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DIGITAL TELEMEDICINE IN IMPROVING HEALTH, SOCIAL, AND ECONOMIC OUTCOMES IN PATIENTS WITH FUNCTIONAL MOTOR DISORDERS

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Abbreviations

FMD: Functional motor disorder

FGD: Functional motor disorder

FND: functional neurological disorders

MS: Multiple Sclerosis

PD: Parkinson's Disease

HC: Healthy Controls

ALS: Amyotrophic Lateral Sclerosis

CNS: Central Nervous System

ST: single task

mDT: motor dual task

cDT: cognitive dual task

vDT: visual-fixation dual task

VR: virtual reality

TOMs: technology-based objective measures

MEMs: Micro Electro Mechanical System

QoL: Quality of Life

IGA: Instrumented Gait Analysis

APA: Anticipatory Postural Adjustments

ADLs: Activities of Daily Living

PNES: non-epileptic psychogenic seizures

RCT: Randomized Controlled Trial

NMSs: Non-Motor Symptoms

EG: experimental group

CG: control group

S-FMDRS: Simplified Functional Movement Disorders Rating Scale

T0: intensive 5-day rehabilitation program

T1: the day after the intensive 5-day rehabilitation program

T2: first follow-up

T3: second follow-up and end of the self-management plan

Introduction

Neurological disorders represent a significant global health burden, ranking as one of the leading causes of death and disability. According to the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2016, these disorders accounted for 276 million disability-adjusted life years (DALYs) and 11.6% of global DALYs, making them the second leading cause of death after heart disease. This substantial impact is due to the increasing prevalence of neurological disorders and the longevity of individuals living with these conditions, despite stabilized age-standardized rates of mortality and DALYs.

Movement disorders are among the most disabling neurological conditions, characterized by impaired gait, postural control, and other motor and non-motor symptoms [1,2]. These disorders can range in severity from subtle impairments to profoundly incapacitating symptoms, significantly reducing patients' quality of life [2–8]. Their recognition is critical, as they can offer insights into underlying pathologies, particularly in early or uncertain clinical presentations [1,2].

Within the spectrum of movement disorders, Functional Motor Disorder (FMD) stands out for its complexity and diagnostic challenges [9]. FMD is a neurological condition where symptoms arise from abnormal functioning of brain networks rather than structural damage. Functional gait disturbances are particularly disabling, affecting 23–45% of FMD patients [1]. These disturbances, along with symptom overlap with other neurological and psychiatric disorders, contribute to diagnostic delays and frequent misdiagnoses. [1,9,10].

Rehabilitation is essential in the management of movement disorders, including FMD. Despite its importance, current rehabilitation systems face critical limitations. Many patients do not receive the evidence-based care they require due to a shortage of specialized professionals. Additionally, the chronic nature of these conditions necessitates continuous rehabilitation support, which is often unavailable in traditional care settings. Innovative approaches are urgently needed to address these gaps and ensure effective long-term management and monitoring. Gait analysis offers a promising solution, providing an objective means to evaluate

and understand abnormal walking patterns in neurological diseases. However, it presents significant challenges in clinical practice, as it is typically conducted in laboratory settings, which do not capture the full extent of disability experienced in ecological environments. This limitation is particularly pronounced in Functional Motor Disorder (FMD), where gait disturbances have been inadequately explored in both supervised (laboratory) and unsupervised (ecological) settings. Expanding this knowledge is especially critical, given the potential for improved diagnostic and therapeutic strategies.
Indeed, quantitative gait assessments have demonstrated their value in enhancing diagnosis, predicting outcomes, and optimizing treatment strategies across various neurological conditions, including Parkinson's disease, multiple sclerosis, and stroke [1,2,9–14]. These assessments provide a more precise and reliable alternative to conventional observational scales, with the potential to identify specific spatiotemporal gait parameters as diagnostic biomarkers [3,15–20].

Moreover, the rapid development of portable and wearable technologies has further expanded the potential of technology-based objective measures (TOMs) in unsupervised environments. These tools are revolutionizing neurological care by facilitating a transition from traditional rehabilitation approaches to digital telerehabilitation. This evolution enhances accessibility to personalized rehabilitation programs and empowers patients with real-time tools to monitor their health. Nevertheless, significant challenges persist, particularly in identifying TOMs that are clinically meaningful and seamlessly integrated into comprehensive telerehabilitation systems. Overcoming these challenges is vital to advancing digital rehabilitation and improving outcomes for patients with FMD.

During the first year of my PhD, I was mainly involved in the work of analyzing the literature on the topic of digital telemedicine, investigating which devices and technologies had been used in an unsupervised environment in individuals with movement disorders, such as Parkinson's and functional motor disorder, and multiple sclerosis. The aim was to provide a state-of-the-art review on telerehabilitation, digital telerehabilitation, and the implementation of digital platforms with wearable devices in the neurological field. Great attention was on wearable devices, which can perform gait analysis. Our research team is focusing on a gait biomarker specific to FMD patients.

Based on the review work on telerehabilitation and the use of wearables on patients with functional motor disorders in the first year, in the second year, we developed a protocol for the combined use of virtual reality and new wearable sensors for gait analysis (FeetMe baropodometric insoles). Based on the results obtained in previous studies carried out by the research team on the importance of the dual task in helping to distract patients by improving their gait and balance performance, the protocol of the study with virtual reality aimed to verify the behavior of patients in a new situation, with great prospects in the field of telerehabilitation. The same study was also subjected to subjects with Parkinson's disease (in its early stages) to compare the results with three different samples: healthy, organic pathological, and neurological pathological, but not organic.

Then, in the third year, we started the TOM project on FMD patients to explore functional motor disorders (FMD) gait and activities in an unsupervised setting. After receiving confirmation of the correctness of the project from the Ethics Committee, we registered the study as a clinical trial and then started taking care of enrolment, explaining the use of wearable technology, and saving and processing data on activity performed at home and monitored with wearable sensors. Due to the limited literature on FMD patients and home monitoring, this feasibility study aimed to compare the effects on motor and non-motor symptoms in the control group (without sensor) and the experimental group outside the hospital setting. No similar studies have been published to date. Another aim was to understand the feasibility, i.e., to evaluate the recruitment and drop-out rates. The study is ongoing, and we estimate that enrollment will conclude by February 2025.

Moreover, during the three PhD years, collaboration with the company (daVi Digital Medicine s.r.l) has been maintained to develop a sensorised t-shirt for upper limb rehabilitation in the neurological field. In the first year, the Vicon system was used for the validation study of the Niurion 1.0 sensorised t-shirt, the first phase necessary to subsequently start a validation study of the Niurion 2.0 sensorised t-shirt. Niurion 2.0 changed its name to Aureha. In the second year, updates between clinicians, engineers, and physiotherapists regarding the development of the sensorised shirt continued. Finally, in the third year, we concluded the drafting of the protocol for using the Aureha sensorised shirt as a digital telerehabilitation tool for rehabilitating patients with upper limb impairments in the neurological field.

1 Functional Motor Disorders

Functional motor disorders (FMD) represent more than 50% of functional neurological disorders (FND), a condition characterized by a prevalence of 50/100.000 inhabitants, which leads to prolonged disability and reduced Quality of Life (QoL)[1,2,5–7]. These disorders present a unique and perplexing challenge as individuals experience many motor symptoms that can't be attributed to organic or structural neurological causes [1].

They often cause prolonged disability and negatively affect the patient's and their caregivers' QoL, leading to significant care costs [1,2,4–6,8,21–23]. FMD is more frequent in women (71%), and the average age of onset varies between 31 and 62 years, with an average age of 46.6 years.

The etiology of FMD is typically understood using a biopsychosocial model, where individuals have different predisposing and precipitating factors for developing symptoms, which are maintained by perpetuating factors. Examples of predisposing factors include biological vulnerabilities in the nervous system, emotional disturbance, or adverse life events [2]. In recent years, attention to these disorders has increased, partly improving the understanding of pathophysiological mechanisms. Understanding FMD pathophysiology and refining clinical assessment are unmet needs to improve patient management and reduce long-term disability.

Most patients with FMD usually manifest more than one symptom (motor and non-motor) simultaneously in varying combinations. Generally, the various symptoms are best interpreted as part of a single disorder rather than being considered stand-alone. Individuals with FMD typically have other comorbid conditions, making it a complex and multidimensional disorder[1]: experiencing many symptoms simultaneously can be challenging for patients and complicate clinicians' clinical-diagnostic framing. So, functional motor disorders are diverse and can vary in clinical presentation. According to the Functional Motor Disorders Registry, the most frequent motor symptom is paresis (43%), followed by tremor (40%), dystonia (28%), and gait disorders (26%). Less frequently occurring are myoclonus (13%), movement disorders in the facial district (10%), Parkinsonism (6%), and tics (2%).

These symptoms can lead to abnormal gait patterns and may directly impact walking ability, negatively affecting patients' QoL [1,2,4–6,8,21–23].

Other Functional Neurological Disorders (FND) associated with FMD include anxiety (52.1%), fatigue (45.1%), and pain (41.9%). Other symptoms include somatosensory symptoms (25.3%), functional visual symptoms (11.4%), and cognitive symptoms (10.9%) (LIMPE Foundation, n.d).

1.1 Functional Gait Disorders

Functional gait disorders (FGDs) are among the most disabling symptoms and impact 23%–45% of patients with Functional Motor Disorders (FMD), either as isolated symptoms or in combination with other motor and non-motor symptoms [24]. Functional Gait Disorders (FGD) significantly negatively affect work performance and social activities [21]. They are persistent in patients with FMD (26.6%), characterized by a complex pattern, and present mainly in older individuals [21].

Functional gait impairment is observed in isolated form in a minority of cases (5.7%), while 36.6% of cases are associated with other functional motor disorders, [21,25,26], mainly visual-functional symptoms or somatosensory disorders [22]. The main gait impairments that can be found in FMDs are:

- wide, slow, and very unsteady steps
- dragged gait (consumption on the inside of the heel)
- tightrope walking with outstretched arms
- crouched gait, often associated with fear of falling
- knee collapse.

Nonnekes et al. (2020) classified functional gait disorders (FGDs) into seven categories:

- *Ataxic gait:* characterized by variability of stance, difficulty walking in a straight line, excessive arm movements, and poor balance
- *Scissor gait*: characterized by frequent crossing of the lower limbs while walking

- *Knee buckling*
- *Antalgic gait:* characterized by an asymmetric reduction of the stance phase (lameness)
- *Weak and hesitant gait*
- *Hemiparetic gate*: characterized by the dragging of a limb
- *Dystonic gait*: characterized by an abnormal trunk or lower limb posture.

Additional gait patterns observed in patients with functional movement disorders (FMD) include [1,4,27–29]:

- '*Walking-on-ice' gait*: characterized by reduced height and stride width
- *Astasia-abasia*: characterized by continuous trunk swaying without falling
- *Tightrope gait*: characterized by walking with abducted upper limbs.

Concerning other organic disease, peculiar FGDs' features are the absence of falls at history (despite a balance disorder being reported), difficulty in standing and walking (despite normal segmental strength, astasia-abasia), and the assumption of postures considered "uneconomical" that, for example, paradoxically make balance more complex (e.g., narrowing the base of support).

Such gait patterns are often altered when distracted or performing non-physiological movements, suggesting the role of compromised higher-level gait control [24]. As FMD, functional gait disorders are characterized by *incongruent* and *inconsistent* symptoms that manifest themselves as a manifestation of different walking patterns in other environments, variation of symptoms in a short period, inability to perform specific movements during medical assessment (which are typically performed during spontaneous activities); onset of symptoms after a minor injury (not congruent with the organic condition); absence of falls in the anamnesis despite a reported balance disorder; difficulty standing and walking despite normal segmental strength; astasia-abasia; and taking of postures considered 'uneconomical' that paradoxically make balancing more complex (e.g. narrowing of the base of support).

Inconsistency refers to gait patterns that can be modified with interfering maneuvers (variations in clinical presentation that can't be reconciled with an organic lesion). In contrast, incongruency refers to gait patterns that can't be traced to those observed in neurological disorders or with organic lesions (e.g., stroke, multiple sclerosis, Parkinson's disease)[24]. Also, in FGD patients, distractibility is possible but often unquantifiable[21,25].

Diagnosis is challenging because no single walking pattern is pathognomonic for FGD. Establishing a diagnosis is primarily based on recognizing positive clinical features of functional gait disorders, such as an antalgic, buckling, or waddling gait, rather than mainly excluding organic gait disorders. Notably, these features can resemble and overlap with organic gait disorders (for example, knee buckling can be seen in idiopathic dystonia) [9]. Therefore, diagnosis relies on clinical assessment to identify specific positive signs, such as inconsistency and incongruence in symptoms [2,27,30].

1.2 FMDs and FGDs pathophysiology

In recent years, numerous neuroimaging, neurophysiological, and behavioral studies have been conducted to investigate the pathophysiological mechanisms underlying functional movement disorders[31]. The functional disturbance can be interpreted as a sensory processing, motor output dysfunction, or both. [21] The pathophysiology of gait functional disturbances (FGDs) is attributed to some leading mechanisms shared with FMDs [21,30,32–34]

I) Excessive internal attentional focus
II) Discordance between expectations/beliefs and actual sensory data
III) An altered Sense of Agency [32].
IV) Autonomic Dysregulation

It is thought to involve heightened activity in the limbic system and to enclose an internal model of symptoms within a predictive coding framework [21]. Also, there appears to be a disconnection in the neural networks responsible for imparting a sense of voluntariness to movements [21]. Indeed, symptoms arise from an abnormal functioning of brain networks rather than structural damage to specific brain regions [35].

A first distinguishing feature in patients with FMD compared to those with 'organic' movement disorders is that in the former, symptoms mainly occur when attention is focused. In contrast, they decrease or disappear without attention [31,32,35]; symptoms tend to increase when the patient places exaggerated attention on their body [35].

The second distinguishing feature is symptom-related beliefs and expectations[32]. Patients with FMD may present symptoms that don't follow the neurophysiological constraints typical of organic diseases; instead, they seem to fit common, intuitive beliefs about brain function.

As a third distinguishing feature, these patients seem to have an altered Sense of Agency, i.e., the conscious and subjective experience of initiating, performing, and controlling a motor action [21,32,33]. Deficits in the Sense of Agency could explain how involuntary movements are experienced by patients [30] up to situations in which the patient experiences a loss of control over their own body, defined as a dissociative crisis [35].

From a neurophysiological point of view, when a healthy subject plans a movement, the motor command is sent from the prefrontal areas, such as the supplementary motor area, to the motor cortex via the movement efferent pathway. In parallel, a feedforward signal is transmitted to the Sense of Agency area (an important hub corresponding to the right temporoparietal junction). Once the movement is executed, the feedback information reaches the Sense of Agency region, where the feedforward and feedback signals are compared. If there is a good match in this comparison, the Sense of Agency, i.e., the feeling of self-attribution of the performed movement, increases. In individuals with FMD, a predominance of the feedforward signal would occur, leading to poor correspondence with the feedback signal and inducing the perception of the movement as non-voluntary.

The hypothesis is that in FMD, the predictive coding doesn't update correctly, perpetuating the dysfunction [35]. Neuroimaging studies have shown that in FMD, there are alterations in the activation of some cerebral regions, including hypoactivity of areas associated with movement preparation, i.e., prefrontal cortex and supplementary motor area, limbic hyperactivity, and abnormal activation of the right temporoparietal junction [23,31,36]. Furthermore, an altered connection between the amygdala and insula would contribute to perceiving movement as involuntary. Genetic factors would have been correlated with an earlier onset of functional disorders and less connectivity between the right amygdala region and the middle frontal gyrus[37]. An epigenetic study also found increased methylation of the gene encoding for the oxytocin receptor (OXTR), which regulates the stress response in patients with FND [21]. Furthermore, several studies have revealed anatomical brain differences, such as minor grey matter and basal ganglia volumes, in patients with FND [21].

1.3 Risk Factors

FMD has a multifactorial origin, and risk factors in adults often include exposure to psychological stress and a history of adversity during childhood [21]. FMD frequently coexists with depression, anxiety, post-traumatic stress disorder, and type B personality traits. Other functional symptomatic disorders, such as chronic pain and irritable bowel syndrome, are also common, suggesting the presence of shared risk factors or mechanisms. The literature indicates that possible pathogenetic and predisposing factors for FMD include psychological, physical, and sexual trauma or stressful events[38].

The study by Tinazzi et al. (2020) shows that physical trauma preceding the onset of the functional disorder can be detected in 37% of cases, and infections and side effects of medication in a smaller percentage. In 9.3% of the patients, childhood-predisposing factors such as psychological trauma (6.1%), physical trauma (2.0%), or both (1.2%) were reported (Stephen et al., 2021). Half of the patients reported precipitating factors such as psychological trauma (27.8%), surgery (15.4%), general anesthesia (8.0%), infections (4.4%), and adverse drug reactions (3.9%). A functional neurological disorder predisposition could also include genetic factors[1].

1.4 Diagnosis and prognosis

Correct and early diagnosis is often a challenge for the clinician, given the variability of the disorders, often in a combined form [1]. Functional gait disorders are characterized by patterns that may resemble organic disorders, at other times, in a bizarre manner. Furthermore, an overlap between the functional component and disorders of organic diseases is common, making the correct diagnosis even more challenging [21].

Significant advances have been made in defining diagnostic criteria based on recognizing positive signs, including inconsistency of symptoms [40]. Inconsistency presents itself, for example, as a spontaneous remission or exacerbation of symptoms over time, a discrepancy between the severity of the disorder objectively assessed during the clinical examination and the limitations that the patient reports during their daily life [2], a variability of the gait pattern when the subject is observed [30,40,41]. Inconsistency is also characterized by the symptom improvement with distraction and worsening with attention [27]. Another key diagnostic feature is a combination of symptoms and signs that don't follow anatomical and physiological rules, thus incompatible with a specific organic lesion. For example, in gait disturbances, it is possible to note an abrupt onset or rapid progression of gait disturbances in the absence of structural trauma or injury, an antalgic gait in the absence of pain, or an unstable gait (as collapsing knees) in the presence of normal quadriceps strength. Positive diagnostic signs for functional weakness include the Hoover sign, the 5th finger abduction sign [21,41], and the entrainment test for tremors [21].

The presence of psychological or psychiatric disorders isn't a sufficient criterion for formulating the diagnosis of FMDs, nor is a diagnostic approach based solely on the fact that symptoms are unusual [42]. Furthermore, variability in movement patterns can be detected by comparing movements initiated with the patient's full attention, movements performed under distraction maneuvers, habitual movements (e.g., moving in a chair), and movements induced by tendon reflexes [21].

Studies indicate that many patients present with persistent symptoms even years after follow-up [33]. Favorable prognostic factors include good physical health, a positive and active social life, perception of effective treatment by the physician, reduction of factors such as stress, and treatment with specific drugs [43]. Other positive prognostic factors are young age and early diagnosis [42]. The main negative prognostic factors include a long duration of symptoms, the presence of personality disorders [42], a belief in the non-reversibility of symptoms, a late diagnosis, multiple physical symptoms, concomitant organic pathology, and advanced age [42].

1.5 FMDs management and rehabilitation

Functional symptoms not attributable to organic causes are potentially more reversible than those due to organic causes [44].

Management consists of three phases: anamnesis, diagnosis, communication, and treatment. An important part is the communication of the diagnosis, in which the physician must be very clear, adopt an inclusive style, and focus more on how the symptoms appear rather than on the cause of the functional impairment [21]. It may be helpful to demonstrate how excessive focus on the affected limb or negative mood tends to exacerbate the symptoms, making it clear to the patient that symptoms are common and potentially reversible, thus repressible, primarily through intensive, specific, and customized rehabilitation treatment. The literature suggests a multidisciplinary intervention involving physiotherapy, cognitive behavioral therapy, pharmacological therapy with botulinum toxin, online education, and self-help [24,31].

Physiotherapy is fundamental in treating patients with FMD [21]. It aims to educate, re-educate, and promote the patient's self-management by addressing predisposing, precipitating, and perpetuating factors in a multidisciplinary context and with a biopsychosocial approach.

Specifically, it helps to normalize beliefs about the pathology, reduce self-directed attention, and break learned abnormal movement patterns.

The rehabilitation treatment consists of three main components:

- *Education of the patient* by facilitating and understanding the diagnosis (using the same terminology used by the neurologist when communicating the diagnosis acts as a reinforcement)

- *Movement reprogramming*, where the rehabilitation treatment must gradually aim at retraining movement by redirecting attention (dual task) and addressing unhelpful beliefs and illness behaviors
- *Supporting self-management*, such as providing a personalized card to perform exercises at home and using telemedicine approaches (text messaging, telephone calls, video calls) and workbooks to complete the rehabilitation pathway.

Intensive rehabilitation interventions (2 hours/day, 5 days) using dual distraction/interference tasks have been reported to be effective, as they can change the patient's attentional state and reprogram movement[45].

To facilitate self-management of symptoms, it is useful to use a diary in which the patient can note different information: description of the diagnosis related to their experience, identification of the triggers and maintenance of symptoms, management strategies, reflections on treatment sessions, techniques used to normalize movement, goals achieved and future goals, as well as plans for achieving them. The positive effects of these rehabilitation trainings have also been reported at follow-ups of up to 2 years [35,46,47]. Furthermore, a physiotherapy program integrated with telemedicine could significantly treat FMD [47].

A recent study investigated self-assessment of improvement in motor symptoms, physical fatigue, and perception of change in FMD after 12 weeks of treatment [48]. This study compared a 12-week telemedicine program with a 12-week self-management program after a 5-day rehabilitation program to improve motor and non-motor symptoms, QoL, and perception of change in FMD patients [48]. It showed an improvement in the three-month follow-up assessment of motor symptoms, physical fatigue, and self-assessed change perception, which was higher in the telemedicine group. No different effect was found between the groups on other dimensions of fatigue, pain, physical and mental health, and gait and postural control. In conclusion, the long-term management and expert monitoring of FMD patients through telemedicine may improve long-term outcomes in motor symptoms and physical fatigue, with a long-term positive impact on the self-assessed perception of change in terms of health [48].

The consensus among experts in the field recommends a multidisciplinary approach to treat motor Functional Neurological Disorders (FND), including Functional Motor Disorders (FMDs) and Functional Gait Disorders (FGDs), involving physicians, physiotherapists, occupational therapists, and psychologists, all within a biopsychosocial framework. Treatment options cited by clinical trials include physiotherapy, cognitive behavioral therapy, and botulinum neurotoxin injections. However, the heterogeneity of these interventions hinders the synthesis of evidence, resulting in a knowledge gap regarding their effectiveness, particularly in a comparative context.

So, advancements also in the field of treatment and rehabilitation of FMD remain poorly understood and inadequately treated. There is a pressing need to enhance our understanding of FMDs' pathophysiology and refine clinical assessment to improve patient diagnosis and reduce long-term disability through dedicated and tailored telemedicine programs [1,9,24].

1.6 Gait Analysis and Gait Impairments in Motor Disorders

Gait is an intricate activity in which lower and higher-level functions are integrated, including cognitive, visuospatial, somatosensory, and motor planning abilities. For instance, we adjust walking speed to personal goals and to safely and autonomously navigate environmental conditions [49,50]. Gait control involves the central and peripheral nervous systems, which promptly activate muscles in physiological gait patterns and rhythm regulation [49,50]. The movement pattern is fine-tuned by visual, vestibular, and proprioceptive systems feedback while involving the locomotor regions in the midbrain, subthalamus, and cerebellum [51]. Routine walking can pose considerable cognitive demands[52]. Furthermore, certain walking activities (changes in speed and direction) may require higher cognitive functions, such as executive processes, and sharp attention to demanding situations, such as multitasking or navigating unfamiliar environments [49,50].

Gait is a cyclic movement of the whole body, made possible by repeating movements of different body segments, maintaining balance, and involving a series of systems, such as musculoskeletal, articular, neuronal, vestibular, visual, and proprioceptive [53]. Several kinematic parameters define gait. At its base is the cadence, defined as the number of steps performed in one minute (step x minute), and the stride time, defined as the interval between two successive stances of the same limb on the ground. The stride cycle establishes the concept of a stride, a phase that occurs when the whole foot of the same limb touches the ground twice in a row, and the idea of a semi-step. This phase occurs between the support of one foot and the support of the same part of the contralateral foot. The step is divided into a stance phase, in which the whole foot is in contact with the ground, and a swing phase, where the foot is lifted off the ground and moved forward.

Observation of gait is a powerful tool for predicting future cognitive decline. Changes in the gait signature reveal key information about the status and progression of numerous underlying health challenges, ranging from neurological and musculoskeletal disorders to cardiovascular and metabolic diseases. Accurate and reliable identification of gait patterns and characteristics in clinical settings and continuous monitoring and assessment over time can serve as both a diagnostic tool and a prognostic measure [54]. This capability facilitates the delivery of tailored treatments, informs predictive outcome assessments, and enhances the practice of precision medicine [17].

Gait Analysis is a multidisciplinary field of study that examines the biomechanics of human locomotion. Instrumented Gait Analysis (IGA) is particularly valuable as it offers precise and accurate quantitative measurements of gait patterns and characteristics. IGA typically involves instrumentation to capture and analyze various human gait parameters, including spatiotemporal, kinematic, and kinetic measures. Traditional IGA systems encompass motion capture systems, force plates, instrumented walkways, and treadmills, while more recent systems incorporate miniaturized wearable sensing technology and computational platforms [17]. The literature on the clinical applicability and effectiveness of IGA suggests that IGA-based quantitative assessments can enhance the diagnosis, prediction of outcomes, and rehabilitation of various gait impairments when compared to conventional observational scales and techniques for assessing gait dysfunction in a wide range of diseases, including MS, PD, Stroke, and Cerebral Palsy ([12–14,17]. Additionally, IGA's economic and non-invasive approach makes it a valuable tool, reducing the need for costly and invasive diagnostic procedures and benefiting patients and healthcare providers [17].

1.6.1 *Gait cycle*

Gait is a fundamental function, essential for life. It is one of the keys to moving around the environment and from one place to another [49,55]. Normal gait is a series of rhythmic, systematic, and coordinated movements of the limbs and trunk that advance the body's center of mass forward. This complex process results from intricate dynamic interactions between the CNS and feedback mechanisms [55,56]. Walking is characterized by individual gait cycles and functional phases.

A gait cycle consists of two main phases, stance and swing. The stance phase corresponds to the duration between heel strike and toe-off of the same foot, constituting approximately 60% of the gait cycle. The swing phase begins with toe-off, ends with heel contact of the same foot, and occupies 40% of the cycle. Each phase includes a sequence of Double Support (both feet in contact with the ground) and Single Support (only one foot in contact with the ground) sub-phases [57].

1.6.2 *Gait parameters*

The aim of gait analysis in individuals exhibiting abnormal walking patterns is to capture motion variations, including postural instability and reduced movement speed, which are crucial in assessing disease progression. The primary objective is to identify features that characterize these variations, allowing for the detection of gait abnormalities associated with the disease and contributing to early diagnosis and clinical management. These distinguishing features are often called “disease-specific” [57].

Gait Analysis involves measuring various spatiotemporal, kinematic, and kinetic features. Spatiotemporal features primarily pertain to distance measurements of different body parts during gait and the duration of various phases. Kinematic features involve the angular movements at joints resulting from the rotational motions of body segments. Instead, kinetic features are related to the forces driving the motion of the legs and feet during gait, providing information about joint moments and powers [58].

Spatiotemporal gait parameters

As mentioned above, spatial (or distance) and temporal parameters characterize an individual's walking pattern during the gait cycle [58]. *Table 1* summarizes the primary spatiotemporal parameters utilized in Gait Analysis and examples of potential pathological variations.

Table 1: Spatiotemporal gait features.

	Feature name	Feature definition	Pathological variations
Spatiotemporal features	Step Length (cm)	Indicates the distance from one foot's initial contact to the contralateral foot's initial contact. Named according to the foot that is in front. For example, the right step length is the distance between the heel strike of the left foot to that of the right foot, or the distance covered by the right lower limb when taking a step. In abnormal gait, the step lengths of the two sides may differ.	Its decrease may be found in patients with Multiple Sclerosis and Huntington's disease [57]. In addition, even patients who underwent orthopedic surgery, such as total hip replacement, may show a decreased step length [57].
	Stride Length (cm)	Defined as a measure of "gait performance", it's the distance between one foot's initial contact and the subsequent contact of the same foot. It includes a step length of the left and right foot.	Its decrease may be found in patients with Multiple Sclerosis, Parkinson's Disease, and Alzheimer's Disease [57].
	Step Width (cm)	Distance between feet, while walking	Its increase may be found in patients with cerebellar disorder [57].
	Step Time (s)	Time duration to complete one step	Its decrease may be found in elderly patients [57].
	Step velocity (cm/sec)	Ratio between distance and time (Step Length/Step Time)	Its decrease might be found in elderly patients [57] .
	Stride Time (s) (or Cycle Time)	Time duration to complete one gait cycle	It may increase in patients with Amyotrophic Lateral Sclerosis [57].
	Stance Time (s)	Time during which the foot is in contact with the ground, from the touch of the heel to the detach of the toe	

	Stance time percentage (%)	Percentage of stance time of a step	
	Swing Time (s)	Time interval between the toe off and the subsequent heel strike of the same foot	
	Swing Time Percentage (%)	Percentage of the swing time of a step	
	Single Support Time (s)	Time duration of the single support phase	Its decrease may be found in patients with Huntington's disease [57].
	Double Support Time (s)	Time duration of the double support phase	An increased double support time may be found in patients with Multiple Sclerosis (MS) and Parkinson's Disease (PD) [57].
	Double support time percentage (%)	Percentage of the step cycle where both feet are in contact with the ground (Double Support).	
	Cadence (steps/min)	Number of steps taken in one minute	Its increase might be found in Parkinson's Disease (PD); meanwhile, its decrease often characterizes Multiple Sclerosis (MS) patients [57].
	Gait speed or velocity (m/sec)	Time required to traverse a specific distance on a level surface	Its decrease may be found in elderly, Parkinson's Disease (PD)/ Multiple Sclerosis (MS) patients [57].

