also introduce substantial computational cost and sensitivity to segmentation errors, which was beyond the scope of the present work. Second, the selection of the functional connectivity metric and its temporal implementation is equally critical. Hassan et al. demonstrated that the combination of inverse solution and connectivity measure significantly impacts the reconstructed brain networks, with certain combinations (e.g., wMNE with phase-based measures such as PLV) providing more physiologically consistent

results. In line with this framework, PLV was selected in the present study as it captures phase synchronization between neuronal populations and is widely used in EEG connectivity analysis. Regarding the temporal implementation, a sliding window approach was adopted to characterize the dynamic evolution of connectivity. The choice of a 50% overlap represents a trade-off between temporal resolution and stability of the estimates. While smaller overlaps reduce redundancy, overlapping windows are commonly recommended in dynamic connectivity analyses to ensure continuity and reduce variability, particularly in short or noisy EEG segments. Importantly, the overlap does not bias PLV estimation itself but rather smooths its temporal trajectory. Finally, the selection of the window length across frequency bands was guided by established criteria in the literature. As recommended in EEG connectivity studies, the window size should be sufficient to capture multiple oscillatory cycles of the lowest frequency of interest to ensure reliable phase estimation. This criterion is essential to avoid spurious synchronization estimates and to ensure that the computed connectivity reflects meaningful neurophysiological interactions. Consistent with this principle, the window length in the present study was defined to include several cycles of the lowest analyzed frequency band, balancing temporal resolution with estimation reliability. In summary, the methodological choices adopted in this study are grounded in established EEG source connectivity frameworks and reflect a deliberate trade-off between physiological plausibility, computational feasibility, and robustness, in line with recommendations from the literature.

## Chapter 7

# Conclusions and Summary

The results demonstrate that BioVRSea effectively captures alterations in postural behavior that are often undetectable through conventional assessments. The paradigm differentiates between adaptive, compensatory, and maladaptive postural responses, providing a sensitive framework for identifying physiological markers across diverse populations. In particular, the integration of EEG-derived brain dynamics, EMG-based muscle recruitment, CoP variability, and HRV measures offers a comprehensive view of the processes underlying balance control.

This work introduces a novel approach for the early-stage detection of Parkinson's disease, identifying changes that may indicate future motor and neural impairments. The EEG-based methodology applied here is rarely used and demonstrates strong potential. Notably, the patterns observed in the biosignals are directly reflected in the BioVRSea paradigm, demonstrating coherence between neural, muscular, and postural measures. Together, these results support the concept of a neurophysiological signature of PC, which can serve as a sensitive marker of early dysfunction.

Although BioVRSea is not intended as a diagnostic device, it shows significant potential as a clinical support system, capable of detecting early signs of dysfunction, monitoring recovery, and guiding further evaluation. By evoking controlled postural challenges while simultaneously recording detailed physiological responses, the paradigm represents a valuable tool for both research and translational applications. Overall, this thesis demonstrates that immersive VR combined with multimodal physiological monitoring offers a powerful and versatile approach for assessing PC, with potential applications in early diagnosis, longitudinal monitoring, and the personalization of therapeutic interventions.

### 7.1 Limitations

While this work provides important insights into PC mechanisms, several limitations should be acknowledged.

One notable limitation concerns the sample sizes across cohorts, which were occasionally unbalanced and may have affected the comparability of results. In particular, the concussion group consisted exclusively of young female athletes, limiting generalization to broader populations. Reliance on self-reported concussion history and the absence of precise information regarding injury timing may have introduced additional variability. Similarly, classification of the Parkinson's disease cohort as 'early-stage' is inherently imprecise due to variability in diagnosis timing and symptom onset.

Another important consideration relates to the multimodal analysis of physiological signals. Although BioVRSea allows simultaneous acquisition of EEG, EMG, CoP, and HRV data, a fully integrated analysis was not systematically applied across all groups, which limited the ability to explore dynamic interactions between neural, muscular, and postural components of balance. The EEG analysis focused on alpha-band dynamics, excluding potential contributions from other frequency bands. Future studies should investigate beta oscillations (motor control), theta oscillations (cognitive control and sensory integration), and delta oscillations (compensatory mechanisms), which may provide additional insights into postural regulation. Furthermore, while the EEG source reconstruction and functional connectivity approach used here (wMNE + PLV) is robust, alternative methods exist, and the lack of a gold standard implies that different methodological choices could produce varying results. Comparative analyses are needed to establish best practices for connectivity-based biomarkers in postural tasks.

A further limitation concerns the practical implementation of the BioVRSea system. Despite its high validity, the complexity of integrating a motion platform with a VR environment limits its applicability in standard clinical settings. Future developments should aim to miniaturize and simplify the system to enhance portability, usability, and scalability, enabling applications in rehabilitation, routine assessment, and longitudinal monitoring.

## 7.2 Future Directions

Future work should aim to validate these findings in larger and more diverse cohorts, evaluate the predictive value of the identified markers longitudinally, and optimize the experimental setup to enhance portability and clinical applicability. Further expansion of multimodal signal analysis will improve both the interpretability and translational utility of the method.

This chapter presents examples of potential future research directions utilizing the BioVRSea paradigm.

One key direction concerns the continuation and expansion of the brain network analysis introduced in Chapter 5. The study of Brain Network States (BNSs) in early-stage Parkinson's disease, conducted within the alpha frequency band, has revealed promising insights into the temporal structure of large-scale brain connectivity during postural tasks. Future work will extend this methodology across other EEG frequency bands, particularly beta, theta, and

delta, which are known to contribute to motor planning, cognitive control, and compensatory mechanisms. This expanded, multi-band analysis will allow for a more comprehensive understanding of cortical network reorganization in both healthy and clinical populations.

In parallel, the research presented in Chapter 4 on early-stage Parkinson's disease has laid the groundwork for a new methodology that combines functional connectivity with postural and neuromuscular data to derive novel biomarkers of PC. A dedicated manuscript is currently in preparation to publish these findings, and this methodology will be applied to additional populations and task conditions to validate its broader applicability.

