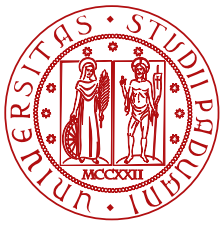

UNIVERSITÀ DEGLI STUDI DI PADOVA

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Department of Information Engineering

Master's Degree in Rehabilitation Bioengineering

Profiling Postural Control in Parkinson's Disease and Concussion Patients during a Virtual Reality Motion Sickness Stimulation

An EMG and Center of Pressure Data Analysis

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Ad maiora semper

Abstract

This master's thesis project is the culmination of six months of research conducted at the Motion Sickness and Postural Control Lab at Reykjavik University.
The aim of this study is to highlight the potential utility of physiological responses to complex postural control tasks in evaluating different conditions and disabilities.

For this purpose, two distinct populations are taken into consideration: individuals afflicted by Parkinson's Disease and patients who have experienced an event of concussion.
A total of 91 subjects was recruited, to participate in the BioVRSea experiment.
Therefore, a comparative analysis was undertaken between each cohort and their respective healthy, age-matched control group. The goal is to discern variations in their response to a complex balancing task, which is implemented through the novel BioVRSea paradigm.

The BioVRSea protocol constitutes a unique and innovative setup that employs a virtual reality environment and a moving platform, to simulate a scenario wherein the tested subject perceives themselves on a boat in the sea, exposed both to visual and motor stimuli. During the experiment different biosignals are measured, including electromyography, center of pressure, electroencephalography, electrocardiogram and electrodermal activity.

This multiscale investigation particularly focuses on Electromyography and Center of Pressure data, for a mainly neuromuscular and biomechanical analysis of postural control.

Subsequently to the complete acquisition of data coming from all healthy and pathological subjects, both electromyographic and force platform's data were pre-processed implementing filtering. Furthermore, data underwent segmentation into different phases of the experiment, called baseline, PRE, MOV and POST phases.

This segmentation into phases follows a subdivision dictated by the experiment's scheduling and stimulation. The baseline corresponds to the phase in which the participant adapts to the virtual reality environment; the PRE phase follows and it is characterized by the only the visual stimuli

through the sea waves scene; then in the MOV phase the platform starts moving according to the sea scene; and in the last segment called POST phase the platform stops moving and the subject is required to balance despite the induced movement provided by the previous segment.

The final step into the data processing included the statistical analysis, which was performed for both Parkinson's Disease and Concussion groups, with respect to their healthy control, in the three main phases of the experiment.

Finally, a detailed discussion of the obtained results is provided.
Significant variations in sway area were observed between healthy individuals and Parkinson's patients, particularly during PRE and POST phases, while no notable difference was evident during MOV phase. In contrast, in the Concussion Study group, sway area values were comparable between healthy and pathological subjects. Nevertheless, distinct features extracted from the data exhibited significant differences between the two groups, primarily in the POST phase. Regarding muscle activity, a notable number of significant parameters were identified, particularly in the PRE and POST phases, specifically involving the tibialis anterior muscle, across both groups.

Key biosignals for the differentiation of pathological subjects were identified. The inclusion of individuals with different conditions, and consequently different balance strategies, increased the relevance of collected data and obtained results. This study contributes to the validation of the BioVRSea protocols a gold standard for the quantitative measurements of motion sickness using bio-signals, advancing its recognition as a tool for the diagnostic of various conditions, and for the training and the rehabilitation for those who suffer motion sickness.

Riassunto

La tesi dal titolo *"Profiling Postural Control in Parkinson's Disease and Concussion Patients during a Virtual Reality Motion Sickness Stimulation: An EMG and Center of Pressure Data Analysis"* approfondisce il tema del controllo posturale umano nelle condizioni di morbo di Parkinson e commozione cerebrale, esaminando l'efficacia di strumenti come l'elettromiografia e la misurazione del centro di pressione per la valutazione dell'equilibrio, tramite l'innovativo protocollo BioVRSea.

Introduzione Le strategie di adattamento motorio costituiscono un sistema complesso di abilità che un individuo utilizza al fine di mantenere o ripristinare l'equilibrio durante alcune attività o situazioni di instabilità.
L'analisi del controllo posturale richiede test strumentati che permettano un'analisi cinetica, cinematica ed elettrofisiologica.

A tal proposito, è stato implementato un nuovo sistema di misurazione detto BioVRSea, per valutare oggettivamente il controllo posturale attraverso diversi biomarcatori.
Questo approccio innovativo prevede di indurre il paziente ad una condizione di instabilità, con lo scopo di misurare segnali cerebrali e muscolari, frequenza cardiaca e centro di pressione, durante un complesso task di controllo posturale. Il BioVRSea mira a diventare un gold standard per la diagnosi di varie condizioni legate al deficit equilibrio.

Obiettivi dello studio L'obiettivo primario del lavoro è quello di quantificare il controllo posturale acquisendo contemporaneamente vari biosegnali per condurre un'analisi completa. Si intende proporre un confronto significativo e oggettivo tra popolazioni sane e popolazioni affette da deficit dell'equilibrio, facendo emergere quali sono le caratteristiche elettromiografiche e del centro di pressione in grado di differenziare questi gruppi. Inoltre, con questo studio si vuole contribuire alla validazione del paradigma BioVRSea come nuovo strumento diagnostico.

Partecipanti Questo studio coinvolge 91 soggetti divisi in due macro-gruppi: un gruppo per lo studio del morbo di Parkinson e l'altro per lo studio delle commozioni cerebrali. Nel gruppo del morbo di Parkinson, 18 pazienti affetti dalla malattia sono stati confrontati con un gruppo di 27 persone sane. Nel gruppo delle commozioni cerebrali invece sono state incluse 23 atlete donne che hanno riportato un evento di commozione, e sono state confrontate con lo stesso numero di donne sane. In entrambi i gruppi, la coorte di pazienti sani è stata abbinata per età media al gruppo patologico corrispondente.
L'inclusione di soggetti affetti da Parkinson o con storico di commozione cerebrale, è dovuto al fatto che entrambe le condizioni hanno delle ripercussioni motorie che possono compromettere il controllo posturale.

Acquisizione dati Dopo aver fornito una descrizione dettagliata della procedura da seguire ed un questionario di suscettibilità alla cinetosi da compilare, i partecipanti sono stati dotati dei sensori necessari per acquisire tutti i diversi biosignali.

L'esperimento è diviso in due fasi principali: nella prima, è stata registrata solo l'attività cerebrale tramite elettroencefalogramma in uno stato di riposo. Nella seconda fase, sono stati aggiunti sensori per registrare segnali fisiologici aggiuntivi, come l'elettromiogramma (EMG), l'elettrocardiogramma (ECG), l'attività elettrodermica (EDA) ed il centro di pressione (CoP). Durante quest'ultima fase, che appunto costituisce il protocollo BioVRSea, i partecipanti sono stati coinvolti in una simulazione virtuale di una barca in mare che, anche per via del movimento di una piattaforma mobile, stimola l'impiego di strategie posturali per mantenersi in equilibrio. Il protocollo BioVRSea, che costituisce quindi la seconda parte dell'intero esperimento, è suddiviso in sei segmenti, ma per lo scopo principale dello studio questi sono stati riassunti in quattro fasi: fase baseline di assestamento e abituazione all'ambiente virtuale, fase PRE di solo stimolo visivo dato da un visore, fase MOV in cui il movimento della piattaforma si aggiunge alla scena virtuale e il soggetto si aggrappa ad una barra per prevenzione, fase POST in cui il movimento si arresta e il partecipante deve rispondere ad una situazione di instabilità senza utilizzare il supporto della barra.

Strumentazione Per quanto riguarda la strumentazione utilizzata, l'attività cerebrale è stata misurata con una cuffia a 64 elettrodi; l'attività muscolare è stata registrata tramite tre sensori EMG wireless collocati nei muscoli gastrocnemio, soleo e tibiale anteriore, sia nella gamba destra che nella gamba sinistra. L'elettrocardiografia è stata effettuata con tre elettrodi ECG e l'attività elettrodermica tramite due sensori EDA, tutti collegati ad un hub wireless. La piattaforma di movimento è stata utilizzata per simulare il movimento di una barca in mare, in sincronia con scene di realtà virtuale mostrate attraverso un visore opportuno, nonché per misurare il centro di pressione durante l'esperimento tramite 2 pedane di forza, ognuna dotata di 4 sensori.

Elaborazione dati Dopo l'acquisizione dei dati, sono state applicate ad essi delle procedure di pre-processing. L'elaborazione dei dati è stata eseguita utilizzando Matlab R2023a, Microsoft Excel e Python 3.12.0. Per questo progetto di tesi sono stati considerati ed analizzati solo i dati elettromiografici e di centro di pressione.

Inizialmente, dal questionario di suscettibilità alla cinetosi sono stati estratti i dati anagrafici e sono stati calcolati degli indici per suddividere i pazienti appartenenti ai due macro-gruppi in: soggetti propensi a riportare sintomi da movimento e soggetti non propensi (l'indice utilizzato per questa classificazione è detto Motion Sickness Index); soggetti influenzati dalla stimolazione data dall'esperimento e soggetti non influenzati (indice BioVRSea Effect).
L'elaborazione dei dati acquisiti ha poi permesso l'estrazione di 43 features EMG e 35 features CoP, per ogni soggetto in studio.

Analisi statistica Dopodiché è stata svolta un'analisi statistica per valutare le differenze significative tra il gruppo patologico e il relativo gruppo sano, durante tutte le fasi dell'esperimento e per entrambe le coorti di pazienti. Quest'analisi comprende una prima parte descrittiva ed esplorativa sulla distribuzione della popolazione utilizzando boxplot e istogrammi e una seconda parte di valutazione della distribuzione di tutte le features estratte, condotta mediante il test di normalità di Shapiro-Wilk. Data la prevalenza di distribuzioni non normali delle variabili, è stato deciso di calcolare i p-values utilizzando il test U di Mann-Whitney, non parametrico. I risultati ottenuti attraverso questo test sono stati poi verificati mediante il test di Kolmogorov-

Smirnov. Infine, è stata implementata la correzione di Bonferroni per i test multipli al fine di migliorare la solidità e l'affidabilità dei risultati.

Risultati L'analisi statistica ha permesso l'identificazione di differenze significative tra gruppi a confronto, offrendo una chiara comprensione dei risultati ottenuti.
Il processing dei dati EMG ha permesso di differenziare tramite attivazione muscolare i pazienti con problematiche di equilibrio e i relativi gruppi di controllo, sia nelle fasi PRE che POST. Non sono state osservate distinzioni significative durante la fase MOV, probabilmente a causa della stabilizzazione fornita afferrando la barra in questa fase dell'esperimento. La distinzione tra i due gruppi è soprattutto evidente nel muscolo tibiale anteriore durante la fase POST, che generalmente ha un coinvolgimento maggiore, rispetto agli altri due muscoli, nel mantenimento dell'equilibrio.
Per quanto riguarda invece l'analisi dei dati CoP sono state osservate variazioni significative nell'area di oscillazione tra individui sani e pazienti affetti da Parkinson, particolarmente durante le fasi PRE e POST, mentre non sono state evidenziate differenze significative durante la fase MOV. Nel gruppo di studio sulle commozioni cerebrali, i valori dell'area di oscillazione erano confrontabili tra soggetti sani e patologici. Tuttavia, distinti parametri estratti dai dati sull'attività muscolare hanno mostrato differenze significative tra i gruppi.

Limiti dello studio Il progetto di tesi presenta alcune limitazioni da considerare per sviluppi futuri dello studio, come per esempio il numero limitato di pazienti inclusi in entrambi i gruppi analizzati; l'omogeneità del gruppo sulle commozioni cerebrali, sia in genere che in stato sociale (tutte le partecipanti erano atlete). Inoltre, nonostante il paradigma BioVRsea mostra grandi promesse nella valutazione quantitativa del controllo posturale, esso presenta anche diverse limitazioni che riguardano principalmente l'accessibilità e l'usabilità nella pratica clinica.

Conclusioni In conclusione, lo studio ha esaminato le differenze nella risposta fisiologica tra pazienti affetti da Parkinson, individui con una storia di commozione cerebrale e i relativi gruppi di controllo, utilizzando il protocollo BioVRSea. L'obiettivo principale era identificare parametri biomedici chiave attraverso l'esperimento, che vuole valutare in modo oggettivo lo

stato patologico. L'esperimento ha fornito importanti spunti su queste condizioni, riuscendo a individuare segnali biologici e pattern distintivi tra gruppi sani e patologici. Lo studio ha inoltre dimostrato capacità diagnostiche, e l'analisi statistica ha evidenziato la potenziale differenziazione tra gruppi patologici e non patologici, esaminando problemi di equilibrio e risposte muscolari durante compiti complessi di controllo posturale. La partecipazione di un considerevole numero di soggetti ha aumentato la rilevanza dei dati raccolti e dei risultati ottenuti.

Il lavoro verrà presentato alla 19esima conferenza *International Symposium on Computer Methods in Biomechanics and Biomedical Engineering (CMBBE)*, che si terrà a Vancouver nell'agosto 2024.

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Abbreviations

PD Parkinson's Disease

EEG Electroencephalography

EMG Electromyography

ECG Electrocardiography

CoP Center of Pressure

VR Virtual Reality

TAL Tibialis Anterior Left

SL Soleus Left

GLL Gastrocnemius Lateralis Left

TAR Tibialis Anterior Right

SR Soleus Right

GLR Gastrocnemius Lateralis Right

PRE Phase of only visual stimuli

MOV Phase of both visual and motor stimuli

POST Phase of only visual stimuli and induced movement

1

Introduction

A fundamental aspect of human motor function is the maintenance of the upright posture, which is essential for everyday activities, such as standing, walking, and interacting with the environment. However, postural control is a complex task that involves the integration of various systems, including the vestibular, visual, and somatosensory systems, to maintain stability and balance [1]. Postural control dysfunctions can have a significant impact on the quality of life of impaired subjects, leading to falls, injuries, and decreased mobility. For this reason, balancing is particularly relevant for neurodegenerative disorder such as Parkinson's Disease and traumatic brain injuries like Concussion.

Parkinson's disease is characterized by the degeneration of dopaminergic neurons in the substantia nigra, leading to motor impairments such as bradykinesia, tremors, and postural instability. Individuals with Parkinson's disease often experience difficulties in maintaining balance and exhibit altered postural control strategies compared to healthy individuals [2].

Similarly, Concussion can disrupt postural control mechanisms due to a jolt to the head that causes the head and brain to move rapidly back and forth. Concussion-related impairments in postural control can manifest as dizziness, unsteadiness, and increased risk of falls, particularly during activities that challenge balance [3]. Understanding the mechanisms underlying postural control deficits in Parkinson's disease and concussion is essential for developing innovative diagnostic approaches, effective interventions, and rehabilitation strategies.