Variability of gait parameters

According to the literature, gait variability features applied to spatiotemporal measurements have proven effective in distinguishing pathological from normal gait patterns [16]

Gait variability is characterized as the fluctuation in gait characteristics between steps. Various methods are proposed in the literature for quantifying gait variability, with the most used methods being [59,60]: Standard Deviation (SD) and Coefficient of Variation (CV), where (CV = [SD/mean] × 100).

Typically, gait variability is low during normal gait. However, increased or decreased variability is frequently observed in populations with gait abnormalities, such as elderly fallers and individuals with neurodegenerative diseases [19]. For instance, Central Nervous System (CNS) impairments, including cognitive functioning and motor performance, have been associated with increased stride time variability. The stride time variability is a sensitive indicator of gait automaticity, as it reflects the ability of the nervous system to generate rhythmic and consistent walking patterns without the need for continuous voluntary control. Recent studies have shown that, under physiological conditions, stride time variability remains relatively stable even during simultaneous cognitive tasks, suggesting that this parameter is strongly related to subcortical and spinal mechanisms of automatic motor control[61].
Furthermore, in FMDs, this parameter does not significantly change under dual-task conditions, unlike other spatiotemporal parameters such as gait speed or stride length. This finding reinforces that stride time variability is closely linked to intrinsic deficits in automatic control circuits rather than cognitive overload[3]. Moreover, low variability in stride time reflects the regular rhythmic nature of automated gait and indicates stable and safe walking. In contrast, reduced step length variability is linked to sensory impairments and balance deficits during walking. So, these values are a clinical indicator of gait stability and potential biomarkers for assessing the loss of automaticity in FMDs and other neurological conditions such as Parkinson's disease and stroke.

All these findings suggest that gait variability is associated with gait impairments and related to balance, mental and functional status, and limitations in QoL.

In *Table 2*, definitions of two primary variability parameters used in Gait Analysis and examples of potential pathological variations will be provided.

Table 2: Variability of gait features

	Feature name	Feature definition	Pathological variations
Variability feature	Stride time variability (StTV)	Mean stride time coefficient of variation, calculated as: stride time SD/ stride time mean	An increased stride time variability may be found in patients with Parkinson's Disease [19,47] and Multiple Sclerosis [19,62]
	Swing time variability (SwTV)	Mean swing time coefficient of variation, calculated as: swing time SD/ swing time mean	An increased swing time variability may be found in patients with Parkinson's Disease [19,47] and Multiple Sclerosis [19,47]

1.7 Gait Analysis and Dual-Task Paradigm in FGDs

As described in the previous section, Functional Gait Disorders (FGDs) exhibit extremely diverse gait patterns, with numerous phenotypes documented in the literature. These phenotypes include slow gait, astasia-abasia, knee buckling, paraparetic gait, ice walking gait, hemiparetic gait, and tightrope gait [1]. This clinical heterogeneity makes it exceedingly challenging to describe a "typical" gait pattern and identify disease-specific parameters [63–65].

For a long time, gait was generally regarded as an automatic process involving little or no higher-level cognitive processes (e.g., attention and executive function). Ambulation is a complex task that also involves 'high-level' cognitive functions such as visuospatial, somatosensory, and executive abilities to adapt movement to individual goals and environmental contingencies safely and autonomously [49,63]. Gait occurs in challenging and destabilizing environments, creating distractions in everyday activities. Often, we walk while talking, even facing some obstacles (pedestrians, cars, sidewalks, rough terrain, etc.). In these situations, therefore, we must plan the action, anticipate any risks, and, if necessary, make changes in the step, all maintaining a standing and stable position while being careful what to say and/or do.

In all these various circumstances, daily walking requires important cognitive resources, mainly executive and supervisory functions. Executive functions refer to different cognitive processes that modulate and use information from the posterior cortical sensory systems to produce behavior [64,65]. These include starting or the intention to act, the planning of action, working memory, and attention. The latter is a dynamic function driven by sensory perception and needs to select a preferred stimulus for a particular action, ignoring the unnecessary and irrelevant ones[53]. Attention processing is required when learning new actions and when it is necessary to consciously change and adjust old motor programs, such as trying to improve a previously acquired motor skill. The integrity of executive functions becomes important to maintain previously learned motor strategies. Also, motor programs must have good perceptual and dynamic integrity. In Figure 1, Mirelman and colleagues (2018) have developed a new model in which an interdependence between locomotion, cognitive functions, and risk of falls in elderly patients and those with neurological organic disease (Multiple Sclerosis, Parkinson's Disease). In these populations, it is possible to notice how the execution of cognitive tasks, concomitant with the gait, can deteriorate their quality and safety by exposing the patient to the risk of falls.

Studies of neurological lesions and motor behavior have highlighted the fundamental role of higher-level cognitive control systems in regulating walking [66,67]. The role of cognitive functions in gait control can be explored through dual-task methodology protocols, in which variations in performance in one or both tasks indicate the magnitude of their cognitive demands [52,68,69].

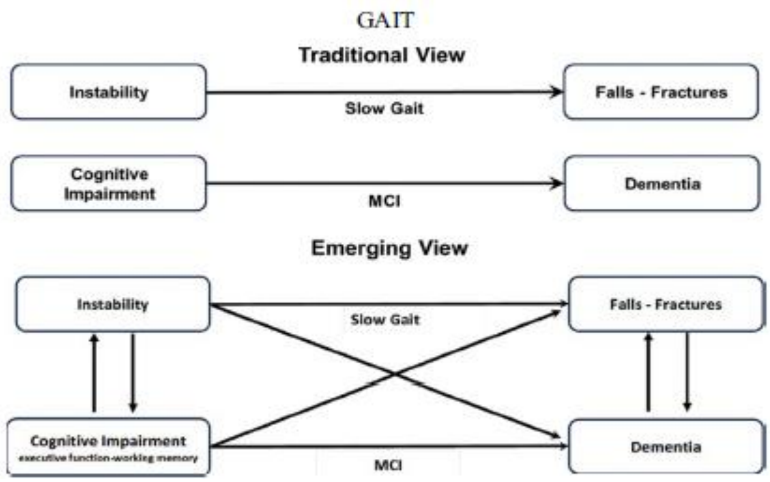


Figure 1: Interaction between gait and cognitive decline (Mirelman et al., 2018)

In this context, the dual-task paradigm is a valuable tool to explore the interaction between gait and attention on the assumption that the simultaneous execution of two tasks (walking and cognitive tasks, for example) may decrease performance on one or both tasks. Examples of changes related to the dual task in the spatiotemporal gait parameters in healthy people, the elderly, and those affected by neurological diseases (Multiple sclerosis, stroke, Parkinson’s disease) are the decrease in gait speed, the decrease in cadence and step length, the increase in step time and stride time variability. So, dual tasks can impair performance, reduce automaticity, and increase the risk of falls in healthy individuals, the elderly, and people with neurological conditions such as Multiple sclerosis, stroke, Parkinson's disease, and dementia [52,68,69] [70]

To date, few studies have explored the dual-task effect on spatiotemporal gait parameters in patients with FMD, finding that the interference of dual-task versus single task affected gait speed, stride length (a measure of gait performance), and stride time variability (a measure of gait automaticity and stability) [70].

1.7.1 *Dual-Task Paradigm in the Real Environment*

The dual-task paradigm can be applied to investigate the relationship between gait and cognition [47,52,65,67,70–73]. Performing two tasks simultaneously (motor and cognitive) may reduce performance on one or both tasks.

Comparing the pathophysiological aspects of FMD and FGDs by way of extension, preliminary evidence indicates that besides providing a valuable tool to evaluate postural and gait disturbances [74–76], the dual-tasking paradigm may offer insight into the complexities of these disorders and help in more effective assessment and management strategies.

Preliminary research by Gandolfi et al. 2023, involving a small cohort of individuals with FGDs, explored for the first time the influence of various dual-tasking conditions (motor, cognitive, visual tasks) on spatiotemporal gait parameters compared with healthy controls[3]. This study investigated dual-task performance as a measure of interference on gait speed, stride length, and stride time variability.

In all, 29 patients with FGDs and 49 healthy controls underwent spatiotemporal gait analysis, performing four conditions: single task, motor, cognitive, and visual-fixation dual-task [3]. Spatiotemporal gait parameters were collected at a self-selected comfortable speed on a 7.92-m electronic walkway (GAITRite, CIR System Inc., Havertown, PA, USA) [3]. Nine spatiotemporal gait measures (mean, standard deviation, and/or variability) spanning lower and high-level gait control and sensitivity to the dual-task effect were extracted [3,16,52,77,78]: gait speed (cm/s), stride length (cm), stride time (s), stride time variability (%), swing time (s), swing time variability (%), double support (s), and step duration (s).

In the single-task condition (ST), participants were instructed to walk comfortably without performing any adjunctive task at their comfortable speed [3]. The motor dual-task (mDT) and the cognitive dual-task (cDT) required walking while executing pronosupination movements with the right hand and serially subtracting seven starting from 100, respectively [3]. The visual-fixation dual task (vDT) focused on a “destination-focused” fixation placed at eye level in front of participant [3]. The single-task condition was completed before the dual-task one [16].

The dual-task effect was a measure of interference of the concurrent task on gait speed, stride length (a measure of gait performance), and stride time variability (a measure of automaticity).

Overall, lower gait speed, shorter stride length, and higher stride time variability were noted in FGDs compared to healthy controls; there was a significant effect of group and Task × Group interaction for the dual-task effect on gait speed and stride length but not for stride time variability.

The results revealed that patients with FGDs exhibited poorer gait performance, characterized by reduced stride length and lower automaticity and steadiness, as indicated by higher stride time variability than healthy control participants [3]. However, dual-task performance affected gait performance but not automaticity and steadiness compared to controls. While dual tasking impacted gait performance in individuals with FGDs, it did not significantly affect gait automaticity and steadiness, marking a distinct contrast with patterns observed in neurological diseases. These observations reveal aspects of higher-level gait control mechanisms in FGD participant [3].

Notably, stride time variability emerged as a potential diagnostic biomarker for FGDs, underscoring the value of further investigating a comprehensive set of spatiotemporal gait parameters and potential gait biomarkers specific to FGDs. This suggests that patients with FGDs have a more automatic gait control under dual-task conditions, relying on lower-level spatiotemporal gait control rather than higher-level control of locomotion, in contrast with other neurological conditions [16,47,58,79,80]. So, these findings shed light on higher-level gait control mechanisms in FGDs and suggest that stride time variability could be a diagnostic and prognostic biomarker.

A motor dual-task requires an internal focus on body movement components to be consciously aware of their movements. The lack of group difference in the vDT condition suggests that both groups could control gait with such a task. Moreover, the vDT didn't increase the dual task effect (DTE, which corresponds to the cost) in either group, suggesting that a visual stimulus doesn't interfere with gait.

It remains to determine whether using a visual stimulus that represents the effect of an action instead of a fixed point could promote an external focus of attention and improve performance by leveraging an automatic gait process, according to the constrained action hypothesis [3].

These findings have implications for clinical practice because understanding the high-level attentional role in the pathophysiology of disturbances can help improve diagnosis and hypothesize potential directional intervention by practicing the executive domain through dual tasking to plan personalized intervention. So, the three types of dual tasking (motor, cognitive, visual) should be integrated with the assessment of FGDs to explore the effects of different types of attentional focus.

Building on these results, Gandolfi et al. (2024) expanded their previous study [3] with a larger sample and a robust statistical methodology to confirm preliminary results, aiming to identify measures of dual-task effects of spatiotemporal gait parameters that best discriminate between the gait performance of FGDs and HC[70]. This is the first study to compare a broad set of objective measures of spatiotemporal gait parameters, and the key findings are threefold. Since that variability in stride time, as a measure of gait automaticity, is not thought to be affected in individuals with FGDs and associated with conserved control of gai [3], unlike neurological disease [16,47,70,81], Gandolfi et al. (2024) included several more spatiotemporal gait measures under different attentional conditions on a single and a dual task for ROC curve analysis [3,16,52,81,82]. The primary diagnosis of FGDs relies on clinical pattern recognition. However, by expanding the scope of gait analysis to include a broader range of gait measures, sensitive indicators of gait impairment could be observed [24,27].

This cross-sectional observational study analyzed high-level spatiotemporal gait control outcomes in 87 patients with FGDs and 48 healthy controls. Spatiotemporal gait parameters were collected at a self-selected comfortable speed on a 7.92-m electronic walkway (GAITRite, CIR System Inc., Havertown, PA, USA) [3]. Nine spatiotemporal gait measures (mean, standard deviation and/or variability) spanning lower and high-level gait control and sensitivity to the dual-task effect were extracted [3,16,27,77,78]: gait speed (cm/s), stride length (cm), stride time (s), stride time variability (%), swing time (s) and swing time percentage (%), swing time variability (%), double support (s), and step duration (s). As done in the previous study, four conditions were tested: single Task (ST), motor (mDT), cognitive (cDT), and a visual-fixation dual-task (vDT) [3]. The task requests and conditions are the same as in the previous study. In this study, to strengthen the results' accuracy and credibility, receiver operating characteristic (ROC) curve analysis was performed, and then the area under the curve (AUC) from the receiver operator characteristic plot and the dual-task effect (DTE) were calculated for each measure. Dual-task interference on the top single-task gait characteristics was determined by two-way repeated measures ANOVA.

It was found that stride time variability and its standard deviation failed to discriminate between the two groups in single and dual-task conditions, and significant Group x Task interactions were observed for swing time SD and stride time on the cognitive dual tasks. Moreover, longer disease duration was associated with poor gait performance and unsteadiness in motor and cognitive DTE. Still, there was an improvement in stride length and swing time on the visual dual tasks.

Building upon Vitorio's findings[16], it seemed that conventional measures such as gait speed and stride length must be revised to capture the FMD-specific functional nature of gait disturbances accurately and that a more focused investigation into specific high-order levels of gait control is warranted for this population. This insight opens new avenues for research into the intricate mechanisms of gait in

FGDs and perhaps other neurological conditions, as a future step to understand and differentiate FGDs from other conditions. Specifically, this study suggests that stride time variability serves as a more indicative biomarker of the structural integrity of gait neurophysiology and should be considered a key gait biomarker in the context of FGDs using motor and visual-fixation dual tasks to retrain correct movement patterns.

So, these measures hold significant potential for refining the selection of gait measures that can effectively discriminate between FGDs and HC and for future clinical trials to evaluate the effects of the intervention. Moreover, these preliminary findings shed light on measures of gait automaticity as a diagnostic and prognostic gait biomarker, as these patients maintain the structural integrity of gait automaticity control [22,40], underlining the importance of early diagnosis and management in individuals with FGDs. These also sought to devise the most effective dual-tasking methods for discriminating between individuals with FGDs and healthy controls and explore possible correlations with disease features.

1.7.2 Dual-Task Paradigm with Virtual Reality

Virtual Reality (VR) is a tool that can be used to treat neurological disorders for rehabilitation purposes [22,81,83,84]. Despite the different definitions of VR proposed depending on the scope of application, the requirements for creating such an experience are immersive, interaction, sensorimotor contingencies, and illusion [82].

Typically, VR exploits vision as the main sensory channel involved and is often sufficient to foster a high degree of immersion, being, for most people, the dominant sense. In addition, factors determining adequate sensory substitution include a wide visual field, three-dimensionality, tracking of head movements, high-resolution screens, and low signal latency between sensor and viewer. Immersive systems, such as the Oculus Rift and the VIVE Pro Eye (HTC), provide an experience closer to reality than non-immersive ones, giving the user the illusion of non-technological mediation and allowing the user to 'feel into' the virtual environment [85].

These systems provide a complete simulated experience and allow interaction and actions to be perceived as real [85,86]. The main difference is how this technology

tracks the movement of the user's body and how its displays guide our perceptive senses. Although there are several theoretical reasons why VR could be useful in treating and diagnosing functional neurological disorders (FNDs), research is still limited [31]. Recently, VR systems have been used to assess and intervene in rehabilitating people with neurological disabilities [82].
VR experiences have shown numerous benefits in neurorehabilitation, including motor and perceptual systems involvement during rehabilitation programs. In addition, using feedback from the body promotes a change in the subject's perception of it [82]. The ability to easily change the virtual environment, measure the task's difficulty, and adapt it according to the patient's abilities are important advantages of VR, as continuous changes and adaptations are essential for cognitive and motor recovery [87,88]. VR use in rehabilitation also offers additional benefits, such as encouraging greater motivation [88].

In neurorehabilitation, VR has been used as a strategy for rehabilitation intervention in different patient categories regarding extrapyramidal disorders and has been tested in patients with Parkinson's disease, pyramidal syndromes, patients with stroke, multiple sclerosis, and cranial trauma [89]. The outcomes considered are the gait, balance, coordination, upper limb function, cognitive function, everyday life activities, and QoL. VR can improve many of these aspects [90].
However, most of these studies have mainly used non-immersive VR devices like Nintendo Wii, Xbox, and others. In the future, home use of VR devices could become an increasingly important component of Telerehabilitation [87,88]: it would keep the patient's interest alive in the rehabilitation program, controlled remotely by the physiotherapist, and significantly reduce costs compared to traditional rehabilitation interventions [90]

There are few studies in the literature where VR is tested, immersive and not immersive, in patients with FMD [31]. The rationale for using VR in the rehabilitation of patients with FMD is interesting and in line with the pathophysiological aspects that characterize the pathology. VR could act at the same time on suggestibility, on careful control of the movement of their own body (increasing the distracting effect), and on the prediction of sensory information, the latter closely linked to the

Sense of Agency [31,84]. Furthermore, VR can help to depersonalize the context, allowing the patient to interact with virtual environments in ways that reduce self-awareness and increase immersion [84]. The greater suggestibility of subjects with FND, meaning a predisposition to respond to communications that induce involuntary changes, could interact with VR to improve patient responses to treatments. It is uncertain whether all patients with functional disorders have the same level of suggestibility.

Gandolfi et al. (2023) found that immersivity facilitates distraction and improves symptomatology in FMD, acting on the reduction of signal feedforward to bring the intensity closer to the sensory feedback signal. This study used a VR-based protocol to assess postural control disorders in patients with FMD in a static condition. It improves postural stability during a cognitive dual task in a 3D virtual environment. A task that requires higher cognitive functions can limit basic perceptual information processing [49]

The illusion of perceiving a place as real involves both perceptive and cognitive systems, which depend on multisensory bottom-up processing, sensory awareness, and top-down forecasting manipulations. Bottom-up multisensory processing is a cognitive strategy in which multisensory inputs are centrally integrated to build self-awareness and respond to the outside world. When multiple sensory modes are congruent, the brain is likelier to believe that information is real (VR headsets, for example, can optimize and enhance visual content). However, multisensory integration alone can't explain why VR illusions can be so strong. In our brains, mechanisms of prediction based on sensorimotor frameworks are more complex: they are based on the comparison of the performance of a motor task and its internal representation [91]. When the afferent inputs correspond to the expected state, the brain is more likely to infer that the afferent input is correct. This model has been used to describe motor learning and self-awareness of voluntary actions.

In VR, when users perform active voluntary motor activities, and their brain matches information from multisensory modes, it creates a strong illusion that is a powerful implication of the sense of agency linked to volition [92]. The illusion can be strengthened through interactions: in this way, the brain can "correct" some sensory deficiencies to make them match the intended state using top-down manipulations [92]. These corrections are so powerful that they can alter the Sense of Agency and produce self-attribution of actions.

Patients with FMD, since present a discrepancy between expectation/belief and actual sensory data, could benefit from this tool: the strong integration and multisensory congruence offered by the immersive VR system, combined with the possibility of interacting with the system, correcting, change their behavior, could affect self-awareness of their voluntary actions and change their Sense of Agency. Brouwer and colleagues (2024) suggest using VR as a promising approach in rehabilitation, multidisciplinary management, and psychotherapy. VR could also implement and complement the existing therapies by improving the effectiveness and accessibility of therapeutic interventions.

So, FMD rehabilitation using the VR context could be very promising as it could act simultaneously on attention, beliefs/expectations, and Sense of Agency, the three key processes involved in the neurobiological pathophysiology of the disorder. In this way, VR rehabilitation would be a powerful tool to promote functional recovery and improve the QoL to a greater extent than traditional one.

In addition to being an advantageous tool for studying the control mechanisms in patients with functional disorders, VR can also be used to develop new strategies to diagnose FND, thanks to the ease of changing scenario-environment-task to a greater level of distraction and suggestibility. In this context, VR has been defined as very interesting for patients with gait disorders and a good strategy for identifying diagnostic biomarkers [29].

Despite these potential benefits, some limitations remain, such as the limited presence of specific research, the difficulty of standardized protocols due to the variability of symptoms in FMD, and the current cost and accessibility of some equipment needed for VR [31].

2.Digital telemedicine

2.1 Telemedicine, Telerehabilitation, and digital medicine

The World Health Organization (WHO) defines rehabilitation as interventions to optimize functioning and reduce disability in individuals with altered health conditions when interacting with their environment. Rehabilitative therapies play an essential role in the healthcare system by providing services to patients with acute or chronic conditions to restore and improve functional capacity, minimize impairment, prevent complications, or slow the disabling effects of chronic diseases. In addition to its fundamental role in achieving clinical outcomes, rehabilitation has an enormous economic and social impact on the healthcare system [97,98]. Motor skills are of primary importance in achieving optimal quality of life. In this direction, the comprehensive optimization of individuals' functional abilities is an important public health goal.

In 2019, it was estimated that 2.41 billion people in the world and 373 million people in the European area had conditions that would benefit from rehabilitation services: most individuals aged 15 to 64 years have impairments due to musculoskeletal conditions, while people older than 65 years suffer predominantly from musculoskeletal conditions, neurological disorders, sensory impairments, and chronic respiratory diseases [99]. As a result, the demand for rehabilitation services has increased in recent years. It is expected to increase gradually due to changes in the general health conditions of the population [99], such as the progressive aging of the population and the spread of chronic diseases, which have generated an increased demand for rehabilitation therapies and programs. However, despite this urgency, the healthcare system has been unable to meet these demands [100] due to the lack of nationwide funding policies and ineffective regulatory pathways to access rehabilitation therapies. As a result, patients face high expenses to avail themselves of the services they need, limited availability of rehabilitation services outside urban areas, and long waiting lists [100–102].

In the past four years, the pandemic situation of COVID-19 has been a significant contributor to the disruption of the rehabilitation sector, exacerbating already-known problems. Within this framework, the use of digital technologies has addressed some of the main critical issues of the emergency, such as overcoming the social distancing that didn't allow for classic in-person therapeutic sessions [103]. The circumstances of COVID-19 emphasized the already existing need for innovative research, especially the importance of remote data collection, which would allow objective assessments of patients' conditions and improve continuity of care by monitoring their progress [103]. In this context, increasing research has been directed toward wearable devices for monitoring and collecting clinical data in hospital and remote settings, which is potentially helpful in planning telemedicine and telerehabilitation interventions.

Telemedicine refers to delivering health care services using innovative technologies, mainly Information and Communication Technologies (ICT), when health professionals and patients are not in the same location. Telemedicine involves securely transmitting medical information and data in text, sound, images, or other forms necessary for patient prevention, diagnosis, treatment, and subsequent follow-up. However, telemedicine doesn't replace traditional healthcare delivery in the relationship between clinician and patient; instead, it could improve effectiveness, efficiency, and appropriateness [103].

Telerehabilitation, conversely, consists of the remote delivery of services and performances intended to enable, restore, or improve the psychophysical functioning of people of all age groups with disabilities or disorders, whether congenital or acquired, transient or permanent, or at risk of developing them. It is a health professional activity, may be multidisciplinary, and, when beneficial to the patient, may require the collaboration of caregivers, family members, and others. Telerehabilitation performances and services are enabled by various information and communication technologies, including hardware and software infrastructure and devices for the management and network exchange of data and images, mobile devices, medical applications, and devices, including wearables, sensors, robotics, virtual reality, and artificial intelligence, and other innovative solutions such as serious games (games or recreational activities used for therapeutic purposes), and digital therapies, in appropriate combination with each other and always within the framework of telemedicine methodologies, organization, and procedures.

Telerehabilitation performances and services can be used in any care and educational setting where the patient is [103].

Moreover, *Digital Telerehabilitation* combines the advantages of Telerehabilitation with the possibility of using digital tools (wearable sensors, digital platform) to monitor functions and activities in real-time and in the real-world environment. Wearable sensors (such as IMUs, accelerometers, and insoles) used during regular assessments can provide objective data on patients' capabilities, complementing the expert subjective judgment of healthcare specialists.

Further, remotely acquiring data shows promise in implementing independent rehabilitative training outside clinics, allowing patients to work more extensively toward recovery. Telerehabilitation in the neurological field could extend specific rehabilitation pathways from hospitalization to the home, allowing better management of patients and their clinical, social, and economic outcomes [104]

It is crucial, especially in FMDs, because of the clinical complexity of patients who require highly qualified personnel, adapting rehabilitation programs over time, and long-term monitoring without impacting health care costs. Besides the limitations caused by COVID-19, the restricted presence of qualified centers for rehabilitating FMDs emphasizes the need to create specific digital telerehabilitation pathways for experts who can reach those without access to such rehabilitative treatment [103].

Thus, Telerehabilitation aims to reduce costs, both for the health care system and the patients themselves; problems with transport and delivery of such services; and most importantly, it aims to provide continuity of treatment pathways, being able to ensure more frequent and constant monitoring, thus leading to potentially better outcomes, delivering more effective and efficient services, with the goal of improved patients' QoL.

While the advancement of telemedicine enables remote interaction with the patient, allowing the physician to check and update clinical pathways remotely and the patient to check their progress directly, Telerehabilitation has not yet taken hold as it's a field in evolution and development. However, the benefits of Digital Medicine and Digital Telerehabilitation must be proven through rigorous research, especially validation through controlled clinical trials.

2.2 Digital transformation of classic rehabilitation

Rehabilitative therapies are essential in the healthcare system since they provide services to patients affected by acute or chronic conditions. They aim to restore and/or enhance functional capabilities, minimize their impairments, prevent complications, or slow the disabling effects of chronic diseases [96].

Besides the core role in achieving clinical outcomes, rehabilitation has a substantial economic and social impact on the healthcare system since it delivers cost-beneficial services for individuals and society [97,105]. It helps patients participate in everyday life, maintaining or restoring their independence as much as possible, and considerably cuts ongoing care costs [104]. It is important to underline that motor capabilities, which depend upon the coordination of different functions of the human body, have a primary relevance in achieving an optimal quality of life [106]. In this direction, the comprehensive optimization of the functional capabilities of individuals is recognized as a primary public health goal [107,108].

In 2019, as mentioned above, 2,41 billion people worldwide had conditions that would benefit from rehabilitative services [108]; consequently, the request for rehabilitation services has increased in recent years and is predicted to rise progressively because of the changes in health conditions [96,99]. For instance, the incremental aging of the population and the spread of chronic diseases have generated a higher demand for therapies [96,99].

Nevertheless, despite this urgency, the healthcare system has not prioritized the rehabilitation sector and has been unable to fulfill those requests [100]. Therefore, patients must face high out-of-pocket expenses, the shortage of rehabilitation services outside urban areas, and long waiting lists [96,100–102].

A positive effect of the COVID-19 pandemic is, from a broader perspective, its implication in the strong call for strengthening health systems and regulatory policies and developing a multidisciplinary rehabilitation workforce, emphasizing the need for innovative research and, most of all, the importance of data collection. In this framework, the use of digital technologies has faced some of the main criticalities of the emergency, such as overcoming the social distancing that has not allowed the carrying out of classical therapeutic sessions [109,110], decongesting the

hospitals, and helping to manage time and resources better both for patients and therapists.
The latter allows us to objectively evaluate patients' condition and improve the continuity of care by monitoring them [103]. In the future, we could support defining reference protocols or pathways for designing and delivering effective rehabilitation therapies.

In this regard, it is necessary to gain clarity on the terminology (Table 10): the term Digital Health applies to all the technologies that engage patients in their health and well-being, but only the subdimension of Digital Medicine provides for evidence-based products and services both for monitoring and intervention, whose outcomes must be demonstrated through clinical studies. In this scenario, while Digital Therapeutics only focuses on the intervention dimension, Digital Rehabilitation or Telerehabilitation concerns monitoring and treatment [111,112]. The latter enables the patients to carry out the therapeutic exercise program in their domestic environment, overcoming the issues related to access to therapies and increasing the sustainability of services. At the same time, physicians can manage more patients, maintaining the continuity of care through telemonitoring and gathering clinical data, which are essential to providing supervision and tailoring therapy according to patients' needs. Thus, the efficiency of care increases while costs are contained [113].
Considering these factors and the exponential improvement and advancement of technologies, the rehabilitation field seems to be truly suitable for digital transformation. Current literature provides evidence about the adequacy and effectiveness of Telerehabilitation, whose outcomes are comparable to or better than conventional methods concerning reducing pain and impairments derived from musculoskeletal conditions [104,109,114] and surgical treatments [113]. Moreover, Telerehabilitation has proved to be an effective means for improving physical activities and fatigue tolerance in patients with neuro-motor disorders [104,109,114]. Telerehabilitation has also increased adherence to exercise-based physical therapy[115] and empowered patients to participate actively in care management.