Furthermore, a new research project has been launched in collaboration with Össur, a leading company in prosthetic innovation. The study aims to investigate cognitive and postural responses in individuals with lower limb amputation using the BioVRSea paradigm. While previous studies have examined cognitive load associated with prosthesis use, systematic comparisons of neuromuscular and postural responses across different prosthetic designs remain limited. This pilot study will assess the feasibility and sensitivity of the BioVRSea setup for quantifying both cognitive and biomechanical responses in this population. Specifically, responses will be compared across three different types of prosthetic feet and benchmarked against data from able-bodied participants. Ultimately, this line of research may contribute to the objective evaluation of prosthetic design and support the development of personalized solutions aimed at reducing cognitive load and improving balance under real-world dynamic conditions.

Together, these future directions aim to establish BioVRSea as a modular and extensible framework for quantitative assessment in complex sensorimotor tasks. The integration of additional EEG bands, the development of new methodologies, and the expansion into novel clinical populations will reinforce the paradigm's utility in both research and clinical contexts.



# Appendices

## CoP Formulas

### Time Parameters

ML and AP components (these axes are referenced to the force platform, not the subject) are multiplied with the physical sizes of the machine to express the measurements in centimeters. Thus, the normalized signals  $AP_N$  and  $ML_N$  are:

$$AP_U[n] = AP_N[n] \cdot (41.5/2) \quad (7.1)$$

$$ML_U[n] = ML_N[n] \cdot (32.5/2) \quad (7.2)$$

Equation (7.3) is used to compute the mean of AP component, while equation (7.4) calculates the mean of the ML component. The parameter N represents the number of samples within the time window. The COP coordinate time series, AP and ML, are commonly used to compute measures of postural steadiness, and characterize the static performance of the PC system.

$$\overline{AP} = \frac{1}{N} \sum_{n=1}^N AP_U[n] \quad (7.3)$$

$$\overline{ML} = \frac{1}{N} \sum_{n=1}^N ML_U[n] \quad (7.4)$$

Even though the moving platform has a predetermined sign for foot placement, individual variations in foot positioning result in the stabilogram being rarely centered. To address this, equations (7.5) and (7.6) are utilized to obtain a centered stabilogram.

$$AP[n] = AP_U[n] - \overline{AP}; \quad n = 1, \dots, N \quad (7.5)$$

$$ML[n] = ML_U[n] - \overline{ML}; \quad n = 1, \dots, N \quad (7.6)$$

The resultant distance RD[n] is the Euclidean distance of sample n from the origin:

$$RD[n] = \sqrt{(AP_n^2 + ML_n^2)}, \quad n = 1, \dots, N \quad (7.7)$$

Total Excursion TOTEX is the summation of the elementary excursion (movement) on the support plane between consecutive samples. It represents the total length of the path followed by the CoP. TOTEX is widely recognized as a reliable measurement in various populations and balance conditions. A smaller path length indicates better postural stability. It is also defined for the AP and ML components.

$$TOTEX = \sum_{n=1}^{N-1} \sqrt{(AP[n+1] - AP[n])^2 + (ML[n+1] - ML[n])^2} \quad (7.8)$$

$$TOTEX_{ML} = \sum_{n=1}^{N-1} \sqrt{(ML[n+1] - ML[n])^2} \quad (7.9)$$

$$TOTEX_{AP} = \sum_{n=1}^{N-1} \sqrt{(AP[n+1] - AP[n])^2} \quad (7.10)$$

The root distance (RD) represents the cumulative radial displacement of the Center of Pressure (CoP) from its mean position:

$$RD = \sum_{i=1}^N \sqrt{(ML_i - \bar{ML})^2 + (AP_i - \bar{AP})^2} \quad (7.11)$$

Where:

- $ML_i$  and  $AP_i$  are the medio-lateral and antero-posterior CoP positions at time  $i$ ,
- $\bar{ML}$  and  $\bar{AP}$  are the mean values of the ML and AP signals over time.

MDIST represents the average distance of the CoP from the center of the trajectory. It has been defined for the AP and ML axes.

$$MDIST = \frac{1}{N} \sum_{n=1}^N |RD[n]|$$

$$MDIST_{AP} = \frac{1}{N} \sum_{n=1}^N |AP[n]| \quad (7.12)$$

$$MDIST_{ML} = \frac{1}{N} \sum_{n=1}^N |ML[n]| \quad (7.13)$$

MVELO is the average velocity of movement (mean velocity of points on the support plane), by dividing the total excursion by the total time T(30 seconds in this analysis).

$$MVELO = \frac{TOTEX}{T} \quad (7.14)$$

$$MVELO_{ML} = \frac{TOTEX_{ML}}{T} \quad (7.15)$$

$$MVELO_{AP} = \frac{TOTEX_{AP}}{T} \quad (7.16)$$

RDIST is the root mean square (RMS) distance from the mean CoP. It is computed for the support plane, ML axis, and AP axis and corresponds to the standard deviation of the trajectory.

$$RDIST = \sqrt{\frac{1}{N} \sum_{n=1}^N RD^2[n]} \quad (7.17)$$

$$RDIST_{ML} = \sqrt{\frac{1}{N} \sum_{n=1}^N ML^2[n]} \quad (7.18)$$

$$RDIST_{AP} = \sqrt{\frac{1}{N} \sum_{n=1}^N AP^2[n]} \quad (7.19)$$

Sample Entropy is a measure of the irregularity or complexity of a time series. It quantifies the probability that similar patterns of length  $m$  remain similar at the next point, within a given tolerance  $r$ , excluding self-matches.

$$\text{SampEn}_{ML}^{(i,k)} = \text{SampEn} \left( \Delta \tilde{ML}_t^{(i,k)}, m = 3, r = 0.3 \right) \quad (7.20)$$

$$\text{SampEn}_{AP}^{(i,k)} = \text{SampEn} \left( \Delta \tilde{AP}_t^{(i,k)}, m = 3, r = 0.3 \right) \quad (7.21)$$

$$\tilde{ML}_t^{(i,k)} = \frac{ML_t^{(i,k)} - \mu_{ML}^{(i,k)}}{\sigma_{ML}^{(i,k)}}, \quad \tilde{AP}_t^{(i,k)} = \frac{AP_t^{(i,k)} - \mu_{AP}^{(i,k)}}{\sigma_{AP}^{(i,k)}} \quad (7.22)$$