Electromyography and Center of Pressure measurements are valuable tools for assessing postural control and identifying abnormalities in motor function. Electromyography allows the quantification of muscle activation patterns during postural tasks, providing insight into the neuromuscular mechanisms of balance control. Center of Pressure data instead, offer objective measures of postural sway and stability, enabling researchers to characterize postural control strategies and identify deviations from normal patterns. Integrating these multiple data provides a comprehensive understanding of the neuromuscular and biomechanical aspects of postural control, facilitating the development of targeted interventions tailored to address specific impairments in balance and stability [4].

The present study aims to capture significant electromyographic and force platform data obtained through the BioVRSea protocol [Fig. 3.4], a unique measurement model designed to assess participants' postural control response. This highly instrumented setup mimics the sensation of imbalance typically experienced on a small boat moving with the sea waves by means of virtual reality, and collects biosignals using several sensors [5].

The BioVRSea paradigm has already been tested on Parkinson's Disease patients and individuals with a history of Concussion, totaling more than 400 participants, including healthy subjects, who were assessed using this innovative setup. The paradigm has already gained relevance in the evaluation of new biomarkers for the purpose of analysing postural control in these two groups of subjects.

1.1 Aim of the Study

In this project, the primary objective is to quantify postural control by concurrently acquiring various biosignals and conducting a comprehensive analysis using the innovative BioVRSea approach.

One key aim is to conduct a meaningful comparison between healthy participants and those diagnosed with Parkinson's Disease or Concussion. This comparison seeks to identify electromyographic and center of pressure features capable of distinguishing between these groups, shedding light on the specific physiological signatures associated with each condition.

Moreover, the overarching objective of the study is to contribute to the validation of the BioVRSea paradigm as a novel diagnostic tool. By elucidating its effectiveness in distinguishing between healthy individuals and those with pathological conditions or injuries, the project aims at enhancing the classification accuracy and diagnostic capabilities of the BioVRSea approach.

Finally, the project aims to advance the quantitative assessment of various physiological responses during postural control tasks. By analysing the correlation between biosignals and postural control mechanisms, the study seeks to pave the way for more effective diagnostic strategies and subsequent therapeutic interventions.

1.2 Thesis Outline

Following an initial introductory chapter aimed at providing an extensive description of the work and outlining the study's objectives, Chapter 2 examines the background information concerning the primary focus of this project: profiling Postural Control in patients with Parkinson's Disease and individuals with a history of Concussion, along with the various assessment methods employed. In addition, it introduces the BioVRSea protocol used for data acquisition.

Chapter 3 outlines the study's structure, including a description of the participants involved in the acquisition, the materials and methods utilized during the data collection, and a detailed explanation of the phases of the experiment. Furthermore, it described the procedures for data processing and statistical analysis.

Results are presented in Chapter 4, which is organized into distinct groups: the Parkinson Study group and the Concussion Study group.

Subsequently, Chapter 5 offers a comprehensive discussion of the obtained results, including an analysis about the limitations of the study.

Finally, this thesis work concludes with Chapter 6, in which the study goals and achievements obtained from this research are summarized.

2

Postural Control

Postural control and adaptation strategies constitute a multifaceted system of abilities aimed at maintaining or restoring balance across various positions and motor activities.
Individuals with a postural control deficit typically undergo an adaptive approach made of exercises tailored to improve the function of remaining capabilities, in order to restore balance as close to normal as possible [6].

Postural control denotes an individual's capacity to sustain balance both in natural settings and when exposed to perturbations.
As a matter of fact, postural control analysis includes both static and dynamic testing. In particular, dynamic postural control is about the body's response to perturbations in the center of mass, providing insights beyond what static testing can reveal [7].

Static balance is routinely evaluated through methods such as the Balance Error Scoring System (BESS) or force plates. The BESS asks individuals to maintain different static postures while evaluators monitor deviations from the desired posture, offering a valuable approach of easily assessing balance impairment. Alternatively, instrumented force plates provide a quantitative analysis of balance by tracking the Center of Pressure during static stances.
Dynamic balance assessments instead, is usually tested using the Star Excursion Balance Test (SEBT), which challenges individuals to maintain balance on one foot while reaching in specified directions with the other foot [7].

2.1 Postural Control Quantitative Assessment

While non-instrumented tests may aid clinicians in diagnosing sensory-motor disorders, they offer only a rudimentary assessment of postural control efficiency. In-depth analysis of postural control performance and associated strategies necessitates the utilization of instrumented tests employing diverse materials, enabling kinetic, kinematic, and electrophysiological analysis to be conducted effectively [4].

2.1.1 Electroencephalography

Electroencephalography (EEG) is the most commonly employed non-invasive method for capturing brain activity, thanks to its high portability and cost-effectiveness, coupled with its superior temporal resolution and low spatial resolution [8]. Since 1875, when the first brain activity was recorded by Richard Caton, the interest in EEG research has grown significantly over the years. It constitutes one of the main diagnostic tools in neurology, neurosurgery and psychiatry, because it leads to the quantification of neuronal activity of the human brain. EEG is also a valuable tool for clinicians and researchers in identifying brain dysfunction-associated diseases [9], [10].

The EEG signal is predominantly produced by cortical pyramidal neurons situated in the cerebral cortex, arranged perpendicular to the brain's surface. The EEG captures neural activity, which results from the combined excitatory and inhibitory postsynaptic potentials of relatively large groups of neurons firing synchronously [11].

EEG signals have a quasi-periodic pattern that reflects the synchronization and desynchronization of neurons, and they are characterized by an amplitude ranging from 0.5 to 100 μV. EEG waveforms are then classified depending on their amplitude, location, frequency, symmetry, and reactivity into four different frequency bands that are described in Table 2.1 [10] [12].

WAVE	RANGE [Hz]	ACTIVITY	AMPLITUDE [µV]
delta	0.5 - 4	tiredness and early stages of sleep; deep sleep	20 - 100
theta	4 - 7	creativity and daydreaming; emotions; meditation and payers; focus and hypervigilance	10
alpha	8 - 12	awake and relaxed; low levels of environmental stimulation	2 - 100
beta	13 - 30	awake and on alert; decision making; hearing and imagination	5 - 10
gamma	30 - 80	brain processing; high levels of thoughts and focus	-

Table 2.1: Differentiation between electroencephalographic frequency bands

EEG signal recording requires the placement of electrodes on the scalp that can capture the inherent and periodic electrical impulses generated by clusters of brain cells. Usually, electrodes are embedded in a cap that follows the ”10–20 International System” [Fig. 2.1], which establishes the correct placement of electrodes and increase the reproducibility of the experiments on different subjects. This protocol is recommended by the International Federation of Clinical Neurophysiology (IFCN) and includes 21 electrodes and 2 anatomical measurements: ”nation-inion distance” and ”ear-to-ear distance” [9]. Electrode positions are designated using a letter-and-number system. The letters correspond to various brain regions: frontal (F), parietal (P), occipital (O), temporal (T), central (C). Subsequently, a numerical value is appended, with even numbers indicating the right hemisphere and odd numbers denoting the left [13].

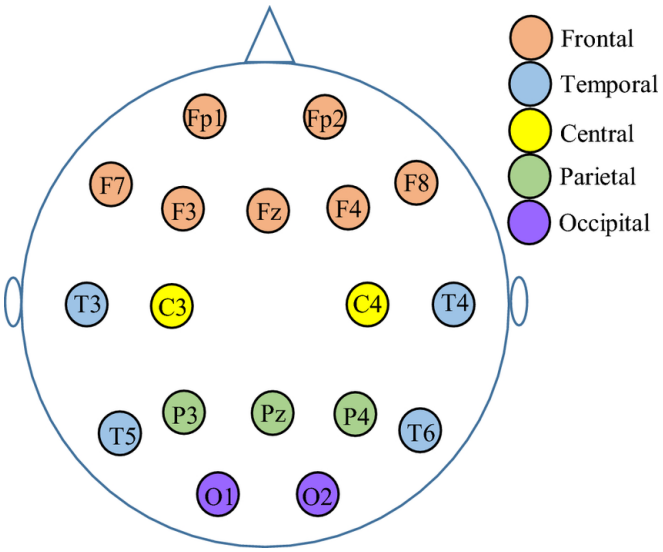

Figure 2.1: 10-20 International EEG System for electrodes' placement

Postural Control assessment by EEG

The central nervous system is fundamental in postural control strategies, since balancing requires the integration of visual, vestibular and proprioceptive sensory. Electroencephalography can underline the different cortical brain activities under different postural perturbations [1]. Parietal cortical areas are strongly implicated in vestibulo-spatial functions, but they are also crucial in proprioceptive cortical processing. Understanding electroencephalographic patterns during a variety of standing postures, with varying levels of difficulty, would facilitate the investigation of clinical conditions where patients only experience feelings of dizziness or instability, without significant changes in postural reflexes [14].

2.1.2 Electromyography

In 1849, Dubois-Reymond observed the presence of electrical activity during voluntary muscle contractions. The inaugural recording of this phenomenon occurred in 1890, coinciding with the introduction of the term ”electromyography” for the first time [15].

The electromyographic signal is generated by the electrical activities produced by skeletal muscles. Electromyography (EMG) serves as a tool for detecting myoelectric signals through electrical measurements. These myoelectric signals originate from motor neurons within the central

nervous system. EMG signal is a diagnostic indicator for muscle injuries, nerve impairments, and muscular dysfunctions stemming from neurological and muscular disorders. Additionally, EMG signals is mainly used for precisely capturing muscle movements in specific scenarios, such as during gate.

In order to measure muscle activity, the most used tool is the non-invasive surface electrode. EMG electrodes work by detecting the change the muscle surface and body skin through electrolytic conduction. EMG signals frequency ranges between 5 Hz and 2 kHz [16].

Electrodes' placement is essential to acquire reliable EMG data. According to the Surface ElectroMyoGraphy for the Non-Invasive Assessment of Muscles (SENIAM), in order to capture an optimum signal each electrode should be placed in a point on a line between two anatomical landmarks, that vary depenDing on the muscle under measurement [17].

Postural Control assessment by EMG

Electromyographic recordings have been widely used for the evaluation of postural function. These recordings allow for the differentiation of parameters into amplitude, temporal, and frequency domains.

Particularly, temporal electromyographic analysis is valuable for discerning postural responses following platform-movement disturbances or anticipatory postural adjustments during voluntary movements, aiding in the identification of bursts of muscle activity.

Amplitude analysis, like RMS or area calculations, can be used to reflect the level of muscle activity in sustaining a particular postural task.

Eventually, frequency domain analysis, which is often used in moving and vibrating platforms, shows a link between frequency of vibration and increased amplitude of muscle activity [4].

2.1.3 Electrocardiography

Electrocardiography (ECG) is able to capture electrical potentials generated by the heart, which are recorded from the body surface to detect and measure differences in electrical activity. The first electrical activity from a human heart was recorded in 1887 by Waller.

ECG constitutes an essential tool in the preliminary evaluation conducted for individuals with with cardiac complaints. It is a non-invasive and cost-effective method to assess arrhythmias and ischemic heart disease [18].

The recording of a precise ECG signal requires the correct placement of electrodes, which are attached to the chest and/or limbs of the patient. For an accurate acquisition, and depending on the situation, different monitoring lead systems are used. The main three configurations correspond to [19]:

- Simple 3 electrode bipolar monitoring, which includes two electrodes for active monitoring and the third one as ground electrode. Electrodes can be attached in three different configurations: lead I, II, and III. it is mostly used in telemetry monitoring;

- Common 5 electrode monitoring, in which four electrodes are placed on the torso corresponding to the limbs, and the one placed on the right lower limb is used as the ground one. The fifth electrode is attache don the chest in a standard position;

- Mason-Likar 10 electrode 12 lead monitoring [Fig. 2.2], mostly used in treadmill testing. Chest electrodes are placed in a standard position, but limb electrodes are transposed to the torso in order to reduce movement artefacts. Right lower electrode serves as the ground.

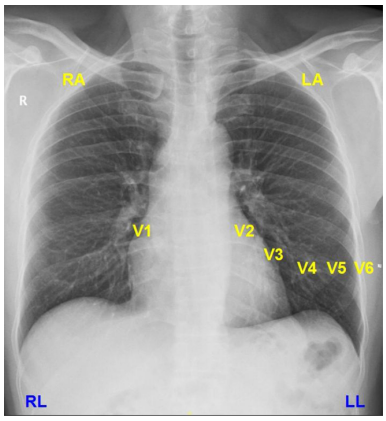

Figure 2.2: Mason-Likar 12 Lead. RA: Right arm, LA: Left arm, RL: Right leg, LL: Left leg. (Left leg and right leg or ground electrode positions are representatory, actual positions are lower than what is shown in the figure)

Postural Control assessment by ECG

The regulation of heart function is crucial for maintaining a stable internal environment in response to external stimuli. Heart Rate Variability (HRV) serves as a clinical metric for quantifying variations in successive heartbeat intervals [20]. Heart biosignal alterations and their correlation to other parameters involved in postural control assessment, such as electromyographic and center of pressure variables, are studied by testing postural control across different challenging tasks [21]. In addition, researchers have found that virtual reality stimulations can cause the increasing of the heart rate.

Despite the extensive literature available on ECG signals, their use in postural control assessment remains limited: their application in the assessment of postural control has not been fully explored or integrated into clinical practice [22]. The introduction of ECG measurement into this data acquisition, marks a progress in postural control investigation: HRV has already demonstrated its efficacy as a valuable biomarker in the classification of healthy and pathological subjects during a complex postural control task.

2.1.4 Force platform

Force platforms represent the predominant tool used for center of pressure measurement. They are widely employed due to their high sampling frequencies and precision, making them the

standard choice for assessing center of pressure.

Force plates are mechanical sensing systems specifically engineered to measure the ground reaction forces and moments associated with human movements. These plates rely on load cells to accurately determine forces exerted. Additionally, they can also provide information regarding the center of pressure, which particularly defines the location of the force vector [23].

Specifically, the position of the center of pressure of the two feet on the ground can be used for the identification of abnormal patterns of foot contact. This type of measure is mainly used in postural studies [24].

Two principal types of force platforms are used for this purpose:

- Uniaxial force plates, equipped with a single-axis load cell that measure only the vertical component (Fz) of the ground reaction force;
- Multiaxial force plates, equipped with load cells, from which the three components (Fx, Fy, Fz) of the ground reaction force and the moment of force acting on the plate can be obtained.

Both types of force paltforms are used in calculating medial-lateral (ML) and anterior-posterior (AP) dimensions of the Center of Pressure during a task of postural control [25].

Postural Control assessment by CoP

A quantitative assessment of postural control is crucial for the evaluation of human abilities in balancing tasks and for the prevention of falls.

One of the most frequently analysed variables in postural studies is the coordinate of the center of pressure, which serves as a tool to help in assessing balance deficits and postural instability associated with impairments. In general, equilibrium is achieved only when the projection of the center of mass on the support surface aligns with the center of pressure position. The objective is that of maintaining the center of mass projection within a safe area [24].