Table 3: Digital Framework Definitions

Digital Health technologies for health	
Digital Medicine evidence-based medical products and services	
Digital Therapeutics Focus on intervention	**Digital Rehabilitation/ Telerehabilitation** focus on monitoring and intervention

Hence, the pandemic has been the catalyst for adopting existing digital solutions, the need for technological advancements, and the urge to provide policies to account for telerehabilitation therapies as an alternative among the common standards [115].

In this regard, it is interesting to note that Italian guidelines about telemedicine have included the term telerehabilitation since 2012. Still, only the statement of 29 April 2022 has approved a protocol for home-based care employing digital technologies. According to this policy, the therapists deliver the treatments remotely and gather clinical data utilizing medical devices (wearable, robotics, and serious games) supplied by the public healthcare system without any substantial difference in the presence of therapeutic pathways. However, it is important to underline that even if the rehabilitation session is performed in a domestic environment, real-time interaction between the patient and the therapist must always be provided.

The next step of the digital revolution in rehabilitation is to allow the patient to perform rehabilitative exercises at home and the therapists to asynchronously evaluate the results, optimizing time and resources while empowering the patients to be actively involved in their therapeutic pathway for greater adherence to the therapy.

2.3 Current Scenario for FMD Rehabilitation

Rehabilitation interventions are an essential part of the treatment of FMD. Large cohort studies and recent randomized controlled trials have provided strong evidence to support their use in managing patients with FMD. Improved knowledge of the pathophysiology of FMDs could further aid the development of specific rehabilitation interventions. In this context, the motor symptoms of FMDs can be considered learned patterns of movement guided by attention and belief. The various symptoms of the FMD patient should be regarded as within a bio-psycho-social disease model in which predisposing, precipitating, and perpetuating factors can be addressed in a multidisciplinary referral context [24,47,116].

Rehabilitation treatment consists of 3 main components:

1) *Education*: facilitating understanding of the diagnosis (using the same terminology used by the neurologist in communicating the diagnosis acts as reinforcement)
2) *Movement reprogramming*: rehabilitative treatment should, therefore, aim to retrain movement stepwise by redirecting attention and addressing unhelpful beliefs and illness behaviors. The effectiveness of intensive rehabilitation interventions (2 h/day, five days) based on movement reprogramming using distracting/interfering tasks that can change the patient's attentional state during movement has been reported in controlled clinical trials.
3) *Supporting self-management*: provide a personalized plan to perform exercises at home, using telemedicine approaches (texting, phone calls, video calls) and a workbook to complete the rehabilitation pathway [24]. The following information should be indicated in the book: an explanation of the diagnosis concerning the patient's personal experience; relevant symptom precipitation and perpetuation factors with management strategies; reflections from treatment sessions; strategies employed during treatment that help normalize movement; goals achieved; future goals and plans to achieve them.

Within the framework of treatment, it is also helpful to consider psychological aspects, especially in cases where symptoms manifest paroxysmally and in the presence of dissociative crises. Among psychological approaches, cognitive behavioral therapy (CBT) is considered one of the most effective therapies for treating dissociative crises and attacks, especially when combined with rehabilitation. CBT aims for the patient to change how they think (about their symptoms) and behave (concerning their symptoms). This approach, therefore, allows learning to recognize the premonitory symptoms of attacks and to apply techniques based on distraction (e.g., counting backward from 100 to 0, taking off seven each time, talking to someone, singing a favorite song) that can help prevent or overcome these attacks. Psychological treatment is also essential in the presence of comorbidities such as anxiety and depression.

2.4 Future Scenario for FMD Rehabilitation

Telemedicine in FMDs effectively reduces motor and non-motor disorders [36,47]. The role of "unsupervised" monitoring remains unexplored, which means collecting objective measures based on the technology (technologies objective measures, TOMs) in patients with FMD at home. The development and availability of portable and wearable technologies are rapidly increasing, expanding the field of TOMs in neurological disorders such as Parkinson's disease [47,117].

To date, there remain substantial challenges in identifying which devices may be most relevant for patients and clinicians and which may help provide an accurate, objective, and real-time assessment to allow a transition from Telemedicine/ Telerehabilitation to Digital Telemedicine/ Telerehabilitation.

With the evolution of digital healthcare, further research is needed to improve device accuracy, assess user acceptability, and integrate these tools into the telemedicine infrastructure [117].

In the literature, there are no studies in which VR, immersive and non-immersive, is tested in FMD patients' rehabilitation. In the future, home use of VR devices could increasingly become a key component of Telerehabilitation [87]. It would keep the patient's interest in the rehabilitation program, controlled remotely by the physiotherapist, and significantly reduce the costs compared to traditional rehabilitation interventions [89].

The rationale for using VR in FMD rehabilitation is interesting and in line with the pathophysiological aspects that characterize the pathology. First, VR could simultaneously act on the prediction of sensory information, on the attentive control of one’s body movement, and on the sense of agency. The illusion of perceiving a place as real involves cognitive and perceptual mechanisms, which depend on bottom-up multisensory processing, sensorimotor awareness, and manipulations of top-down prediction. The bottom-up multisensory processing is a cognitive strategy in which multisensory inputs are centrally integrated to build an understanding of self and respond to the outside world. When more sensory modes are congruent, the brain is more inclined to believe that the information is accurate (VR headsets, for example, can optimize and improve the visual content). However, multisensory integration alone can’t explain why VR illusions can be so strong. In our brains, more complex prediction mechanisms based on sensorimotor frameworks take place: they are based on the comparison between the performance of a motor task and its internal representation. When the relevant inputs correspond to the expected state, the brain is more likely to infer that the afferent input is correct. This model was used to describe motor learning and self-awareness voluntary actions.

In VR, when users perform voluntary motor activities actively, and their brain matches information from multisensory, it creates a strong illusion that comes from a powerful implication of agency linked to volition [91]. The illusion can be enhanced through interactions: using top-down manipulations, the brain can "correct" some sensory deficiencies to match the intended state [91]. These corrections are so powerful that they can alter the sense of agency and produce self-attribution of actions.

Patients with FMDs present a mismatch between expectation/belief and real sensory data, so they could benefit from this tool: strong integration and multisensorial congruence offered by the immersive Virtual Reality system, combined with the possibility to interact with the system and correct or modify their behavior, may affect self-awareness of their voluntary actions and change their Sense of Agency.

In addition, the VR context could be enriched with dual-task tasks (motor or cognitive) that could affect expectations and attention: when performing a task that requires superior cognitive functions, the brain is busy and, therefore, has less opportunity to focus on assessing basic perceptual information. It is worth noting that the playful context would always reward patient performance by improving recovery motivation [118,119].

Conversely, despite VR presenting promising opportunities for FMD rehabilitation, it is essential to acknowledge some potential limitations and barriers to its widespread application. First, not all patients may tolerate VR environments due to the risk of cybersickness, which can cause symptoms such as dizziness, nausea, or visual discomfort, potentially limiting session duration or adherence. Moreover, FMD patients may present with significant psychological comorbidities, such as severe anxiety or dissociative tendencies, making immersive VR experiences less suitable or even counterproductive. Additionally, accessibility issues remain challenging, as VR-based rehabilitation often requires specialized equipment, trained personnel, and infrastructure that may not be readily available in all clinical settings. Finally, there is a need for further evidence on long-term outcomes and generalization to real-life functional improvements, as much of the existing literature focuses on short-term efficacy. Therefore, although VR is a highly promising tool, it should be considered part of a personalized rehabilitation strategy, carefully tailored to each patient's clinical profile, preferences, and potential contraindications.

In conclusion, considering these possible limitations, FMD rehabilitation using VR context could be the best rehabilitation approach as it acts simultaneously on attention, beliefs/expectations, and agency, the three key processes involved in the neurobiological pathophysiology of the disorder. In this way, VR rehabilitation would be a powerful tool to promote functional recovery and improve quality of life compared to traditional rehabilitation. Furthermore, it could be argued that VR tools could positively influence patient outcomes, increasing motivation and participation in rehabilitation programs.

3.TOMs and Wearable devices

In the past five years, there has been a significant increase in the study and development of wearable devices, thanks to an improvement in technological devices or other needs and contingencies outlined above.

Technologies Objective Measures (TOMs) are wearable devices designed to objectively detect and quantify body movements and spatial orientation using advanced digital sensors, such as IMUs (Inertial Measurement Units) or triaxial accelerometers (for example, Axivity) [119]. These devices, worn directly on the body, allow precise monitoring of various movement parameters, offering detailed measurements not only about posture and motor activity but also of energy expenditure and intensity of physical activity during the day. It also provides valuable information, for example, on movements during sleep.

There are different types of TOMs. The most studied and documented in the literature are IMUs and, more generally, accelerometers, smartwatches, smartphones, and baropodometric insoles. IMUs and accelerometers can acquire a wide variability of data, even in everyday activities, but they are complex enough to monitor and discriminate differently. Processing acceleration data makes it possible to extrapolate specific movement and gait analysis information. Baropodometric insoles, which allow the collection of precisely barometric data, are essential in monitoring and treating many pathologies. Finally, smartphones and smartwatches still enable data collection, albeit limited from a therapeutic point of view. The collected data can be saved on their internal memory in all these devices and later hand-delivered or transmitted to digital platforms [120,121].

The increased development and availability of wearable and portable technologies are rapidly expanding the field of TOMs in neurological disorders [119]. TOMs minimize intra- and inter-variability in clinical assessments of motor and non-motor symptoms, improving the accuracy of clinical endpoints in neurological diseases such as PD [119].

Critical unmet needs for the integration of TOMs into clinical and research practice are the identification and validation of endpoints relevant to individual patients, acquisition of motor and non-motor activities from an ecological environment, integration of various sensor data into open-access platforms and common language, and the definition of a regulatory pathway for the approval of TOMs. The current lack of intelligent multi-domain and multi-sensor technologies to measure a wide range of relevant changes in real-time continues to represent a significant constraint for integrating technology into the assessment of motor and non-motor functional disability, as shown in Parkinson's disease [121].

The fields of use for such technologies are still limited in clinical research, as algorithms to analyze data collected from these devices are still being developed. In the literature, there are studies on TOMs about the treatment and rehabilitation of patients suffering mainly from Movement Disorders, particularly Parkinson's disease [117]. Other current limitations in using TOMs in clinical trials on neurodegenerative disorders are difficulty identifying and analyzing relevant endpoints for clinicians, standardizing measurements and procedures, and creating a single platform for integrating data and algorithms from devices [122].

There is a need to facilitate the regulatory approvals that should enable the integration of TOMs into clinical studies [122].

Tables 11 and 12 summarize the TOMs' pros and cons for patients and physiotherapists, highlighting the opportunities and challenges associated with their integration into clinical trials on neurodegenerative disorders.

Table 4: Pros and cons of using TOM's Wearable Devices for the patient.

Pro	Cons
More Autonomy: Devices provide real-time feedback, helping the patient monitor progress even without the direct supervision of a therapist	**Uncomforting:** Some patients may find bulky devices uncomfortable, reducing adherence to use
Increased motivation: Feedback on continuing progress can increase motivation and commitment to the programmed rehabilitation	**Possible Privacy Issues:** Devices collect personal data that, if not correctly handled, can raise privacy and confidentiality problems
Access to information about your state: Devices give a thousand people awareness of owners' improvements and areas to be enhanced	**Need for familiarization**: The patient must learn how to use the device, which can require time and initial support

Support for Rehabilitation Continuity: Devices facilitate continuity treatment at home without the need for frequent visits.	**Patient Costs**: In some cases, the patient can't sustain the devices' costs, representing an economic burden
Reduction of Clinical Visits: Devices allow remote progress monitoring, reducing the need for frequent movements.	**Reliability of Devices:** Measurement errors or malfunctions can compromise the quality of data and, therefore, the effectiveness of monitoring

Table 5: Pros and cons of using TOM's Wearable Devices for the therapist.

Pro	Cons
Continuous monitoring: Devices allow continuous monitoring of the patient's activities	**Cost:** Buying and maintaining devices can be expensive, and engraving on the budget
Objective Data: Quantities data on movement and motor functions, facilitating analysis results	**Necessary training**: It requires training for both the physiotherapist and the patient, increasing time and costs
Personalization of Therapy: It allows the program to be adapted to be rehabilitative according to the needs and specifications collected from the data	**Complexity Management of the Data**: Data collection and analysis involves ethical issues and security, besides requesting technical skills
Patient Feedback: **I**t improves patient engagement by providing real-time feedback on progress	**Possible patient resistance:** Some patients may find it uncomfortable or invasive to wear devices
Documentation of results: It facilitates the documentation of progress and is helpful for clinic evaluations and communications with other professionals	**Reliability of Devices:** Some devices may have measurement errors or failures, reducing the reliability of the collected data

Currently, the integration of wearable devices such as TOMs into rehabilitation pathways is closely linked to the presence of multidisciplinary teams in which the figure of an engineer is included, which is essential for the technical management of the devices. The engineer supports installing, maintaining, and resolving technical problems, ensuring the devices operate with maximum precision and reliability.

This collaboration facilitates technological integration and allows clinicians to focus on the therapeutic aspect while the engineer is responsible for operational and technical aspects. In addition, the data collected by the devices is processed and made available in detailed reports, providing clinicians with objective and easily interpretable information on the patient's condition and progress. These reports are valuable for adapting rehabilitation programs to patients' needs and optimizing therapeutic results through real-world data analysis.

By providing patients with such devices to perform specific rehabilitative exercises independently, physicians and physical therapists can manage more patients while maintaining continuity of care through telemonitoring and collecting essential clinical data to provide oversight and tailor therapy to the patient's needs. Considering these factors and thanks to the exponential improvement and advancement of technologies, the rehabilitation field appears well suited for digital transformation. Current literature provides evidence of the appropriateness and potential effectiveness of Telerehabilitation. In addition, the latter effectively improves physical activities and fatigue tolerance in patients with neuro-motor disorders [123]. Telerehabilitation has also increased adherence to exercise-based therapy and empowers patients to actively manage their care and treatment pathway. Greater adherence and more active participation consequently result in the improved treatment itself.

The next step in the digital revolution in rehabilitation could be to ensure better accessibility of collected data by physicians and therapists, leading to greater treatment effectiveness. In addition, the research aims to focus on low-cost rehabilitation training systems that can be easily used in home settings, even by inexperienced patients, outside of any clinical setting, achieving a trade-off between cost and effectiveness and increasing patient adherence to therapy.

In this context, our work will focus on wearable devices in neurology, especially in patients with chronic diseases who need continuous and consistent treatment and monitoring over time to ensure the best possible quality of life for them functionally, socially, and psychologically.

3.1 Accelerometers and IMUs technologies

Inertial Measurement Unit (IMU) is an electronic device used to calculate and report the same acceleration, angular velocity, and direction of the body, which can be achieved by using the combination of three sensors: a gyroscope, a magnetometer, and an accelerometer.

Triaxial gyroscopes measure angular velocity, triaxial accelerometers capture linear accelerations, and magnetometers capture the intensity and direction of magnetic fields. This information can determine whether an object is moving, translating, rotating, or tilting the floor. All these parameters are expressed in a coordinate system, and their fusion can be applied to obtain the orientation of these coordinates in a global reference frame for a specific outcome.

The advantages of IMUs are low cost, small volume, lightweight, low power consumption, high reliability, and relatively long data recording duration [123]. In addition, in the context of digital Telerehabilitation, they enable the collection of data, which has proven to be essential in two main scenarios: during the rehabilitation session, the acquired data can be used in real-time to adapt the parameters of the therapeutic session through artificial intelligence algorithms, according to the patient's needs and abilities. At the same time, the raw data stored during the rehabilitation sessions can be visualized and processed later by the therapist to analyze the progress of the patient's health conditions and better plan the next steps of the rehabilitation pathway. Like most wearable devices, they provide objective, quantitative data that allow the therapist to advance clinical considerations and further personalize therapy, making the rehabilitation process patient specific.

Possible critical issues could be the proper application and fixation of the sensors on the previously established body segments on which the patient or caregiver must be instructed, the accuracy of the calibration of the sensors themselves, and the synchronization between inertial devices if more than one is included in the acquisition protocol. Another issue is their placement, which depends strictly on the monitoring target selected for the patient. The number of sensors that must be worn is being investigated to achieve the best possible accuracy of outcomes, ease of use, and application for the patient. In the literature, it tends to range from 1 to 5.

As previously mentioned, the potentiality of serious game-based technologies must be coupled with systems that collect objective data during the rehabilitative session. Significant attention has been paid to inertial measurement units (IMUs) as alternative low-cost tools for human motion tracking, which require easy setup compared to optoelectronic systems. Even if this latter remains the gold standard for motion analysis, it implicates data acquisition in laboratory settings [123,124].

Furthermore, IMUs' advantages include small volume, lightweight, low power consumption, high reliability, and relatively long-life service [120]. Consequently, IMUs have been widely used in sensors-based medical devices to provide accurate kinematics measurements: they are easy to use even by non-expert operators and allow data collection outside the laboratory framework.

Inertial sensors are generally composed of three-axial gyroscopes, which measure angular velocity, three-axial accelerometers for the acquisition of linear accelerations, and they can also integrate magnetometers for the acquisition of intensity and direction of magnetic fields (in this case, they are referred to as MIMU). All these parameters are expressed in a technical coordinate system associated with the inertial sensor case: their fusion using a Kalman filter or a complementary filter can be applied to obtain the orientation of these technical coordinates in a global reference frame [125] Inertial sensors can be affected by various sources of error, so it is essential to apply calibration techniques to improve accuracy and reliability.

Generally, two primary sources of errors (Figure 3) can affect measurements' accuracy and precision. The first depends on the measurement, while the other results from the sensor misalignment concerning human segments. It is worth noticing that motion-tracking technologies used to estimate human joint angles should be attached to the body and rigidly linked to it. However, soft tissue artifacts can appear and affect the accuracy of measurements.

Regarding the system, a further classification can be identified. Sources of noise include random errors that are difficult to compensate for, such as turn-on errors, random noise, and drift caused by long-term operations. Several specific calibration techniques are exploited to compensate for the noise coefficients due to the measurement system itself, given that the sensor fusion algorithm already provides some of these adjustments. Deterministic errors caused by inaccurate calibration or incorrect conversion parameters in the accelerometer datasheet can also occur [126].

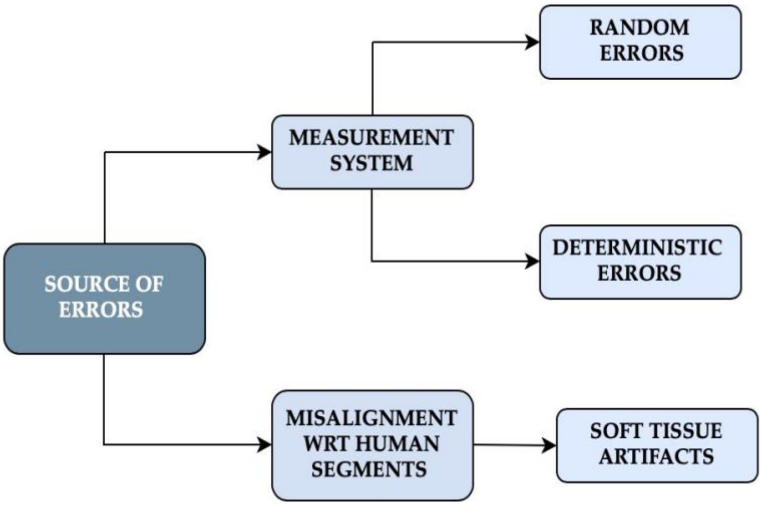


Figure 2: Schematic representation of the typical source of errors in IMUs.

Different categories of calibration procedures have been proposed for the errors resulting from the sensor misalignment concerning the orientation of body segments. Each has advantages and disadvantages in terms of simplicity, speed of implementation, and presumed accuracy. The choice also depends on the application and the subject's physical ability or pathological impairments [120].

In this framework, autonomous calibration procedures can be performed without the assistance of high-precision instruments. They exploit external references such as the local gravity field, the rotational angular velocity of the earth, and the uniform magnetic field to estimate orientations [120].

Static calibration requires the subject to adopt one or two postures during which body segments are anatomically neutral. On the other hand, sensor-to-segment (STS) calibration methods provide for the definition of the axes related to the functional joints since the segment orientations are estimated from parameters collected during precise movements performed around the desired axis. It is necessary to underline that they rely on the hypothesis that the subjects perform a pure rotation as much as possible during the proposed movement [124].

Usually, the different calibration approaches are mixed to achieve the correct orientation by retaining the advantages of static methods for some computation while increasing accuracy in axis definition employing functional methods.

Therefore, when digital sensor-based technologies are used to perform and support rehabilitation therapies, there is a need to identify a trade-off between the desired reliability of measurements and executability by patients.

3.1.1 *Axivity AX-6*

The AX6 is a low-cost logging 6-axis inertial movement sensor (IMU). It comprises a 6-axis movement sensor and a nonvolatile flash memory chip linked by a USB-enabled microcontroller, a temperature sensor, an ambient light sensor, a real-time clock (RTC), and a lithium polymer battery. The light sensor can help determine wearing periods, providing useful environmental data. The temperature sensor measures the internal device temperature, indicating the sensor's external environment, and the LED, emitting different light colors, is controlled via the microprocessor. It is used to tell what state the sensor is in, distinguishing between charging, standby, recording, or communicating to a host computer. The LED also has a "silent" logging mode where the LED is off during recording operation. Through the USB connection with the computer, it's possible to interact with the microprocessor, negotiate battery charging, and keep the time precise. A summary of its specifications is reported in Figure 4.

It's characterized by a charge time of approximately 120 minutes, and the sensor will record for 7 days of continuous 6-axis IMU data at 100 Hz or 34 days of continuous data at 50 Hz. The device is suitable for use in various environments, is water resistant up to 1.5 meters, and is CE safety mark approved. It's used in different applications in human movement science, such as sports research, instrumented environments, digital interaction, and activity recognition.

Regarding the technology and the data acquisitions, the AX6 is a data logger capable of recording raw data from integrated sensors. It features a state-of-the-art 6-axis movement sensor measuring linear acceleration and angular velocity at high precision.

According to the study design and protocol, AX devices could be attached in different sites, mainly on the wrist or on the lumbar, and a typical study protocol might be to configure a device to record within a specific interval, then give the device to be worn by a participant for the specified period without removing it. The maximum duration of a single recording depends on the device and configuration, but this is almost one or two weeks for a typical rate of 100 Hz. If a longer recording is required, a replacement configured unit could be mailed with instructions to swap them over and return the first unit. Whenever a unit is returned, the data can be downloaded, the device recharged, then reconfigured, and sent out to another participant.

Physical Parameter	
Dimensions	23 x 32.5 x 8.9 (mm)
Weight	11g
Environmental Protection	
Moisture Ingress	IPx8 1.5m for 1hr
Dust Ingress	IP6x
Typical Capabilities	
Memory	1024Mb flash non-volatile
Accelerometer Sample Rate	12.5 - 1600Hz Configurable
Battery Life	7+ days @ 100Hz, Accel & Gyro 31+ days @ 50Hz, Accel only
Accelerometer Range	±2 / 4 / 8 / 16 g Configurable
Gyroscope Range	±125/250/500/1000/2000 dps Configurable
Sensor Resolution	16 bit, Accel and Gyro

Figure 3: Axivity AX-6 specifications

According to the study design and protocol, AX devices could be attached at different sites, mainly on the wrist or lumbar. A typical study protocol provides two initial stages: first, the device configuration is to record within a specific interval, and then the device is to be worn by a participant for the specified period without removing it. The maximum duration of a single recording depends on the device and configuration, but this is almost one or two weeks for a typical rate of 100 Hz. If a longer recording is required, a wearable replacement is necessary. The data can be downloaded whenever one is returned, the device recharged, reconfigured, and sent out to another participant.

This tiny device contains two closely coupled MEMs (Micro Electro Mechanical System) sensors, an accelerometer, and a gyroscope. The accelerometer detects linear acceleration (movement) and orientation changes. The gyroscope measures angular velocity (rotation). Both sensors have three high-precision measurement axes. The sensors can be sampled at configurable rates and precision. All sensor locations and orientations are identical to the AX3 for maximum compatibility. All data is stored in its raw unaltered format on the embedded flash memory. The device is ideal for collecting longitudinal movement data. To date, as reported by Salaorni et al. (2024), AX devices have been used in many studies and the neurological field.

An open-source OMGUI Configuration and Analysis Tool is available and free to download to analyze raw data. It’s an application designed to provide different functionalities such as setting up and configuring sensors for recording, downloading, and visualizing recorded data from wearable devices, providing an easy-to-use interface to convert binary accelerometer recordings, and providing access to validated analysis algorithms on recorded data. Figure 5 reports the sensor, its internal composition, and an overview of the OMGUI interface once the device is connected.

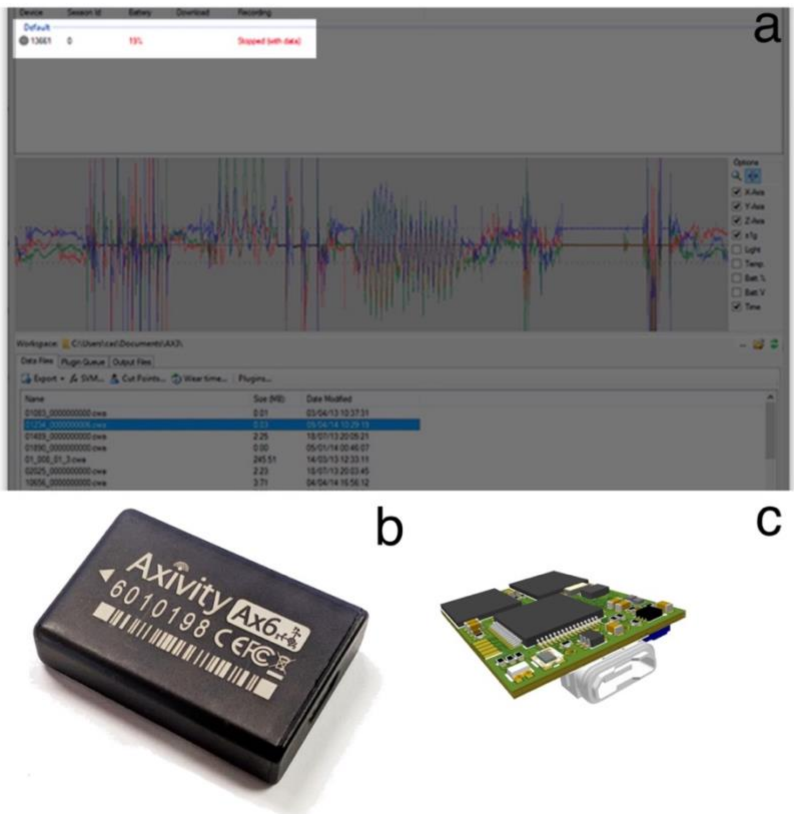


Figure 4: OMGUI interface and AX-6 hardware: a) overview of OMGUI interface once the sensor is connected to the computer after a period of data registration; b) external hardware design, c) internal hardware design

The AX devices record raw, high-frequency data directly from an underlying movement sensor - this ensures the dataset remains useful for any future analysis that you may want to perform. The raw can be loaded into many languages/processing environments, such as MATLAB, R, Phyton, C, and other languages, or indirectly via another file format. The devices are implementations of the Open Movement project (openmovement.dev), and the other components (such as electronic designs, device firmware, supporting software, and documentation) are all open-source and freely available. So, published algorithms can be applied to process the raw data and derive metrics. Some simple analysis methods are available through the open-source OmGui configuration tool; instead, for a richer analysis, there are alternatives. The most popular option in research is the open-source *GGIR* package, which includes sleep analysis and can produce more visual reports. Other analysis toolsets include: biobankAccelerometerAnalysis (from Oxford Wearables Group, Oxford University; Academic Use Licence; but not currently compatible with AX6 data); pampro (MRC Epidemiology, Cambridge University; but not compatible with AX6 data), and mobgap (currently in development).

Moreover, any available algorithm designed to process raw data might also be used, e.g., from a published description of an approach to handling the raw data or open-source code. In addition to the open source software and documentation, other organizations offer expertise in analyzing data from Open Movement devices, including McRoberts, which provides analytics using Open Movement sensors, Dr. Vincent van Heers (author of GGIR analysis package), which offers consulting on movement data including Open Movement sensors, and Dr. Rob Thompson which provides consulting on animal movement.

3.1.2 *Telerehabilitation with IMUs, virtual reality, and serious game*

The sections above highlight the advantages and opportunities of applying serious games and inertial measurement units. Combining these innovative technologies within the framework of neuromotor rehabilitation can stand as a worthwhile and effective means to meet the needs of patients, clinicians, and society.