*Notation:*

$\Delta \tilde{ML}_t^{(i,k)}, \Delta \tilde{AP}_t^{(i,k)}$ : normalized sway velocity (ML/AP)

$\tilde{ML}_t^{(i,k)}, \tilde{AP}_t^{(i,k)}$ : normalized CoP position time series

$\mu, \sigma$ : mean and standard deviation used for normalization

The Complexity Index (CI) is computed as the sum of multiscale sample entropy values across different time scales  $s$ :

$$CI_{ML} = \sum_{s=1}^S \text{MSE}(ML_{\text{Diff}}, m, r, s) \quad (7.23)$$

$$CI_{AP} = \sum_{s=1}^S \text{MSE}(AP_{\text{Diff}}, m, r, s) \quad (7.24)$$

where:

- $ML_{\text{Diff}}, AP_{\text{Diff}}$ : normalized incremental time series;
- $m$ : embedding dimension (e.g.,  $m = 2$ );
- $r$ : tolerance threshold (e.g.,  $r = 0.15 \cdot \sigma$ );

- $S$ : number of scales (e.g.,  $S = 6$ ).

$$\Delta \tilde{M}L_t^{(i,k)} = \tilde{M}L_{t+1}^{(i,k)} - \tilde{M}L_t^{(i,k)} \quad (7.25)$$

$$\Delta \tilde{A}P_t^{(i,k)} = \tilde{A}P_{t+1}^{(i,k)} - \tilde{A}P_t^{(i,k)} \quad (7.26)$$

ML Complexity Index is computed over Medio-Lateral (ML) sway velocity.

$$CI_{ML}^{(i,k)} = \sum_{s=1}^6 \text{SampEn} \left( \Delta \tilde{M}L_t^{(i,k)}, m = 2, r = 0.15, s \right) \quad (7.27)$$

AP Complexity Index is computed over Antero-Posterior (AP) sway velocity.

$$CI_{AP}^{(i,k)} = \sum_{s=1}^6 \text{SampEn} \left( \Delta \tilde{A}P_t^{(i,k)}, m = 2, r = 0.15, s \right) \quad (7.28)$$

The major axis length of the ellipse is computed from the first principal component (PCA) of the centered CoP trajectory:

$$L_{\text{major}} = \sqrt{(x_2 - x_1)^2 + (y_2 - y_1)^2} \quad (7.29)$$

Where  $(x_1, y_1)$  and  $(x_2, y_2)$  are the endpoints of the first PCA component at the 95% confidence interval.

The minor axis length of the ellipse is computed from the second principal component (PCA) of the centered CoP trajectory:

$$L_{\text{minor}} = \sqrt{(x_4 - x_3)^2 + (y_4 - y_3)^2} \quad (7.30)$$

Where  $(x_3, y_3)$  and  $(x_4, y_4)$  are the endpoints of the second PCA component at the 95% confidence interval.

The area of the confidence ellipse is computed as:

$$A_{\text{ellipse}} = \pi \cdot \frac{L_{\text{major}}}{2} \cdot \frac{L_{\text{minor}}}{2} \quad (7.31)$$

Where  $L_{\text{major}}$  and  $L_{\text{minor}}$  are the full lengths of the major and minor axes, respectively.

The orientation of the ellipse's major axis with respect to the ML axis is computed using the PCA coefficients:

$$\theta_{\text{ellipse}} = \cos^{-1}(\text{PC}_{1,ML}) \quad (7.32)$$

Where  $\text{PC}_{1,ML}$  is the first component of the first eigenvector from PCA, representing the direction of maximum variance.

$$SD_{AP} = \sqrt{\frac{1}{N} \sum_{i=1}^N (AP_i - \bar{AP})^2} \quad (7.33)$$

$$SD_{ML} = \sqrt{\frac{1}{N} \sum_{i=1}^N (ML_i - \bar{ML})^2} \quad (7.34)$$

$$\begin{cases} SD_{\text{magnitude}} = \sqrt{\frac{1}{N} \sum_{i=1}^N \left( \sqrt{ML_i^2 + AP_i^2} - \bar{M} \right)^2} \\ \bar{M} = \frac{1}{N} \sum_{i=1}^N \sqrt{ML_i^2 + AP_i^2} \end{cases} \quad (7.35)$$

**Standard Deviation of Direction (Circular Statistics)** The standard deviation of the direction is computed using circular statistics applied to the heading angle differences between consecutive points in the CoP trajectory.

Let the direction (heading) at each time step be:

$$\theta_i = \arctan \left( \frac{\Delta AP_i}{\Delta ML_i} \right)$$

Then, the heading change between time steps is:

$$\Delta\theta_i = \theta_{i+1} - \theta_i$$

The standard deviation of these circular differences is given by:

$$SD_{\text{direction}} = \sqrt{-2 \ln \left| \frac{1}{N-1} \sum_{i=1}^{N-1} e^{j\Delta\theta_i} \right|} \quad (7.36)$$

Where:

- $\Delta\theta_i$  is wrapped to the interval  $[-\pi, \pi]$ ,
- $e^{j\Delta\theta_i}$  maps angular differences to the unit circle,
- The result quantifies variability in direction changes, independent of magnitude.

**Magnitude Entropy** Magnitude entropy quantifies the complexity of the sway magnitude time series, based on normalized incremental CoP displacements:

$$M_i = \sqrt{(\Delta ML_i)^2 + (\Delta AP_i)^2} \quad (7.37)$$

$$\text{Magnitude Entropy} = \text{SampEn}(M, m, r) \quad (7.38)$$

Where:

- $M$  is the time series of CoP displacement magnitudes,
- $m = 3$  is the embedding dimension,
- $r = 0.3 \cdot \text{std}(M)$  is the tolerance.

Direction entropy is computed as the sample entropy of heading angle changes between consecutive CoP displacements:

$$\theta_i = \arctan \left( \frac{\Delta AP_i}{\Delta ML_i} \right) \quad (7.39)$$

$$\Delta \theta_i = \text{wrap}(\theta_{i+1} - \theta_i) \quad (7.40)$$

$$\text{Direction Entropy} = \text{SampEn}(\Delta \theta, m, r) \quad (7.41)$$

Where:

- $m = 3$  is the embedding dimension,
- $r = 0.3 \cdot \text{std}(\Delta \theta)$  is the tolerance,
- $\text{wrap}(\cdot)$  ensures angular continuity within  $(-\pi, \pi)$ .