The center of mass consolidates the overall weight distribution of a body and it is calculated as the weighted average position of each body segment in three-dimensional space. Its vertical projection onto the ground is called center of gravity. Conversely, the Center of Pressure (CoP) is the point where the plantar ground reaction force is applied and it is typically measured via a force platform [25], [Fig. 2.3].

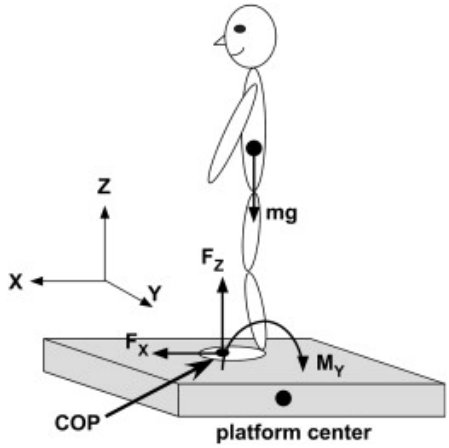

Figure 2.3: Computation of the Center of Pressure coordinate, based on forces and moments of force measured by a typical force platform

The CoP variables that can be obtained from the force platform recordings, are considered as a gold standard for assessing balance performance.
The evaluation of human balance typically involves examining spontaneous sway and induced sway of posture by means of a force plate, for the assessment of static upright posture and dynamic balance.

Typically, static balance assessment necessitates the individual to stand on a stable support surface, maintaining the CoP within this surface. usually, the subject is asked to complete several tasks, such as standing on one foot, closing the eyes, or using an elastic cushion. Conversely, reactive balance assessment often involves an induced sway balance test that commonly is achieved by a moving platform [25].

The force platform enables the recording of center of pressure deflection, facilitating the plotting of a stabilogram, which illustrates the CoP displacement in the AP and ML directions [26].

Researchers commonly evaluate the performance of balance control systems also by measuring various temporal parameters extracted from the center of pressure. Additionally, ellipse areas is also a valuable and assessed tool in posturography research. Further variables of interest in postural control assessment include the CoP path length, or total distance traveled by the center of pressure during a task; the distance between the maximum and minimum CoP peak points in the two directions, also called CoP amplitude; the average CoP speed; standard deviation and root mean square as variability indexes of CoP motion track; the sample entropy or time series complexity measures [27].

2.2 The BioVRSea paradigm for Postural Control Assessment

A novel measurement setup called BioVRSea was implemented to objectively assess postural control by means of different biomarkers. This novel approach indeed, includes multiple biosignals that work simultaneously to quantify balancing skills of each subject participating in the experiment. The paradigm is based on brain and muscle signals, heart rate and center of pressure measurements during a complex postural control task induced by a moving platform and a virtual reality environment [28].

This unique experimental setup was introduced to invoke and asses motion sickness and postural control during a virtual reality experience, coupled to a moving platform, to analyze individual fluctuations and changes in physiological functions [29] (see Fig. 3.4 for a graphical explanation).

The first aim of the BioVRSea setup was finding a general postural analysis prototype, that would take into consideration lifestyle, symptoms and general information, together with the analysis of the various biosignals. All these data would help in creating a multimetric profile, in order to obtain accurate and specific figures, related to postural control and motion sickness, for each participant.

Therefore, the creation of multimetric motion sickness profiles could be used not only to support

decision-making, but also for the assessment and diagnosis of pathologies under specific physiological conditions. The BioVRSea aims at becoming a gold standard and a main diagnostic tool for the assessment of various diseases.

The paradigm has already demonstrated its ability of individuating pathological and non pathological subjects, both in Parkinson's Disease [30] and Concussion condition [5]. Nevertheless, the BioVRSea paradigm was created with the primary objective of establishing a comprehensive profile to collect precise and specific data concerning postural control and motion sickness. The main goal was to gain deeper insights into the mechanisms driving motion sickness, ultimately leading to the development of novel strategies for its prevention and rehabilitation.

Motion Sickness Motion sickness is defined as a set of autonomic symptoms caused by inconsistent sensory impressions under conditions of motion, such as cold sweats, pallor, nausea, and vomiting. All these symptoms are caused by a stress reaction to the motion [31].
It is estimated that over one-third of the population suffers from this condition.

This syndrome is predominantly experienced by individuals during passive travel (for instance, a passenger in a car or boat), and it is characterized by feelings of discomfort or illness as the ones mentioned above. It is estimated that more than one-third of the population experiences this condition. The fact of feeling sick in motion has been more common in recent years with the use of video games; in particular, vertical motion with respect to gravity and roll of the body and head are prominent features causing motion sickness, as stated by Golding and colleagues [32].

According to this, motion sickness is caused by a mismatch between visual, vestibular, and somatosensory inputs [33], [32]. In passive locomotion the physical movements perceived by the vestibular system do not match the expected signals from the visual system. Purely visual stimuli can also lead to sensory conflict, as it can be experienced in Virtual Reality experiments where visual motion is perceived, but the vestibular signal does not match it. Other studies have shown correlations between the degree of motion sickness and physiological biosignals such as electroencephalogram, skin conductance, heart rate, blood pressure and body temperature [34].

2.3 Parkinson's Disease

Parkinson's Disease (PD) is defined as a neurological condition characterized by severe difficulties in movement, cognitive function, sleeping, pain management, and other health-related issues.
It is a progressive disease, lacking a definitive cure; however, therapies and medications exist to alleviate symptoms [35].

According to the World Health Organization, the incidence of PD has doubled over the last 25 years, estimating in 2019 a number of over 8.5 million individuals affected by PD, which marks an 81% increase since 2000. It is the second most common neurodegenerative disorder after Alzheimer disease.

While predominantly afflicting older individuals, it can also affect younger demographics, with men exhibiting a higher susceptibility than women [35].

As a complex neurodegenerative syndrome, PD affects various motor and non-motor neural circuits. Its due to two major pathologic processes: the premature and selective loss of dopamine neurons, and the accumulation of Lewy bodies which are composed of α-synuclein proteins. Patients affected by this disease encompass both motor and non-motor symptoms: when motor symptoms manifest, pathological examination reveals a 30–70% loss of cells in the substantia nigra [36].

2.3.1 Diagnosis

The accurate diagnosis of Parkinson's Disease is crucial for prognostic, therapeutic, and clinical research purposes.
However, several clinicopathological investigation based on data from brain bank materials of UK and Canada, revealed the misdiagnose of this disease in approximately 25% of patients, mainly because of symptoms that can also be associated to further conditions or, typically, seniority [35].

Diagnosis of Parkinson disease is based on clinical features from history and examination. History can include the reporting of motor and non-motor symptoms from the patient [35].

Motor Symptoms

Parkinson's disease is a neurodegenerative disorder characterized by a spectrum of motor symptoms, reflecting dysfunction within neural structures responsible for action selection, motor sequencing, and coordination and execution of movement [37]. PD is associated to primary and secondary motor symptoms, which are predominantly due to progressive degeneration of nigral dopaminergic neurons. Diagnosis of the disease typically occurs upon the emergence of initial motor symptoms [38].

The primary medication used to treat Parkinson's Disease is Levodopa, known for its efficacy. However, a notable side effect associated with Levodopa is the induction of dyskinesia, another motor symptom that significantly impacts the quality of life for patients [39].

Bradykinesia Bradykinesia refers to slowness in the execution of movements and gestures and to the reduced amplitude of movement. This symptom is due to the failure of basal ganglia and the cortical regions responsible for initiating and executing movement commands. This results in severe issues with self-paced movements, delayed reaction times, and abnormal brain activity before movement onset. In addition, patients often exhibit reduced muscle activity. Bradyknesia is often associated to Akinesia, which instead refers to the absence of movement, that also characterizes subjects with PD [40]. Bradykinesia can also result in a lack of facial expression and reduced amplitude in handwriting [41]. This symptom has been shown to be the most strongly correlated with dopamine deficiency that characterize PD patients. Consequently, it is the symptom that most aids in the diagnosis of the disease [36].

Resting tremor Tremor is one of the most prevalent symptoms in PD and is reported to affect up to 75% of patients during their disease course, and its response to dopaminergic medications varies.

The majority of patient exhibits tremor during rest, but sometimes this is also observable while walking. Tremor has an important effect on quality of life, impacting on simple daily activities when occurs [42].

Tremor commonly affects only one side of the body, typically manifesting in one hand, although it can also involve the feet or jaw. Usually it appears as an early symptom of the disease, sometimes it also disappears over time [43].

Rigidity Rigidity, or stiffness, refers to an involuntary elevation in muscle tone and may manifest as the initial symptom of Parkinson's disease. It affects up to 90% of PD patients.

Rigidity can impede muscle flexibility and relaxation, resulting in discomfort, muscle cramps, and difficulty in balancing [44].

Rigidity can manifest unilaterally or bilaterally, impacting the hips and ankles (limb rigidity), as well as the neck and trunk (axial rigidity). This stiffness can affect both flexor and extensor muscle tone equally [45].

Postural instability Postural instability denotes a compromised response to balance disturbances, indicating a condition in which the patient is at risk of falling because unable to spontaneously correct imbalance. Balance disorders typically manifest in the later stages of Parkinson's disease and affect the body's axis. Symptoms become evident during walking or when changing direction [46]. Unlike motor symptoms, balance disorders do not typically improve with dopaminergic therapy. Consequently, physiotherapy emerges as a crucial intervention for managing this condition [47].

Gait dysfunction Gait pattern in PD patients is characterized by slower walking, diminished arm swing, shorter step length, postural instability, and diminished coordination between arm and trunk movements. Gait impairment constitutes the mayor risk of falling; as a matter of fact, prospective studies have revealed that 70% of individuals with PD experience at least one fall within a year, with 39% experiencing recurrent falls [48].

Non-motor Symptoms

While motor symptoms may be somehow controlled with dopaminergic therapy, non-motor symptoms are hard to treat. Additionally, these features have a significant role in both the diagnosis and management of the disorder, and they may precede the development of motor symptoms [49].Non-motor symptoms are common in all stages of the disease [50].

Cognitive disorders Cognitive dysfunction stands as a major clinical non-motor symptom of PD. This feature includes mild cognitive impairment and dementia, notably characterized by executive dysfunction. Often, it coincides with impairment across other cognitive domains, which are typically categorized into two main groups. One group involves issues with planning, working memory, and executive function; the second group is instead related to disturbances in attention, semantic verbal fluency, and visual spatial ability [51].

Autonomic dysfunction Autonomic dysfunction frequently manifests in Parkinson's disease due to the loss of dopamine-producing cells and the presence of microscopic protein deposits in the brain (Lewy bodies) [44].

Symptoms of autonomic dysfunction are among the most debilitating and significantly reduce the quality of life in PD patients. These individuals may experience gastrointestinal malfunction, constipation and weight loss, orthostatic hypotension, urinary disturbance, skin problems and sweating, dry eyes, sialorrhea and dysphagia [52].

Olfactory dysfunction Olfactory dysfunction is one of the non-motor disorder that are usually reported from PD patients many years before the first motor manifestations, and consequently it is an early and sensitive marker of the preclinical phase of the disease. It affects 90% of cases, and seems to persist over time despite drug therapies [53].

Psychiatric symptoms Psychiatric symptoms in PD include depression, anxiety, hallucination, delusion, apathy, anhedonia and impulsive and compulsive behaviors. They characterize the majority of PD patients, having a significant impact on their quality of life [54].

Fatigue Fatigue is usually defined as the complete lack of energy and an exhaustive sense of tiredness, which severely affects the quality of life. Fatigue worsens as PD progresses, often accompanied by other non-motor symptoms such as psychiatric ones [55].

There is no correlation between fatigue and the stage of the disease or the duration of the condition. However, fatigue could be a side effect of dopaminergic medications, and energy levels may also depend on dosage and timing of therapy [44].

Disease Assessment Scale

The diagnosis of PD also necessitates determining the stage at which a patient is situated. Parkinson's Disease can be subdivided into five different stages of development. This differentiation follows the Hoehn-Yahr staging system published in 1967, wherein stages are primarily based on clinical observation of motor symptoms. The scale helps in describing the progression of the disease, also allowing to measure the severity of the case [56]:

- Stage 1, Unilateral involvement only (symptoms on one side), usually with minimal or no functional disability;
- Stage 2, Bilateral or midline involvement without impairment of balance;
- Stage 3, Mild to moderate bilateral disability with impaired postural reflexes. The patient is physically independent;
- Stage 4, Severely disabling disease. The patient is still able to walk or stand unassisted
- Stage 5, Confinement to bed or wheelchair unless aided.

There is a growing need to quantify the characterizing PD factors, for objectively assess the disease [2].

Due to its progressive nature, PD symptoms worsen over time and can severely affect the quality of life of the patient. Symptoms can be divided in motor symptoms and non-motor symptoms [57].

Therapy

Today's available treatments for Parkinson's Disease include supportive care (physical therapy, occupational therapy, etc.), pharmacologic therapy, and surgery.

The goal of drug therapy for PD is to compensate for the deficiency of dopamine in the striatum by emulating physiological stimuli. Levodopa® (L-dopa) is the primary treatment and works by elevating dopamine levels in the brain, which is crucial factor for the regulation and synchronization of body movement. In the majority of cases, individuals with the disease exhibit positive responses to treatment. Nonetheless, in a minority of patients, treatment efficacy is limited and, over time, the level of disability increases, severely impacting on normal daily activities [58].

2.3.2 Postural Instability in Parkinson's Disease

Postural instability, as the most incapacitating aspect of PD, has become the primary challenge in the disease's management.

Patients affected by Parkinson's Disease commonly exhibit a certain level of postural instability attributed to ineffective coordination. Postural instability denotes the inability to maintain balance, stemming from the loss of postural reflexes, including balance reactions, trunk rotation, and the adoption of a flexed posture.

Existing treatment strategies such as drugs, surgery and physiotherapy, fail to address postural instability, leading to increased morbidity.

Even in the initial phases of the disease, before reaching Hoehn-Yahr stage 3, individuals with PD may have a diminished capacity for postural adaptation to maintain their support base when subjected to potentially destabilizing external forces [2].

Identifying postural instability specific risk factors could help in accurate diagnosis, facilitating effective screening and disease monitoring. Some of the measurable factors for the assessment of postural instability in PD patients are fear of falls, biomechanical variables (for instance, center of pressure, center of gravity, center of mass), gait analysis variables, age, postural reflexes,

defective perception of orientation, impulsivity, and serum vitamin D levels [2].

2.4 Concussion

A concussion, also known as mild traumatic brain injury (mTBI), is a temporary functional neurological disturbance resulting from a blow to the head or transmitted force, which usually it's briefly and spontaneously resolved [59]. Approximately 42 million people worldwide experience a concussion event annually [60].