As previously mentioned, inertial sensors have proven to be portable, affordable, and reliable tools for kinematic analysis. Under these features, they have been exploited to implement easily manageable devices. Furthermore, they provide for data gathering, which has turned out to be essential in two main scenarios: during the rehabilitation session, acquired data can be used in real-time to adapt parameters of the therapeutic session (as the difficulty levels of the objectives to be reached) through artificial intelligence algorithms, according to the needs and capabilities of the patient. At the same time, data stored during the rehabilitative sessions can be remotely visualized by the therapist to analyze the progress of patients' health conditions. Moreover, the therapist relies on objective data to advance clinical considerations and tailor the therapy, making the rehabilitative process patient specific. Accessing data offline also allows the therapist to be constantly aware of the patients' advancements and/or needs, improving continuity of care. Through digital rehabilitation technologies, patients are encouraged to adhere to the training program and be autonomous since such therapeutic solutions do not strictly require real-time monitoring by professionals.
Indeed, when acquired data is used for these purposes, the sensors must be accurately calibrated, and the sources of error must be reduced to an acceptable minimum. Furthermore, sensors should be rigidly fixed to the underlying body segments to measure the human joint angles. However, soft tissue artifacts misalign the sensors' coordinate system concerning the anatomical segments. Thus, there is a need to perform suitable STS calibration procedures to compensate for such inaccuracies and to estimate reliable joint angles. The STS calibration can be applied through several methods: protocols reported in the literature vary regarding movement performed (flexion/extension, abduction/adduction) and amplitude of motion (submaximal, maximal, or not mentioned) [127]. Besides the protocol chosen to perform the STS calibration, the validity and accuracy of the IMU-based system for data acquisition and STS misalignment compensation must be compared to the optoelectronic system, considered the gold standard for motion analysis [125,128].

For example, Zabat M. et al. (2005) proposed an IMU-based STS that integrates multiple static postures of upper limbs in all anatomical planes to evaluate the variation of the misalignment between sensors and body segments in joint angle measurements [125,129]. A comprehensive STS calibration based on multiple steps showed significant improvement in joint angle measurement on the mechanical model and human joint angle compared to those obtained from attached sensors after technical calibration [127]. Thus, a general statement could be that the more rigorous and the less sensitive to soft tissue artifacts the placement of the IMU sensors is, the better the quality of the final joint angle estimation [129,130].
Moreover, in their feasibility study on a wearable biofeedback suit to promote and monitor aquatic exercises, Gandolla et al. (2020) performed an STS calibration in two steps (static calibration step and dynamic calibration step), acquiring and processing data using quaternions. This results in improved computational efficiency, which is crucial for real-time applications and avoiding singularities, especially in body motion estimation.
Ligorio et al. (2017) also introduced a functional two-step procedure to perform the STS calibration on shoulder and elbow joints based on accelerometer and gyroscope data only [130]. Results showed a general agreement between ROMs estimated by the sensors and optoelectronic systems and that the results were reasonably close to the expectations. Moreover, a practical solution was proposed to automatically correct the inaccuracies caused by soft tissue artifacts. In conclusion, this protocol can be proposed as an alternative to current approaches for indoor application.

Regarding serious games, the literature has proved them to be a valuable solution for engaging patients and increasing their adherence to the therapy. The patient is encouraged to perform rehabilitation exercises presented as tasks in virtual environments employing avatars displayed on the screen. Rajkumar et al. (2021) examined a wearable inertial sensor-based system for assessing the upper limb ROM based on exergames regarding usability features and resulted that most of the users found the virtual coach-based tutoring system to be easy to use (82% strongly agreed) and well-integrated (82% agreed or strongly agreed), revealing that they would be confident in using it (88% strongly agreed) and would like to use it (82% agreed or strongly agreed) [131].

One of the main requirements is the design of an intuitive interface to increase the ease of use even by non-experienced patients. Despite their value and accuracy in delivering the therapy and collecting parameters, it is worth explaining that developed games require the intended users to comply with therapeutic regimens and perform the rehabilitation program at home instead of abandoning it as with many existing home rehabilitation programs. The satisfaction of target users with these technologies directly affects their adherence and motivation and, subsequently, the clinical outcomes [131].

Thus, general feedback and preferences for VR rehabilitation games can be assessed through surveys or tailored questionnaires to guide their future development. For example, Garske et al. (2021) conducted a usability study on a serious game for motor rehabilitation of upper limbs, aiming to evaluate usability from the perspective of physiotherapists and patients [132,133]. In addition to surveys, House of Quality analysis has been used for usability outcomes processing, a design-management method to enable product design based on customers' desires. The participants showed a general willingness and optimism toward the serious game under investigation and the hurdles limiting its adoption by both clinics and users.

Another study by Baluz R. et al. (2022) aimed to evaluate the user experience relative to the developed rehabilitative game, demonstrating the positive attitude of physiotherapists and patients and indicating that the game can be used in a clinical trial to be compared with other rehabilitation techniques [133].

In this scenario, it is fundamental to focus the research on measurement tools that can ensure data accuracy and a high level of usability to increase adherence and satisfaction of the intended users, therefore improving clinical outcomes.

3.2 Insoles technologies

Baropodometric insoles are wearable devices capable of detecting pressure forces applied to them and reaction forces generated by the contact of one surface with another, in the specific case of the foot with any surface. They allow the detection of pressure and load applied to different areas of the foot and the distribution of the load under dynamic and static conditions.

Digital baropodometric measures load distribution on the feet during resting and walking. The latter has a significant influence on the walking pattern but also balance in a static position. Incorrect weight distribution can affect the mechanics and proper function of the entire body. It gradually can extend to problems in the foot, knees, hips, and spine, resulting in poor balance conditions in static and dynamic gait and an increased fall risk.

Such devices require insertion into shoes, which can be an obstacle in some situations. However, baropodometric data from a rehabilitation perspective is important in starting diagnosis, monitoring, and planning the treatment plan [120].

The FeetMe ® baropodometric insoles are a wearable medical device that combines 16-foot pressure sensors, accelerometers, and gyroscopes to evaluate the spatiotemporal parameters of the path. An integrated microcontroller calculates the spatial and time parameters of the path in real time. Second, according to the study of Farid et al. (2021), FeetMe ® is the first device that is entirely autonomous and can calculate these parameters without external calculation sources.

Feetme insoles are easy to apply, thanks to an app installed on wearable devices, and they can be used for balance and gait assessment in both clinical and home environments. Once installed inside shoes, the insoles, equipped with pressure and inertial sensors, can accurately calculate a range of gait parameters with each step. FeetMe provides the application with real-time biofeedback directly installed on the smartphone and a dashboard that allows remote monitoring and rehabilitation and evaluation programs. To be used, once connected to the application via Bluetooth, one must go through the calibration process, register the subject to create a specific folder for the tests performed, and finally, choose the type of test to be submitted. If assessments are to be performed, one can choose between posturographic tests, i.e., stabilometry with open or closed eyes, and dynamic tests, i.e., walking tests such as free walking, 10-metre tests, and six-minute tests. If rehabilitation sessions are to occur, static, dynamic, and long-term programmed exercises are available.

Regardless of the tool used, the phases of the gait cycle and the corresponding times are precisely identified using pressure sensors inside the insoles, and distances are estimated by the high-performance built-in algorithms that gather information from the inertial sensors. The result is a high-precision recording of spatiotemporal parameters.

Once the test recording is finished, the data is automatically saved, and a PDF with the test report and analysis, obtained using neural networks and artificial intelligence, is displayed.

Through the FeetMe Mobility dashboard, designed to provide easy access and in real-time, patient data can be used to download raw data of different spatiotemporal gait or balance parameters. The inertial and pressure sensors extract useful parameters for gait and balance analysis, including plantar pressure measurements, the center of pressure evolution, ground reaction force, spatiotemporal rhythm, variability, and asymmetry parameters. On the dashboard, in addition to the raw data, a report is provided in which it is possible to have a summary of the progress of the test and a frame-by-frame visualization of the test itself in terms of pressure, load management, and any asymmetries.

Therefore, this medical device can collect real-time gait data to assess an individual's health status and disability levels with physiotherapy intervention.

FeetMe insoles have been validated as medical devices, and their usability in Parkinson's, post-stroke, and elderly subjects has been verified.

3.3 Smartphone and smartwatch

Smartphones and smartwatches are ubiquitous devices, a significant advantage since they are now globally spread. The ease of use and convenience of wearing them require less training and familiarization to the patient using them. On the other hand, they have a significantly reduced capacity for data collection regarding measurable parameters compared to IMUs, accelerometers, and insoles, as they possess accelerometers inside them. Still, their location during use doesn't allow discrimination of specific parameters and outcomes. Data collection is based on the number of steps, speed of gait, and thus also activity time. Despite their limitations, they are functional and valuable in gait analysis[120]

3.4 Clinical applications

Motion acquisition systems (motion capture and force platforms) are the gold standard for motion analysis. These systems are typically used to assess parameters that characterize gait, but they are expensive, non-portable, and usable only in laboratory settings. Recent studies support using IMUs or other wearables to objectively assess the movement of people with disabilities, demonstrating their validity over motion capture systems [134].

In the clinic, five main application areas of wearable devices have been analyzed and studied: early diagnosis, tremor analysis, body movement analysis, motor fluctuations (such as ON-OFF phases in PD patients), home and long-term monitoring. The aim is to obtain an overview of the pathology at each stage of development, from the beginning of the disease (first symptoms) to the disease progression, with an analysis of the most common disorders. It would improve the management of the most complicated situations (i.e., motor fluctuations), general symptomatology, and long-term remote monitoring. Wearable sensors could be essential in helping clinicians with early diagnosis, differential diagnosis, and objective quantification of symptoms over time.

Relative to diagnosis, in people with neurological diseases, such as PD, the neurologist diagnoses the condition by asking the patient to perform tasks defined in the MDS-UPDRS [135] and assessing the patient through visual examination [136]. This subjective assessment is based on the physician's experience and can vary from one neurologist to another, sometimes making the diagnosis inaccurate or uncertain. In addition, invasive neuroimaging techniques with high healthcare costs are generally adopted to confirm the diagnosis. For these reasons, several research groups have been working in recent years to find a method to objectively quantify patients' motor performance during the proposed MDS-UPDRS III items, as motor symptoms generally lead the neurologist to the diagnosis. These devices must be tested comprehensively, not only for the typical items proposed in MDS-UPDRS III (diagnosis) but also for ADLs and other tasks of daily living [137], so that their use can be extended for a greater range of use in neurological disorders.

Wearable sensors have demonstrated their potential relative to body motion analysis, especially in detecting posture, gait, and asymmetry [137]. Using inertial sensors combined with advances in short-range communication technologies (e.g., Bluetooth) meets the needs of people with chronic conditions due to their low power consumption, non-invasiveness, lightweight, and ease of use [138].

In patients with neurological diseases, symptoms of postural instability are common and can lead to complications, worsened QoL, and an increased risk of accidents and falls, further worsening the overall situation. Sant 'Anna et al. (2011) focused on gait analysis and evaluation of both leg movements and arms sway, showing that the asymmetry between the left and right sides in people with PD is more significant than in HC, particularly for the upper limbs [139,140]. The idea is to recognize pathologically abnormal postures and attitudes as early as possible to make interventions at the earliest stage. Using inertial sensors on different body parts seems promising for objectively estimating gait parameters [140]. Parisi et al. (2016) focused on developing a comprehensive biomechanical analysis to measure parameters such as joint range of motion, ankle dorsiflexion, toe flexion, and other parameters. They studied the advantages of using these features in artificial intelligence algorithms [20].

Trojaniello et al. (2014) confirmed that a single IMU placed on the lower back (lumbar area) can discriminate gait parameters but showed impaired gait impairments in healthy subjects [141]. In contrast, Del Din et al. (2016) obtained good results in pathological subjects, claiming that a single accelerometer on the lower back is sufficient to measure gait characteristics, including asymmetry and variability [140,142]. The placement and number of sensors remain an open question.

In Parkinson's patients, IMUs have been used alone or with other sensors to improve the detection of FOG (freezing of gait) events. Another study proposed applying the IMU to the wrist, as upper limb movement is highly correlated with FOG events.

Additional information on gait cadence may improve the sensitivity and specificity of FOG event detection, avoiding the detection of false events [142]. Another study proposed a dynamic neural network to capture the time-varying nature of FOG, as the method allowed them to learn how representative features of FOG events can change over time. The difficulty of detecting FOG is its unpredictability, making it preferable to test wearable sensors in everyday situations and not while performing structured tests (e.g., TUG tests) in clinical settings.

In this direction, a smartphone-based system could be a viable solution, allowing patients to use the system during daily activities without inconvenience [142].
Smartphone-based solutions or smartwatches can be innovative in wearability because sensors are hidden in standard tools and can accurately count steps. However, these solutions don't allow for measuring clinical features of interest, such as stride length; therefore, complete motion analysis and direct comparison with other systems are impossible and should be implemented with other sensing units. For this purpose, baropodometric insoles could be integrated into other devices to obtain a complete picture of the gait pattern.
For future implementations, the gait analysis results must be shown immediately after the test is performed through the development of semi-automated operations or dedicated applications available on smartphones to enable real-time gait analysis.

So, sensor-based systems can improve the diagnosis of neurological patients in the early stages of the disease by measuring parameters not accurately identified by traditional tests and distinguishing between mild and moderate stages. In recent work, Baston et al. (2016) proposed using IMU to quantify postural strategy and gait dispersion between HC and Patients with Parkinson's Disease at different stages of the disease [143]. In contrast, Mancini et al. (2016) focused on APA (Anticipator Postural Adjustments) before gait onset and the first step, a state that is not easily observed with the naked eye [143,144]. The system resulted in high test-retest reliability for HCs and patients, and data measured by IMUs were highly correlated with those derived from validated systems.
Thus, the wearable sensor approach would generally allow a more straightforward quantification of postural alterations than the conventional protocol with a force

platform, which is more expensive and non-transportable. APA and postural sway, both in ML (mediolateral) and AP (anteroposterior) directions, are the most analyzed features that can differentiate patients with postural and HC disorders in the early stages of the disease [145], as well as between mild and severe PD groups for differential diagnosis or between ON/OFF groups.
Such sensors have also been used to measure tremors. From a technical point of view, using triaxial inertial sensors can provide a detailed investigation of tremor detection. Since tremor assessment is based on the neurologist's visual examination, technological solutions that quantify disease severity and therapy efficacy provide an optimal solution with low invasiveness and reliability.
Relative to motor fluctuations affecting neurological patients, in literature, several articles reported studies on using an inertial sensor to monitor them, especially in an advanced stage of disease, and to assess response to therapy. Patel et al. (2020) proposed monitoring motor fluctuations, assessing dyskinesia and bradykinesia, and measuring acceleration intensity, modulation, frequency, regularity, left- and right-sided coordination, and entropy in continuous monitoring. These studies identified the different motor states and quantified treatment efficacy and symptom features (bradykinesias, dyskinesias, freezing of gait, and others).

Therefore, allowing the system to be used at home in an unsupervised setting is critical.
For example, studying and identifying motor fluctuations in PD patients is challenging in long-term management. When a patient is in the OFF phase, their condition may be considered critical. The patient may be prone to FOG events with a risk of falls, significant tremors, and general difficulty performing daily activities. Usually, this situation doesn’t occur when the patient is undergoing inpatient medical examination or outpatient monitoring. Hence, monitoring the subject at home during the day is essential to identify and prevent these critical events.
Finally, related to home and long-term monitoring, the European research project CuPiD, for example, developed a system consisting of IMUs and a smartphone-based application to provide an efficient home gait training application for people with disabilities [145]. The system improved gait and balance in people with disabilities more effectively than traditional home-based gait intervention and

follow-up checks. Other works, however, required the performance of ADLs or similar daily activities, while other work aimed to monitor patients, possibly even overnight continuously. In measurements, a wide range of characteristics has been extracted for long-term home monitoring, including statistical and frequency characteristics, gait parameters, and many others.

In addition, to ensure optimal management during home monitoring, it's necessary to develop and provide user-friendly interfaces that allow physicians and patients to stay in touch, adopting a telemedicine service to exchange information, advice, and therapeutic adjustments based on the data collected. Real-time and automated assessment of patient performance are other cornerstones for developing an adequate remote support and monitoring system. It makes it possible to assess the status of patients on demand, including evaluating any changes due to modification of pharmacological or rehabilitative treatment or progression of pathology, as well as objective assessment of the effectiveness of the therapy adopted [117].

4. Niurion for upper limb rehabilitation

The upper limb is a complex human body structure with a morphology that enables precise movements and a broad range of motion (ROM) across joint angles, as illustrated in Figure 6. When motor dysfunctions of the upper extremities occur and ROM becomes restricted, daily activities (ADLs) are often performed using compensatory movements or assistance from caregivers and adaptive devices, which can negatively impact the quality of life [146]. Additionally, trunk stabilization plays a critical role in the accuracy and quality of upper limb movement [147].

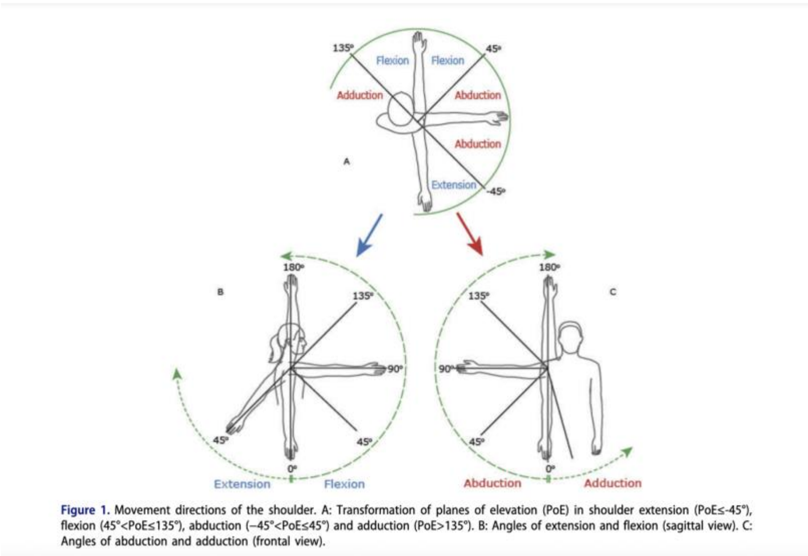


Figure 5: Directions of the shoulder movements. On the upper side, the transformation of planes of elevation (PoE) in shoulder extension, flexion, abduction, and adduction; on the lower left side, the angles of extension and flexion (sagittal view); on the lower right side, the angles of abduction and adduction (frontal view)

Rehabilitation to maintain or restore upper limb capabilities is fundamental to improving functionality and reducing the medical burden on families and society. Upper limb rehabilitation is a rapidly advancing field in modern neurorehabilitation [148]. Traditional therapy involves repetitive motion exercises administered by medical professionals, but it often requires extensive time due to limited human and technological resources [149]. Consequently, emerging technologies like robotic devices aim to enhance patient engagement and treatment efficacy [150]. However, these solutions often require clinical settings and specialized personnel and are costly for healthcare systems and patients.

Research is increasingly focused on developing affordable upper-limb rehabilitation systems that non-expert patients can use outside hospitals. These systems strive to balance cost-effectiveness with therapeutic efficacy while promoting patient adherence. In collaboration with daVi Digital Medicine s.r.l. (Verona, Italy), a protocol was created to evaluate the accuracy of NiuRion, a digital rehabilitation device.

4.1 Niurion hardware and software

NiuRion, later rebranded as Aureha, is a digital rehabilitation device designed to assist patients with neuromotor disorders or musculoskeletal conditions, such as variations in muscle tone or reduced strength. It enables home-based rehabilitation sessions using a sensorized shirt integrated with gamified software. Developed by P2R s.r.l. (Play To Rehab), NiuRion provides medical interventions and measures therapy outcomes. Key benefits include improved upper limb functionality, personalized exercises, and enhanced adherence to treatment through gamification.

Physicians can monitor therapy progress in real-time through a dedicated software interface, leveraging data from sensors embedded in long-sleeved shirts made of 95% viscose and 5% elastane. These shirts feature five numbered and color-coded pockets for sensor placement (Figure 7).

NiuRion software includes two interfaces: one for patients and another for physicians. Physicians can customize therapy by locking or unlocking exercises, analyzing session scores, and comparing results to ensure continuity of care. Instead, patients use their interface to control an avatar in a virtual environment, guided by vocal and visual instructions during a calibration phase. Initially, patients choose a game level and complete a tutorial, followed by specific movements repeated three times to set an initial ROM target. During sessions, patients strive to reach or exceed these targets, which are progressively adjusted by the algorithm to encourage improvement. While not clinically significant, game scores help patients track progress and motivate adherence. Graphical and numerical session data representations are available for patients and physicians (Figure 8).

Figure 6: Niurion hardware

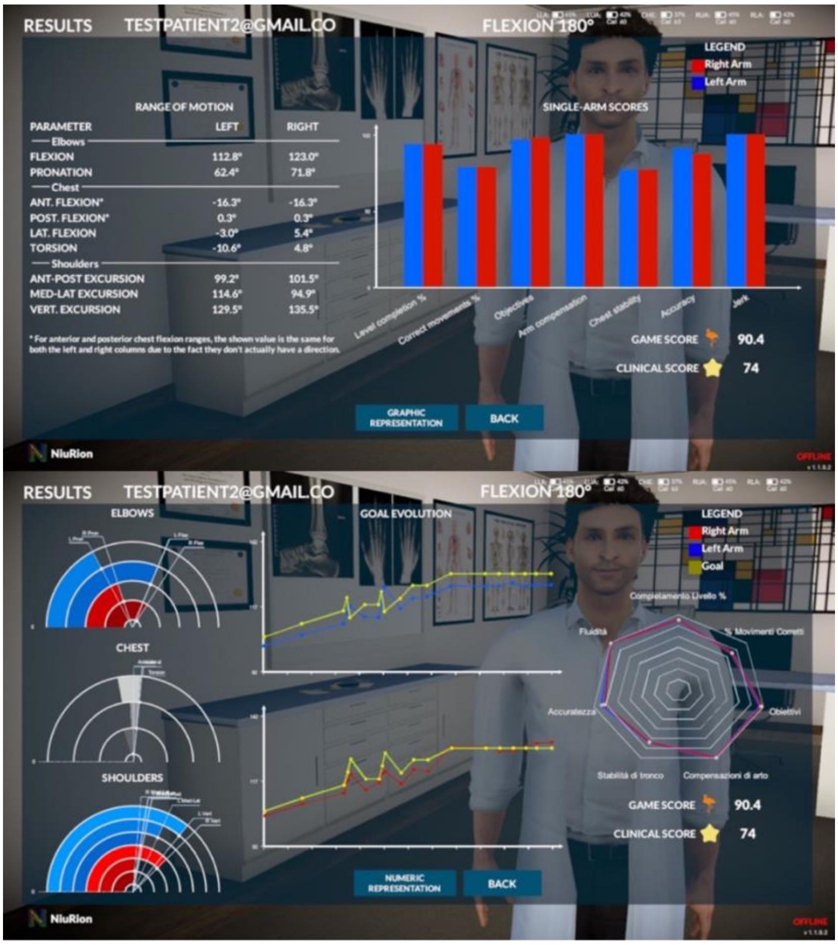


Figure 7: Numerical and graphical results representation

Outcomes parameters comprehend the measures of joint angles and the calculation of the seven scores: achievement of the objective (%), trunk strategies of compensation measured (average inclinations of the trunk in the principal planes), arm strategies of compensation, accuracy (displacement from the predefined trajectory), movement fluidity (as jerk, the derivative of acceleration measure), percentage of the completion of the level, rate of correct movements calculated (as amount of target reached for all the objectives).

The average over the entire session is computed for all five scores and shown in the graphical and numerical representations of the results; instead, the clinical score is calculated as the weighted average (depending on the parameters considered relevant for each exercise from the physiotherapists) comprehensive of all the individual scores.

NiuRion demonstrates promise as an innovative device that enables home-based therapy with asynchronous monitoring by therapists and promotes continuity of care. Moreover, NiuRion grants continuity of care, which is core to attaining an effective clinical outcome.

While NiuRion provides joint angle estimations based on sensor orientations in 3D space, it relies on the calibration phase (before starting exercises) to align sensor data with anatomical reference frames. So, anatomical joint angles obtained from the orientation of the body segments to the sensors are attached, but it's an estimation and not an absolute reference.

For this reason, this pilot confirmatory study aimed to assess the accuracy and robustness of the Niurion sensor and algorithm with an optoelectronic system, which assumed the gold standard. It also evaluated NiuRion's advantages, limitations, and usability to define the features to be improved in further device versions.

This wearable device was in the preliminary development stage, so the study was classified as an early feasibility clinical investigation.

4.2 Confirmatory study protocol

A validation protocol was designed to assess NiuRion as a measurement device following the Sensor-to-Segment (STS) calibration procedure, which defines axes related to functional joints. NiuRion data from selected movements were compared to simultaneous measurements from the Vicon Nexus system, a gold standard of motion-tracking standard.

Using Vicon's Upper Limb Model (ULM) plug-in for precise kinematic descriptions, 20 healthy subjects (11 females, nine males) wore NiuRion shirts fitted with 24 passive markers placed by a single researcher to minimize operator-dependent errors (Figure 9). Sensors were activated before connection to ensure consistent calibration settings, and exercises followed a metronome set at 21 bpm for synchronization.

The sensors were turned on before the connection with the computer and have remained switched on for the entire acquisition duration to rely on the same calibration procedure setting and the exact orientation of offset quaternions, which change every time sensors are switched on. Moreover, a synchro movement (flexion of the elbow starting from N-pose with thumbs pointing forward in the sagittal plane) has been performed at the beginning and at the end of each acquisition to obtain a better synchronization among the Vicon and sensor signals in the post-processing and data analysis procedures.

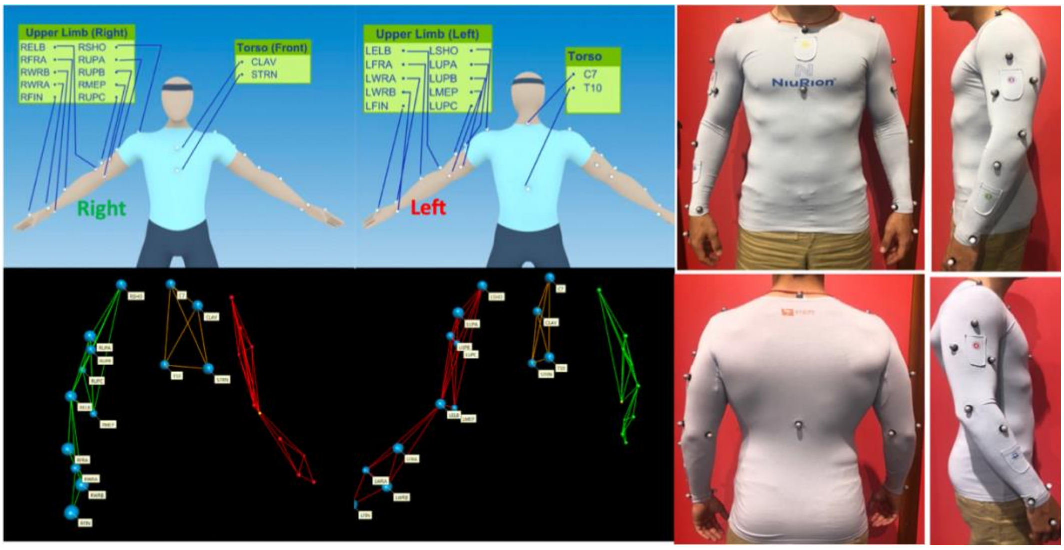


Figure 8: Markers' placement in the validation protocol and kinematic Vicon model

Different exercises were executed after the calibration phase of the NiuRion sensors and subsequent alignment between the reference frames of NiuRion and Vicon system environments.
First, a humeral flexion at 90° was repeated 10 times as the target movement in level 4 of NiuRion. Then, the subject performed a simultaneous left and right elbow flexion until 90° for 10 repetitions, as the target movement in level 2 of NiuRion.

To analyze data, once acquired, outputs from NiuRion and Vicon have been imported into MATLAB. Vicon measurements have been resampled at 50 Hz, corresponding to the sensor sampling frequency. Then, datasets were synchronized thanks to the calibration phase, and, finally, averaging the 10 repetitions, one single movement repetition was obtained.
Concerning the ULM model, joint angles have been represented by Euler angles according to the following conventions:

- XZY convention for shoulder joints (flexion/extension, abduction/adduction, internal/external rotation).
- XZY for the elbow's joints, corresponding to flexion/extension, carrying angle (always set to zero), and pronation/supination.

To relate sensor and Vicon data to the same coordinate system, the Vicon anatomical reconstructed reference frame has been used as the anatomical reference frame in the STS calibration procedure.
The comparison between joint angles acquired by NiuRion sensors and Vicon has consisted of a within-subject cross-sectional design since the same measures have been acquired with two different systems for 20 healthy participants.
At first, the maximum of the absolute values of each joint angle along the three axes of rotation have been computed to identify the widest ROM performed during the tests. The mean of these ROMs acquired by sensors has been calculated among the 20 tests for every axis of rotation, and they have been compared to Vicon-derived measurements to assess the consistency of the movements to the requests and gain a preliminary insight into the accordance between measures collected by the two

systems. Then, the Pearson correlation coefficient was calculated for ROMs associated with the joints under investigation (left shoulder, right shoulder, left elbow, and right elbow).