Magnitude entropy is the sample entropy of the magnitude (or modulus) of the Center of Pressure (CoP) displacement vectors. The CoP movement can be represented as 2D vectors from the origin to each ML/AP point. The magnitude of these vectors is:

$$|V(t)| = \sqrt{ML(t)^2 + AP(t)^2} \quad (7.42)$$

This metric quantifies how complex or variable the *amplitude* of sway is over time.

- High entropy: sway magnitudes are irregular or unpredictable.
- Low entropy: sway magnitudes are regular or repetitive.

Entropy is computed over the modulus of CoP velocity (i.e., the difference of normalized ML/AP). This captures the complexity of *movement intensity*, not position.

Direction entropy is the sample entropy of the sway *direction*, i.e., the angle of movement at each time point. The instantaneous direction (heading) is computed as:

$$\theta(t) = \arctan \left( \frac{\Delta AP(t)}{\Delta ML(t)} \right) \quad (7.43)$$

The change in heading (heading change) is:

$$\Delta \theta(t) = \theta(t+1) - \theta(t)$$

This measures how predictable or variable the *direction of sway* is over time.

- High entropy: sway directions change unpredictably.
- Low entropy: sway direction is constrained or repetitive.

Direction entropy is useful for detecting compensatory strategies, e.g., rigid, unidirectional sway in neurological disorders.

Multivariate CI is the complexity index computed over a multivariate signal, in this case, CoP represented by both ML and AP components.

CoP is treated as a bivariate signal:

$$\mathbf{X}^{(i,k)}(t) = \begin{bmatrix} \Delta ML^{(i,k)}(t) \\ \Delta AP^{(i,k)}(t) \end{bmatrix}, \quad t = 1, \dots, T$$

Multivariate multiscale entropy (mvMSE) is computed across scales  $s = 1, \dots, 6$ :

$$\text{MMSE}^{(i,k)}(s) = \text{mvMSE}(\mathbf{X}^{(i,k)}, m = 2, r = 0.15, s)$$

The Multivariate Complexity Index is then:

$$\text{CI}_{\text{Multivariate}}^{(i,k)} = \sum_{s=1}^6 \text{MMSE}^{(i,k)}(s) \quad (7.44)$$

Since CoP sway is inherently bivariate (ML + AP), analyzing them together captures interaction effects and complexity patterns that univariate metrics miss.

Let  $r_i = \sqrt{ML_i^2 + AP_i^2}$  denote the radial distance of the  $i$ -th point from the origin.

$$\text{Antero Magnitude} = \max_{AP_i > 0} r_i \quad (7.45)$$

$$\text{Antero Angle} = \arctan\left(\frac{AP_{\max}}{ML_{\max}}\right) \quad (7.46)$$

$$\text{Postero Magnitude} = \max_{AP_i < 0} r_i \quad (7.47)$$

$$\text{Postero Angle} = \arctan\left(\frac{AP_{\min}}{ML_{\min}}\right) \quad (7.48)$$

$$\text{Left Magnitude Maximum} = \max_{ML_i < 0} r_i \quad (7.49)$$

$$\text{Left Angle} = \arctan\left(\frac{AP_{\text{left}}}{ML_{\text{left}}}\right) \quad (7.50)$$

$$\text{Right Magnitude Maximum} = \max_{ML_i > 0} r_i \quad (7.51)$$

$$\text{Right Angle} = \arctan \left( \frac{AP_{\text{right}}}{ML_{\text{right}}} \right) \quad (7.52)$$

**Root Mean Square (RMS)** The Root Mean Square (RMS) quantifies the average amplitude of the CoP displacement in the AP and ML directions:

$$\text{RMS}_{AP} = \sqrt{\frac{1}{N} \sum_{i=1}^N AP_i^2} \quad (7.53)$$

$$\text{RMS}_{ML} = \sqrt{\frac{1}{N} \sum_{i=1}^N ML_i^2} \quad (7.54)$$

Where:

- $AP_i$ ,  $ML_i$  are the centered antero-posterior and medio-lateral displacements at time  $i$ .
- $N$  is the number of time samples.

**Fractal Dimension using Higuchi Method** The Higuchi Fractal Dimension (HFD) quantifies the complexity of a time series based on self-similarity at different temporal resolutions. It is calculated by measuring the average length of the signal at different scales.

Let  $X = \{x_1, x_2, \dots, x_N\}$  be the CoP trajectory in either the ML or AP direction.

$$L_m^{(k)} = \frac{1}{k} \sum_{i=1}^{\lfloor \frac{N-m}{k} \rfloor} |x_{m+ik} - x_{m+(i-1)k}| \cdot \frac{N-1}{\lfloor \frac{N-m}{k} \rfloor \cdot k} \quad (7.55)$$

The average curve length for each scale  $k$  is:

$$L(k) = \frac{1}{k} \sum_{m=1}^k L_m^{(k)} \quad (7.56)$$

Finally, the Higuchi Fractal Dimension is estimated as the slope of the log-log plot:

$$\text{HFD} = \frac{d \log(L(k))}{d \log(1/k)} \quad (7.57)$$

Where:

- $k$  ranges from 1 to  $K_{\text{max}}$  (maximum number of intervals),
- $L(k)$  is the average signal length for scale  $k$ ,
- The slope is computed via linear regression on  $\log(L(k))$  vs.  $\log(1/k)$ .