Given the wide array of definitions regarding concussion, the Mild Traumatic Brain Injury Committee of the American Congress of Rehabilitation Medicine, revised by the World Health Organization, identified different diagnostic criteria to assess this condition [61].

The major cause of sustaining concussion is the participation is sports: millions of athletes of all ages may face the risks of multiple concussion during their career. An estimation of 1.6 to 3.8 million sports-related concussions occur annually only in the United States alone; however this constitutes an underestimation due to all the events of concussion which are not clinically reported.

Sports such as football, rugby, ice hockey, and wrestling present a higher risk of concussion than others [62].

2.4.1 Diagnosis

According to the diagnostic criteria mentioned above, for an injury to be classified as a concussion, it should be characterized by a Glasgow Coma Scale score between 13 and 15, along with the presence of at least one of the following symptoms during the 30 minutes after the injury [61]:

- loss of consciousness < 30 minutes;
- post-traumatic amnesia < 24 hours;

- impaired mental state at time of accident (confusion, disorientation, etc.);
- transient neurological deficit (focal signs, epilepsy, or non-surgical intracranial injury).

Despite of this indication regarding symptoms that will be discussed below, there is no objective way to diagnose a concussion. In research, concussion assessments typically involve questionnaires structured according to the latest consensus on the definition of concussion. For instance, the fifth edition of the Concussion Assessment Tool is currently used [3].

While a concussion can be diagnosed even in the absence of structural damage, studies have revealed structural damage occurring after a concussion, which is also potentially contributing to prolonged symptoms. 25% of patients experiencing a concussion exhibit persistent difficulties [63], also called post concussion symptoms, developing a sever Post-Concussion Syndrome.

Symptoms

After a biomechanical force is imparted to the brain, several acute symptoms characterized and help in distinguishing a concussion. Typical symptoms and signs include [3]:

- Somatic symptoms (headache), cognitive symptoms (slowed reaction times), emotional symptoms;
- Physical signs, such as loss of consciousness, amnesia, neurological deficit;
- Balance problems, also resulting in gait impairments;
- Behavioural changes (irritability);
- Sleep/wake disturbance, including somnolence and drowsiness.

Some people suffer Post-Concussion Syndrome (PCS), that is the development of one of the eight following symptoms within four weeks after the event of mild traumatic brain injury:

headache, dizziness, fatigue, irritability, sleep problems, concentration problems, memory disorders and emotion perturbations [60].

Recovery

While most cases of concussions resolve spontaneously, they can lead to persistent psychological, physical, and cognitive complications, as well as protracted recovery times.
Clinical recovery includes the return to normal activities (school, work, and sport) after injury, but operationally it involves the resolution of post-concussion-related symptoms and a return to clinically normal balance and cognitive functioning.
Recovery typically occurs within the first 24-72 hours following the event; additionally, for most people, these cognitive and balance impairment rapidly improve and the athlete returns to sport in two weeks [3].

The concept of a prolonged rest following injury is the common therapy recommended to patients with a Post-Concussion Syndrom. However, there is no empirical evidence of its efficiency. Multiple studies are instead demonstrating the effectiveness of an active approach to recover concussion.

2.4.2 Postural Instability in patients with History of Concussion

The most typical clinical consequence to the event of concussion, is the observation of impaired postural control.

Postural control relies on the integration of sensory information from the somatosensory, visual, and vestibular systems. In healthy individuals, these systems work harmoniously to adjust motor patterns. Concussed individuals instead, experience postural control decrements due to deficits in visual and vestibular system functioning, particularly with eyes closed.

These balance deficits typically resolve within approximately 3 days post-injury, but many investigations demonstrate that changes in postural control persist long after the more evident symptoms' resolution [64].

Since the maintenance of balance requires these multiple neural networks and structures of the brain, in the context of concussion there is a direct association with decreases in static stability compared to not-injured individuals.

Concussion has been demonstrated to induce alterations in Center of Pressure dynamics, mostly during upright standing, which is evidence of postural instability. These changes manifest as increased sway displacement, velocity, and regularity, and reduced entropy measures [65].

The perception of concussion as a temporary injury rather than a pathological condition raises questions about the long-term effects on postural stability. It remains uncertain whether the acute deficits in postural stability, observed immediately after the injury, ever completely restore to measures of stability prior to the concussive impact.

In healthy individuals, keeping an upright posture is automatic and doesn't need much effort. However, after a concussion, stability deficits increase, especially when attention is divided between cognitive tasks and posture maintenance. Even after cognitive symptoms resolve, subjects who experienced concussion show static and dynamic stability deficits, even months later.

Until now, there hasn't been much research on long-term impairments of postural stability in individuals who have had concussions [65].

3

Materials and Methods

3.1 Participants

A total number of 91 subjects was involved in this study [Table 3.1]. The entire thesis project has been divided into two main branches that will be labeled in this work as Parkinson Study group and Concussion Study group.

	Number of subjects	Female	Male	Age
Parkinson	18	7	11	67.2 ± 7.6
Healthy Elderly	27	14	13	63.4 ± 5.5
Concussion	23	23	0	28.6 ± 5.7
Healthy Young	23	23	0	30.3 ± 8.4

Table 3.1: Population distribution, divided into Parkinson Study group and Concussion study group. Age is reported as mean ± standard deviation)

In the Parkinson branch, forty-five participants underwent the acquisition.
Eighteen subjects were diagnosed with Parkinson's Disease (age 67.2 ± 7.6), and they were matched with a Healthy Control group of twenty-seven people (age 63.4 ± 5.5).

Forty-six participants underwent the study making part of the Concussion branch.
Twenty-three female athletes had a self-reported history of concussion (age 28.6 ± 5.7), instead

twenty-three young females were taken as their Healthy Control group (age 30.3 ± 8.4) [Fig. 3.1].

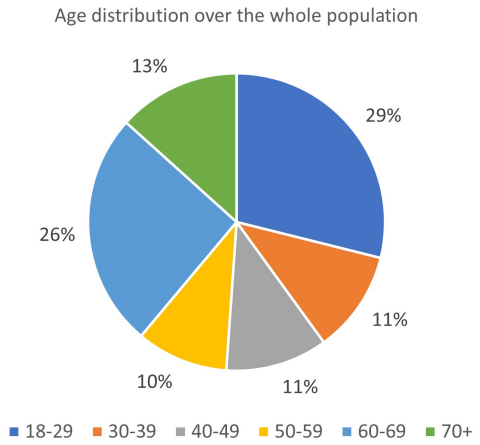

Figure 3.1: Age distribution over the whole population composed by 91 participants. Parkinson's Disease subjects are all over 50 years old, instead Concussion subjects are all under 50 years old.

For simplicity, the healthy control group for Parkinson's Disease will be termed "Healthy Elderly", while the healthy control group for Concussion will be designated as "Healthy Young".

In both cohorts, the healthy control was age-matched to the respective pathological group. In the Parkinson Study group, 46.7% of the participants were female; whereas in the Concussion study group, all participants were female [Fig. 3.2], [Fig. 3.3].

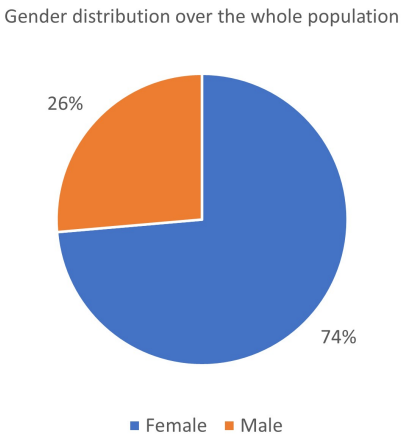

Figure 3.2: Gender distribution over the whole population composed by 91 participants. Female = blue; Male = orange

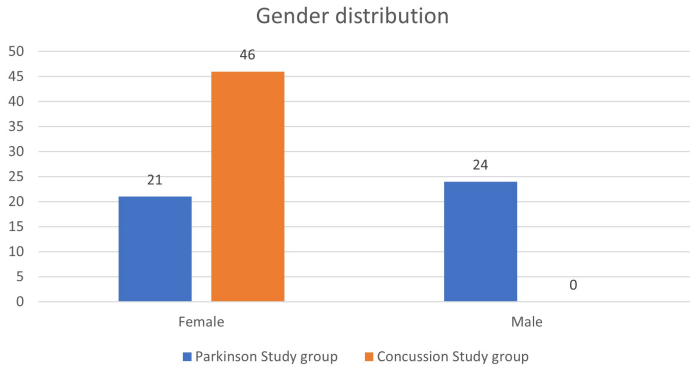

Figure 3.3: Gender distribution for both Parkinson Study group (blue) and Concussion Study group (orange)

The study was conducted at the Motion Sickness and Postural Control Laboratory of Reykjavik University.

3.2 Data Acquisition

All participants were provided with written information detailing the study before affixing their signature to a declaration of informed consent. The study protocol received approval from the Icelandic National Bioethics Committee (no:17-183-S1).

At the beginning, participants were instructed on the procedural aspects, whereby the entire experiment is divided into two principal segments.

In the initial phase, only recording of brain activity was conducted through electroencephalogram (EEG) during a resting state. This session lasted 10 minutes, during which the subject was asked to maintain a seated position with eyes closed during the first five minutes, followed by observing a visual stimulus on a monitor for the subsequent five minutes.

During the second phase, participants were provided with supplementary sensors to record additional physiological signals, named electromyogram (EMG), electrocardiogram (ECG) and electrodermal activity (EDA). This phase involved engaging them in a complex task of postural control, which included two distinct types of stimulation: a visual stimulation through a virtual reality system, and motion stimulation via a moving force platform that additionally measures

the Center of Pressure (CoP) data.

A detailed explanation of the protocol will be provided below.

It is crucial to emphasize that, for the purpose of this study, only electromyography and center of pressure signals will be processed and analysed. Specifically, only the second phase of the whole experiment, referred to as the BioVRSea experiment, will be considered.

3.2.1 The BioVRSea protocol

The just mentioned protocol which is used to measure the subject's response to a task of postural control is called BioVRSea protocol.

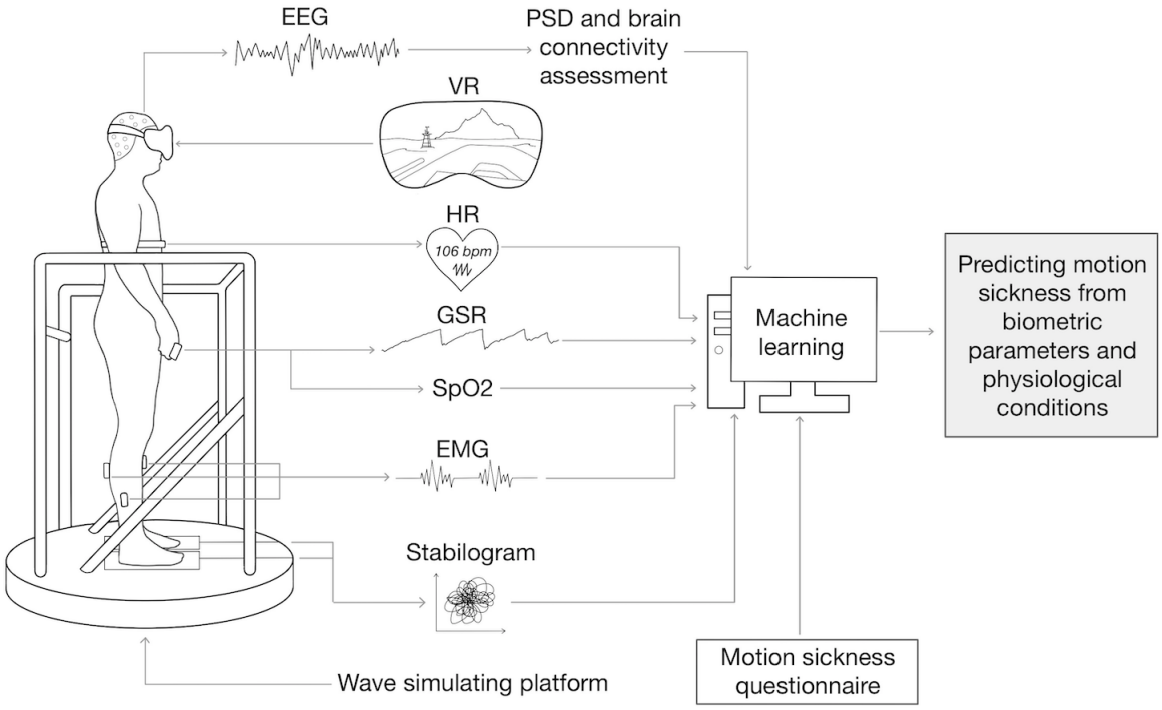

Figure 3.4: BioVRSea paradigm

All participants that underwent the study, took part in this experiment, which introduces a unique multi bio-metric system that combines virtual reality with a moving platform [Fig. 3.4].

The system is designed to imitate the sensation of being at sea on a small boat, a situation involving different balance strategies.

The experiment combines the acquisition of different biosignals, measured by many sensors which will be presented below, with the aim of studying the physiological response of the individual to this unbalanced situation, through several metrics. For the analysis of data acquired with the explained method, machine learning techniques were used with the aim of classifying pathologies based on self-reported (Motion sickness questionnaire) and measured parameters [Fig. 3.5].

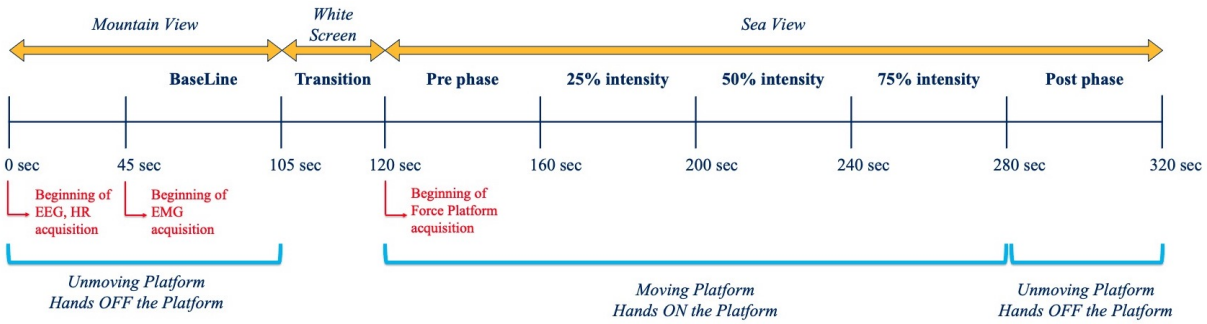

Figure 3.5: BioVRSea scheduling

The protocol of the experiment is divided into six segments: baseline (BL), pre-phase (PRE), 25% phase, 50% phase, 75% phase, post-phase (POST) [Table 3.2], in which different biosignals are measured, such as electromyogram (EMG), pressure center (CoP) and electroencephalogram (EEG). Subjects faced the experience of different stimuli: visual stimulation (Phase of only visual stimuli (PRE)), motor stimulation (Phase of both visual and motor stimuli (MOV)), balance control (Phase of only visual stimuli and induced movement (POST)).