The elbow's carrying angles have always been zero in Vicon measurements. Therefore, the comparison of ROMs along the Z-axis has not been assessed. Moreover, Root Mean Squared Errors for parameters related to the X, Y, and Z axes have been calculated to evaluate the incidence of differences in measures between the joints and the axes.

Results have shown that the STS calibration procedure is a valuable instrument for the computation of anatomical joint angles, which could be more useful for a reliable assessment of ROMs during rehabilitation sessions concerning measurements relying on the sensors' position in 3D space only. The calibration procedure has compensated for the misalignment between the sensors and the body segments, producing the expected anatomical joint angles. The calibrated signals reproducing 90° humeral flexion have maintained the predominant component of rotations on the X anatomical axis for the left and right shoulder, significantly reducing the angles related to the Z-axis. Moreover, the procedure has minimized left and right elbow flexion angles coherently with the expected outcomes: the anatomical angle between shoulder and elbow joints during humeral flexion with straight arms should be negligible. However, when significant internal/external rotations have occurred in raw data, the STS calibration procedure has not managed to minimize them, and therefore, angle components around the Y-anatomical axis have been not negligible Concerning the comparison of off-line calibrated data from NiuRion sensors to Vicon Nexus optoelectronic system, measurements acquired by them have shown to be highly correlated to the predominant axis of the movement (X-axis) both for humeral flexion and elbow flexion and this has been demonstrated by significant Pearson's coefficients.

The correlation of measurements related to the Z-axis and Y-axis, which refers to abduction/adduction and rotations, haven't been significant: these results have accounted for discrepancies between the two measurement systems. Of course, an ideal humeral or elbow flexion could not be performed entirely in the sagittal plane, leading to the presence of angles in the other axis of rotation.

Moreover, inaccuracies due to soft tissue artifacts, especially concerning the upper arms, could affect the estimation of shoulder joint angles for inertial sensors and Vicon systems. Significant rotation values in Vicon outcomes were probably due to the markers placed on the shirt instead of the subjects' skin.

The divergence of the measurements in the Y-axis and Z-axis could be explained by the calibration protocol implemented in MATLAB and applied on sensors, which is different from the protocol exploited by the Upper Limb Plug-in to compute joint angles. In the STS procedure, the longitudinal axis of the anatomical reference frames (correspondent to the reaction to gravity from accelerometer readings) has been considered a reference unit vector to estimate the calibration quaternion. Instead, the longitudinal axis of anatomical coordinates provided by Vicon is not strictly vertical, so when these coordinate systems are exploited as anatomical reference frames in the STS calibration protocol, the observed unit vectors in the sensor's reference frame do not always correspond to the orientation of the reaction to gravity. From measuring the longitudinal direction during the STS calibration, all the other steps follow with the risk of introducing inaccuracies resulting in measurement errors.

Errors in the Z-axis and Y-axis, which occur in the comparison of NiuRion with the Vicon system, cannot be considered negligible since they reduce the accuracy of the inertial sensors' measurement system. Besides the presence of soft tissue artifacts and the mismatch between protocols for anatomical axis reconstruction, it is interesting to notice that significant components in the non-preferential axes of movements occur in raw data. Although STS has reduced them, the calibration has not minimized them completely.

Thus, criticalities may have occurred because of insufficient accuracy of the initialization procedure performed in MATLAB. Moreover, besides the angular-grid algorithm implemented in the STS calibration protocol, which has increased accuracy in estimating the mediolateral axis for simulated data, it has not produced significant improvements in real-world settings, suggesting further algorithm optimization.

Results from this work have suggested that STS calibration is an essential procedure for assessing anatomical joint angles, even though some criticalities exist.

In assessing NiuRion from both a technical and usability perspective, results have suggested it as a promising digital rehabilitation device. The combination of effective strategies for optimizing the initialization and the calibration procedure could demonstrate its reliability as a portable measurement system suitable for home-based applications. Measurements should be precise enough to reveal improvements in patients with impairments such as limited ROMs during the therapeutic pathway. Moreover, data acquired by NiuRion should be suitable and reliable for therapists to monitor the progress of the therapy and deliver rehabilitation interventions tailored to patients' needs.

In this regard, the usability study has provided promising results from both the patients' and therapists' perspectives, proving that NiuRion is also easy for non-expert patients to use.

A further design of the NiuRion shirt is being developed, considering the involvement of integrated sensors on the shirt to overcome difficulties in placing the sensors in patients' pockets.

In conclusion, patients, therapists, and the healthcare system could benefit from integrating NiuRion in standard rehabilitative interventions since it could significantly contribute to the digital transformation already in place.

5. Wearable devices for gait and posture monitoring in people with movement disorders and MS: a Systematic Review

The rapid development and accessibility of portable and wearable technologies significantly enhance the scope of technology-driven objective measures (TOMs) in managing neurological disorders. These advancements can potentially revolutionize patient care by providing more precise and continuous monitoring of motor functions. However, significant challenges remain in identifying TOMs that are clinically meaningful, ensuring their reliability for real-time gait and activity assessment in everyday life settings, and integrating them into telerehabilitation systems to facilitate a transition toward digital rehabilitation.

This systematic review was conducted to address these gaps by analyzing the use of wearable devices for monitoring gait and posture in patients with movement disorders and Multiple Sclerosis. The primary aim was to synthesize state-of-the-art knowledge regarding the clinical populations targeted, the types of devices utilized, and the specific clinical purposes for which these technologies were employed. By doing so, we sought to provide a foundation for enhancing the adoption of wearable technologies in clinical practice and advancing their integration into digital health systems[117].

We registered the protocol of this systematic review in the PROSPERO database (CRD42022355460). We followed the Preferred Reporting Items for Systematic Reviews and Metanalyses (PRISMA) guidelines during the review process (ref PRISMA).

5.1 Search Strategy and Data Collection

We conducted a literature search from May 2022 to September 2022. PubMed, SCOPUS, COCHRANE LIBRARY, and SPORTDiscus databases were selected as the source of research. Specifically, search strategies have been defined using specific terms and keywords in the title or abstract. In particular, the terms ‘movement disorders,’ ‘multiple sclerosis,’ ‘wearable technology,’ ‘gait,’ and ‘posture’ were combined:

- **PubMed**: ((((telerehabilitation OR "remote rehabilitation" OR "virtual rehabilitation" OR "home rehabilitation" OR telemedicine OR "virtual medicine" OR "mobile health" OR mhealth OR telehealth OR "tele referral") AND (accelerometer OR imu OR "inertial measurement unit" OR smartphone OR smartwatch OR "wearable device" OR "wearable technology" OR "wearable electronic device" OR "wearable sensor")) AND (gait OR postur* OR "musculoskeletal equilibrium")) AND ("MULTIPLE SCLEROSIS" OR "Movement Disorder" OR "Dyskinesia Syndrome" OR "Etat Marbre" OR "Status Marmoratus" OR Akathisia OR Acathisia OR "Angelman Syndrome" OR "Puppet Children" OR Dyskinesia OR "Abnormal Movement" OR Hemiballismus OR Hemiballism OR "Involuntary Movement" OR Asterixis OR Ballismus OR Chorea OR Choreiform OR Choreatic OR Dystonia OR distonic OR "Vitus Dance" OR "Acanthocytosis" OR "Levine Critchley Syndrome" OR "Writer Cramp" OR "Oppenheim Ziehen Disease" OR "Progressive Torsion Spasm" OR "Childhood Torsion Disease" OR "Brueghel Syndrome" OR "Essential Tremors" OR "Familial Tremor" OR "Hepatolenticular Degeneration" OR Pseudosclerosis OR "Wilson Disease" OR "Hepatocerebral Degeneration" OR "Westphal Strumpell Syndrome" OR "Copper Storage Disease" OR "Progressive Lenticular Degeneration" OR "Neurohepatic Degeneration" OR "Multiple System Atrophy" OR "Multisystem Atrophy" OR "Olivopontocerebellar Atrophies" OR "Olivopontocerebellar Atrophy" OR "Dejerine Thomas Syndrome" OR "Presenile Ataxia" OR "Olivopontocerebellar Degeneration" OR "Shy Drager Syndrome" OR "Dysautonomic Orthostatic Hypotension" OR "Dysautonomia Orthostatic Hypotension Syndrome" OR "Progressive Autonomic Failure" OR "Idiopathic Orthostatic Hypotension Shy Drager Type" OR "Striatonigral Degeneration" OR "Striatonigral Atrophy" OR "Striatonigral Atrophies" OR "Pantothenate Kinase-Associated Neurodegeneration" OR "Pantothenate Kinase Associated Neurodegeneration" OR "Hallervorden Spatz Syndrome" OR "Neurodegeneration With Brain Iron Accumulation 1" OR "Pigmentary Pallidal Degeneration" OR "Juvenile Onset Neuroaxonal Dystrophy" OR "Hallervorden Spatz Disease" OR "Pigmentary Pallidal Atrophy" OR "Parkinsonian Disorders" OR "Parkinsonian Syndrome" OR "Parkinsonian Syndrome" OR "Parkinsonian Disease" OR Parkinsonism OR "Parkinson Disease" OR "Ramsay Hunt Paralysis Syndrome" OR "Lewy Body Disease" OR "Lewy Body Dementia" OR "Parkinson Disease" OR "Paralysis Agitans" OR "1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine

Poisoning" OR "MPTP Neurotoxicity Syndrome" OR "MPTP Induced Degeneration of the Striatum" OR "Progressive Supranuclear Palsies" OR "Steele Richardson Olszewski Syndrome" OR "Richardson Syndrome" OR "Steele Richardson Olszewski Disease" OR "Progressive Supranuclear Palsy" OR "Progressive Supranuclear Ophthalmoplegia" OR "Tic Disorder" OR "Tourette Syndrome" OR "Tourette Disease" OR "Tourette Disorder"))

- **SCOPUS:** "MULTIPLE SCLEROSIS" OR "Movement Disorder" OR "Dyskinesia Syndrome" OR "Etat Marbre" OR "Status Marmoratus" OR Akathisia OR Acathisia OR "Angelman Syndrome" OR "Puppet Children" OR Dyskinesia OR "Abnormal Movement" OR Hemiballismus OR Hemiballism OR "Involuntary Movement" OR Asterixis OR Ballismus OR Chorea OR Choreiform OR Choreatic OR Dystonia OR distonic OR "Vitus Dance" OR "Acanthocytosis" OR "Levine Critchley Syndrome" OR "Writer Cramp" OR "Oppenheim Ziehen Disease" OR "Progressive Torsion Spasm" OR "Childhood Torsion Disease" OR "Brueghel Syndrome" OR "Essential Tremors" OR "Familial Tremor" OR "Hepatolenticular Degeneration" OR Pseudosclerosis OR "Wilson Disease" OR "Hepatocerebral Degeneration" OR "Westphal Strumpell Syndrome" OR "Copper Storage Disease" OR "Progressive Lenticular Degeneration" OR "Neurohepatic Degeneration" OR "Multiple System Atrophy" OR "Multisystem Atrophy" OR "Olivopontocerebellar Atrophies" OR "Olivopontocerebellar Atrophy" OR "Dejerine Thomas Syndrome" OR "Presenile Ataxia" OR "Olivopontocerebellar Degeneration" OR "Shy Drager Syndrome" OR "Dysautonomic Orthostatic Hypotension" OR "Dysautonomia Orthostatic Hypotension Syndrome" OR "Progressive Autonomic Failure" OR "Idiopathic Orthostatic Hypotension Shy Drager Type" OR "Striatonigral Degeneration" OR "Striatonigral Atrophy" OR "Striatonigral Atrophies" OR "Pantothenate Kinase-Associated Neurodegeneration" OR "Pantothenate Kinase Associated Neurodegeneration" OR "Hallervorden Spatz Syndrome" OR "Neurodegeneration With Brain Iron Accumulation 1" OR "Pigmentary Pallidal Degeneration" OR "Juvenile Onset Neuroaxonal Dystrophy" OR "Hallervorden Spatz Disease" OR "Pigmentary Pallidal Atrophy" OR "Parkinsonian Disorders" OR "Parkinsonian Syndrome" OR "Parkinsonian Syndrome" OR "Parkinsonian Disease" OR Parkinsonism OR "Parkinson Disease" OR "Ramsay Hunt Paralysis Syndrome" OR "Lewy Body Disease" OR "Lewy Body Dementia" OR "Parkinson Disease" OR "Paralysis Agitans" OR "1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine Poisoning" OR "MPTP Neurotoxicity Syndrome" OR "MPTP

Induced Degeneration of the Striatum” OR “Progressive Supranuclear Palsies” OR “Steele Richardson Olszewski Syndrome” OR “Richardson Syndrome” OR “Steele Richardson Olszewski Disease” OR “Progressive Supranuclear Palsy” OR “Progressive Supranuclear Ophthalmoplegia” OR “Tic Disorder” OR “Tourette Syndrome“ OR “Tourette Disease” OR “Tourette Disorder” AND gait OR postur* OR "musculoskeletal equilibrium" AND accelerometer OR imu OR "inertial measurement unit" OR smartphone OR smartwatch OR "wearable device" OR "wearable technology" OR "wearable electronic device" OR "wearable sensor" AND telerehabilitation OR "remote rehabilitation" OR "virtual rehabilitation" OR "home rehabilitation" OR telemedicine OR "virtual medicine" OR "mobile health" OR mhealth OR telehealth OR "tele referral"

- **COCHRANE LIBRARY**: ("Wearable Electronic Devices"[Mesh] OR cloth* OR shirt OR telemedicine) AND ((("Posture"[Mesh] OR "Postural Balance"[Mesh]) OR ("Gait"[Mesh])) AND (("Movement Disorders"[Mesh]) OR ("Multiple Sclerosis"[Mesh]))) AND "y 10"[Filter]
- **SPORTDiscus**:((gait)+OR+(posture))+AND+(((wearable+AND+devices))+OR +(shirt)+OR+(telemedicine)+OR+((smart+AND+cloth*)))+AND+((Parkinson) + OR +(dystonia))

We included studies published within the last decade, from 2012 to August 2022. The focus was on adult patients diagnosed with Movement Disorders (such as Parkinson’s disease, Dystonia, Functional Motor Disorders, and Huntington’s chorea) and Multiple Sclerosis, considering both acute and chronic phases of these conditions. Studies involving other neurological or psychiatric conditions, pediatric populations, or healthy adults were excluded.

Only studies utilizing wearable devices for gait and posture monitoring in real-life settings as part of telemedicine approaches were included, while those involving robotic devices were excluded. Eligible study designs comprised case series, randomized controlled trials (RCTs), quasi-randomized controlled trials (quasi-RCTs), controlled clinical trials (CCTs), and observational studies written in English. Conversely, case reports and single-case studies were not considered.

We also excluded studies on upper limb function, animal models, wearable devices used solely in controlled laboratory settings, and e-health applications. To qualify, studies needed to involve adult participants in either the early or chronic stages of movement disorders or Multiple Sclerosis and assess gait and posture using wearable technology in naturalistic environments [151,152]. Exclusion criteria encompassed studies involving participants younger than 18, those evaluating gait and mobility exclusively in hospital or laboratory settings, and those centered on e-health applications. A summary of all inclusion and exclusion criteria is provided in Table 13.

Table 6: Synthesis of inclusion and exclusion criteria

Inclusion criteria	- Any wearable devices used for monitoring gait and posture combined with telemedicine. - Adult patients affected by Parkinson's disease, Dystonia, Functional Motor Disorders, Huntington Corea, and Multiple Sclerosis. - RCTs, quasi-RCTs, CCTs, and observational studies.
Exclusion criteria	- Other neurological diseases - Psychiatric diseases, Children, Healthy adults. - All studies not considering telemedicine intervention, devices for upper limb - Animals - All studies considering robotics devices - All studies considering e-health applications - Case reports

PICO criteria were population (P) movement disorders and multiple sclerosis; intervention (I) wearable technology; comparator (C) not applicable; outcome (O) gait and posture. The PICO model used for this review is reported in Table 14.

Table 7: PICO Model

P (Participants)	Movement Disorders and Multiple Sclerosis
I (Intervention)	Wearable Devices, Telemedicine
C (Comparator)	/
O (Outcome)	Gait and Posture

Two independent reviewers screened records, starting with titles and abstracts, to determine their eligibility for inclusion. Any disagreements that arose during this phase were resolved through discussion. The same two reviewers extracted data from the selected full-text articles and systematically organized them using a predefined data extraction sheet. The screening process was conducted concurrently using the Rayyan online platform to enhance efficiency and reliability.

The data extraction sheet was structured into three subsections: study characteristics and clinical aspects, technical aspects, and telemonitoring and teleconsulting.
The first is study characteristics and clinical aspects. This section captured information such as the year of publication, the first author's name, the study title, the clinical population under investigation, and the study design. Additionally, demographic and clinical details of the population were recorded, including age, sex, symptom/pathology onset, rating scales used, dropout rates, and patient feedback. The primary findings and gait outcomes identified as potential biomarkers of functional impairment in real-world settings were also documented.

The second is technical aspects. This subsection contained information focused on details of the wearable devices used. Information included the type and name of the sensors, their number and placement, acquisition mode and setting, data storage, and cloud utilization. The acquisition protocol was detailed, covering the duration of recordings, the nature of tasks or tests performed, and the specific outcomes measured. Furthermore, information about telemonitoring components such as hardware and software specifications, algorithms employed, sensor placement, input and output data, tasks, and the outcomes of interventions and teleconsulting was collected.

The third is telemonitoring and Teleconsulting aspects. The final subsection addressed factors such as user engagement, interoperability with other smart devices or platforms, and the interpretation of data. This included patient feedback, synchronization capabilities with external devices or platforms, and the use of specific data algorithms (as referenced in Tables 15 and 16).
To evaluate the quality of included studies, the Study Quality Assessment Tools developed by the National Heart, Lung, and Blood Institute were employed (available at: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). Additionally, the evidence levels of the studies were rated using the 5-item Oxford CEBM scale (accessible at: https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence.2011, pp. 1–7).

5.2 Results

The flow chart of the review process is presented in Figure 10. A total of 140 records were initially identified from MEDLINE (n = 47), SCOPUS (n = 91), and SPORTDiscus (n = 2), with no records retrieved from the Cochrane Library. Following duplicate removal (n = 34), 106 unique records were screened for eligibility [121,144,145,153–158]. Based on the inclusion criteria, 99 records were excluded due to inappropriate study design (n = 58), outcome measures (n = 23), population characteristics (n = 5), or their focus on e-health applications (n = 13). Consequently, 12 studies were included in the final review [144,153–160].

Tables 15 and 16 summarize the main findings of the studies, including their clinical, technical, telemonitoring, and teleconsulting features. Table 15 also details the evidence levels assigned based on the OCEBM framework, while Table 16 provides an overview of each study's clinical and technical characteristics.

Of the included studies, 11 (91.6%) were observational in design, with one study classified as a randomized controlled trial (RCT) (8.3%) [145]. Four studies (41.6%) were published within the past six years [154,156,160], while five (41.6%) were published between 2011 and 2014 [121,155–157,160,161]. One study each was published in 2015 (8.3%) [158] and 2016 (8.3%) [145].

Regarding study populations, all included studies focused on patients with Parkinson's disease (PD) (n = 12; 100%), with no studies addressing functional motor disorders (FMDs) or multiple sclerosis (MS). Nearly all studies (n = 11; 91.6%) evaluated gait during free-living conditions, while one study (n = 1; 8.4%) assessed gait during a specific test (2-Minute Walking Test) conducted in a naturalistic setting [145]. Regarding wearable devices, 33.3% of studies (n = 4) [121,144,156,157] utilized a single sensor, whereas 56.7% (n = 8) employed two or more sensors [154–156,158,161,162].

The most used sensors were triaxial accelerometers (41.6%) %) [121,155–158,160,161], followed by IMUs (5.0%) [79,89,142–145,163], smartphones (8.3%) 142, instrumented socks (8.3%) [154], and small wearable devices (8.3%) [153]. Figure 11 presents an overview of the studies, highlighting publication year (A), population sample (B), and wearable device types (C).

Across all studies, 663 participants were included, with 533 in experimental groups (range: 9–155 participants per study) and 141 in control groups (range: 0–65 participants per study). The mean age of participants was 62.4 years (SD = 3.2), with females comprising 17% of the sample (n = 89). Disease duration was reported in 66.6% of studies (n = 6) [153,154,157,160,161], with an average duration of 7.75 years (SD = 2.8). Neurological severity, measured using the Hoehn and Yahr (H&Y) scale, was reported in all studies (n = 12), with scores ranging from 1 to 5 (Table 14); the mean PD duration ranged from 4 to 10 years (Table 14).

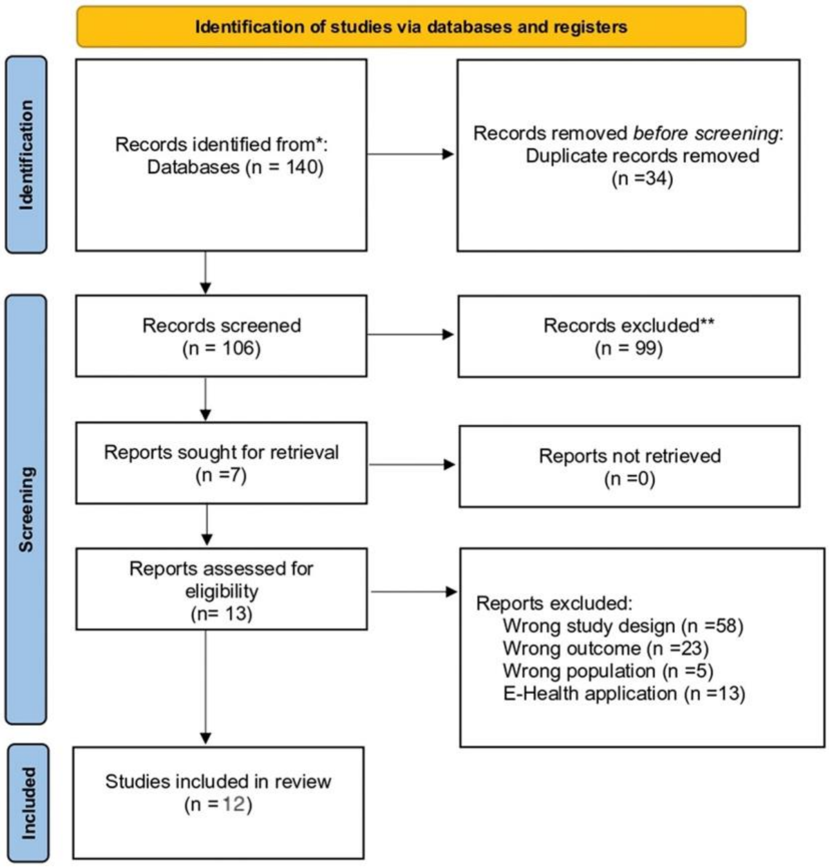


Figure 9: Flow diagram

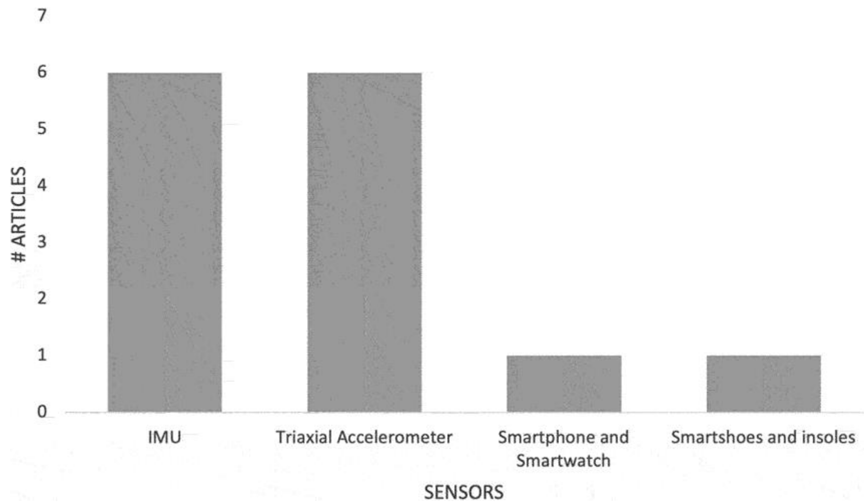


Figure 10: Summary of the studies

Primary gait outcomes included gait cycle duration (38.5%; n = 5) [139,154,157,159] and acceleration amplitude (30.76%; n = 4) [154,155,157,159]. Other gait parameters assessed included cadence, velocity, double support, number of steps, freezing of gait (FoG), turning movements, and postural sway (Tables 15 and 16). Data from pressure sensors provided additional insights into foot pressure, total force, ground reaction force, center of pressure, and sway area. Only one study used insoles [154].
The number of steps and bouts, freezing of gait, turning step count/ angle/ duration, and turning frequency were extracted from the acceleration patterns. Eight studies used these data to extract patterns and differentiate activities performed during data acquisition, such as walking, sitting, lying in bed, or climbing stairs [153,154,157,158].
The pressure-sensor studies extracted foot pressure and acceleration, total force, ground reaction force, center of pressure, and postural sway area.

Almost all studies (n = 11, 91.6%) recorded gait during free daily activities; only one recorded it during a protocol involving balance and gait tests (n = 1; 8.4%) [145]. In three studies, TOMs were used to detect freezing of gait and gait abnormalities related to the risk of falls [145,160,161]. Assessment of fall risks was monitored in five studies [121,144,153,155,157].
Moreover, studies differentiated by the clinical characteristics extracted from daily life activities monitoring. Three focused on turning [139,144,156,157], two on falls [121,156], two on numbers of freezing of gait episodes [145,153], two quantified the amount of exercise during the activity of daily living [154,157], and the other two on motor

fluctuations [155,158]. Only two studies reported the number of dropouts [157], while one rated patient feedback on a Likert-like scale [145].

The most used wearable devices were triaxial accelerometers (Opal inertial sensors). Instead, the most used IMU was Axivity A3. The mean number of sensors was 3.3 (excluding insole devices), and the recording durations in home environments varied, averaging 19.5 hours/day (SD = 7.05). Wearable devices were predominantly placed on the lower back (L5), which was the sole placement site in four studies (33.3%) [121,144,145,155] and used in combination with other locations in four studies (33.3%) [153,154,157,158].

Regarding data acquisition, most studies (83.3%) relied on offline recording and storage using SD cards or internal sensor memory [121,144,145,155 _ 153,154,157,158]. One study employed wireless data transmission (8.3%) [155], and another used a smartphone app as a hardware component for data collection (8.3%) [145]. Data analysis was generally performed offline using software such as MATLAB.

Telemonitoring was primarily conducted asynchronously, with only one study incorporating real-time feedback through a dedicated smartphone app [145]. Continuous monitoring was performed in participants' home environments, with teleconsulting features reported in select studies

Table 8: Studies Involving Patients with Parkinson's or Huntington's Disease.