## Spectral Features

$$\text{Total Power} = \sum_{j=1}^N PSD(f_j) \cdot \Delta f \quad (7.58)$$

$$\text{Mean Frequency} = \frac{\sum_{j=1}^N f_j \cdot PSD(f_j)}{\sum_{j=1}^N PSD(f_j)} \quad (7.59)$$

$$\text{Median Frequency} = f_m \quad \text{such that} \quad \sum_{f_j \leq f_m} PSD(f_j) \geq 0.5 \cdot \sum_{j=1}^N PSD(f_j) \quad (7.60)$$

$$\text{Spectral Variance} = \frac{\sum_{j=1}^N (f_j - \text{Mean Frequency})^2 \cdot PSD(f_j)}{\sum_{j=1}^N PSD(f_j)} \quad (7.61)$$

$$\text{Peak Frequency} = f_k \quad \text{such that} \quad PSD(f_k) = \max_j PSD(f_j) \quad (7.62)$$

## EMG Formulas

Average Amplitude Change ACC

$$AAC = \frac{1}{N} \cdot \sum_{i=1}^{N-1} |x_{i+1} - x_i| \quad (7.63)$$

Average Energy

$$AE = \frac{1}{N} \cdot \sum_{i=1}^N (x_i)^2 \quad (7.64)$$

Absolute Value of the Summation of the Exponential Root

$$ASM = \frac{1}{N} \cdot \sum_{i=1}^N |(x_i)^p| \quad (7.65)$$

where

$$p = \begin{cases} 0.5 & \text{if } 0.25N \leq i \leq 0.75N \\ 0.75 & \text{otherwise} \end{cases} \quad (7.66)$$

Absolute Value of the Summation of the Square Root

$$ASS = \sum_{i=1}^N \sqrt{|x_i|} \quad (7.67)$$

Coefficient of Variation

$$CV = \frac{SD}{\bar{x}} \quad (7.68)$$

Difference Absolute Mean Value

$$DAMV = \frac{\sum_{i=1}^{N-1} |x_{i+1} - x_i|}{N-1} \quad (7.69)$$

Difference Absolute Standard Deviation Value

$$DASDV = \sqrt{\frac{\sum_{i=1}^{N-1} (x_{i+1} - x_i)^2}{N-1}} \quad (7.70)$$

Difference Variance Value

$$DVARV = \frac{1}{N-2} \cdot \sum_{i=1}^{N-1} (x_{i+1} - x_i)^2 \quad (7.71)$$

Enhanced mean absolute value

$$EMAV = \frac{1}{N} \cdot \sum_{i=1}^N |(x_i)^p| \quad (7.72)$$

where

$$p = \begin{cases} 0.75 & \text{if } 0.2N \leq i \leq 0.8N \\ 0.5 & \text{otherwise} \end{cases} \quad (7.73)$$

Enhanced wavelength

$$EWL = \frac{1}{N} \cdot \sum_{i=1}^N | (x_i - x_{i-1})^p | \quad (7.74)$$

where

$$p = \begin{cases} 0.75 & \text{if } 0.2N \leq i \leq 0.8N \\ 0.5 & \text{otherwise} \end{cases} \quad (7.75)$$

New Zero Crossing (FZC) è definita come il numero di attraversamenti della soglia dinamica  $T$ , calcolata come segue:

$$T = \frac{2}{5} \sum_{i=1}^{10} x_i \quad (7.76)$$

Il numero totale di attraversamenti  $FZC$  è dato da:

$$FZC = \sum_{i=1}^{N-1} w_i \quad (7.77)$$

dove il peso  $w_i$  è definito come:

$$w_i = \begin{cases} 1, & \text{se } (x_i > T \wedge x_{i+1} < T) \vee (x_i < T \wedge x_{i+1} > T) \\ 0, & \text{altrimenti} \end{cases} \quad (7.78)$$

Kurtosis

$$KURT = \frac{x^4}{SD^4} \quad (7.79)$$

Integrated EMG

$$IEMG = \sum_{i=1}^N | x_i | \quad (7.80)$$

Interquartile Range

$$IQR = Q_3 - Q_1 \quad (7.81)$$

Log CV

$$LCOV = \log(COV) \quad (7.82)$$

Log DAMV

$$LDAMV = \log(DAMV) \quad (7.83)$$

Log DASDV

$$LDASDV = \log(LDASDV) \quad (7.84)$$

$$L_1 = \frac{1}{n} \sum_{i=1}^n X_{(i)} \quad (7.85)$$

$$L_2 = \frac{1}{n-1} \sum_{i=1}^n (i-1) \cdot (X_{(i)} - X_{(1)}) \quad (7.86)$$

$$L_3 = \frac{1}{(n-1)(n-2)} \sum_{i=1}^n (i-2)(i-1) \cdot (X_{(i)} - 2X_{(1)}) \quad (7.87)$$

$$L_4 = \frac{1}{(n-1)(n-2)(n-3)} \sum_{i=1}^n (i-3)(i-2)(i-1) \cdot (X_{(i)} - 3X_{(1)}) \quad (7.88)$$

Log Teager Kaiser Energy Operator

$$LTKEO = \log\left(\sum_{i=1}^N N - 1(x_i)^2 - x_{i-1} \cdot x_{i+1}\right) \quad (7.89)$$

Mean Absolute Deviation

$$MAD = \frac{1}{N} \cdot \sum_{i=1}^N |x_i - \bar{x}| \quad (7.90)$$

Mean Absolute Value

$$MAV = \frac{1}{N} \cdot \sum_{i=1}^N |x_i| \quad (7.91)$$

Maximum Fractal Length

$$MFL = \log\left(\sqrt{\sum_{i=1}^{N-1} (x_{i+1} - x_i)^2}\right) \quad (7.92)$$

Modified Mean Absolute Value

$$MMAV = \frac{1}{N} \sum_{i=1}^N w_i \cdot |x_i| \quad (7.93)$$

where  $w_i$  is defined as:

$$w_i = \begin{cases} 1, & \text{se } 0.25N \leq i \leq 0.75N \\ 0.5, & \text{altrimenti} \end{cases} \quad (7.94)$$

Modified Mean Absolute Value 2

$$MMAV2 = \frac{1}{N} \cdot \sum_{i=1}^N w_i \cdot |x_i| \quad (7.95)$$

where

$$p = \left\{ \begin{array}{ll} 1 & \text{if } 0.25N \leq i \leq 0.75N \\ \frac{4i}{N} & \text{if } i < 0.25N \\ \frac{4(i-N)}{N} & \text{otherwise} \end{array} \right\} \quad (7.96)$$