However, for the main purpose of this study these phases were then summarized into four main segments of the experiment [Table 3.3]:

- baseline (BL), in which the sole stimulus presented to the participant is the visual stimulus. In this stage, the participant is exposed to a virtual reality scene featuring a mountain view. The supporting platform remains stationary throughout this phase and the subject stands with their arms along their body;

Time [s]	Segment	VR scene	Hands positioning	Platform state
0-120	Baseline	Mountains	by side	Stationary
120-160	PRE	Sea	by side	Stationary
160-200	25%	Sea	on bars	Moving
200-240	50%	Sea	on bars	Moving
240-280	75%	Sea	on bars	Moving
280-320	POST	Sea	by side	Stationary

Table 3.2: BioVRSea Experimental Paradigm

- pre-phase (PRE), in which the virtual reality screen switches to a sea scene, with solely a visual stimulus, and the moving platform remains inactive during this period. The subject is asked to grasp the bar in front of them, preparing for the following phase [Fig. 3.6];
- mov-phase (MOV), that includes the three aforementioned phases in which the platform undergoes motion at different percentages of maximal wave amplitude (25%, 50% and 75%). This phase incorporates both visual and motor stimuli;
- post-phase (POST), in which the platform stops moving and the only stimulus is provided by virtual reality; in this segment the subject is required to lower their hands and adapt to an induced movement provided by the motion experienced in the preceding segment.

Time [s]	Segment	VR scene	Platform state	Stimulus
0-120	Baseline	Mountains	Stationary	None
120-160	PRE	Sea	Stationary	Visual
160-280	MOV	Sea	Moving	Visual and Motion
280-320	POST	Sea	Stationary	Visual

Table 3.3: BioVRSea stimuli

Multiple recent studies have underscored the significance of the BioVRSea setup in facilitating cohort differentiation and enabling pathological assessment [28], [29].

Figure 3.6: Example of a participant during the experiment. The participant is wearing all the sensors required for data acquisition. Technicians are assisting the participant in grasping the bar in front of them, just before the platform begins its motion for the MOV phase

3.2.2 Experimental Setup

The data acquisition process during the BioVRSea experiment requires precise placement of each sensor and adequate use of each instrument. Consequently, following a detailed description of the protocol and the completion of a pre-experiment questionnaire, participants are equipped with requisite sensors designed to capture all the diverse biosignals.
A comprehensive elucidation of the instrumentation is presented below.

Questionnaire

At the beginning of each acquisition, general information were collected by means of the Motion Sickness Susceptibility Questionnaire (MSSQ) inspired by the one proposed by Golding (2006b) [66], which is considered as the benchmark for assessing symptoms and proneness associated with motion sickness.

This included general questions regarding age, gender, lifestyle and health condition, other questions about motion sickness to be answered before the acquisition as indication of a general personal history, and after the acquisition to assess the personal response to the virtual and moving environment. These questions mainly concerned the feelings of general discomfort such as nausea, dizziness, sweating and increased salivation, which could appear in the subject during a passive movement action. An additional section asked particular questions about a person's condition after experiencing a concussion (only for subjects belonging to the Concussion group).

Electroencephalography

Brain activity was acquired by means of the CA-204-64 wet electrode cap, named EegoTM mylab (ANT Neuro, Hengelo, the Netherlands) at a sampling frequency of 4096 Hz. The cap was lightweight and flexible, composed by 64 Ag/AgCl electrodes [67].

A conductive gel was applied to each electrode with a blunt needle syringe to reduce the impedance between the scalp and each electrode. An impedance lower than 40 kΩ was considered sufficiently conductive. The EEG amplifier (ANT Neuro, Hengelo, The Netherlands) was connected to the cap and to a tablet [Fig. 3.7].

Figure 3.7: EEG wet cap and Amplifier

Electromyography

Muscle electrical activity was measured by means of six wireless EMG sensors by KineLive (Kiso ehf, Reykjavik, Iceland) with a sampling frequency equal to 1600 Hz. Muscles under observations were Tibialis anterior (TA), Gastrocnemius Lateralis (GL) and Soleus (S), for both right and left leg [Fig.3.8].

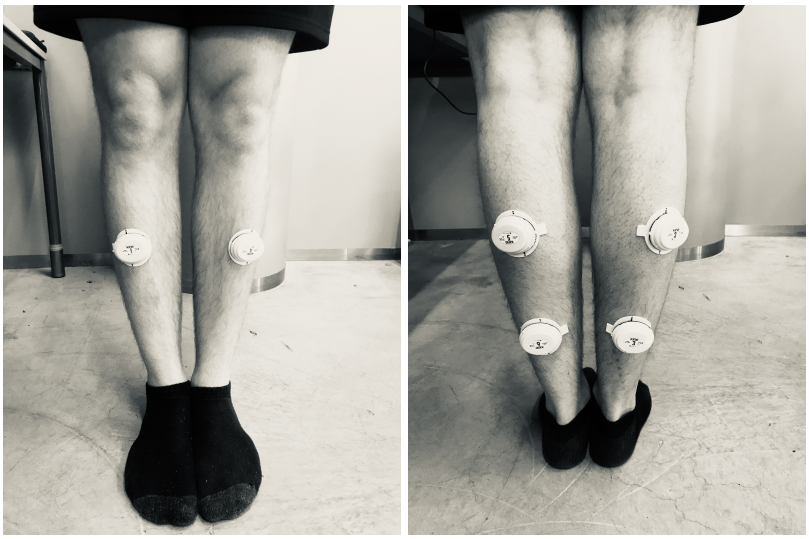

Figure 3.8: EMG sensors' placement

Electrocardiography

The electrocardiography was carried out by the BiosignalsPlux Explorer Kit, which contained three ECG sensors. The three sensors were connected to a wireless 4-channel BioSignalsPlux HUB to acquire ECG data throughout all the phases. The ECG electrodes were placed on the chest of the subject from the Right Ar, (RA) to the Left Foot (LF), as illustrated in the configuration in figure 3.9. This electrode placement allows for accurate measurements during the experiment.

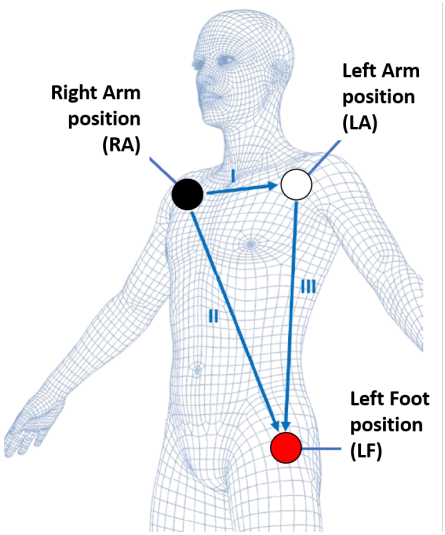

Figure 3.9: ECG electrodes' placement

Force Platform and Virtual Reality Goggles

The platform that was used to simulate the motion of a small boat in the sea, was moving in combination with the virtual reality scene that the subject could see through the goggles.

The platform by Virtualis (Clapiers, France) [Fig. 3.13] is provided with two force plates with 4 sensors each, that measured the center of mass at a sampling frequency of 90 Hz. The subject was asked to stand with the feet over the two force plates, in order to acquire information about the center of mass the antero-posterior and medio-lateral axis [Fig.3.10].

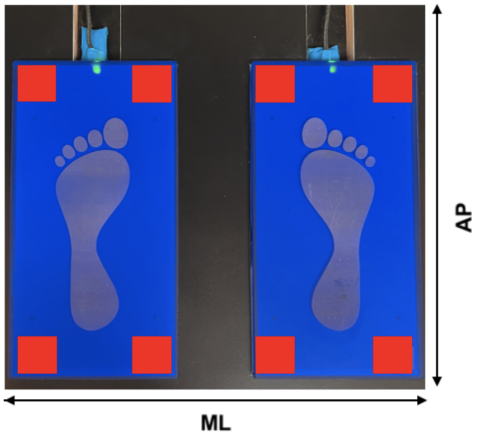

Figure 3.10: Force plates on the platform, red boxes representing the sensors' location

During the experiment, the force platform recorded the movement of the center of pressure (CoP), also called the stabilogram, which is the projection of the subject's center of mass onto the plane of the platform.

The virtual reality goggles named VIVE Focus (HTC, New Taipei, Taiwan) were set to show waves and mountains scenarios [Fig. 3.11].

Figure 3.11: Virtual Reality goggles and base stations

It is important to state that before starting with each data acquisition, the platform protocol must be selected distinguishing between "light" and "hard" protocols.

In the so called light protocol of the experiment, subjects are stimulated by a wave of 1 Hz frequency with an amplitude of 0.6, whereas in the so called hard protocol, they were simulated by a wave of 3 Hz frequency with an amplitude of 0.5.

The choice of one protocol is based on the initial assessment of the subject's condition, but careful consideration is given to an evenly alternated distribution of these protocols.

The participants were instructed to stand with their arms along the body, for the first part of the acquisition in which no platform movement was present. After the first 35 seconds of sea simulation in quiet standing, participants were asked to hold onto the bar in front of them. The platform then began synchronized movement with the sea scene in the Virtual Reality (VR)

goggles [Fig. 3.12]. For the last forty seconds of the experiment, after two minutes of motion, the platform stopped and the subject was asked to balance without holding onto the bar, as shown in Figure 3.6.

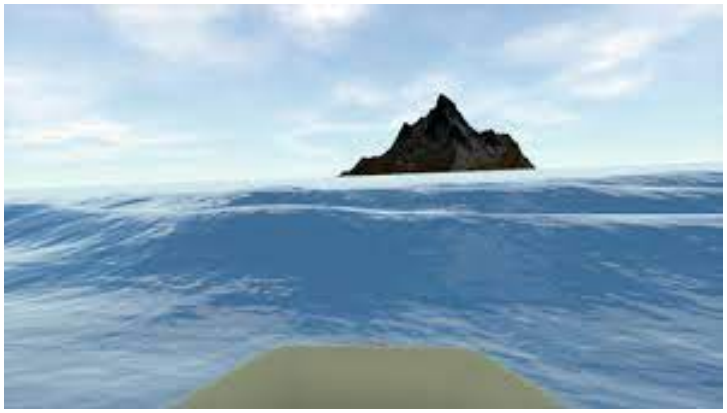

Figure 3.12: Sea simulation scene

Figure 3.13: Platform by Virtualis used for the BioVRSea experiment

3.3 Data Processing

Subsequently to data acquisition, pre-processing procedures were implemented to streamline signal analysis and eliminate noise components without compromising information integrity. The objective of the data analysis was to discern variations in postural control strategies between cohorts of healthy individuals and those in a pathological condition, such as Parkinson's Disease patients and Concussion subjects.

In this study, just EMG and CoP data were analysed, in combination with a descriptive analysis on the questionnaire given to participants. Moreover, the analysis will be conducted separately for the Parkinson Study group and the Concussion Study group.

Data processing was performed using different tools, such as Matlab R2023a, Microsoft Excel and Python 3.12.0.

3.3.1 Questionnaire data

Initially, the Motion Sickness Susceptibility Questionnaire was used to extract general data. Subsequently, the questionnaire aimed at assessing the predisposition for motion sickness.

In this study, "Proneness" is defined as a subject's inclination to experience motion sickness, while "BioVRSea Effect" denotes the impact of the BioVRSea experiment. These conditions are attributed to individuals based on their responses to specific questionnaire sections. From their answers then, two indexes have been calculated for each participant, in order to evaluate the motion sickness proneness condition and the experiment effect.

Motion Sickness Proneness Index The Motion Sickness Proneness Index is a binary assessment tool formulated from responses pertaining to an individual's susceptibility to motion sickness and their inclination toward different modes of transportation and entertainment systems. The categories that are considered for evaluating motion sickness are:

- Car

- Bus
- Train
- Aircraft
- Small boat
- Ship
- Swing
- Roundabout
- Funfair

Each category is assigned a score ranging from 0 to 3, depending on the subject's answer:

Value	Meaning
Nan	Never travelled/Not applicable
0	Never felt sick
1	Rarely felt sick
2	Sometimes felt sick
3	Frequently felt sick

These scores are then added together and divided by the total number of categories (a maximum of 9), resulting in a value known as MSpr_SUM. The Motion Sickness Proneness Index is then computed based on the sum: if the MSpr_SUM is higher than 9, then Motion Sickness Proneness Index is 1 (= prone to motion sickness), otherwise it is assessed as 0 (= not prone to motion sickness).

$$MotionSicknessPronenessIndex = \frac{\sum(Transport.or.Entertainment) * 9}{9 - \sum(NaN)} \tag{3.1}$$

Once the Motion Sickness Proneness Index was calculated for each participant, it was possible to arrange Table 3.4.

MS Proneness IDX	Parkinson	Healthy Elderly	Concussion	Healthy Young	Total
Prone subj.	4	8	15	9	36
Not prone subj.	14	19	8	14	55

Table 3.4: Population subdivision into Motion Sickness Prone subjects and those not Prone to Motion Sickness

In the Parkinson Study group, 20% of patients with Parkinson's Disease were Prone to Motion Sickness, with respect to a 30% in their healthy elderly controls; whereas in the Concussion Study group, 65% of participants with history of Concussion were Prone to Motion Sickness, instead only a 39% of Healthy Young controls were prone to it.

BioVRSea Effect Index The BioVRSea Effect Index instead, refers to the difference between the motion sickness symptoms that the participant feels before the experiment, and those which are experienced after it. Symptoms are grouped as follows:

Index	Symptoms
General discomfort (IGenDis)	General discomfort
Dizziness-Vertigo Index (IDizzVer)	Dizziness, Vertigo
Stomach Index (Isto)	Increased salivation, Sweating, Nausea
Fatigue Index (Ifatig)	Fatigue, Eye strain, Difficulty focusing or concentrating
Head Index (Ihead)	Blurred vision, Headache

A score ranging from 0 to 3 was assigned to the subject's response about each symptom:

To calculate the BioVRSea Index, at first the average from the individual responses of each

Value	Meaning
0	Not at all
1	Some days
2	More than half of the days
3	Almost every day

index is computed; then the maximum among the averages is calculated; at the end a binary classification into two groups (below and above 1/3 of the maximum) is determined. This procedure is followed both for answers given before the experiment and answers given after it.

At this point, the difference between the results obtained prior and post acquisition is calculated for each of the 5 symptoms groups. Then all the differences are summed, obtaining the MS_DIFF_Sum value, and the BioVRSea Index is extracted: if the sum is higher than 0, then the index is 1 (= affected by the BioVRSea experiment), otherwise it is assessed as 0 (= not affected by the BioVRSea experiment).