Author, year	Wearable	Study design	No. of Subjects, PD duration, H&Y score	Feature extracted	Setting	Monitoring duration	Main finding/ biomarker	CEBM Level of Evidence	Quality assessment
Safarpour et al., 2022[144]	IMU, instrumented socks	Observational	N=31 N=17 dyskinesia N=13 FoG, 8.6 ±5.9 yrs, 2.1 ± 0.4 Exclusion criteria: dementia. MOCA mean score 27 (2.7)	Activity amount Gait quality Turn quality	Free-living	1 week (at least 8 h/day)	No. of walking bouts and turns correlated with rigidity subscore	3	Poor
Ginis et al., 2016 [144]	Smartphone (2 apps with feedback: ABF gait app, FOG cue app), docking station, IMUs	RCT	N=38 EG=20 CG=18, n.a, stages II to III in ON state. Inclusion criteria: MOCA > 23, cognitive assessment (Color Trail test CTT A and B).	Primary outcomes: Gait speed under usual and DT conditions in the lab. Secondary outcomes: Gait, Balance, HR-QoL, FOG severity, NFOG-Q, Ziegler protocol	Gait training for 30 min (2MWT, Mini BESTes, VF scores sitting and walking, FSST, FES-I, Physical activity scale) QoL SF-36	30 min 3 times/week for 6 weeks and follow up assessment after one month	Gait speed under usual and dual-task conditions, MiniBESTest, FSST, Likert Scale	2	Good
Cavanaugh et al., 2012 [156]	Accelerometer and gyroscope	Observational	N=33, 4.4 ± 4.21 yrs, Stage I-IV No measures of cognitive status	Ambulatory activity: mean no. of daily steps, step count, intensity of activity measures (moderate intensity in min., peak activity index, maximum output)	Free-living	1 week, Follow-up after 1 year	Amount of activity (total no. of steps), intensity of activity (step rate), frequency of activity (total no. of activity bouts), duration of activity (total minutes of stepping of percentage of the day spent inactive)	3	Fair
Nakae et al., 2011 [164]	Triaxial accelerometer activity meter	Observational	N=9, 9.18 ± 2.23 yrs, n.a., Exclusion criterion: severe dementia with difficulty understanding the task	Gait velocity, cadence, frequency of falls, modified falls efficacy scale	Free-living	24 h	Total impulse value, amount of physical activity (time spent sitting and supine position)	3	Poor

Cancela et al., 2011[154]	Triaxial accelerometer, accelerometer, and gyroscope	Observational cohort	N=10, n.a, n.a., Exclusion criterion: dementia	Gait characteristics (Macro): volume, pattern, variability of ambulatory bouts. Discrete gait characteristics (Micro): step frequency, stride length, entropy	Gait recording in OFF and ON phase, unsupervised	n.a.	Entropy (a measure of uncertainty or unpredictability associated with a specific variable, a measure of the disorder) and arm swing	3	Poor
Kannellos et al, 2023 [158]	IMUs	Observational	N=20, 6.1 ± 5.7 yrs, n.a., No measures of cognitive status	Bradykinesia (right and left arm), wrist tremor, leg tremor, gait impairment, FoG, postural instability, time spent with dyskinesia, time spent in OFF state	Free-living	30-min interval recording during daily life	Bradykinesia (right and left arm), wrist tremor (right and left), leg tremor (right and left), gait impairment, >FoG, postural instability, time spent with dyskinesia, time spent in OFF state	3	Good
Mancini et al., 2021[162]	IMUs	Observational	N=48, 9.8 ± 5.10 yrs, n.a., No measures of cognitive status	FoG features	Free-living	7 days	Algorithm to detect no. of FoG episodes, percentage of time spent freezing and its variability (over 7 days of unsupervised daily life setting), average turning duration (s), average turn peak velocity (°/s), and coefficient of variation (CV) calculated for turn peak velocity. For measuring walking: gait speed, the pitch angle of the foot at initial contact (°) was an indicator of shuffling and variability of the pitch angle of the foot at initial contact	3	Good

Del Din et al., 2019 [155]	Triaxial accelerometer	Observational	N=342, of which 277 fallers (=155 older adults and 122 PD) and 65 Non-fallers = (50 older adults and 15 PD). n.a., n.a., Exclusion criterion: MMSE <21 and <24	Behavioral outcomes Macro: volume of walking (total and % of walking time per day, no. of bouts/steps per day), mean AB length Micro gait characteristics (n=14: pace, rhythm, variability, asymmetry, postural control) for each walking bout	Free-living	1 week	Macro and micro-gait characteristics	3	Poor
Iluz et al., 2014 [120]	Accelerometer and gyroscope	Observational	N=40, 5.3 ± 3.50 yrs, 2.54 ± 0.66, Cognitive assessment by MMSE 29.18 (1.21)	Peak difference, frequency above threshold, entropy, no. of steps, maximum amplitude (g), maxim amplitude (deg/s)	Free-living	3 days	Missteps	3	Poor
El-Gohary et al., 2014[157]	IMUs	Observational	N=30 PD=12 HC=18, n.a., n.a., No measures of cognitive status	Hourly frequency of turn, duration of each turn, no. of steps to complete turn, peak/average rotational turning rate and jerk, variability of measures throughout day and week, capture of walking/turning events in free activities	Free-living	1 week (16 h/day)	Turn metrics: duration, peak and mean velocity, no. of steps to complete a turn, and body jerk during a turn	3	Fair

Mancini et al. 2015 [159]	IMUs	Observational	N=32 EG=13 CG=19, n.a.,n.a. Exclusion criterion: dementia	Hourly frequency of turning, duration of each turn, no. of steps to complete turn, peak/average rotational turning rate, activity rate as a percent of the time in a day when walking/turning	Free-living	1 week	Turning metrics: no. of turns per hour, turn angle amplitude, turn duration, turn mean velocity, and number of steps per turn	3	Fair
Mancini et al., 2018 [143]	Triaxial and gyroscope	Observational	N=84 (N=69 freezer N=15 non-freezer), 4.90± 2.80 yrs, (freezer) 7.60 ± 4.40 yrs, (non- freezer) 2.4 ± 0.5, Inclusion Criterion: MMSE >24	No. of turns in 30 min, turn angle amplitude, turn duration, mean/peak turn velocity, turn jerkiness, turn mediolateral range of acceleration (m/s^2)	Free-living	3 days	No. of turns per 30 min, turn angle amplitude, turn duration, mean and peak turn velocity, turn jerkiness, turn mediolateral range of acceleration	3	Fair

Abbreviations: EG denotes Experimental Group, CG Control Group, HC Healthy Controls, MoCA Montreal Cognitive Assessment, MMSE Mini-Mental State Examination, MDS-UPDRS MDS-Unified Parkinson's Disease Rating Scale, LEDD Levodopa Equivalent Dose, HY Hoen & Yahr, PDQ-39 Parkinson's Disease Questionnaire, PPMI Parkinson's Progression Markers Initiative, CTT Color Trail Test, VF Verbal fluency, 2MWT 2 Minute Walk Test, MiniBESTest mini-Balance Evaluation Systems Test, FSST Four Square Step Test, FES-I Falls Efficacy Scale-International, SF-36 Form 36 Health Survey, GDS Geriatric Depression Scale, MFI Multidimensional Fatigue Inventory, FTSTS Five Times Sit to Stand, VAS Visual Analog Scale, IC initial ground contact, DT dual task, FOG freezing of gait, NFOG-Q New-FOG questionnaire.

Table 9: Digital Systems in Studies Involving Patients with Parkinson's Disease

				Systems (Telemedicine) for remote data acquisition. Telemonitoring						**Teleconsulting**
Author, year	**Hardware / Software**	**Sensor placement (no.)**	**Input source**	**Input**	**Tasks**	**Output (content)**	**Output users**	**Intervention outcomes**	**Algorithm/validated before in the lab**	
Gait and Posture										
Safarpour et al., 2022[144]	IMU (Opal sensors) and instrumented socks (APDM)/ Offline registration and data analysis	Lower back (1), feet (2), socks (1 pair)	n.a.	MDS-UPDRS, MoCA, MDS-UPDRS PIGD, H&Y, rigidity, FoG, LED	Analysis of data from free-living gait/daily monitoring to generate measure of MDS-UPDRS rigidity and Postural Instability and Gait Difficulty (PIGD) subscores	Quantification of activity, quality of gait, and turns to examine rigidity and PIGD MDS-UPDRS subscores in the context of objective gait and balance measures through wearables at home	n.a.	Potential surrogates for rigidity and PIGD are not yet ready for implementation in telehealth or remote clinical trial administration. Still, they are a starting point for creating data collection algorithms for partially instrumented MDS-UPDRS-mobile scores.	Algorithm used in Mancini 2018/validated by El-Gohary 2013/n.a.	No
Ginis et al., 2016[144]	Smartphone (Galaxy S3-mini. Samsung) (2 apps), docking station and IMUs (Exl-s3, EXEL)/ App (ABF-gait)	Ankles (2)	n.a.	MDS-UPDRS, H&Y, MoCA, Color Trail Test (CTT) A and B, VF scores, VF scores while sitting and walking, SF-36	Gait training for 30 min (2MWT), MiniBESTest, FSST, FES-I, and PASE to provide people with PD real-time feedback on gait performance	Primary: gait speed under usual and dual-task (DT) conditions. Secondary: gait, balance HR-QoL, FOG severity. Conventional gait training analyzed in the home environment.	5-item Likert Scale to investigate whether participants found the CuPiD system user-friendly (from 1 to 5)	Both groups improved on primary outcomes (single and dual-task gait speed) at post-test and follow-up. EG improved more in terms of balance than the conventional one. The system is feasible for unsupervised home use and has proved an effective approach to gait and balance training in PD.	The online automatic algorithm developed and validated by Casamassima et al. 2014	App (ABF-gait app and FOG-cue app)
Cavanaugh et al., 2012[156]	Accelerometer and gyroscope (Stepwatch)/ Offline registration and data analysis	Ankle (1)	n.a.	UPDRS III, H&Y, 10MWT, 6MWT	Analysis of data from Free-living gait/daily monitoring to explore natural, long-term changes in daily ambulatory activity and to compare the responsiveness of ambulatory activity parameters to clinical	Mean daily steps and step counts, intensity of activity measures (moderate-intensive minutes, peak activity index, maximum output) to investigate changes in ambulatory activity	n.a.	The study documented natural decline in function potentially associated with disease progression by analysis of ambulatory activity parameters	Custom algorithm written in MatLab (MathWorks, Natick, MA, USA)	No

					measures of gait and disease severity	parameters and clinical measures.				
Nakae et al., 2011 [164]	Triaxial accelerometer and activity meter (MicroStone)/ Offline registration and data analysis	Abdomen (2)	n.a.	UPDRS	Analysis of Free-living gait/daily monitoring to evaluate and characterize physical activities of PD patients	Gait velocity, cadence, frequency of falls, and modified falls efficacy scale used as indices for evaluating physical activities	n.a.	Understanding the type of activities and how much time spent sitting or lying can help to increase physical activities and prevent falls in home-bound patients	n.a.	No
Cancela et al., 2011 [154]	Triaxial accelerometer, accelerometer, and gyroscope (n.a.)/ Sensors for wireless data transmission and data analysis	Limbs (5), belt (1)	n.a.	UPDRS	Gait recording during the OFF and ON phases to detect differences between the two states; variables to focus on continuous gait impairment assessment with a belt accelerometer	Macro: volume, pattern, and variability of ambulatory bouts Micro:14 discrete gait characteristics, step frequency, stride length, and speed arm swing and entropy. Identifying which of them characterized both states more accurately in an unsupervised environment.	n.a.	The system can provide detailed and accurate status of impairment and develop a continuous monitoring system to identify different phases of disease during the day (alert physician when the patient enters the OFF phase, indicating the need for adjusting medication intake).	PC with the application for detection of activities, custom algorithm implemented/ n.a.	No
Kannellos et al, 2023 [158]	IMU sensors (PDMonitor)/ Offline registration and data analysis	Shanks (2), wrists (2), waist (1)	n.a.	MDS-UPDRS, H&Y	30-minute interval recording during daily life. Analysis of free-living gait/daily monitoring	Bradykinesia (right and left arm), wrist tremor, leg tremor, gait impairment, FoG, postural instability, time spent with dyskinesia, time spent in OFF state		Moderate-to-strong correlations for most symptoms (bradykinesia, rest tremor, gait impairment, FoG) and fluctuating conditions (dyskinesia and OFF). Development of an index that can remotely measure patient quality of life: in-office examination only partially reveals most PD symptoms and cannot accurately capture daytime fluctuations and quality of life	PDMonitor algorithms/validated in the lab by Antonini et al. 2023	
Mancini et al., 2021 [162]	**FoG**	Feet (2), lumbar area (1)	n.a.	MDS-UPDRS, H&Y, PDQ-39	Analysis of data from free-living gait/daily monitoring	FoG features during 7 days of unsupervised, daily life settings walking and turning features		Objective measures of freezing in PD using inertial sensors on the feet in the lab matched well with clinical scores. Results found during daily life are promising but need validation. Objective measures of FoG with wearable	New open-source algorithm/validated in lab phase by Study I	

								technology during community living help manage this mobility disability in PD		
Falls										
Del Din et al., 2019 [155]		Lower back (1)	n.a.	H&Y, MDS-UPDRS	Analysis of data from free-living gait/daily monitoring to explore associations in free-living gait in fallers and non-fallers with and without PD	Macro: volume of walking (total and percentage of walking time per day, number of bouts, steps per day), mean AB length. Microgait characteristics (pace, rhythm, variability, asymmetry, and postural control) for each walking bout. Macro and micro need to compare findings concerning fall risk and pathology.	n.a.	Generic differences and disease-specific differences in macro and micro characteristics that inform a nuanced understanding of fall risk and intervention across groups	Custom algorithm written in MatLab (MathWorks, Natick, MA, USA)	No
Iluz et al., 2014 [120]	Accelerometer and gyroscopes (Dynaport) / Offline recording and data analysis	Lower back (1)	n.a.	UPDRS in OFF phase, H&Y, Pull test, TUG, DGI, BBS, 4-square step test, MMSE	Analysis of data from free-living gait/daily monitoring to detect missteps and improve evaluation of fall risk	Peak difference, frequencies above the threshold, entropy, number of steps, and maxim amplitude for a comparison of the likelihood of event detection between fallers and non-fallers	n.a	Automatic fall risk assessment in a home environment with potential advantages over routine clinical assessment. A method that can automatically detect events and quantify frequency could help to monitor and better evaluate fall risk together with conventional assessment	Custom algorithm to detect missteps validated in the lab	No
Turning										
El-Gohary et al., 2014[157]		Pelvis (1), feet (2)	n.a.	UPDRS III	Analysis of data (algorithm) from free-living gait/daily monitoring to detect differences between turn characteristics in PD subjects and controls	Hourly frequency of turning, duration of each turn, number of steps needed to complete a turn, peak and average rotational turning rate and jerk, and variability of these measures throughout the day and week to prove	n.a.	An inertial system using three wearable sensors can measure locomotor activities and characterize turns in the home throughout the day and week	Custom inertial algorithm/validated with laboratory data	No

						wearable sensors as possible instruments to help clinicians and patients in determining who is at risk of falls			
Mancini et al. 2015 [159]	IMUs (Opal sensors)/ Offline recording and data analysis	Pelvis (1), feet (2)	n.a.	UPDRS in the ON phase	Analysis of data from free-living gait/daily monitoring	The hourly turning frequency, duration of each turn, number of steps needed to complete a turn, and peak and average rotational turning rate are also included. Activity rate (percentage of time spent walking or turning compared to the total monitoring time per day)	n.a.	There were no differences between PD and control groups for observed turns, whereas PD patients had impaired turning quality compared to healthy controls; there was higher variability within the day and across days in PD patients compared to controls. There are no differences in overall activity between PD patients and controls	The algorithm used in El-Gohary 2013/validated in the lab
Mancini et al., 2018 [143]	Triaxial accelerometer and triaxial gyroscope (Dynaport) / Offline recording and data analysis	Lower back (1)	n.a.	H&Y, UPDRS III, MMSE	Analysis of data from free-living gait/daily monitoring	Number of turns per 30 min, turn angle amplitude, turn duration, mean and peak turn velocity, turn jerkiness, and turn mediolateral range of acceleration	n.a.	Quality but not quantity of turning at home differs between freezers and non-freezers; no. of turns is similar in the two groups. Mean jerkiness, mean, and variability of mediolateral jerkiness are more significant in freezers than in non-freezers	The algorithm used in El-Gohary 2013/validated in the lab

Abbreviations: EG denotes Experimental Group, CG Control Group, HC Healthy Controls, MoCA Montreal Cognitive Assessment, MMSE Mini-Mental State Examination, MDS-UPDRS MDS-Unified Parkinson’s Disease Rating Scale, LEDD Levodopa Equivalent Dose, HY Hoen & Yahr, PDQ-39 Parkinson’s Disease Questionnaire, PPMI Parkinson's Progression Markers Initiative, CTT Color Trail Test, VF Verbal fluency, 2MWT 2 Minute Walk Test, MiniBESTest mini-Balance Evaluation Systems Test, FSST Four Square Step Test, FES-I Falls Efficacy Scale-International, SF-36 Form 36 Health Survey, GDS Geriatric Depression Scale, MFI Multidimensional Fatigue Inventory, FTSTS Five Times Sit to Stand, VAS Visual Analog Scale, IC initial ground contact, DT dual task, PIGD Postural Instability and Gait Difficulty, FOG Freezing of Gait, NFOG-Q New-FOG questionnaire, DGI Dynamic Gait Index, TUG Time Up and Go, BBS Berg Balance Scale, MSWS-12 Multiple Sclerosis Walking Scale-12

5.3 Discussion and Future area of focus

This literature review highlights the increasing adoption of Telemonitoring Systems (TOMs) combined with telemedicine for monitoring gait and balance in patients with movement disorders, particularly Multiple Sclerosis (MS). These technologies have proven valuable for patients and healthcare professionals, providing accurate, real-time, and objective gait and postural control assessments in real-world settings. A key aspect of advancing telemedicine toward becoming "digital medicine" lies in the effective integration of data. The growing interest in home-based rehabilitation, primarily through wearable sensors, is closely tied to clinicians' need to enhance the quantity and quality of assessments for patients with Parkinson's Disease (PD), whose evaluations are increasingly conducted outside clinical settings, aided by recent technological advancements. Since 2016, both researchers and healthcare providers have recognized the substantial potential of wearable devices, with their advantages becoming particularly evident during the COVID-19 pandemic [165]
Despite this progress, a noticeable gap in the literature remains concerning patients with Functional Movement Disorders (FMDs), suggesting that this complex and disabling condition is not sufficiently studied. [9] Nonetheless, there is emerging evidence that telemedicine may provide promising outcomes for these patients, and developing protocols for wearable devices integrated with telemedicine for FMDs remains a critical, unmet need [47].

Most reviewed studies were observational, with only one moderate-quality Randomized Controlled Trial (RCT) identified. This highlights the importance of conducting further confirmatory studies with rigorous methodologies. The studies included in the review varied in sample size (ranging from 9 to 220 patients), monitoring duration (from 30 minutes to 24 hours per day), and weekly monitoring periods (from 1 to 7 days), all of which are critical factors in assessing disease progression and predicting motor behaviors, such as falls or freezing of gait episodes [145].

While TOMs have been widely used to detect gait and balance disturbances in PD patients during daily activities, their applications extend beyond diagnosis to evaluating pharmacological treatment effects and rehabilitation outcomes. Recent studies have focused on developing digital biomarkers for PD, emphasizing the need for more refined tools to track disease progression. Although consensus exists on the utility of home-based gait and balance monitoring for assessing neurological severity and disability in movement disorders, further investigation is required to identify specific biomarkers for PD and MS and refine markers for gait and balance within rehabilitation contexts [145,161,166].

One of the challenges identified in this field is the variability in the type and number of wearable devices used across studies, along with differences in sensor sampling rates and algorithms, which complicates the comparison and generalization of results. Despite the promise of wearable devices, there is still no clear consensus on the optimal number, type, and placement of sensors for assessing motor symptoms in movement disorders [167].

The most used devices in the studies reviewed were Inertial Measurement Units (IMUs) [144,153,157–159,162] and triaxial accelerometers. [120,154–157,159] Many studies utilized multiple sensors, often placed on the lower back (L5) or the mid-waist, though the number and placement of sensors depended on the specific goals of the study. Recent research has increasingly focused on using a single sensor worn on a belt, which offers greater patient independence and minimizes risks associated with improper placement or synchronization errors. Insoles, which are worn inside shoes, are another promising solution for improving wearability, allowing for unrestricted movement. However, they come with challenges, including higher costs and potential patient discomfort, especially when they prefer walking barefoot or wearing slippers. Insoles may be acceptable for most patients but may not be suitable in certain ecological contexts, such as walking barefoot [167]. Another issue with wearables is the discomfort of wearing multiple sensors, although patients generally tolerate wearing up to three on-body sensors. Despite these challenges, the data derived from wearable sensors remains highly valuable. One study confirmed the reliability of data captured by wearables using video recordings, reinforcing the accuracy of wearable technology in providing real-time, objective monitoring [167].

In terms of outcomes, studies commonly focused on spatial-temporal gait parameters, including gait speed [144,153,154,156,157,164], gait cycle duration [153–157], gait amplitude [153,156,157,160], and step count [120,154–157,159]. These metrics are essential for evaluating functional status and quality of life in patients with PD or MS[67]. However, gait speed alone does not fully capture mobility in individuals with movement disorders [156]. Additional measures, such as stride time and freezing of gait (FoG) episodes, are necessary to assess symptom severity and fall risk in more complex environments [144,153,154,156,157,164].

Motor activities such as climbing stairs, lying in bed, or sitting in a chair have also been examined as indicators of patient independence and disability levels. Although long-term monitoring in ecological settings provides important insights, some parameters remain difficult to assess in laboratory environments [143,153,157,159].

Wearable technologies are proving to be invaluable tools in identifying biomarkers that allow for a deeper understanding of movement disorders, particularly in PD. These biomarkers, which address various aspects of gait, posture, and mobility, are instrumental in tracking disease progression and guiding clinical decision-making. One critical area of research is understanding the mechanisms behind falls. While self-reported fall data has traditionally been used, wearable sensors offer a more precise method of capturing gait abnormalities and missteps that could indicate a higher risk of falls. Studies by Del Din et al. (2019) and Iluz et al. (2014) contributed to this area by analyzing gait variability and the occurrence of missteps in PD patients, which can offer heightened sensitivity in identifying individuals at risk of falls, especially in dual-task situations [130].

The role of turning mobility in PD and MS patients has also been explored. Turning is a complex motor task involving cognitive and executive functions, and impairments in this area can indicate broader mobility issues. Studies by El-Gohary et al. (2014) and Mancini et al. (2018, 2019) underscored the significance of turning metrics, such as duration and step count, as key biomarkers for assessing mobility in PD patients. Mancini's research compared data from laboratory and home settings revealed that patients with PD exhibit distinct turning velocities, which can help evaluate motor fluctuations and medication effects [168,169]

Finally, studies focusing on turning quality have shown that PD patients with freezing episodes exhibit smaller turning angles, which could trigger FoG. This highlights the importance of assessing both the quantitative and qualitative aspects of turning, as they offer valuable insights into disease progression and help identify subgroups of patients who may be at higher risk of falls or mobility impairments [153]. The studies found that the variability metrics associated with turning tended to decline as the disease progressed: more significant variability seemed to indicate compensatory behavior for impaired postural control during turning, whereas less variability indicated deterioration of adaptive skills needed for posture maintenance during locomotion. These insights underscore the imperative of a nuanced approach to turning behavior in unsupervised environments by evaluating quantitative and qualitative measures as pivotal biomarkers for movement disorder assessment, particularly in PD.

Mancini et al. applied an innovative automated algorithm for detecting and objectively characterizing freezing of gait (FoG) episodes using inertial sensors placed on the feet [160]. Their study included initial lab tests and unsupervised home-based monitoring. During home monitoring, the study revealed notable differences in FoG episodes between patients who experienced them and those who did not. Specific FoG indicators, such as the percentage of walking time spent in a frozen state and its variability, showed distinct patterns between these subgroups. The algorithm's efficacy was influenced by sensor placement, demonstrating robust detection capabilities when sensors were positioned on the feet. It accurately identified both brief (2–5 seconds) and extended (>5 seconds) FoG episodes. However, its performance declined when the sensors were placed on the shins. Despite its promise in detecting FoG, the algorithm had limitations, including the time required (several seconds) to identify a FoG episode, making it less suitable for real-time interventions. Future research should focus on long-term unsupervised monitoring in real-life settings and follow-up studies with PD patients, including those who do not experience FoG at baseline, to further substantiate these findings. In addition to FoG, the study explored other relevant biomarkers, such as walking-related parameters. The average pitch angle at initial foot-ground contact was smaller in 'freezers' compared to 'non-freezers,' suggesting a tendency for a shuffling gait and higher fall risk among the 'freezers.' Moreover, the 'freezers' exhibited smaller turning angles, emphasizing the need to examine turning characteristics in this subgroup. These biomarkers contribute to a nuanced evaluation of gait and balance, particularly in PD patients susceptible to FoG. The integration of wearable technology and advanced algorithms offers the potential for valuable insights into managing movement disorders, enabling more personalized intervention strategies and telemonitoring systems.

The studies by Cancela [154] and Kanellos [158] demonstrated that wearable technology-based sensors can accurately capture motor fluctuations in PD patients. Biomarkers such as entropy and arm swing proved useful in identifying variations in motor symptoms. Cancela's study investigated motor symptom variations in PD patients during ON and OFF states [154]. The study explored multiple variables—step frequency, stride length, entropy, and arm swing—and observed significant differences between the ON and OFF phases. Arm swing and entropy were found to be more reliable biomarkers. A decrease in entropy during the ON phase indicated increased signal predictability compared to the OFF phase. However, the study cautioned that these variations were not directly correlated with scores on the Unified Parkinson's Disease Rating Scale (UPDRS), implying that clinical evaluation might not fully capture motor fluctuations. The study also highlighted the need for multifaceted sensor systems and personalized algorithms for accurate data interpretation. Additionally, shoe-measured leg length as an input variable introduced an element of variability based on patient footwear.
Kanellos et al. (2023) examined the limitations of diary-based self-reporting for capturing daily variations in PD symptoms. Instead, they employed a sensor-based in-home monitoring system, which proved valuable for assessing motor symptoms in an unsupervised environment. They found a strong correlation between clinical assessment and in-home monitoring for symptoms such as freezing of gait, resting tremor, and dyskinesia. The correlation was moderate for gait impairment, postural instability, and bradykinesia, indicating that daily symptom fluctuations could affect clinical evaluation. The study also noted a moderate correlation between rigidity (a symptom typically not captured by inertial sensors) and bradykinesia

during in-home recordings, demonstrating the diverse utility of sensor-based monitoring. Additionally, the system effectively measured the percentage of time patients spent in the OFF phase, providing valuable data for tailoring treatment plans. Continuous monitoring significantly enhanced symptom management for PD patients.

These studies emphasize the critical role of sensor-based systems in understanding the nuances of PD symptoms and their daily fluctuations. These technologies enhance patient health literacy and empower clinicians to offer personalized treatment options. While traditional clinical evaluations remain essential, they provide only a snapshot of symptom dynamics and overall quality of daily life.

The studies by Safarpour et al. (2022), Cavanaugh et al. (2012), and Nakae investigated biomarkers for gait, balance, and physical activity in PD patients. These biomarkers included the number of steps, activity intensity, frequency, and duration. Safarpour et al. conducted a study on rigidity and subscores on the Postural Instability and Gait Difficulty (PIGD) MDS-UPDRS in objective gait and balance measures for PD patients [153]. They found that rigidity was best predicted by the quantity of gait and turning (number of walking bouts), indicating that patients with greater rigidity and higher MDS-UPDRS III scores exhibited less overall activity in daily life. The PIGD subscore was most accurately predicted by a combination of gait quantity and quality, as well as postural sway, indicating a more complex mobility pattern. Although these surrogates for rigidity and PIGD are not yet ready for use in telehealth or remote clinical trials, they provide valuable data for developing data collection algorithms for a partially instrumented MDS-UPDRS mobile score.

Cavanaugh's study focused on the physical activity patterns of PD patients over an extended period, particularly ambulatory activity [156]. The study aimed to determine whether objective measures reflecting natural ambulatory behavior could be more responsive to disability progression in PD than traditional clinical measures. The findings revealed that PD patients experienced a decline in ambulatory activity over time, as evidenced by lower daily step counts and reduced stepping activity intensity. The decline was particularly noticeable in the minutes spent in moderate-intensity ambulatory activity. This study underscored the importance of ambulatory activity monitoring in assessing exercise and physical activity behavior changes.

Nakae et al. found that PD patients exhibited a total impulse (an index of physical activity) lower than young individuals but comparable to elderly individuals. Similarly, the amount of physical activity in PD patients was relatively like that of elderly individuals, indicating that PD patients maintained a relatively good ability to perform activities of daily living (ADL).
Ginis et al. described a system called CuPiD, consisting of a smartphone with two apps, two IMUs, and a docking station, designed to promote gait training in unsupervised home settings for PD patients. The CuPiD system provided real-time feedback while stimulating corrective actions and promoting self-efficacy. Participants using the CuPiD system showed improved balance, gait speed under usual and dual-task conditions, dynamic stability, and gait stability compared to controls. Overall, the CuPiD system was well-tolerated and user-friendly, making it a practical solution for gait and balance training in PD.

The dropout rate and patient feedback on using TOMs were rarely reported. While the dropout rate indicates the applicability of TOMs in real-life settings, patient feedback provides information on device acceptability. Both aspects are important for intelligent long-term home monitoring and prolonged device use. Only two studies reported dropout rates and associated reasons [144,156], while one provided patient acceptance data [145]. Ginis et al. [145] reported two dropouts in the experimental group. Responses to a Likert-like scale indicated that the wearable device (CuPiD system) was considered user-friendly, with average scores above four on a 5-point scale [145]. Cavanaugh et al. [156] reported four dropouts due to data recording issues but did not provide patient feedback. The lack of information on dropout rates and patient feedback limits our understanding of the real-world applicability of these devices and how to improve their technical features for larger-scale use [170]. These aspects should be systematically reported because PD patients are generally older and have limited technical skills compared to MS patients.

Wearable technology enables healthcare providers to remotely assess patients in their natural environment, capturing real-world data that may be missed during hospital visits. Ecological assessment offers a holistic view of a patient's daily life, allowing for more personalized and effective interventions. Applying the classification taxonomy for telemedicine proposed by Lee et al., we focused on telemonitoring and teleconsultation via wearables as the first step toward real-world telehealth management [152]. Biomarkers derived from wearable technology allow for continuous and detailed assessment of motor skills and mobility in patients with movement disorders. This information can guide clinical decisions, monitor therapy effectiveness, and enhance quality of life. The implementation of wearable technologies in clinical practice, particularly for telemonitoring, teleconsultation, and tele-education, marks a significant step toward personalized care for individuals with movement disorders. Teleconsultation was reported in one study [145], conducted asynchronously via an app, and synchronous feedback on performance was provided to encourage patient adherence to the intervention. The study showed that balance and quality of life improved in the experimental group, which received synchronous feedback, while deterioration was noted in the control group. This highlights the importance of monitoring during rehabilitation and providing feedback, even asynchronously [145]. Finally, synchronous monitoring is a crucial feature.

Given that systematic literature reviews are subject to potential risks of bias, we applied measures to minimize bias: comprehensive search strategies, explicit inclusion and exclusion criteria, and rigorous assessment of study quality. Multiple authors performed data extraction, analysis, and discussion independently, and discrepancies were resolved through discussion, ensuring a balanced interpretation of the data.