Mean Value of the Square Root

$$MSR = \frac{1}{N} \cdot \sum_{i=1}^N \sqrt{x_i} \quad (7.97)$$

$$SD1 = \sqrt{\frac{1}{2} \cdot \text{Var}(x_{n+1} - x_n)} \quad (7.98)$$

$$SD2 = \sqrt{2 \cdot \text{Var}(x_n) - \frac{1}{2} \cdot \text{Var}(x_{n+1} - x_n)} \quad (7.99)$$

$$RatioSD = \frac{SD1}{SD2} \quad (7.100)$$

Root Mean Square

$$RMS = \sqrt{\frac{1}{N} \cdot \sum_{i=1}^N (x_i)^2} \quad (7.101)$$

Standard Deviation

$$SD = \sqrt{\frac{1}{N-1} \cdot \sum_{i=1}^N (x_i - \bar{x})^2} \quad (7.102)$$

Skewness

$$SKEW = \frac{\sum_{i=1}^N (x_i - \bar{x})^3}{(N-1) \cdot SD^3} \quad (7.103)$$

Single Square Integral

$$SSI = \sum_{i=1}^N (x_i)^2 \quad (7.104)$$

Absolute Value of Temporal Moment

$$TM = \frac{1}{N} \cdot \sum_{i=1}^N |(x_i)^p| \quad (7.105)$$

where  $p \in \mathbb{N}$  and commonly  $p = 3$

Variance

$$VAR = \frac{1}{N-1} \cdot \sum_{i=1}^N (x_i - \bar{x})^2 \quad (7.106)$$

Variance of EMG

$$VARE = \frac{1}{N-1} \cdot \sum_{i=1}^N (x_i)^2 \quad (7.107)$$

Variance Order

$$VO = \sqrt{\frac{1}{N} \cdot \sum_{i=1}^N (x_i)^p} \quad (7.108)$$

where  $p \in \mathbb{N}$  and commonly  $p = 2$

Waveform Length

$$WL = \sum_{i=2}^N |x_i - x_{i-1}| \quad (7.109)$$

Power

$$p_i = \frac{1}{M} \cdot (X_i)^2 \quad (7.110)$$

Mean Frequency

$$F_{MN} = \frac{\sum_{i=1}^M f_i \cdot p_i}{\sum_{i=1}^M p_i} \quad (7.111)$$

Median Frequency

$$F_{MD} = \frac{1}{2} \cdot \sum_{i=1}^M p_i \quad (7.112)$$

Total Power

$$P_T = \sum_{i=1}^M p_i \quad (7.113)$$

Mean Power

$$P_{MN} = \frac{1}{M} \cdot \sum_{i=1}^M p_i \quad (7.114)$$

Peak Power

$$P_{max} = \max(p_i) \quad (7.115)$$

Peak Frequency

$$F_{max} = \max(f_i) \quad (7.116)$$

Kurtosis Frequency

$$F_{kurt} = \frac{F_{MN}^4}{F_{SD}^4} \quad (7.117)$$

Skewness Frequency

$$F_{skew} = \frac{\sum_{i=1}^M (f_i - F_{MN})^3}{(M-1) \cdot F_{SD}^3} \quad (7.118)$$

## ROI-Node-RSN Mapping

Table 7.1: Regions of Interest (ROIs) and their Functional Network Associations

| ROI | Label              | Acronym | RSN   | ROI | Label                | Acronym   | RSN   |
|-----|--------------------|---------|-------|-----|----------------------|-----------|-------|
| 1   | l.bankssts         | l.BSTS  | Other | 29  | l.middletemporal     | l.MTG     | DAN   |
| 2   | r.bankssts         | r.BSTS  | Other | 30  | r.middletemporal     | r.MTG     | DAN   |
| 3   | l.cACC             | l.cACC  | SAN   | 31  | l.paracentral        | l.paraC   | MOT   |
| 4   | r.cACC             | r.cACC  | SAN   | 32  | r.paracentral        | r.paraC   | MOT   |
| 5   | l.cMFG             | l.cMFG  | SAN   | 33  | l.pericalcarine      | l.periCAL | Other |
| 6   | r.cMFG             | r.cMFG  | SAN   | 34  | r.pericalcarine      | r.periCAL | Other |
| 7   | l.cuneus           | l.CUN   | VIS   | 35  | l.postcentral        | l.postC   | MOT   |
| 8   | r.cuneus           | r.CUN   | VIS   | 36  | r.postcentral        | r.postC   | MOT   |
| 9   | l.entorhinal       | l.ENT   | Other | 37  | l.posteriorcingulate | l.PCC     | DMN   |
| 10  | r.entorhinal       | r.ENT   | Other | 38  | r.posteriorcingulate | r.PCC     | DMN   |
| 11  | l.superiorfrontal  | l.sFG   | Other | 39  | l.precentral         | l.preC    | MOT   |
| 12  | r.superiorfrontal  | r.sFG   | Other | 40  | r.precentral         | r.preC    | MOT   |
| 13  | l.fusiform         | l.FUS   | VIS   | 41  | l.precuneus          | l.PCUN    | DMN   |
| 14  | r.fusiform         | r.FUS   | VIS   | 42  | r.precuneus          | r.PCUN    | DMN   |
| 15  | l.inferiorparietal | l.IPL   | Other | 43  | l.rACC               | l.rACC    | DMN   |
| 16  | r.inferiorparietal | r.IPL   | Other | 44  | r.rACC               | r.rACC    | DMN   |
| 17  | l.ITG              | l.ITG   | DAN   | 45  | l.rMFG               | l.rMFG    | SAN   |
| 18  | r.ITG              | r.ITG   | DAN   | 46  | r.rMFG               | r.rMFG    | SAN   |
| 19  | l.pOPER            | l.pOPER | DAN   | 47  | l.SPL                | l.SPL     | Other |
| 20  | r.pOPER            | r.OPER  | DAN   | 48  | r.SPL                | r.SPL     | Other |
| 21  | l.isthmuscingulate | l.iCC   | DMN   | 49  | l.STG                | l.STG     | AUD   |
| 22  | r.isthmuscingulate | r.iCC   | DMN   | 50  | r.STG                | r.STG     | AUD   |
| 23  | l.lateraloccipital | l.LOG   | VIS   | 51  | l.SMAR               | l.SMAR    | SAN   |
| 24  | r.lateraloccipital | r.LOG   | VIS   | 52  | r.SMAR               | r.SMAR    | SAN   |
| 25  | l.LOF              | l.LOF   | DMN   | 53  | l.TP                 | l.TP      | Other |
| 26  | r.LOF              | r.LOF   | DMN   | 54  | r.TP                 | r.TP      | Other |
| 27  | l.LING             | l.LING  | VIS   | 55  | l.TT                 | l.TT      | Other |
| 28  | r.LING             | r.LING  | VIS   | 56  | r.TT                 | r.TT      | Other |