The calculation of the indexes was performed on Microsoft Excel for both the Parkinson group and its healthy control, as well as for the Concussion group and its healthy control.

Also after the BioVRSea Effect Index calculation, Table 3.5 was arrenged.

BioVRSea Effect IDX	Parkinson	Healthy Elderly	Concussion	Healthy Young	Total
Affected subj.	7	13	19	16	55
Not affected subj.	11	14	4	7	36

Table 3.5: Population subdivision into subjects affected by BioVRSea experiment and those not affected by the experiment

In the Parkinson Study group, 39% of patients with Parkinson's Disease have shown to be affected by the BioVRSea experiment, compared to 48% among their Healthy Elderly controls. Meanwhile, in the Concussion Study group, 83% of participants with a history of Concussion were affected by the experiment, whereas only 70% of Healthy Young controls exhibited the effect.

3.3.2 EMG data

The EMG data processing consisted of pre-processing the raw data and extracting features of interest for the purpose of recognizing signal patterns and representing their characteristics.

At first, the EMG acquired signals underwent a segmentation into phases of interest: Baseline, PRE, MOV, POST. A 20-second window was applied to Baseline, PRE, and POST phases, whereas the MOV phase utilized a wider window of 100 seconds. This decision was driven by the MOV phase's predominant duration of 2 minutes in the overall experiment, in contrast to the shorter durations of the PRE and POST phases during acquisition.

Then the raw segmented data were filtered using a 4th-order Butterworth filter and a discrete Fourier transform of the filtered signal was applied.

Subsequently, seven spectral parameters and thirty-six features in the time domain were computed.

The extracted features can be categorized into frequency-domain and time-domain based on their magnitude. The total number of EMG features extracted is 43 [Table 3.6].

Total Power (PT)
Maximum Power (Pmax)
Maximum Frequency (Fmax)
Median Frequency (FMD)
Mean Frequency(FMN)
Frequency Kurtosis (Fkurt)
Frequency Skewness (Fskew)
Average Amplitude Change (AAC)
Average Energy (AE)
Absolute Value of the Summation of the Exponential Root (ASM)
Absolute Value of the Summation of the Square Root (ASS)
Coefficient of Variation (CV)
Difference Absolute Mean Value (DAMV)
Difference Absolute Standard Deviation Value (DASDV)
Difference Variance Value (DVARV)
Enhanced Mean Absolute Value (EMAV)
Enhanced Wavelength (EWL)
New Zero Crossing (FZC)
Kurtosis (KURT)
Integrated EMG (IEMG)
Interquartile Range (IQR)
Log CV(LCV)
Log Detector (LD)
Log DAMV (LDAMV)
Log DASDV (LDASDV)
Log Teager Kaiser Energy Operator (LTKEO)
Mean Absolute Deviation (MAD)
Mean Absolute Value (MAV)
Maximum Fractal Length (MFL)
Mean (MN)
Median (MD)
Modified Mean Absolute Value (MMAV)
Modified Mean Absolute Value 2 (MMAV2)
Mean Value of the Square Root (MSR)
Root Mean Square (RMS)
Standard Deviation (SD)
Skewness (SKEW)
Single Square Integral (SSI)
Absolute Value of Temporal Moment (TM)
Variance (VAR)
Variance of EMG (VARE)
Variance Order (VO)
Waveform Length (WL)

Table 3.6: 43 Electromyographic (EMG) Features

All the features were individually computed for each muscle (Tibialis Anterior Right (TAR), Tibialis Anterior Left (TAL), Gastrocnemius Lateralis Right (GLR), Gastrocnemius Lateralis Left (GLL), Soleus Right (SR), Soleus Left (SL)), for each patient in both the Parkinson and Concussion studies. Subsequently, these features were compiled into six distinct Excel files and, since they were extracted for each of the four phases, within each Excel file they are organized into separate sheets (Baseline, PRE, MOV, POST).

3.3.3 CoP data

The CoP data processing involved filtering the signal through a Savitsky-Golay filter with a window size of 7 [68]. Data were divided into intervals, corresponding to the ones chosen for the EMG data analysis: PRE, MOV and POST. For the center of pressure analysis, the Baseline phase was excluded due to the absence of a sea simulation during this period.

The CoP analysis incorporated a series of multi-scale entropy measurements, known for their significance in assessing CoP data, particularly in the evaluation of pathological subjects [69]. 35 parameters were extracted from the stabilogram to evaluate the subject's postural control response during the experiment. The CoP features are detailed in [Table 3.7] and they are based on geometrical, statistical (related to the entropy) and velocity properties.

Consecutive movement samples on the support plane (TOTEX)
Consecutive movement samples on ML plane(TOTEX-ML)
Consecutive movement samples on AP plane(TOTEX-AP)
Square Root Distance between a point and the plane origin (RD)
Mean Distance in Medio-lateral Direction (MDIST-ML)
Mean Distance in Antero-posterior Direction (MDIST-AP)
Mean Velocity on support plane (MVELO)
Mean Velocity on ML plane (MVELO-ML)
Mean Velocity on AP plane (MVELO-AP)
Root Mean Square Distance respect to origin (RDIST)
Root Mean Square Distance in Medio-lateral Direction (RDIST-ML)
Root Mean Square Distance in Antero-posterior Direction (RDIST-AP)
Medio-lateral Sample Entropy (ML-SampEn)
Antero-posterior Sample Entropy (AP-SampEn)
Medio-lateral Complexity Index (ML-CI)
Antero-posterior Complexity Index (AP-CI)
Ellipse Area
Ellipse angle
Ellipse Main Axis Length
Ellipse Minor Axis Length
Standard Deviation in Antero-posterior Direction (SD AP)
Standard Deviation in Medio-Lateral Direction (SD ML)
SD Magnitude
SD Direction
Magnitude Entropy
Direction Entropy
Multivariate Complexity Index (Multivariate CI)
Antero Magnitude
Antero Angle
Postero Magnitude
Postero Angle
Left Magnitude Maximum
Left Angle
Right Magnitude Maximum
Right Angle

Table 3.7: 35 Center of Pressure (CoP) Features

3.4 Statistical Analysis

For both the Parkinson and the Concussion study a statistical analysis was performed to assess significant differences between the pathological group and its healthy control, within all the phases of the experiment.

This statistical assessment not only shed light on group differences but also contributed to the overall validation and robustness of the BioVRSea paradigm, enhancing the credibility of the study's findings.

At first, a descriptive and exploratory analysis about the population distribution was performed using boxplots and histograms, with information resulting from the Motion Sickness Susceptibility Questionnaire.

After that, for both the EMG data and the CoP data, the statistical analysis was conducted using the same methodology, which encompassed several steps that will be explained in detail.

It is crucial to highlight that the statistical analysis of the EMG and CoP data was executed across all four phases considered in the experiment. Specifically, concerning the electromyography, the activation of tibialis anterior, soleus and gastrocnemius lateralis, for left and right legs, was analysed for all the obtained features.

An initial assessment for normality was conducted through the computation of a normality test, the *Shapiro-Wilk test*, aiming to evaluate the distribution characteristics of all the features that were extracted in both the EMG and CoP dataset.

Shapiro-Wilk test The Shapiro-Wilk test is a hypothesis test used for small samples. Its null hypothesis assumes that the sample originates from a normal distribution, while the alternative hypothesis contends that it deviates from normality.

It assesses the degree of conformity between the sample data and a normal distribution by ordering and standardizing (setting a mean (μ) of 0 and a standard deviation (σ) of 1) the sample

[70].

Due to the prevalence of non-normal distribution of both EMG and CoP features, it was decided to compute p-values using the *Mann-Whitney U test*, suitable indeed for non-normally distributed data. This statistical analysis aimed to facilitate a comparison between participants with pathological conditions and their healthy controls, discerning any significant differences. The results obtained through this test were then validated by the *Kolmogorov-Smirnov test*.

The analysis was also employed for the comparison of subjects prone to motion sickness with those not prone to it, as well as those susceptible to the BioVRSea experiment and those not susceptible to it. For the sake of completeness, the groups under comparison are reiterated below:

- Parkinson group with Healthy Elderly control (healthy subjects over 54 years old)
- Concussion group with Healthy Young control (healthy subjects between 21 and 46 years old)
- Prone group with not prone group, in the Parkinson Study group
- Prone group with not prone group, in the Concussion Study group
- BioVRSea affected group with BioVRSea not affected group, in the Parkinson Study group
- BioVRSea affected group with BioVRSea not affected group, in the Concussion Study group

Mann-Whitney U test The Mann-Whitney U test is a non-parametric statistical method that involves ordering the data in each group from the lowest to the highest values. Subsequently, the entire dataset undergoes ranking. The summation of ranks is then computed for each group, leading to the determination of U by the formula:

$$U = min(U',U") \tag{3.2}$$

where U' stands for the Mann-Whitney statistic for one group (controls, or not prone, or not BioVRSea affected), while U" is the Mann-Whitney statistic for the other one (pathological, or prone, or BioVRSea affected).

To establish the level of significance for comparing the two groups, the z-score and p-value are calculated and an alpha is set. In this case, alpha was set at 0.05, making any p-value less than alpha considered significant [71].

Additionally, the *Bonferroni correction* for multiple tests was implemented to enhance the robustness and reliability of the results, since the Mann-Whitney U test was computed for multiple times (n) both for EMG (n = 43) and CoP (n = 36) data.

Bonferroni correction The Bonferroni correction method is widely used for its simplicity in addressing multiplicity. It involves multiplying the unadjusted p-values by the number of primary outcomes, because of the increased risk of a type I error when making multiple statistical tests. Is a rather conservative method for handling the chance of error in multiple testing [72].

4

Results

The execution of a comprehensive statistical analysis and the generation of graphical representations of it, assisted in differentiating the compared groups. This facilitated the identification of significant differences, providing a clear understanding of the obtained results, which will be exposed and subsequently discussed within this work.

The findings will be presented as categorized into two sections: Parkinson Study group and Concussion Study group, further segmented into EMG Results and CoP Results.

4.1 Parkinson Study group

In the Parkinson branch of the study, data were collected from 45 participants. Among them, 18 subjects were diagnosed with Parkinson's Disease, and they were matched by age with a Healthy Control group comprising 27 participants. This paragraph will be subdivided in two sections: findings derived from the electromyographic analysis and results from the center of pressure analysis.

4.1.1 EMG Results

The EMG data were analyzed by comparing them between the Parkinson patients (18 individuals) and their healthy age-matched controls (27 individuals), across the different segments of the experiment. The activation of the tibialis anterior, soleus and gastrocnemius lateralis muscles, in both right and left legs, was examined for all the obtained features (43 EMG features).

From the computation of the Mann-Whitney U test, it resulted that significant findings (p-value < 0.05) appeared during the PRE and POST phases, in which there was only visual stimuli through VR and no platform movement was performed.

Instead, there were no significant differences between groups in the MOV phase.

In particular, a high number of features shown a significant difference in the last segment of the experiment, that is the POST phase.

All significant features, however, were adjusted and resulted with no significance after the correction procedure (p-value $< 0.05/43$, that is p-value < 0.001163).

In terms of muscle activity, there was a clearly higher engagement of the tibialis anterior muscle, with respect to the involvement of the gastrocnemius lateralis and the soleus. Specifically, during the PRE phase, 4 features (AAC, DAMV, LDAMV, SKEW) were found to be significant (p-value = 0.040326) in the TAL muscle, and 1 feature (FZC) in the TAR muscle (p-value = 0.014515).

During the POST phase instead, 31 features in the TAL muscle [Table 4.1] and 30 features in the TAR muscle [Table 4.2] demonstrated a significant difference between the groups. Furthermore, within this segment, the GLR muscle emerged as one additional muscle capable of distinguishing between the compared groups.

31 significant EMG features	p-value
PT	0.01989
Pmax	0.02115
AAC	0.01547
AE	0.01989
ASM	0.00695
ASS	0.00979
DAMV	0.01547
DASDV	0.01756
DVARV	0.01756
EMAV	0.01547
EWL	0.01361
IEMG	0.00915
IQR	0.00979
LD	0.00979
LDAMV	0.01547
LDASDV	0.01756
LTKEO	0.02115
MAD	0.00915
MAV	0.00915
MFL	0.01756
MMAV	0.00979
MMAV2	0.00745
MSR	0.01046
RMS	0.01989
SD	0.01989
SSI	0.01989
TM	0.01046
VAR	0.01989
VARE	0.01989
VO	0.01989
VAR	0.01649

Table 4.1: Statistical analysis: TAL muscle Features in POST phase analysis with p-value < 0.05 after performing Mann-Whitney U test

30 significant EMG features	**p-value**
PT	0.04033
Pmax	0.02537
AAC	0.02693
AE	0.04033
ASM	0.01756
ASS	0.03812
DAMV	0.02627
DASDV	0.04506
DVARV	0.04506
EMAV	0.01756
EWL	0.023889
KURT	0.02693
IEMG	0.04033
LDAMV	0.02693
LDASDV	0.04506
LTKEO	0.04264
MAD	0.04033
MAV	0.04033
MFL	0.04264
MMAV	0.03602
MMAV2	0.03211
MSR	0.01989
RMS	0.04033
SD	0.040326
SSI	0.04033
TM	0.04033
VAR	0.04033
VARE	0.04033
VO	0.04033
VAR	0.02857

Table 4.2: Statistical analysis: TAR muscle Features in POST phase analysis with p-value < 0.05 after performing Mann-Whitney U test

To give a graphical example of this difference, the comparison boxplots of the Root Mean Square for the left tibialis anterior muscle were made [Fig. 4.1, to give evidence of the significant difference between the Parkinson and the Healthy group. This metric is used in EMG postural control assessment because of its ability in showing the level of muscle activity in sustaining a particular balancing task.

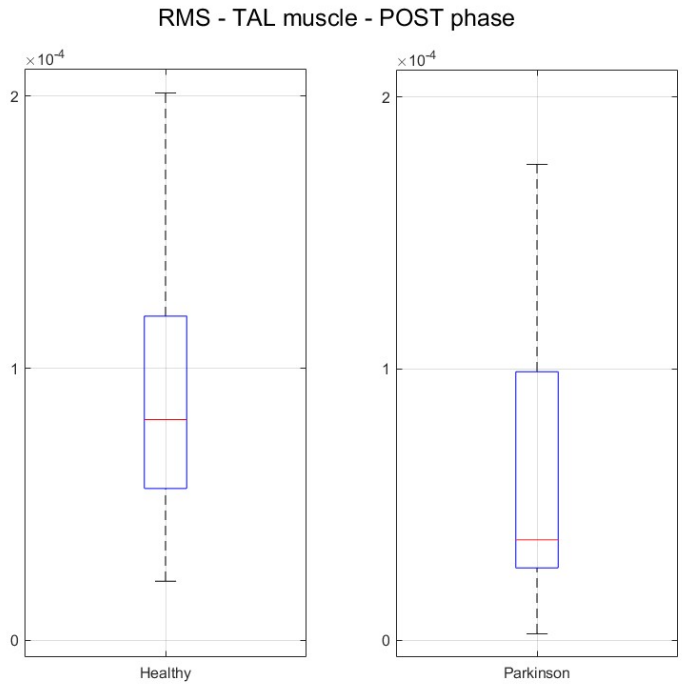

Figure 4.1: Statistically significant Root Mean Square for TAL muscle in POST phase (p-value = 0.01989)

4.1.2 CoP Results

The CoP data were also analyzed by comparing them between the Parkinson patients and their healthy controls, across all the segments of the experiment which are considered in this work.