A significant limitation of our review is not the inclusion of keywords such as 'reliability' and 'validity' (referring to TOMs) in our initial search strategy. Then, due to the relatively small number of studies on wearable technologies for gait assessment in ecological environments in movement disorders and MS, we cannot recommend the type of TOMs to assess gait and mobility in such patients. More research is needed to evaluate the validity of wearables during free-living walking and mobility assessment in persons with movement disorders and MS. Moreover, few studies measured cognitive status [143,144,153,155,158]. This missing patient characteristic may lower the quality of the studies since cognitive impairment has been studied as a significant conditioner of motor parameters[171].

In conclusion, the review comprehensively overviews current technological applications for monitoring gait and balance in patients with movement disorders and Multiple Sclerosis in an ecological setting. Digital technology provides a means to objectively, frequently, and remotely assess various aspects of movement disorders in a natural environment. Wearable devices may enable earlier identification of individual diseases and may be more sensitive to disease progression, facilitating the identification of disease-modifying treatment and the planning interventions for assistance and preventive measures.
Wearable devices may provide personalized treatment and clinical management; however, better digital outcomes and tool validation are needed. In most cases, digital devices collecting large amounts of data are complex for clinicians to interpret and validate. IMUs and accelerometers, for example, require ad hoc statistical analysis to extract and identify characteristics potentially useful for clinicians and that best discriminate between subjects and groups (as patients and healthy controls) [162]. Because they mimic generalization in real-life clinical settings, the use of digital technologies is limited in contexts where clinicians and engineers collaborate.

Recent work in machine learning has examined automatic assessment of performance [172]. Alternatively, the use of deep may be more accurate for correctly classifying symptoms and subjects; however, comprehensive studies are needed to explore this potential [173]. Our findings suggest that future research should prioritize studies with larger samples, longer remote monitoring periods and follow-up, assessment of new patient populations (as FMDs and at an advanced stage of disease), comparison with patient-reported outcomes; digital device data

standardization and the development of real-time platforms; assessment of non-motor features for more holistic disease characterization; and clinical trials to monitor therapeutic rehabilitation programs over the medium to long term in home settings in comparison with programs conducted in clinical settings to assess differences in outcomes (efficacy), adherence, and sustainability.
Finally, digital and technological applications could change approaches in managing motor disorders patients, holding enormous potential for improving their QoL and monitoring the effects and outcomes of therapy and rehabilitation during disease progression.

6. Evaluation of gait disorders in patients with functional motor disorders via a protocol of immersive virtual reality: a cross-sectional study in 104 subjects

This observational cross-sectional study aimed to assess the effects of an immersive virtual reality protocol on the mechanisms of gait control in subjects with functional motor disorder (FMD) in comparison with healthy subjects (HC) and subjects with organic neurological disease, Parkinson's disease (PD), through the analysis of specific gait spatiotemporal parameters. The subjects with a clinically defined diagnosis of functional motor disorder were recruited based on the diagnostic criteria of Gupta & Lang (2009) and selected at the Parkinson's Disease and Movement Disorders Unit of AOUI Verona; instead, the group of patients with Parkinson's disease (PD) was recruited if reported a level below three on the scale Hoen & Yahr.

Specifically, the questions we want to answer were:

I. Can an immersive virtual reality change spatiotemporal gait parameters in patients with FMD?
II. What differences in the spatiotemporal gait parameters emerge between HC and FMDs?
III. Can biomarkers be identified to distinguish patients with FMD from HC?
IV. What are the differences observed in gait patterns among patients with FMD and those with organic neurological diseases such as Parkinson's disease?

According to the literature, we hypothesized that VR could act on the "high-level" gait control mechanisms, which are dysfunctional in patients with FMD, responsible for modulating crucial aspects such as attentive focus, beliefs, and Sense of Agency. Immersive VR could modify the spatiotemporal gait parameters in patients with FMD compared to the control group (HC) and patients with Parkinson's disease, with effects depending on the type of concurrent task (dual task). With this study, we tried to improve the FMD diagnosis and provide new knowledge for developing more effective rehabilitation strategies.

The study provided each participant with a single experimental session to evaluate spatiotemporal gait parameters, performed both in a real environment and in a

virtual environment, developed by a team of engineers (Khymeia, Italy). This study was part of the Joint Project 2019, a collaboration between the University of Verona and Khymeia Group, a company with long experience in VR.
The inclusion criteria were age 18; Simplified Functional Score Movement Disorders Rating Scale (S-FMDRS) for the item relating to the gait (gait subitem) more than 2 (total score 0-6, with higher scores indicating a more severe); Mini-Mental State Examination (MMSE) more than 23. In addition, for subjects with Functional motor disorder (FMD), additional criteria for inclusion were a clinical diagnosis of a functional motor disorder, functional motor symptoms in the lower limbs (at least one of the following: tremor, weakness, dystonia, and sensory symptoms), presence of functional gait disorders (FGDs), including slow gait, astasia-abasia, knee buckling, para-paretic gait, "ice-walking" gait, half-way walk, "tightrope gait" and others types.
The exclusion criteria were the presence of non-epileptic psychogenic seizures (PNES), the need for assistive devices to maintain a standing posture, comorbidities that interfere with walking, non-acceptance of the diagnosis, and comorbidity with other organic pathologies. The severity of the gait disorder was assessed through the subheadings of the S-FMDRSs, which are related to the severity and duration of the gait disorder. All the clinical and demographic variables were collected at the time of enrollment.

As mentioned above, the evaluation protocol was carried out in two different environments: real and virtual. In the first case, the experimental context was represented by a corridor on the eighth floor of Borgo Roma Hospital (Verona, Italy), with a width of 2.5 meters and a length of at least 15 meters. A visual fixation point was placed at the end of the corridor, at eye level.
About the VR, two scenarios were developed:

- A *virtual corridor:* a faithful VR representation of the real corridor accurately reproducing the dimensions, colors, and spatial arrangement. There is a red cross as a fixation point in this scenario, exactly as in the real environment, and no sound effects were expected. The only difference from the real environment was the participant's visor use.

- An *urban environment*: a VR urban setting, complete with buildings, streets, and pedestrians. Background sounds (horn and engine rumble) have been added to promote greater immersivity. The environment contained fixed elements, such as trees, buildings, and traffic lights, and mobile elements, such as pedestrians. Also, as in the other scenario, a red cross was used as a fixation point. According to the study of Corbetta et al. (1991), the speed of pedestrians was regulated on three levels.

For VR, it was used an immersive VIVE Pro Eye (HTC Corporation), with a resolution of 1440 x 1600 pixels per eye, a field of view of 110 diagonal degrees, and stereoscopic stimuli rendered by an Nvidia GeForce GTX 1060 graphics card. The display was powered by a portable battery, receiving the signal from four infrared bases that delimited the physical space in which the immersive virtual scenario was recreated.

6.1 Study Protocol

The experimental protocol involved six consecutive tasks presented randomly (Figure 2). Specifically, Tasks 1 and 2 were always randomly executed before Tasks 3, 4, 5, and 6, which were then performed randomly. Participants were instructed to freely walk along the corridor, about 15 steps (strides), wearing the FeetMe baropodometric insoles® and, where required by the tasks, an immersive virtual reality headset (VIVE Pro Eye). The wearable insoles are a medical device combining 16 plantar pressure sensors, accelerometers, and gyroscopes, were used. An integrated inertial measurement unit calculates the spatiotemporal parameters of the path in real time. According to the study by Farid et al. (2021), FeetMe® is the first device to calculate these parameters without external calculation sources. At the beginning of each Task, subjects received verbal instructions to focus their attention on the interfering task [93]. In VR tests, eye tracking allows to monitor the maintenance of the fixation point during the test.

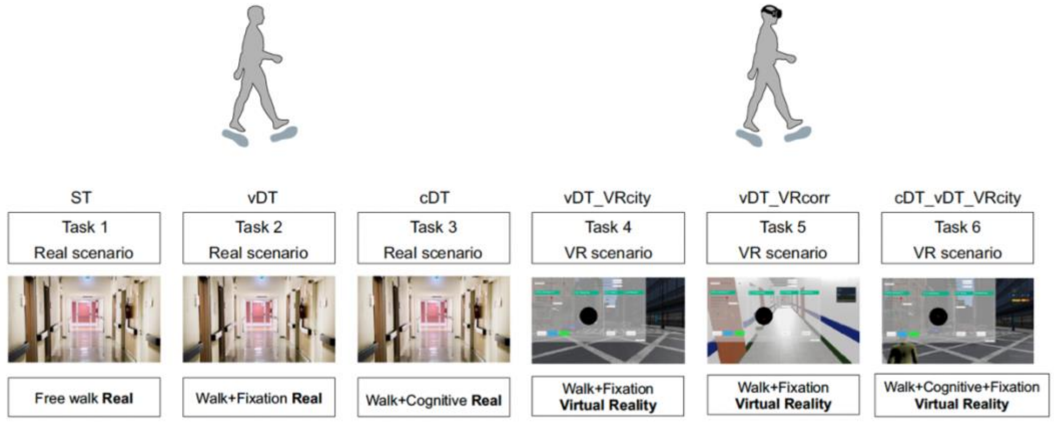


Figure 11: Experimental protocol: from Task 1 to 6. Task1: single task in the real environment, Task 2: visual dual task in the real environment, Task 3: cognitive dual task in the real environment, Task 4: visual dual task in VR environment (city), Task 5: visual dual task in VR environment (corridor), Task 6: cognitive and visual dual task in VR environment (city).

The different subject implications during tasks are listed and described below:

- *Task 1*, defined as "Free Walk Real" (single Task, ST), was performed in a real environment (a corridor of at least 15 m) in which the participants walked at self-velocity without any additional task. This Task allowed us to evaluate the gait patterns in single-task conditions in a real environment.
- In *Task 2*, defined as "Walk with Fixation Real" (visual dual Task, vDT), performed in the same real environment as Task 1, the participant walked at their self-velocity while maintaining the fixation on the red cross drawn on an A4 sheet, fixed at eye-level [79]. This Task allowed us to evaluate the gait patterns in conditions of visual-fixation dual-task in a real environment.
- *Task 3*, defined as "Walk with Cognitive Real" (cognitive dual Task, cDT), was performed in the real environment, and the participant walked at their self-velocity while performing a cognitive task consisting of execution of subtracting number 7 in series from 200, enunciating the counting. This Task evaluated the gait patterns under a cognitive dual task in a real environment.
- *Task 4*, defined as "Walk with Fixation Virtual Reality in 3D City" (visual dual Task in VR, vDT_VRcity), required the participant to walk in a virtual reality environment simulating a city. After 10 seconds of familiarization with the scenario, they had to walk at their self-velocity, fix the virtual red cross, and ignore moving elements (e.g., pedestrians). This Task allowed us

to evaluate the gait patterns of the visual-fixation dual-task conditions in a virtual environment with distractors.

- *Task 5*, defined as "Walk with Fixation Virtual Reality Corridor" (visual dual Task in VR, vDT_VRcorr,) was performed in a 3D virtual environment that faithfully reproduces the real corridor. After 10 seconds of familiarization, the participant walks at self-velocity, fixing a virtual red cross, without performing other tasks. The only difference to Task 2 was the use of the VR headset. This Task evaluated the gait patterns of visual-fixation dual-task conditions in a virtual environment.
- In *Task 6*, defined as "Walk with cognitive Virtual Reality in 3D City" (cognitive and visual dual Task in VR, cDT_vDT_VRcity), the participant walked through an urban virtual scenario (the same as Task 4), wearing the VR headset. During the task, the subjects counted the number of pedestrians visible in the scene without moving their heads. This Task evaluated the gait patterns in cognitive dual-task conditions in a virtual environment.

Through the FeetMe Mobility dashboard, designed to provide easy access in real-time to the patient data, it was possible to extrapolate and measure the following gait spatiotemporal parameters: step duration, stride time, stance time, single support time: the interval between the toe off and the heel strike of the other foot, double support time, swing time, step length, stride length, gait speed, cadence, swing time percentage, stance time percentage, double support time percentage.
The raw data in .csv format were used for a more detailed analysis to derive further outcome measures. Using a developed script in Matlab®, only the columns of the variables of interest were processed and analyzed.
From the parameters listed above, it was possible to calculate standard deviations (SD) as a measure of gait variability, obtaining the following metrics: Step duration SD, Stride time SD, Stance time SD, Single Support time SD, Double Support time SD, Swing time SD, Step length SD, Stride length SD, Gait speed SD, Cadence SD, Swing time percentage SD, Stance time percentage SD, and Double Support time SD. In addition, it was possible to calculate two specific measures of variability: swing time variability, using the formula Swing time SD / Swing time, and stride time variability, using the formula Stride time SD / Stride time.

Among all the spatiotemporal parameters provided by the insoles, the outcome measures of our interest were:

- Gait speed and its SD, as measures of the gait velocity and its variability
- Stride length and its SD, as measures of the stride length and its variability
- Cadence and its SD, as measures of the number of steps in the time and its variability
- Step duration and its SD as a measure of step time and its variability
- Stride time and Stride time var, as measures of the time of step and its variability
- Swing Time and Swing time variability, measures of oscillation time and its variability
- Stance time as a measure of the time spent
- Swing time percentage as a measure of the percentage of oscillation time
- Double support time and its SD, measures of double support time and its variability.

The descriptive analysis included the frequency (number, %) for categorical variables and the mean (± standard deviation, SD) for continuous variables. The parameters considered were: "number of subjects," "age," "sex," "height," "weight," and "BMI" (body mass index). For FMD, information on symptoms was also collected, including the presence of tremors, hyposthenia, dystonia, myoclonus, facial disorders, Parkinsonism, tic, walking ataxia, speech/voice disorders, swelling disorders, PNES (non-psychogenic seizures) and comorbidities. In addition, scores on the S-FMDRS scale for severity and duration of Symptoms in the lower limbs (left and right) and gait were registered.

Comparison between groups (HC, FMD, PD) was performed using the Pearson test for the sex variable and variance analysis (ANOVA) for the age variable, with Tukey post-hoc test and Bonferroni correction, to identify significant differences between groups. The non-parametric Kruskal-Wallis test was used when the data didn't meet the assumptions of normality, as was the post-hoc Dunn test. To assess which spatiotemporal gait measures best discriminated between patients (HC, FMD, PD) with different tasks, a ROC curve analysis (Receiver Operating Characteristic, curve of the operating characteristics of the receiver) was performed, comparing the pairs (for a total of 3 analysis), namely FMD vs HC, FMD vs PD and HC vs PD. The area under the curve (AUC) values have been sorted from highest to lowest. A rough guide to interpreting the usefulness of a biomarker, based on AUC, is as follows: 0.9-1.0 (excellent); 0.8-0.9 (good); 0.7-0.8 (moderate); 0.6-0.7 (poor); 0.5-0.6 (insufficient).

In addition, it was found interesting to assess which variables in the dual task didn't allow discrimination between the HC and FMD groups (AUC < low) but allowed discrimination of HC from other organic pathologies (e.g., HC vs PD) with a discrete AUC. The calculation was performed based on the difference between the values of AUC. This may indicate an improvement in performance in subjects with FMD (or non-worsening) that deviated from the typical behavior of organic pathologies (e.g., PD), which in this case may lead to performance deterioration. As reported by Bitterlink et al. (2003), this operation was possible, but the differences between AUC values may only be used for descriptive purposes, and it wasn't possible to determine whether these differences were statistically or clinically significant.

An ANOVA was conducted for repeated measurements with the group factors (patients with FMD, healthy controls, patients with Parkinson's disease), tasks (6 tasks), and the 'Group X Task' interaction for all measures of the gait, applying the Tukey post hoc test with Bonferroni correction. This analysis was used to identify the significant differences in outcome measures that best discriminated groups in ROC analysis.

6.2 Results

In total, 104 subjects were enrolled. The physiological, demographic, and educational level descriptions are shown in Table 3. Further information on the functional motor disorder (FMD) group regarding their symptoms is given in Table 4. The healthy control group sample included 42 individuals, predominantly female (n = 30; 71.43%) and with an age average of 37.05 ± 15.77 years. The sample of FMD subjects consisted of 30 individuals, predominantly female (n = 21; 70%), with an age average of 38.33 ± 13.85 years, following the higher prevalence of female sex and youth age in individuals with FMD [1,3,67]. The Parkinson's disease (PD) sample was composed of 32 individuals with a lower prevalence of female sex (n = 11; 34.38%) and mean age of 65.44 ± 7.43 years, following the highest prevalence of male sex and adult/senile age in individuals with Parkinson's disease (Parkinson's Foundation, n.d.).

The non-parametric Kruskal-Wallis test found a significant difference in the 'age' factor between the three groups of subjects (HC, FMD, and PD) (chi-squared = 50.55; $P < 0.001$). Post-hoc analysis using the Dunn test showed significant differences in the age factor between HC and PD groups ($Z = -5.89$; P-adjusted < 0.001) and between FMD and PD ($Z = -6.48$; P-adjusted < 0.001), but no differences between the HC and FMD groups ($Z = 0.10$; P-adjusted = 1). Pearson's Chi-Squared test for categorical variables found a significant difference in the 'sex' factor between the three groups (HC, FMD, PD) (chi-squared = 12.25; $P = 0.002$). The post-hoc test for proportions with Bonferroni correction showed significant differences between the PD group with HC ($P = 0{,}010$) and FMD ($P = 0{,}032$), highlighting a higher prevalence of male individuals in the PD group. In contrast, no differences between the HC and FMD groups were found ($P = 1$).
The significant age difference between the PD and the other two groups (HC and FMD) represented an important experimental bias. Therefore, the results that compare the PD group with the two groups, HC and FMD, should be interpreted with caution, and further studies will be needed to eliminate age bias and obtain more reliable conclusions.

Table 10: Physiological, demographic, and educational level information

	HC (n=42)	FMD (n=30)	PD (n=32)
Age, years (± SD)	37.05 ± 15.77	38.33 ± 13.85	65.44 ± 7.43
Female, %	71.43	70.00	34.38
Schooling, years (± SD)	15.33 ± 3.21	13.83 ± 2.96	11.25 ± 3.52
Height, m (± SD)	1.71 ± 0.07	1.68 ± 0.09	1.70 ± 0.07
Weight, kg (± SD)	68.07 ± 10.97	66.40 ± 15.24	75.55 ± 12.53
BMI (± SD)	23.29 ± 3.70	23.48 ± 4.72	26.06 ± 3.86

Table 11: *Additional information of subjects with FMD: symptoms in the lower limbs, indicated as AAII (tremor, hyposthenia, dystonia, myoclonus, Parkinsonism, tic, gait ataxia), comorbidity, score at S-FMDRS scale. In symptoms in the lower limbs, "x" indicates bilaterality of the symptom, "dx" only on the right, and "sx" only on the right left. In 'gait ataxia,' the type of symptom (e.g., knee buckling) or not is specified with "x." In the S-FMDRS score, the gravity and duration of symptoms are specified*

									S-FMDRS					
	AAII symptoms							Comorbidity	AI sx		AI dx		Gait	
# Subject	Tremor	Hyposthenia	Dystonia	Mioclone	Parkinsonism	Tics	Gait Disorders		severity	duration	severity	duration	severity	duration
32		x		xx			slow gait	Meningioma, gliosis, vascular abnormality	2	2	2	1	1	3
33	x	x	dx	x	x			no	0	0	2	2	1	3
34	x	x	x				knee bucling sx	no	3	3	2	3	2	3
35	x	x	x				slow gait	no	3	3	3	3	3	0
44	x	x					x	no	1	3	1	3	0	2
56		x	x				slow gait, knee buckling	no	3	2	3	2	3	2
56	sx	x					knee bukling sx	no	2	2	0	0	2	1
60		x					x	no	0	0	2	2	1	0
68				x			x	no	2	1	2	1	0	2
69		dx					x	no	0	0	2	2	2	3
73	x	x	x			x	knee bukling dx	no	2	3	2	3	2	0
81		x						no	0	0	4	1	0	0
83			x					no	2	2	2	2	0	0
85	x							no	2	2	2	2	0	0
87		x					postural instability, slow gait	no	2	2	2	2	0	2
88	dx	x					x	no	0	0	2	3	1	0
93		dx						no	0	0	1	2	0	0
92				sx				no	3	3	0	0	0	3
94		x					bilateral knee bukling	no	3	3	3	3	3	2
97							knee buckling	no	0	0	0	0	2	0
100		sx						no	1	1	0	0	0	3
102	x		x	x			x	patellar chondropathy	0	0	0	0	1	0
103		x						no	1	2	1	2	0	0
106						x	knee buckling	neoplasia	0	0	1	1	0	0
110	x			x				no	1	1	1	1	0	0
111		sx						no	1	2	0	0	0	0
122	x	x						no	2	1	2	1	0	0
123	sx	sx					knee buckling	epilepsy	1	3	0	0	1	3
125	x	x					knee buckling sx	fibromyalgia	1	2	1	2	1	3
126	x	x	x					no	3	2	1	1	2	2

6.3 Discussion

In this study, we investigated the effect of virtual reality (VR) protocol on spatiotemporal gait parameters by comparing, for the first time, individuals with functional gait disorders (FMD), individuals with motor impairments of organic origin (PD), and healthy control subjects (HC). VR might contribute to a better understanding of the pathophysiological mechanisms underlying FMD, representing a potentially promising tool for their diagnosis and treatment [29].

We found that several measures could distinguish between individuals with FMD and HC subjects, specifically three gait parameters within the pace domain (gait speed, step duration, and stride length) and one automaticity measure (swing time variability). These findings were supported by the AUC values greater than 0.75 and statistically significant results in the ANOVA, particularly under Virtual Reality conditions, reflecting a worsening gait performance among FMD patients (i.e., lower values in pace-related measures and higher values in variability measures).

Interestingly, no significant differences were observed between HC and FMD subjects in the cognitive dual-task performed in the real environment. In our study, the experimental setting and the cognitive demand of the cognitive dual-task in the real environment may have contributed to a reduction in the excessive attentional focus that FMD subjects tend to place on their own body [2,62,94], leading to an improvement in automaticity and rendering their gait performance more like that of HC. It is assumed that such an effect would not be achieved in other VR-based dual tasks due to their lower cognitive demand, as none of them involved mental arithmetic operations during gait. Similarly, a recent study investigating the effect of VR in FMD patients reported an improvement in postural stability during a dual task, but only in the condition requiring a higher attentional load [89]. From what was observed, none of the measured parameters could discriminate between HC from PD. We hypothesize that a specific measure distinguishing functional motor disorder from organic neurological conditions (such as PD) is still missing. Such a measure could be combined with those already capable of discriminating HC from FMD to develop a stronger diagnostic method for FMD. According to the literature, stride time variability may represent a promising candidate for this purpose. Still,

this study might have influenced this parameter by levodopa treatment in PD patients, potentially limiting its discriminative power.
Another critical point is the significant age difference between the PD and the other two groups (HC and FMD). Results comparing PD to the other two groups (HC and FMD) should be interpreted cautiously. Further studies are necessary to control for age-related factors and to obtain more reliable conclusions.

Based on these observations, the results of the gait parameters can be summarized in three points. Firstly, the stride time variability had no effective differentiating performance between groups, neither in single-task conditions nor in dual-task in any of the analyzed environments (real and virtual), confirming this value as a possible biomarker of neurobiological integrity of the pathway [3,94]. AUC values were found to be discrete (AUC > 0.7) only in two of the dual tasks with VR, in comparison between HC and FMD, in one dual-task condition in VR between HC and PD, and in no way between FMD and PD, as reported in Tables 5 and 6. However, the analysis of the variance to repeated measurements (ANOVA) didn't show any significant difference among the factors considered (group, task, and interaction 'Group X Task), highlighting the trend toward the stability of the measurement of the stride time variability in all conditions analyzed., as reported in Table 7. This result is consistent with what has been observed in previous studies [3,94], where the stability of the measurement is confirmed both in single and double tasks, comparing healthy subjects and FMD under a different experimental protocol compared to this study protocol. Sandri et al. (2024) and Gandolfi et al. (2023a) hypothesized the possibility of using the measurement of stride time variability as a biomarker for the diagnosis of FMD as an indication of the integrity of the automatic gait in the FMD. This appearance would contrast with the worsening (increase) of the same measure in dual-task tasks in patients with other organic pathology, such as Parkinson's disease and multiple sclerosis, since the dual-task affects the automaticity of the walk, increasing the variability of step time [52,70]. According to our data, the stride time variability is doubtful as an autonomous measure for distinguishing a neurological pathology of functional origin from a neurological pathology of organic origin.

Table 12: AUC values for HC vs FMD. AUC values resulted from ROC analysis for six tasks on 16 spatiotemporal gait parameters by comparing HC and FMD. High values indicate that a discriminating capacity is greater. Task 1 =ST; 2 = vDT; 3= cDT; 4 = vDT_VRcity; 5 = vDT_VRcorr; 6 = cDT_vDT_VRcity.

HC vs FMD	task 1	task 2	task 3	task 4	task 5	task 6
Gait_speed	0.755	0.791	0.705	0.785	0.803	0.770
Stride_length	0.789	0.825	0.745	0.792	0.833	0.787
Cadence	0.648	0.709	0.633	0.737	0.743	0.714
Step_duration	0.649	0.713	0.660	0.775	0.753	0.739
Stride_time	0.652	0.710	0.637	0.727	0.744	0.715
Swing_time	0.666	0.719	0.658	0.729	0.753	0.667
Stance_time	0.629	0.698	0.611	0.721	0.720	0.714
DoubleSupp_time	0.603	0.658	0.576	0.701	0.677	0.707
Swing_time_%	0.528	0.556	0.511	0.591	0.637	0.652
Gait_speed_SD	0.500	0.599	0.476	0.626	0.519	0.498
Stride_length_SD	0.562	0.567	0.633	0.512	0.618	0.558
Cadence_SD	0.618	0.573	0.556	0.569	0.718	0.696
Swing_time_var	0.781	0.755	0.633	0.773	0.832	0.820
Step_duration_SD	0.572	0.619	0.639	0.578	0.564	0.600
Stride_time_var	0.634	0.610	0.593	0.381	0.736	0.717
DoubleSupp_time_SD	0.589	0.516	0.535	0.551	0.636	0.592

Table 13: AUC values for HC vs PD. AUC values resulted from ROC analysis for six Tasks on 16 gait spatial parameters by comparing HC and PD. High values indicate that a discriminating capacity is greater. Task 1 = ST; 2 = vDT; 3 = cDT; 4 = vDT_VRcity; 5 = vDT_VR; 6= cDT_vDT_VRcity

HC vs PD	task 1	task 2	task 3	task 4	task 5	task 6
Gait_speed	0.621	0.749	0.673	0.692	0.652	0.692
Stride_length	0.742	0.823	0.759	0.779	0.733	0.777
Cadence	0.644	0.511	0.512	0.569	0.565	0.589
Step_duration	0.616	0.536	0.555	0.512	0.528	0.469
Stride_time	0.641	0.515	0.528	0.569	0.567	0.417
Swing_time	0.667	0.540	0.511	0.592	0.585	0.644
Stance_time	0.611	0.547	0.543	0.553	0.541	0.460
DoubleSupp_time	0.502	0.600	0.594	0.506	0.512	0.567
Swing_time_%	0.610	0.630	0.642	0.597	0.588	0.709
Gait_speed_SD	0.495	0.576	0.594	0.513	0.503	0.658
Stride_length_SD	0.518	0.474	0.663	0.512	0.447	0.670
Cadence_SD	0.553	0.526	0.695	0.640	0.698	0.777
Swing_time_var	0.777	0.774	0.763	0.759	0.783	0.866
Step_duration_SD	0.736	0.729	0.688	0.735	0.712	0.703
Stride_time_var	0.566	0.525	0.657	0.401	0.669	0.739
DoubleSupp_time_SD	0.621	0.411	0.498	0.602	0.588	0.468

Table 14: ANOVA of the gait parameters in performance discrimination between HC, FMD, and PD (group: FMD vs. HC vs. PD; Task: 1-6).