## Phase-Locking Value (PLV) Calculation

The dynamic Phase-Locking Value (PLV) dynamic connectivity matrices are computed using the function:

$$N = \left\lfloor \frac{\text{NumberofSamples} - \text{OverlapWindow}}{\text{TotalWindow} - \text{OverlapWindow}} \right\rfloor$$

where:

$$\begin{cases} \text{NumberofSamples} &= \text{EpochDuration} \times \text{SamplingRate} \\ f_{\text{Interest}} &= f_{\text{min}} + \frac{(f_{\text{max}} - f_{\text{min}})}{2} \\ \text{TotalWindow} &= \left\lfloor \frac{6}{f_{\text{Interest}}} \times \text{SamplingRate} \right\rfloor \\ \text{OverlapWindow} &= \left\lfloor \frac{\text{OverlapPercentage}}{100} \times \frac{6}{f_{\text{Interest}}} \times \text{SamplingRate} \right\rfloor \end{cases}$$

This function takes as input:

- *EpochDuration*: EEG time series with dimensions  $[n_{\text{channels}}, n_{\text{samples}}]$ .
- *SamplingRate*: The EEG sampling frequency.
- *fmin*, *fmax*: The lower and upper-frequency limits of the band of interest.
- *OverlapPercentage*: The percentage of overlap between time windows.

The number of dynamic matrices (N) generated for each frequency band depends on the *length* of each analysis window and on the *overlap* between consecutive windows. Following [125], each window spans six cycles of the band's center frequency to ensure reliable phase estimation.

In our implementation, the *Epoch Duration* was 273s, the *Sampling Rate* was 1024Hz, and the *Overlap Percentage* between consecutive windows was set to 50%, providing a balance between temporal resolution and the stability of the phase-locking estimates.

| Band         | Frequency parameters (Hz) |                  |                       | Window parameters (samples)          |                                   |                     |
|--------------|---------------------------|------------------|-----------------------|--------------------------------------|-----------------------------------|---------------------|
|              | $f_{\text{min}}$          | $f_{\text{max}}$ | $f_{\text{Interest}}$ | TotalWindow<br>(samples per segment) | OverlapWindow<br>(samples shared) | N<br>(PLV matrices) |
| Delta        | 1                         | 4                | 2.50                  | 2457                                 | 1228                              | 226                 |
| Theta        | 4                         | 8                | 6.00                  | 1024                                 | 512                               | 545                 |
| <b>Alpha</b> | <b>8</b>                  | <b>13</b>        | <b>10.5</b>           | <b>585</b>                           | <b>292</b>                        | <b>953</b>          |
| Beta         | 13                        | 30               | 21.5                  | 285                                  | 142                               | 1953                |
| Gamma        | 30                        | 45               | 37.5                  | 163                                  | 81                                | 3408                |

## Calculation of the Alpha Band

Epoch Duration = 273 s; Sampling Rate = 1024 Hz; Overlap = 50%.

Number of Samples =  $273 \times 1024 = 279552$  samples.

$f_{\min} = 8$  Hz;  $f_{\max} = 13$  Hz  $\Rightarrow f_{\text{Interest}} = 10.5$  Hz.

Total Window =  $\lfloor 6/10.5 \times 1024 \rfloor = \lfloor 585.14 \rfloor = 585$  samples

Overlap Window =  $\lfloor 0.5 \times 585.14 \rfloor = \lfloor 292.47 \rfloor = 292$  samples

$$N = \left\lfloor \frac{279552 - 292}{585 - 292} \right\rfloor = \left\lfloor \frac{279260}{293} \right\rfloor = \lfloor 953.10 \rfloor = \mathbf{953}.$$

## Computational Methods for BNS Metrics

Description of the metrics employed in the analysis of BNSs, with corresponding formulas and interpretations.

| Parameter         | Formula                                                                                                                                                                                                                                                                                                                                                                      | Description                                                                                                                        |
|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| <i>Coverage</i>   | $\text{Coverage}_i = \frac{T_i}{T_{\text{total}}}$ <p>where <math>T_i</math> is the total time state <math>i</math> was active, and <math>T_{\text{total}}</math> is the total analysis time.</p>                                                                                                                                                                            | Coverage represents the proportion of time a BNS is active relative to the total time.                                             |
| <i>Duration</i>   | $\text{Duration}_i = \frac{T_i}{N_i}$ <p>where <math>T_i</math> is the total time state <math>i</math> was active, and <math>N_i</math> is the number of times state <math>i</math> was activated.</p>                                                                                                                                                                       | Duration is the average time a BNS remains active before switching to another.                                                     |
| <i>GEV</i>        | $\text{GEV}_i = \frac{\sum_{t \in i} \text{GFP}(t) \cdot \text{CC}(t)^2}{\sum_t \text{GFP}(t)}$ <p>where <math>\text{GFP}(t)</math> is the Global Field Power at time <math>t</math>, and <math>\text{CC}(t)</math> is the spatial correlation between the map at time <math>t</math> and the template map of state <math>i</math>.</p>                                      | GEV represents the proportion of the Global Field Power explained by each BNS, indicating how well each state represents the data. |
| <i>GFP</i>        | $\text{GFP}(t) = \sqrt{\frac{1}{N} \sum_{i=1}^N (V_i(t) - \overline{V}(t))^2}$ <p>where <math>V_i(t)</math> is the voltage at sensor <math>i</math> at time <math>t</math>, <math>\overline{V}(t)</math> is the mean voltage across all sensors, and <math>N</math> is the total number of sensors.</p>                                                                      | GFP quantifies the variance of the EEG signal at a given time point, providing a measure of the strength of brain activity.        |
| <i>GMD</i>        | $\text{GMD}(t) = \sqrt{\frac{1}{N} \sum_{i=1}^N \left( \frac{V_i(t)}{\sqrt{\sum_{i=1}^N V_i^2(t)}} - \frac{V_i(r)}{\sqrt{\sum_{i=1}^N V_i^2(r)}} \right)^2}$ <p>where <math>V_i(t)</math> and <math>V_i(r)</math> are the voltages at sensor <math>i</math> at times <math>t</math> and <math>r</math>, respectively, and <math>N</math> is the total number of sensors.</p> | GMD quantifies the dissimilarity between two topographical voltage distributions over time.                                        |
| <i>Occurrence</i> | $\text{Occurrence}_i = \frac{N_i}{T_{\text{total}}}$ <p>where <math>N_i</math> is the number of times state <math>i</math> was activated, and <math>T_{\text{total}}</math> is the total analysis time.</p>                                                                                                                                                                  | Occurrence measures how many times a specific BNS appears within a time window.                                                    |
| <i>TP</i>         | $T_{ij} = \frac{N_{ij}}{\sum_j N_{ij}}$ <p>where <math>T_{ij}</math> is the transition probability from state <math>i</math> to state <math>j</math>, <math>N_{ij}</math> is the observed transitions from <math>i</math> to <math>j</math>, and <math>\sum_j N_{ij}</math> is the total transitions from <math>i</math> to any state.</p>                                   | TP describes the probabilities of transitioning between different BNSs over time.                                                  |