The data collected by the platform on the CoP allow to plot the ellipse that best represents how each individual changes the balance point, during an unstable movement.

For this purpose, to have a first visual comparison of the groups, ellipse areas were graphically represented in the three different main segments of the experiment [Fig. 4.2]. Ellipse Areas plotting shows a clear distinction between compared individuals in the Parkinson Study group. Healthy subjects resulted having a wider sway area with respect to pathological patients, especially in phases that exclusively involved visual stimuli (PRE and POST phases). This difference, during these segments, attained statistical significance (p-value < 0.05).

In contrast, there was no discernible distinction in terms of sway area during the MOV phase, which also included motor stimuli through the force platform.

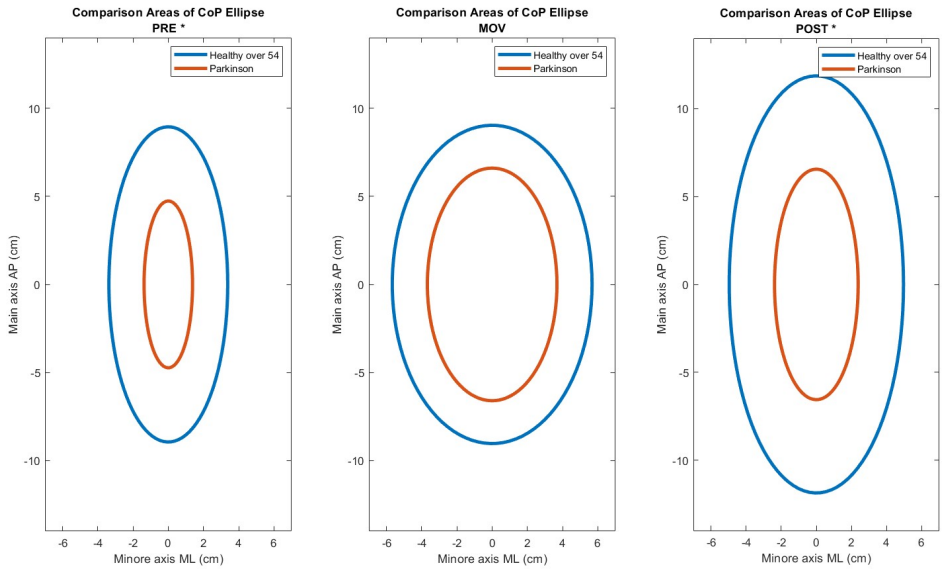

Figure 4.2: Comparison of Ellipse Areas among Parkinson patients (solid orange line) and healthy controls (solid blue line) across the PRE, MOV, and POST phases (those marked with * represent a significant difference between groups)

In particular, a comparison bar plot [Fig. 4.3] for ellipse related features has been made, giving evidence about the significant difference between the two groups during PRE and POST phases, according to the Mann-Whitney U test [Table 4.3], [Table 4.4].

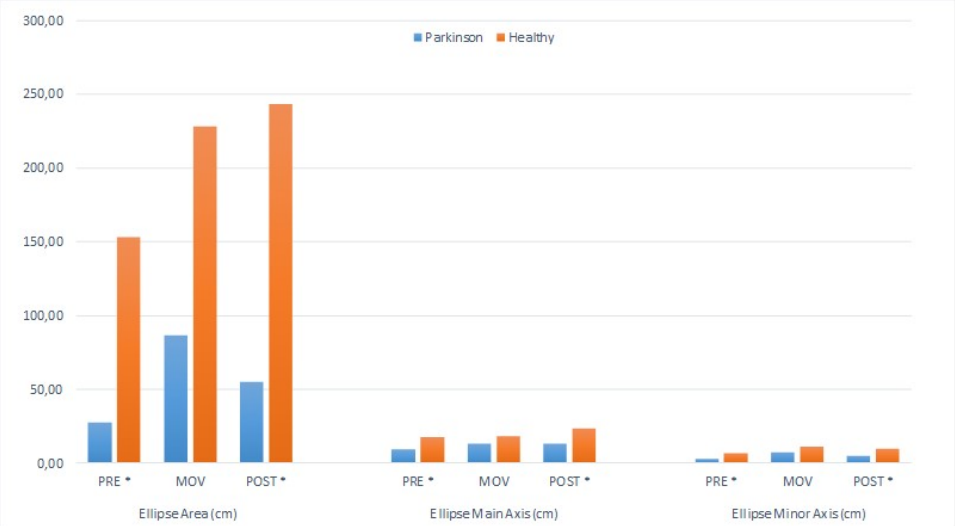

Figure 4.3: Comparison of Ellipse features values among Parkinson's patients (orange) and healthy controls (blue) during PRE, MOV, and POST phases

Significant Ellipse features	**p-value**
Ellipse Area	0.01452
Ellipse Main Axis	0.00745
Ellipse Minor Axis	0.03211

Table 4.3: Statistical analysis: Ellipse Features in PRE phase analysis with p-value < 0.05 after performing Mann-Whitney U test

However, it should be remarked that only Ellipse Area and Ellipse Main Axis in the POST phase resulted being statistically significant when applying a Bonferroni correction for multiple tests (p-value < 0.05/35 = 0.001428).

Generally, following the Mann-Whitney U test computation, differences between the mentioned groups are evident in 29 features during the PRE phase and 26 features during the POST phase. In contrast, only 11 features out of 35 exhibit such differences in the MOV phase.

Significant Ellipse features	p-value
Ellipse Area	0.00047
Ellipse Main Axis	0.00043
Ellipse Minor Axis	0.00345

Table 4.4: Statistical analysis: Ellipse Features in POST phase analysis with p-value < 0.05 after performing Mann-Whitney U test

Specifically, the Total Excursion (TOTEX), measured in centimeters, reaffirms the earlier findings with a p-value of 0.019890 during the PRE phase and a p-value of 0.001121 in the POST phase. A visual representation of this is presented in Fig. 4.4.

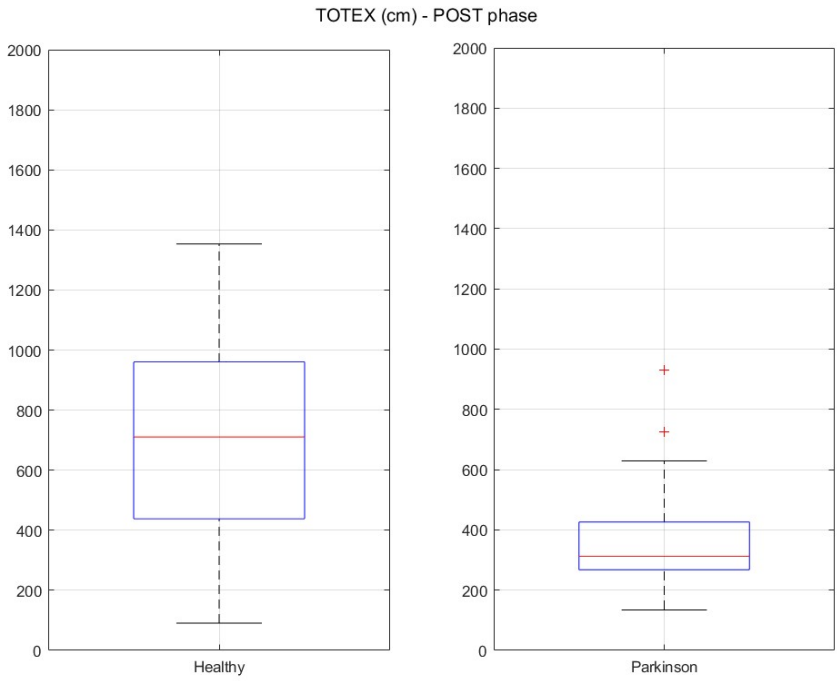

Figure 4.4: Statistically significant Total Excursion after Bonferroni correction in POST phase (p-value = 0.001121)

4.2 Concussion Study group

In the Concussion branch of the study, data were collected from 46 participants. Among them, 23 subjects were included in the group of patients with a history of concussion, and they were matched by age with a Healthy Control group comprising 23 participants. This paragraph will be subdivided in two sections: findings derived from the electromyographic analysis and results from the center of pressure analysis.

4.2.1 EMG Results

In addition to the analysis conducted for the Parkinson Study group, the EMG data for the Concussion Study group underwent the same examination by comparing individuals with unhealthy conditions to their healthy age-matched controls. The comparison was carried out across the different segments of the experiment. The activation of the tibialis anterior, soleus and gastrocnemius muscles, in both right and left legs, was examined for all 43 EMG obtained features.

From the computation of the Mann-Whitney U test, it resulted that significant features (p-value $<$ 0.05) mostly appeared during the PRE and POST phases, in which the participant was subjected only to a visual stimuli. In particular, a high number of features shown a significant difference during the POST phase. Instead, only 2 features indicated a significant difference between groups in the MOV phase.

In terms of muscle activity, during the PRE phase mainly the tibialis anterior and the soleus muscles were involved in the balancing task. But the principal result regarded the POST phase in which there was a higher engagement of the tibialis anterior muscle, with respect to the involvement of the other two recorded muscles.

Specifically, during the POST phase, 5 features demonstrated a significant difference between the groups in the TAL muscle, and 25 features in the TAR muscle. The common features between TAL and TAR muscles are ASM, KURT, MMAV, MMAV2.

However, it should be remarked that none of these results was statistically significant when

applying a Bonferroni correction for 43 tests (p-value < 0.05/43, that is p-value < 0.001163).

4.2.2 CoP Results

Also for the Concussion Study group, the CoP data were analyzed across all the segments of the experiment which are considered in this work, performing a comparison between the two populations.

From the CoP data collected by the platform, it was possible to plot the ellipse that best represents each group behavior during the experiment, for PRE, MOV and POST segments [Fig. 4.5].

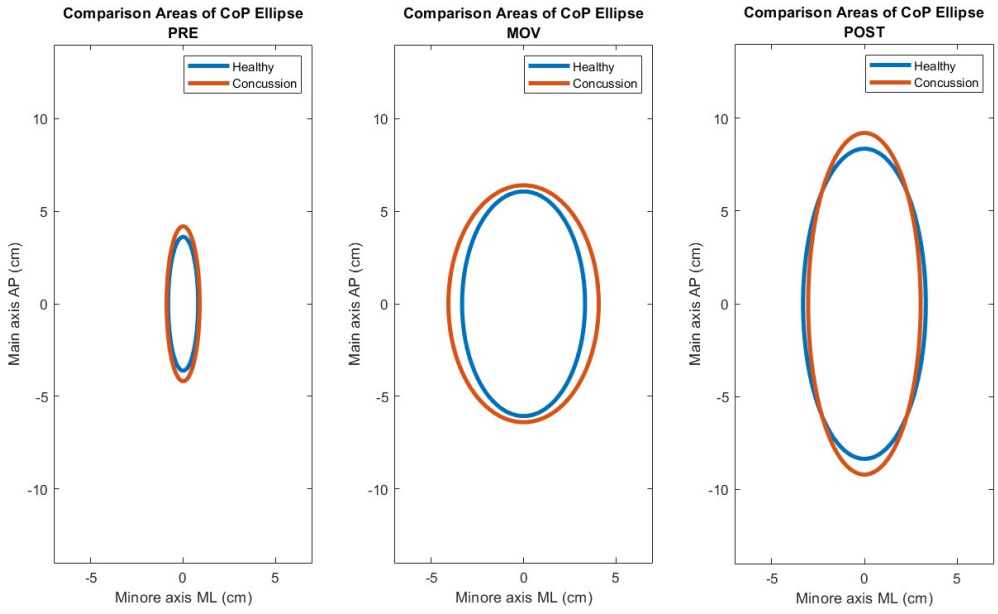

Figure 4.5: Comparison of Ellipse Areas among Concussion patients (solid orange line) and healthy controls (solid blue line) across the PRE, MOV, and POST phases

Ellipse Areas resulted comparable between groups, showing instead a normal differentiation between phases.

In fact, after conducting the Mann-Whitney U test, it was found that none of the ellipse features exhibited statistical significance (p-value < 0.05) in all three phases [Fig. 4.6].

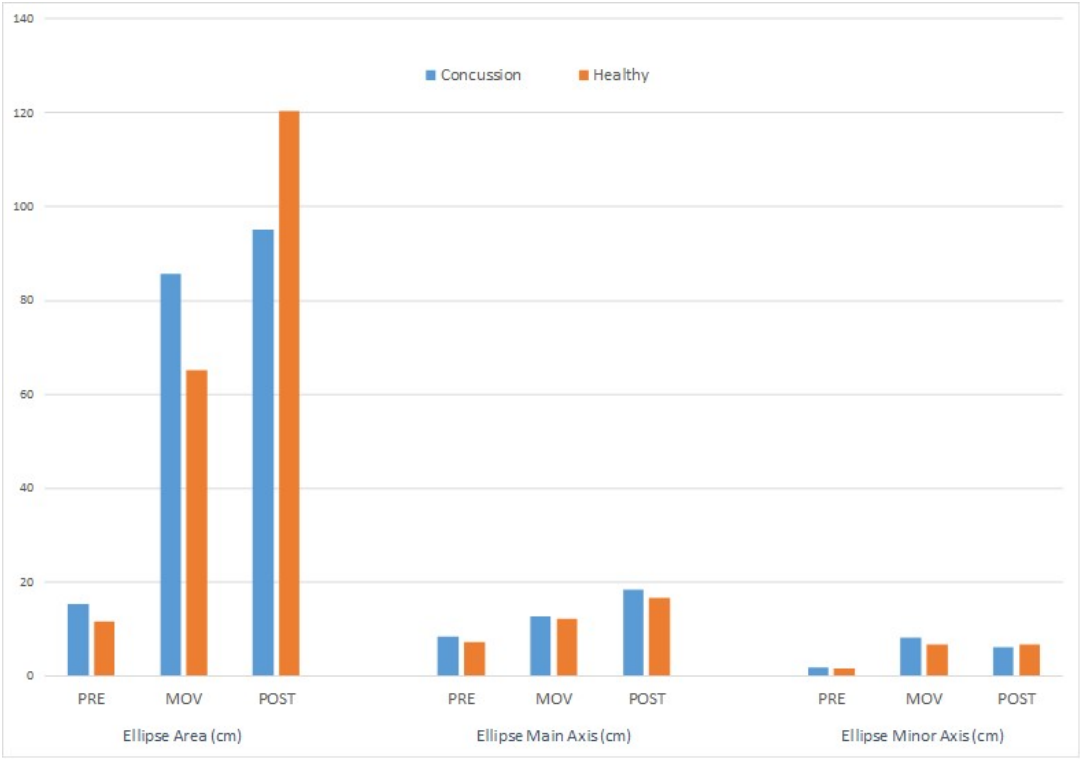

Figure 4.6: Comparison of Ellipse features values among Concussion's patients (orange) and healthy controls (blue) during PRE, MOV, and POST phases

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 and two during the moving platform phase. These findings lack significance in the context of result discussions.