## Statistical Result of Coverage

Coverage p-values and adjusted p-values after FDR correction for different BNSs across phases (BL, PRE, MOV, POST) in the CTR - PD contrast.

| BL Phase |         |                  | PRE Phase |         |                  | MOV Phase |         |                  | POST Phase |         |                  |
|----------|---------|------------------|-----------|---------|------------------|-----------|---------|------------------|------------|---------|------------------|
| BNS      | p-value | Adjusted p-value | BNS       | p-value | Adjusted p-value | BNS       | p-value | Adjusted p-value | BNS        | p-value | Adjusted p-value |
| 4        | 0.024   | 0.143            | 2         | 0.003   | <b>0.019*</b>    | 2         | 0.006   | <b>0.036*</b>    | 4          | 0.018   | 0.109            |
| 1        | 0.178   | 0.337            | 3         | 0.077   | 0.231            | 5         | 0.100   | 0.300            | 2          | 0.086   | 0.259            |
| 6        | 0.201   | 0.337            | 1         | 0.271   | 0.541            | 3         | 0.159   | 0.319            | 1          | 0.459   | 0.854            |
| 3        | 0.229   | 0.337            | 5         | 0.504   | 0.673            | 6         | 0.723   | 0.904            | 3          | 0.570   | 0.854            |
| 5        | 0.281   | 0.337            | 6         | 0.561   | 0.673            | 1         | 0.769   | 0.904            | 5          | 0.859   | 0.944            |
| 2        | 0.671   | 0.671            | 4         | 0.815   | 0.815            | 4         | 0.904   | 0.904            | 6          | 0.944   | 0.944            |

## Statistical Result of Occurrence

Occurrence p-values and adjusted p-values after FDR correction for different BNSs across phases (BL, PRE, MOV, POST) in the CTR - PD contrast.

| BL Phase |         |                  | PRE Phase |         |                  | MOV Phase |         |                  | POST Phase |         |                  |
|----------|---------|------------------|-----------|---------|------------------|-----------|---------|------------------|------------|---------|------------------|
| BNS      | p-value | Adjusted p-value | BNS       | p-value | Adjusted p-value | BNS       | p-value | Adjusted p-value | BNS        | p-value | Adjusted p-value |
| 1        | 0.082   | 0.372            | 2         | 0.032   | 0.174            | 2         | 0.038   | 0.228            | 6          | 0.324   | 0.877            |
| 6        | 0.124   | 0.372            | 1         | 0.058   | 0.174            | 1         | 0.566   | 0.793            | 1          | 0.513   | 0.877            |
| 4        | 0.607   | 0.672            | 6         | 0.450   | 0.678            | 5         | 0.581   | 0.793            | 2          | 0.553   | 0.877            |
| 5        | 0.615   | 0.672            | 5         | 0.452   | 0.678            | 6         | 0.626   | 0.793            | 5          | 0.615   | 0.877            |
| 3        | 0.653   | 0.672            | 4         | 0.815   | 0.978            | 4         | 0.661   | 0.793            | 3          | 0.730   | 0.877            |
| 2        | 0.672   | 0.672            | 3         | 1.000   | 1.000            | 3         | 0.885   | 0.885            | 4          | 0.975   | 0.975            |

## Statistical Result of Duration

Duration p-values and adjusted p-values after FDR correction for different BNSs across phases (BL, PRE, MOV, POST) in the CTR - PD contrast.

| BL Phase |         |                  | PRE Phase |         |                  | MOV Phase |         |                  | POST Phase |         |                  |
|----------|---------|------------------|-----------|---------|------------------|-----------|---------|------------------|------------|---------|------------------|
| BNS      | p-value | Adjusted p-value | BNS       | p-value | Adjusted p-value | BNS       | p-value | Adjusted p-value | BNS        | p-value | Adjusted p-value |
| 5        | 0.042   | 0.253            | 1         | 0.312   | 0.727            | 5         | 0.096   | 0.231            | 4          | 0.035   | 0.210            |
| 3        | 0.111   | 0.261            | 6         | 0.327   | 0.727            | 6         | 0.134   | 0.231            | 6          | 0.244   | 0.724            |
| 4        | 0.130   | 0.261            | 3         | 0.440   | 0.727            | 4         | 0.165   | 0.231            | 1          | 0.362   | 0.724            |
| 6        | 0.400   | 0.601            | 4         | 0.485   | 0.727            | 3         | 0.168   | 0.231            | 3          | 0.548   | 0.768            |
| 1        | 0.750   | 0.893            | 2         | 0.682   | 0.757            | 1         | 0.192   | 0.231            | 2          | 0.702   | 0.768            |
| 2        | 0.893   | 0.893            | 5         | 0.757   | 0.757            | 2         | 0.366   | 0.366            | 5          | 0.768   | 0.768            |

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