Conversely, during the POST phase of visual stimuli, in which the movement of the patient is induced by the memory of the previous segment of the experiment, 6 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 below [Fig. 4.7].

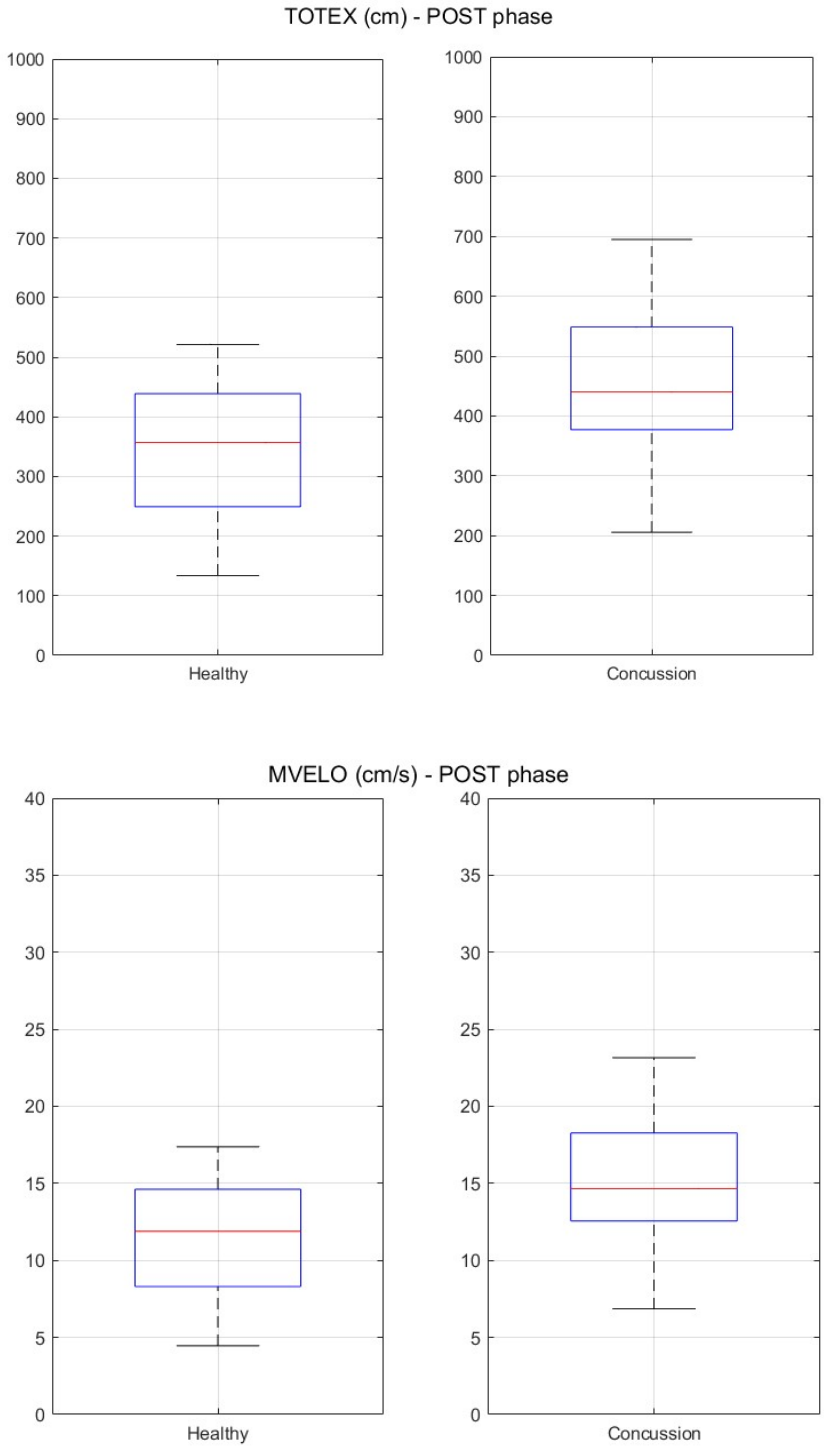

Figure 4.7: Statistically significant features, Total Excursion and Mean Velocity, in POST phase (p-value = 0.016636)

5

Discussion and Limitations

The BioVRSea experiment involved the recruitment and participation of eighteen individuals with Parkinson's Disease, whose response to the protocol was compared with that of twenty-seven healthy people aged over 54.

Similarly, the same approach was applied to twenty-three individuals with a history of Concussion, and their responses were compared to an equivalent number of healthy young participants.

Several statistical procedures were implemented to discern the distinguishing factors between the pathological groups and their respective healthy age-matched controls.

The principal aim of the overall analysis was to enhance understanding of the mentioned conditions by identifying the biosignals that most effectively discriminate between healthy group and pathological, and interpreting them physiologically.

5.1 Muscle Activation

The statistical analysis revealed significant differences in muscle activation between Parkinson patients and healthy controls in both PRE and POST phases. Instead, no significant distinctions between groups were noted in the MOV phase.

This is probably due to the fact that during the MOV phase, in which the participant is subjected to both visual and motor stimuli, the individual moves with the platform, holding its bar, so a real difference between the two groups is not expected.

Furthermore, the observed increase in the number of features explaining a substantial difference between individuals with Parkinson's disease and healthy subjects in the POST phase may directly result from the induced movement caused by the platform's motion in the previous phase.

Similarly to the Parkinson Study group, individuals with a history of concussion also showed no significant difference between healthy and unhealthy participants during the MOV phase, likely due to the stabilization provided by holding onto the bar.

The act of stabilizing by gripping a bar primarily engages the upper limbs' muscles rather than those in the legs, which, instead, simply follow the movement. This phenomenon is observed in both healthy individuals and those with compromised postural control abilities. It explains why, during the MOV phase, no significant difference was observed between the healthy controls and pathological groups.

EMG data were used to investigate the activation of tibialis anterior, soleus and gastrocnemius lateralis muscles. In particular, significant differences in muscle responses were observed when analyzing postural control responses in the PRE phase with only visual stimuli and in the POST phases following induced stimulation.

Considerable results were provided by tibialis anterior muscles, both in left and right legs, allowing an excellent differentiation between the two cohorts, with particular evidence during the POST phase [Table 4.1], [Table 4.2].

As a matter of fact, these result are consistent with several studies regarding better involvement of tibialis anterior muscle in balancing during a task of postural control, rather than other muscles such as gastrocnemius lateralis or soleus, as the primary dorsiflexor of the foot [73],[74].

Furthermore, the notable distinction between healthy and unhealthy participants may be attributed to the characteristic weakness and stiffness of the tibialis anterior muscle in Parkinson's Disease, leading to a diminished capacity to utilize this muscle in the context of postural control [75].

In particular, the Root Mean Square (RMS) extracted from the tibialis anterior muscle provided evidence of differentiation between the Parkinson and Healthy groups, since it reflects the level of muscle activity required to sustain a specific postural task. The comparison boxplots [Fig. 4.1] illustrated a lower RMS for the Parkinson group, which typically indicates reduced muscle activity or decreased muscle force production during the measured period. This reduction may suggest muscle fatigue or neuromuscular inhibition [76].

Correspondingly to the Parkinson's group, in the Concussion Study group the discrimination using EMG signals between the two groups relies on data from the tibialis anterior muscle while participants were required to maintain postural control in the POST segment.

According to previous studies, this result could indicate postural control and balance inabilities, deriving in a more active muscle when trying to stabilize in an unstable environment [77].

5.2 Center of Pressure

The assessment of postural control strategies is crucial, and the center of pressure distribution serves as a significant tool in this regard. As a subject responds naturally to a stimulus by swaying, the coordinates of the CoP change.

Certain medical conditions, such as Parkinson's disease or an event of concussion, can interfere with the capacity to maintain balance when stimulated.

As anticipated, individuals with Parkinson's disease exhibited reduced postural sway [Fig. 4.2], [Fig. 4.3], mainly during phases in which the only stimuli was given by virtual reality (PRE and POST phases).

Typically a smaller area is instead associated with better postural balance. However, excessively narrow CoP displacement may indicate rigid posture control [25].
As a matter of fact, the observed reduction in ellipse area among Parkinson's patients suggests a potential impairment in their ability to adapt postural strategies in response to an occurring stimulation. Moreover, the absence of statistical significant differences in the dynamic segment of the experiment, the MOV phase, is consistently influenced by the diminished instability arising

from the patients gripping the bar in front and consequently moving according to the platform's motion.

These findings, emphasizing a diminished sway area in individuals with the pathology, may be attributed to various factors. Conditions such as Parkinson's Disease can impede the capacity to sustain balance. Additionally, patients often experience muscle rigidity, potentially contributing to decreased confidence in mobility and subsequently resulting in fear of falling [78]. Furthermore, the reduced sway area observed in patients with motor impairments could be attributed to their tendency to maintain the center of mass within a safer range, which typically lies lower compared to that of healthy subjects [79]. These factors may explain the observed reduction in sway during the BioVRSea experiment.

In contrast, within the Concussion Study population, the distinction between groups is not statistically significant; rather, it is nearly comparable [Fig. 4.5], [Fig. 4.6]. This is attributed to the composition of the Concussion Study group, including young female athletes. Half of these individuals have a self-reported history of concussion, categorizing them as the unhealthy subjects in this cohort. Nonetheless, they remain young and physically active individuals, matched in age with healthy controls.

However, as previously stated, two primary components in the analysis of displacement and velocity have demonstrated significance during the POST phase, contributing to the relevance of this study. These features specifically refer to Total Excursion (cm) and Mean Velocity (cm/s).

In line with earlier findings [80], individuals with a history of concussions consistently exhibit modifications in the displacement and velocity of the CoP signal, extending beyond the period of clinical recovery or return to play. Notably, the substantial differences in Total Excursion and Mean Velocity between those with concussions and their healthy controls are considered significant. This is because a larger displacement (higher TOTEX) combined with a faster adjustment (higher MVELO), characterizes individuals who exhibit greater postural instability. This is consistent with these results which demonstrate the impact of Concussion in the alterations in Center of Pressure dynamics [65].

5.3 Limitations of the Study

Despite its novelty, the study presents some limitations that merit consideration.

Firstly, the number of patients included in both Parkinson and Concussion Study groups was limited. Although the dataset is expanding with daily new acquisitions, obtaining more accurate and reliable findings would benefit from a larger sample size.

Secondly, the Concussion Study group population consisted solely of young female athletes. While previous studies have shown that findings regarding the BioVRSea experiment are not affected by gender, a larger and more heterogeneous cohort would enable a wider and more valuable analysis.

Additionally, recruiting only athletic participants for the Concussion Study group may affect the generalizability of the results.

Furthermore, there was no information available regarding the timing of traumatic injury events in the Concussion Study group. Understanding the timing of these events would be helpful in identifying potential differences between fast-recovered individuals and those with Post-Concussion Syndrome. Another aspect regarding the Concussion Study group is that the self-reported nature of the concussion condition by the participants may introduce inaccuracies in reporting, impacting the reliability of the data collected regarding concussion history and related symptoms. Consequently, there may not have been significant differences observed between Concussion patients and their healthy controls.

Another obstacle concerns the Parkinson Study group, whose recruited patients are classified as ”early-stage Parkinson’s Disease patient”, but this definition has no absolute value. Indeed, depending on the timing of diagnosis, a patient’s physiological state may vary from others. For example, some individuals may promptly seek assessment upon experiencing early symptoms, while others might underestimate or feel embarrassed about initial signs, resulting in a delay in their first diagnosis. However, once diagnosed, both patients would be classified as ”early-stage”.

While the BioVRSea paradigm shows great promise in quantitative assessment, it also presents several limitations that warrant attention. One of the primary limitations stems from the com-

plexity of the system itself, which poses challenges for replication in hospital or clinic settings. The BioVRSea paradigm requires specialized equipment, such as the moving platform, which is not readily available in clinical environments. This underscore the importance of further research and development to streamline the BioVRSea paradigm and enhance its accessibility and usability in clinical practice.

6

Conclusions

This analysis aimed to identify biosignal response distinctions among Parkinson's patients, individuals with history of Concussion, and their corresponding healthy age-matched controls, using the BioVRSea protocol. The primary objective of this study was to discover key biomedical parameters through the BioVRSea experiment, which should objectively assesses a pathological status.

The BioVRSea experiment, provided valuable insights into the physiological aspects of these conditions. The study successfully identified pivotal biosignals and patterns, shedding light on the distinctive features between healthy and pathological groups. This represents a significant advancement in the quantitative evaluation of conditions such as Parkinson's Disease and Concussion, since in both condition there is an increasing need for a precise quantification of the characterizing factors of these impairments [2], [63].

In addition to recent publications [28], [74], this study further demonstrates, with satisfactory results, the diagnostic capabilities of the novel BioVRSea setup, which represents an innovation based on the simultaneous analysis of multiple biosignals and the integration of virtual reality.

The statistical analysis conducted in this study revealed the potential to differentiate between pathological and non-pathological groups, by examining balance problems and muscle responses during complex tasks of postural control. This differentiation was achieved through

a multi-faceted approach, whcih included the analysis of electromyography, heart rate, center of pressure, electroencephalography and electrodermal activity. Moreover, the analysis of the various phases of the experiment underscored its capacity to offer robust insights into behavioral patterns when individuals are exposed to different stimuli or combinations thereof.

A considerable number of subjects (91), participated in the experiment. The inclusion in this thesis work of individuals with different conditions, lifestyles and ages, and consequently different postural control responses, increased the relevance of both the data collected and the results obtained.

The study revealed significant findings regarding how a pathological condition, such as Parkinson's Disease or a history of Concussion, affects postural control. These insights are crucial for the BioVRSea protocol, aspiring to establish itself as a gold standard and a primary diagnostic tool for the assessment of various diseases.
Finally, the analysis and its results contributed to the validation and robustness of the BioVRSea paradigm.

In conclusion, these findings are currently under submission for presentation at the 19th International Symposium on Computer Methods in Biomechanics and Biomedical Engineering (CMBBE), scheduled to take place in Vancouver in August 2024.

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