Gait measure	**Main effect/interaction**	**F**	**P**
Pace domain			
Gait speed (cm/s)	Group	12.68	<0.001
	Task	77.65	<0.001
	Group x Task	3.32	<0.001
Stride length (cm)	Group	16.77	<0.001
	Task	70.07	<0.001
	Group x Task	3.86	<0.001
Step duration (s)	Group	8.88	<0.001
	Task	21.55	<0.001
	Group x Task	2.16	0.019
Rhythm domain			
Stride time (s)	Group	7.71	<0.001
	Task	16.87	<0.001
	Group x Task	1.21	0.283
Swing time (s)	Group	8.75	<0.001
	Task	26.52	<0.001
	Group x Task	1.06	0.390
Phase domain			
Swing time (%)	Group	1.72	0.185
	Task	25.73	<0.001
	Group x Task	2.40	0.009
Variability measures			
Gait speed SD (cm/s)	Group	1.00	0.372
	Task	7.03	<0.001
	Group x Task	1.59	0.106
Stride length SD (cm)	Group	2.66	0.075
	Task	8.12	<0.001
	Group x Task	1.97	0.034
Swing time variability (a.u.)	Group	9.83	<0.001
	Task	10.18	<0.001
	Group x Task	3.36	<0.001
Step duration SD (s)	Group	5.95	0.004
	Task	1.35	0.241
	Group x Task	0.23	0.993
Stride time variability (a.u.)	Group	0.37	0.692
	Task	1.79	0.113

Group x Task	1.21	0.280

Secondly, the swing time variability (SWT) effectively differentiated HC from FMD and PD in most tasks, worsening performance in subjects with neurological disorders. However, this measurement never distinguished the three categories of subjects during the cognitive dual task in a real environment (cDT) despite ROC curve analysis showing a good ability to discriminate between HC and PD (AUC > 0.7) but without achieving significance in the post-hoc test. The result is inconsistent with previous studies [3,52] that report an opposite trend: the cognitive dual task worsened the swing time variability, suggesting a negative impact of cognitive Task on this measure of gait automaticity. The cDT is a mental monitoring task during which subjects must keep information in memory while performing a mental process [2,62]. In our study, the experimental setting and the cognitive demand of the cognitive dual task in the real environment (cDT) may have favored a reduction in the excess of attention that FMD subjects place on their body [2,62,94], correcting positively the measure of automaticity and making the results more like those of healthy subjects. It is assumed that the same effect wouldn't be achieved in the other virtual reality dual tasks for the lower cognitive demand that characterized them since no other task involved the execution of minded mathematical operations during the gait. Similarly, a recent study on the effect of VR in patients with FMD showed an improvement in postural stability during a dual task, but only in the condition of greater demand for attention [95]. The tendency for a worsening of swing time variability in subjects with Parkinson's disease could be statistically confirmed by a sample of subjects. However, the significant age difference between the PD and other groups remains influenced by our study, representing a relevant bias. If further studies could be conducted on subjects with organic neurological disorders but without the typical age bias in comparison between FMD and PD (for example, a comparison between FMD and MS), it could be argued that the swing time variability is worse in cases of subjects with organic neurological disorders involved in cognitive dual tasks, becoming a potential biomarker for differential diagnosis of FMD.

It is known that the performance of people with organic neurological disorders worsens during cognitive dual tasks [2,52,62]. Specifically, in Parkinson's disease, it is known that the stride-to-stride variability significantly increases compared to healthy subjects of the same age [95]. However, it is not clear why, in the study, this measure didn't show a significant worsening. It is assumed that in the early stages of disease (Hoehn & Yahr 1 and 2), the stride-to-stride variability can remain stable since motor compensation mechanisms maintain a general gait relatively constant. On the contrary, the increase in swing time variability could be linked to specific neurological alterations that involve fine motor control. In the early stages of the disease, the neural circuits involved in planning and executing movements, such as those of the motor cortex and the basal ganglia, would already show signs of deterioration. Instead, in subjects with FMD, the stability of the stride time variability, associated with a worsening of the swing time variability, could be due to the high sensitivity of the swing time variability to disturbances in coordination and voluntary motor control, negatively affected by excessive attention to their body. On the contrary, the stride time variability is a more global measure of gait stability, thus reflecting a level of control of the more automatic movement. Stride time variability could be considered a less directly modulated parameter by attention fluctuations and conscious control, resulting in less alteration in FMD. Conversely, swing time variability could be linked to a higher level of neurological control than stride time variability. Both are considered part of the "high-level" mechanisms of gait control.

These discussions are supported by several studies showing that the various gait parameters respond to different control mechanisms[52,96]. Specifically, gait speed has been associated with a "high level" cognitive control system as it is easily influenced by tasks involving executive functions [3,52]. The swing time variability seems to depend on balance control mechanisms, distinguished from those responsible for the gait pattern mechanisms, which are more automatic as the adjustment of stride time variability, linked to sequential contraction and relaxation mechanisms of the muscle involved [95].

Thirdly, immersive VR could represent an additional strategy for distinguishing subjects with functional neurological disorders from those with neurological disorders of organic origin. The results of the ROC curves have highlighted how some of the spatiotemporal gait parameters, relative to the pace domain and rhythm, have shown discrete discriminating ability (AUC > 0.7) in dual tasks in the virtual environment (vDT_VRcity, vDT_VRcorr, cDT_vDT_VRcity) comparing the HC and FMD groups, but not between HC and PD. For example, the measurement of step time showed higher values in subjects with FMD than those with HC and PD in all tasks, with significant differences in post-hoc analysis in dual tasks in virtual reality (vDT_VRcity and vDT_VRcorr), as reported in Table 8 and 9. The step time is known to be influenced by dual tasks [84].

Based on current knowledge, it is assumed that VR may positively influence the pathophysiological mechanisms of FMD, reducing/ eliminating differences with HC through the simultaneous effect on the prediction of sensory information, the attentional control of the body movement, and the suggestibility (Sense of Agency) to which is added the depersonalization of the context, characteristic of a VR environment [31,84,94].

Table 15: Mean values and standard deviation of some parameters used for repeated measurements ANOVA. Task 1 = ST; 2 = vDT; 3 = cDT; 4 = vDT_VRcity; 5 = vDT_VRcorr; 6= cDT_vDT_VRcity.

	Task 1	Task 2	Task 3	Task 4	Task 5	Task 6
Gait Speed						
HC	1.234 ± 0.165	1.255 ± 0.183	1.063 ± 0.229	1.108 ± 0.209	1.092 ± 0.206	1.064 ± 0.217
FMD	1.012 ± 0.287	0.975 ± 0.280	0.862 ± 0.276	0.830 ± 0.294	0.796 ± 0.267	0.813 ± 0.263
PD	1.174 ± 0.198	1.100 ± 0.209	0.896 ± 0.258	0.997 ± 0.208	0.989 ± 0.231	0.893 ± 0.254
Stride Length						
HC	1.385 ± 0.112	1.394 ± 0.118	1.290 ± 0.134	1.286 ± 0.147	1.286 ± 0.140	1.270 ± 0.150
FMD	1.201 ± 0.202	1.180 ± 0.195	1.115 ± 0.203	1.070 ± 0.220	1.042 ± 0.200	1.066 ± 0.197
PD	1.265 ± 0.164	1.227 ± 0.170	1.090 ± 0.218	1.138 ± 0.182	1.145 ± 0.202	1.051 ± 0.243
Step duration						
HC	578.321 ± 87.843	569.816 ± 71.829	623.260 ± 103.223	582.197 ± 70.216	601.933 ± 72.190	606.111 ± 70.946
FMD	616.893 ± 93.574	632.083 ± 103.969	682.887 ± 119.731	687.980 ± 112.868	695.496 ± 114.536	694.207 ± 111.093
PD	547.321 ± 40.938	570.315 ± 56.612	638.243 ± 111.720	594,299 ± 95.189	600.565 ± 95.373	624.349 ± 173.303
Swing Time var						
HC	3.720 ± 1.204	4.069 ± 2.357	5.762 ± 2.972	5.256 ± 3.219	4.787 ± 1.979	5.314 ± 2.817
FMD	9.983 ± 11.382	9.645 ± 11.143	10.269 ± 10.223	11.726 ± 10.701	12.606 ± 10.906	10.935 ± 8.380

PD	5.840 ± 3.133	6.298 ± 4.235	9.669 ± 5.455	7.462 ± 3.800	7.456 ± 3.367	10.172 ± 5.047
Step duration SD						
HC	147.160 ± 310.967	145.399 ± 225.654	183.321 ± 177.813	157.955 ± 167.379	158.246 ± 174.421	180.734 ± 175.770
FMD	119.591 ± 188.714	118.618 ± 183.801	118.533 ± 164.555	123.565 ± 159.809	131.189 ± 170.495	137.576 ± 175.369
PD	32.118 ± 14.742	37.388 ± 20.211	63.287 ± 47.077	47.380 ± 22.219	45.100 ± 21.352	68.235 ± 62.994
Stride Time var						
HC	0.024 ± 0.008	0.027 ± 0.015	0.041 ± 0.025	0.091 ± 0.359	0.032 ± 0.016	0.039 ± 0.022
FMD	0.039 ± 0.041	0.039 ± 0.038	0.049 ± 0.026	0.058 ± 0.062	0.068 ± 0.094	0.056 ± 0.023
PD	0.026 ± 0.010	0.028 ± 0.018	0.109 ± 0.296	0.042 ± 0.021	0.040 ± 0.016	0.062 ± 0.036

Table 16: Post-hoc analysis for gait speed, stride length, step time, swing time variability, step time SD. Different letters indicate significant differences in pair comparison (P<0.05). Task 1 = ST; 2 = vDT; 3 = cDT; 4 = vDT_VRcity; 5 = vDT_VRcorr; 6= cDT_vDT_VRcity

Gait speed						
	task 1	task 2	task 3	task 4	task 5	task 6
HC	a	a	a	a	a	a
FMD	b	b	a	b	b	b
PD	ab	ab	a	ab	ab	ab
	HC	FMD	PD			
task 1	a	a	a			
task 2	a	a	b			
task 3	b	b	cd			
task 4	b	b	c			
task 5	b	b	c			
task 6	b	b	d			
Stride length						
	task 1	task 2	task 3	task 4	task 5	task 6
HC	a	a	a	a	a	a
FMD	ab	b	b	ab	ab	b
PD	b	b	b	b	b	b
	HC	FMD	PD			
task 1	a	a	a			
task 2	a	ab	a			
task 3	b	bc	bc			
task 4	b	c	b			
task 5	b	c	b			
task 6	b	c	c			
Step time						
	task 1	task 2	task 3	task 4	task 5	task 6
HC	ab	a	a	b	b	a
FMD	a	a	a	a	a	a

PD	b	a	a	b	b	a
	HC	FMD	PD			
task 1	ab	c	c			
task 2	b	bc	b			
task 3	a	ab	a			
task 4	ab	ab	ab			
task 5	ab	a	ab			
task 6	ab	ab	ab			
Swing time variability						
	task 1	task 2	task 3	task 4	task 5	task 6
HC	b	b	a	b	b	b
FMD	a	a	a	a	a	a
PD	ab	ab	a	ab	ab	a
	HC	FMD	PD			
task 1	b	b	c			
task 2	ab	b	c			
task 3	a	ab	ab			
task 4	ab	ab	bc			
task 5	ab	a	bc			
task 6	ab	ab	a			
Step time SD						
HC	a					
FMD	ab					
PD	b					

In conclusion, this is the first study that compares a wide range of spatiotemporal gait parameters, analyzed in both single and dual tasks, performed in two different environments (real and virtual reality), to identify measures that best discriminate individuals with Functional Movement Disorders (FMD), motor disorders of organic cause (PD) and healthy controls (HC).

The study's main innovations are two:

I. The introduction of immersive Virtual Reality as an evaluative environment to distinguish between FMD and HC

II. Including individuals with an organic neurological disease (PD) as a comparison for gait parameters expands knowledge from previous studies that included only individuals with FMD and HC [3,94]. Subjects in the early stages of Parkinson's (stage 1-2 Hoen & Yahr) may develop motor symptoms that significantly interfere with daily activities but maintain a certain degree of independence (Parkinson's Foundation, n.d.).

Moreover, this study highlights the importance of a multidimensional approach that involves immersive virtual reality in assessing FMD patients' gait through specially developed protocols on the pathophysiology of disorders. Results suggest that the effect of VR, rather than reducing the performance differences between FMD and HC, can identify specific gait parameters that cannot be detected by observation, which could help facilitate early and correct diagnosis of FMD. These results don't exclude that VR can also find application in rehabilitation [31,95].

The results highlight both the prospects and the critical points of VR, underlining the need for further studies to better understand the effectiveness of VR and develop specific evaluation and treatment protocols for FMD patients.

7. Implementing a Digital Telerehabilitation protocol for improving motor and non-motor outcomes and quality of life in patients with Functional Motor Disorders: a feasibility 2-arm parallel randomized controlled trial

Based on results from systematic reviews and studies on FMD-specific biomarkers, this is the first study investigating FMD behaviors in an ecological setting using wearable devices. This is an ongoing study supported by the Verona Brain Foundation.

The primary aim of this study is to implement and assess the feasibility of the steps that need to take place as part of the main confirmatory study on comparing the effects of a Digital Telerehabilitation program, including TOMs (Technological Objective Measurements), on motor symptoms severity and duration in patients with FMDs. The secondary aim is to compare the training effects on non-motor symptoms (such as pain, fatigue, anxiety, and depression), the self-perception of clinical change and Health-Related Quality of Life, and health care costs.

This is an experimental single-blind randomized-controlled trial (RCT) with 2-parallel arms comparing the effects between the experimental (EG) and control group (CG).

After the screening, a simple randomization list is generated by a physician using an automated randomization system (allocation ratio 1:1) to assign eligible patients to either the EG or the CG, and the group allocation is kept concealed.

All patients receive the same individualized intensive 5-day rehabilitation program (2 hours/day, 5 days/week, 1 week) by a qualified physiotherapist in collaboration with the USD Parkinson's Disease and Movement Disorders Unit of Verona[174–176].

All the patients undergo four clinical evaluations: before the intensive 5-day rehabilitation program (T0), the day after the intensive 5-day rehabilitation program (T1), after 12 weeks (at the end of the self-management plan, T2), and 24 weeks (follow-up, T3). During the hospitalization period, on T0 days, which corresponds to the second day of admission, and T1, which corresponds to the day of discharge, specific assessments of the gait and balance are given to the patients, and the same are performed at follow-ups at three and six months, respectively, T2 and T3. At the end of the in-hospital rehabilitation, the therapist instructs the patient to follow an individualized self-rehabilitation program based on specific indications.

In particular, a stabiliometric platform (Tecnobody, Dalmnine, Italy) is used for the balance analysis and is carried out in three tests: single task (a simple balancing with fixing of the cross on the screen), motor dual-task (hand prono-supination and fixing of the cross on the screen), and cognitive dual-task (subtractions of number 7 while always maintaining the fixing of the cross on the screen). All three tests are divided into two parts: a first, open eyes, and a second, closed eyes. Thanks to the relationship between the performance with eyes closed and that with eyes open, it is possible to obtain the Romberg index, a parameter used to evaluate the balance quality.
Instead, wearable devices, specifically the FeetMe baropodometric insoles, are used for gait analysis, equipped with inertial sensors (IMU) and pressure sensors, which can derive spatiotemporal gait parameters. These parameters are useful because they provide performance information, such as cadence, gait speed, stride length, swing, and stride time, as well as automaticity parameters, such as swing and stride time variability. These devices are used during four walk tests at a comfortable patient velocity along the hospital corridor, over 10 meters. As for the stabilometric evaluation, also for the gait analysis different tests, including single and dual tasks, are executed: single task (free walking at comfortable velocity without any other request), motor dual task (free walking and hand prono-supination), cognitive dual task (subtraction with number seven while walking), and visual dual-task (free walking and fixation of the cross at the end of the corridor at eye level).

After intensive rehabilitation treatment of 5 days (2 hours/day, 5 days/week, for 1 week), EG patients are encouraged to perform the self-management plan at home with the same duration and intensity as CG (1 hour/session, three sessions/week, 12 weeks). Compared to the control group, the experimental group patients are equipped with a wearable sensor that must be worn for a whole week, 24 hours a day, to monitor daily activities' performance remotely.
These wearable digital devices are specifically the Axivity AX6, a 6-axis recording accelerometer, which allows objective information to be collected on the patient’s

motor activity. After hospitalization (T1), each patient of the EG receives a sensor for monitoring movement data such as activity level, number of steps, distance covered, and sleep monitoring. After the week of acquisition, the data is transmitted to the research center for processing through specific processing programs developed by the sensor platform (OMGUI Configuration), with which spatiotemporal gait parameters are extracted. An external platform (McRoberts B.V., Netherlands) is also used to obtain data on physical activity, energy expenditure, and night rest. Instead, the subjective assessment of the patient's motor activity is collected from clinical questionnaires focusing on gait and level of activity, like the control group.

From the processing of sensor data, at the end of the 7 days of Monitoring, it is possible to collect the following information (reported in Figure 12):

- *Activity level*: discrimination between inactive behavior (sitting or lying down), static (standing up, shuffling), movement (walking, climbing the stairs, or cycling), and not worn sensor indication.
- *Amount of movement*: number of periods considered, such as the number of measurements made by the wearable device in predetermined time intervals.
- *Total time*: the amount used to perform each item in the activity column expressed in hours and minutes.
- *Average of 24 hours*: average of time (expressed in hours and minutes) use average daily (considering as interval 7 days of acquisition) for each activity in the Activity column
- Relative time: based on the ratio of the time spent on each activity to the total time of all activities performed, for example, 48 hours total.
- *Average MI* (movement intensity): indicates the average acceleration of the body during physical activity.
- *Total and relative energy expenditure*: based on the type of activity done (lying, sitting, standing, walking, shuffling, stair walking and cycling)
- *Total Kcal consumption*: as the sum of BMR (Basal Metabolic Rate), DIT (Diet-Induced Thermogenesis), AEE (Axitivity Energy Expenditure) contributor

As previously mentioned, the device also detects information concerning energy expenditure, the energy expenditure expressed in metabolic activity equivalent (MET). The parameters that are provided are basal metabolic rate (BMR), diet-induced thermogenesis (DIT), activity-related energy expenditure (AEE), total energy expenditure (TEE), physical activity ratio (PAR), and level of physical activity (PAL). These parameters are given concerning the activity performed and total energy spent, considering all periods of activity and inactivity.

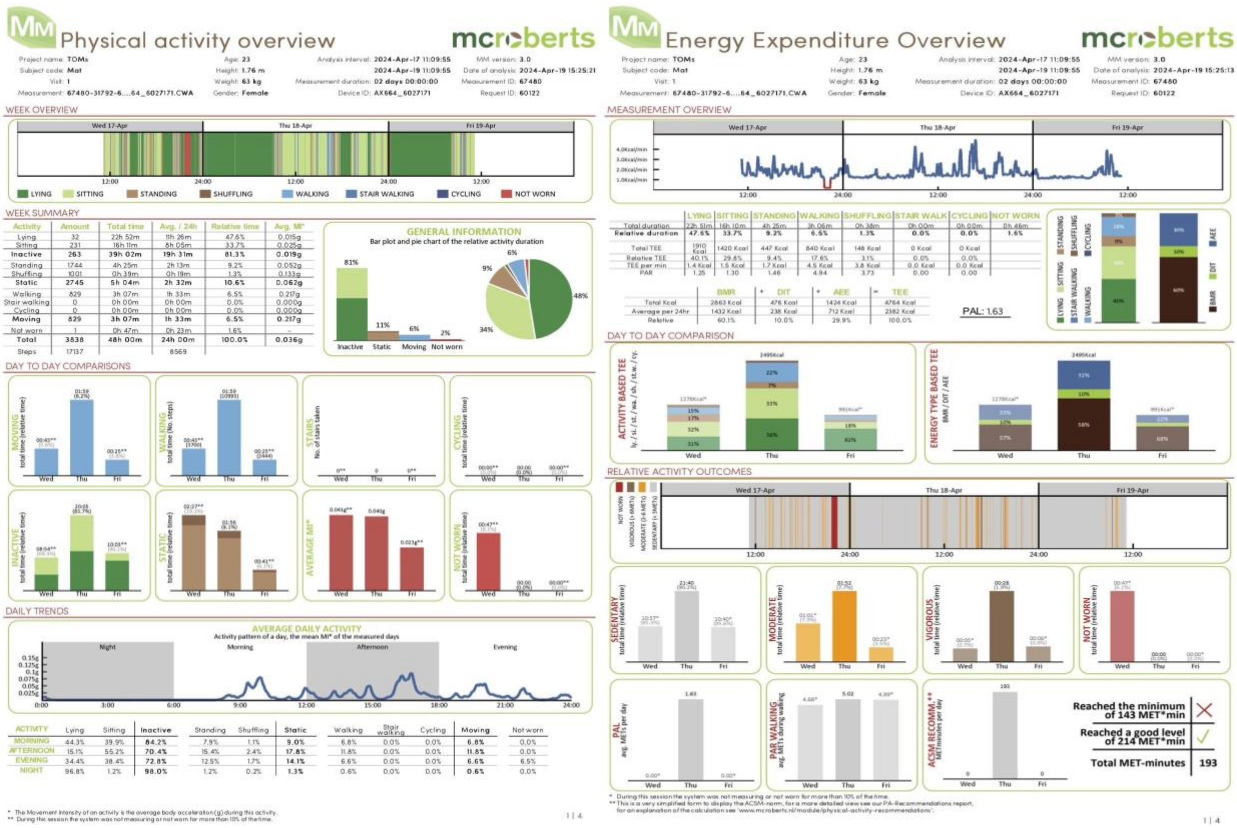


Figure 12: Example of reports from McRoberts platform using Axivity AX6 data regarding physical activity and energy expenditure

For this study, it is considered useful to analyze the Average TEE for 24h, which is the mean value of total energy expenditure for each day of acquisition, the PAL, which is the value obtained from the ratio between TEE and BMR, and the total MET, which is the average metabolic consumption over the acquisition period.

As regards sleep data, the data processed can provide information on the quality of sleep, positions taken during the night, intensity and time of movement, the number and duration of transitions, and the type of position taken (for example, prone, supine, right or left side). This study considers deepening the parameter analysis describing movement during sleep.

The study was conducted based on the Helsinki Declaration. They followed the Good Clinical Practice and Consolidated Standards of Reporting Trials (CONSORT). The local Ethics Committee, "Ethical Committee for Clinical Trial (CESC) of the Provinces of Verona and Rovigo" (159CET), approved and registered the study as a Clinical Trial (NCT06274281).

7.1 Experimental protocol

Patients with a definite diagnosis of FMD were enrolled at the USD Parkinson's Disease and Movement Disorders, AOUI Verona. The flow diagram is reported in Figure 13.

The same inclusion and exclusion criteria as the main study were published in our previous work [177]. The selection criteria are given in Table 17. Sociodemographic data, clinical history, and clinical manifestations of functional disorders are collected at enrollment (T0): age, sex, work, schooling, previous "organic" and "non-organic" diagnosis before final diagnosis, number of clinicians, investigations, symptoms, associated symptoms (for example. pain, cognitive), psychiatric diagnosis, neurological and non-neurological comorbidities, previous clinical examinations related to functional disorders.

One physician with experience in assessing motor and non-motor symptoms in FMD patients, blinded to group assignment, evaluates participants at all time points. To maintain blindness, the examiner doesn't ask for information about treatment from patients or caregivers, and the latter are instructed not to provide information outside the examiner's questions.

After ascertaining that the inclusion/exclusion criteria have been met, discussing the protocol, and obtaining informed consent, randomization is actuated, and patients are randomized in the Experimental (EG) and Control Group (CG). One physical therapist is employed for the EG and CG training during the intensive 5-day rehabilitation program to ensure adherence to the rehabilitation program between the two groups. Exercises are performed to restore normal movement patterns within a multidisciplinary etiological framework, according to a validated rehabilitation protocol for FMD [176,178,179].

Another physiotherapist and a biomedical engineer are trained and dedicated to delivering Digital Telerehabilitation to the EG. At this stage, an operator conducts a training session (only for EG) on using the telemonitoring system.

Patients are also suggested to visit a self-help website (https://neurosymptoms.org/it_IT/) to guide them in actively participating in the healing process and understanding their symptoms through video consultation and sharing of experiences of other patients.

The treatments are adapted to the needs of each patient, following the general principles of treatment in physiotherapy for FMD:

1. Education and exploration of how symptoms affect movement and posture
2. Retrain the movement using strategies based on redirection of attention
3. Development of a self-management plan.

Gradual and non-specific exercises are part of the rehabilitation program to address reduced exercise tolerance, fatigue, and chronic pain.

At the end of the intensive rehabilitation treatment of 5 days, patients receive an individualized home self-management path to facilitate the acquisition of educational components of the program and promote the involvement of the patient's in-home treatment.

Home self-management is implemented during the 5-day intensive rehabilitation program with exercises tailored to the patient's needs and conditions, with the same duration, dose, and intensity between EG and CG (1 hour/day, 3 days/week, 12 weeks). However, once outside the hospital, the EG group patients are monitored remotely (monitor movement as activity level, number of steps, and distance covered) using a wearable accelerometer (Axivity AX6) positioned on L5 for one week, fixed with a medical patch. The same acquisition has to be done three times: at the first week after discharge, at 12 and 24 weeks (T2 and T3, respectively). Instead, the CG group patients are without it. In fact, at the end of hospitalization (T1), each patient in the control group doesn't receive wearable sensors (Axivity AX6) for movement data monitoring. All participants are discharged with a return appointment at 12 and 24 weeks after hospitalization days. For both group patients, the subjective evaluation of their motor activity is collected through clinical diaries focusing on gait and activity level.

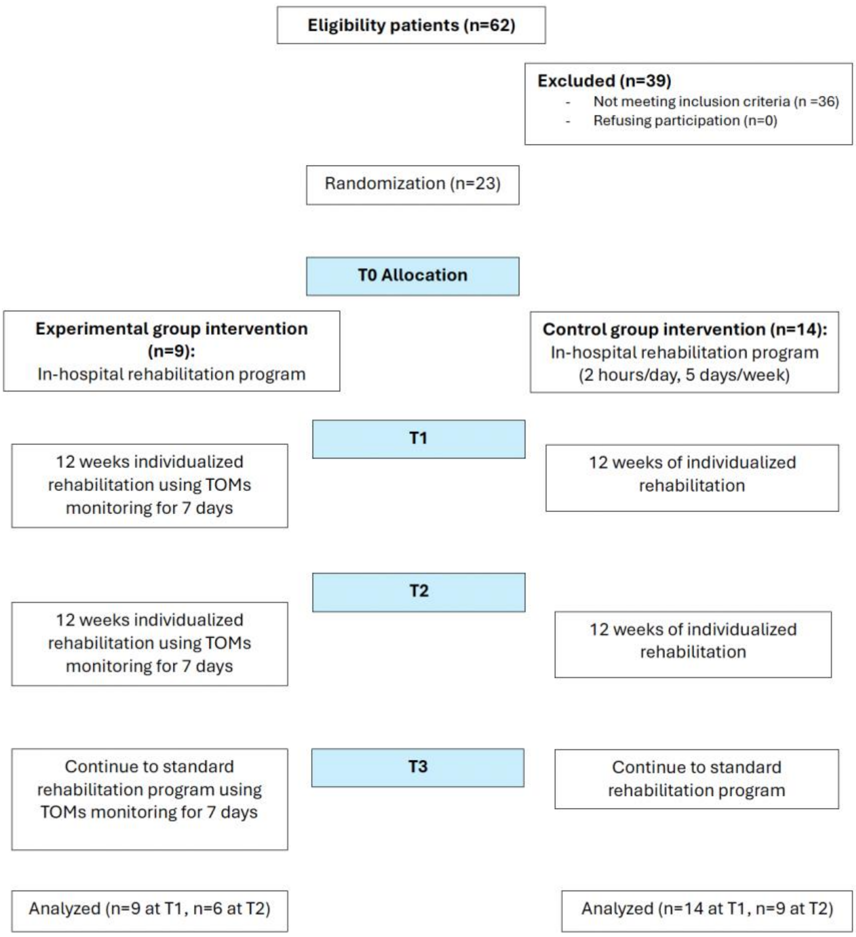


Figure 13: Flow diagram of patients' enrollment

Table 17: Inclusion and Exclusion Criteria for Patients' participations

INCLUSION CRITERIA	EXCLUSION CRITERIA	DROPOUT
A clinically definite diagnosis of FMDs based on Gupta and Lang diagnostic criteria [176] with the presence of distractibility maneuvers and a demonstration of positive signs [180]	Unable or refuse to attend the consecutive 5-day rehabilitation treatment. Patients give their written informed consent after being told about the experimental nature of the study.	The patients who will not attend all the sessions and/or won't undergo all clinical and instrumental assessments will be considered dropouts.
The presence of one (isolated FMDs) or more clinical motor symptoms (combined FMDs), including weakness, tremors, jerks, dystonia, gait disorders, and parkinsonism [180]	Prominent cognitive and physical impairment that precludes signing the informed consent for participation in the study.	The data analysis will consider all selected and randomized patients ("Intention-To-Treat" analysis).
Age ≥ 18 years	Prominent dissociative seizures	

Acceptable level of digital skills	Mini-Mental State Examination <23/30 [180]	
Severity and duration of motor impairment ≥1 scored with the Simplified Functional Movement Disorders Rating Scale (SFMDRS) [181,182]	Vulnerable populations: the study can't include pregnant women patients in an emergency	
Acceptance of the diagnosis	Patients continue expressing doubt over the diagnosis.	

7.1.1 *Planned procedures and collected information*

In this section, all procedures and collected information are reported and schematized (Table 18).

At enrollment:

- Check the patient's eligibility for the study according to the inclusion/exclusion criteria.
- If eligible, patients sign the informed consent, and the following clinical and demographic variables are collected: age, sex, job, schooling, previous diagnosis, symptoms, associated symptoms (i.e., pain, cognitive), psychiatric diagnosis, neurological and non-neurological comorbidities, medical history (i.e., last clinical exams related to FMDs and therapies) and concomitant medications.
- Patient randomization by a clinician (MG) using an automated randomization system (www.randomization.com) (allocation ratio 1:1) to either the EG or CG.

At visits 1 (T0) and (T1), secondary endpoints are collected; at visits 3 (T2), primary and secondary endpoints; and at visits 4 (T3), secondary endpoints are collected.

Visit details:

- *T0: before the intensive 5-day rehabilitation program*

  Baseline-T0 examination (approximately 90 minutes): medical history; verification of inclusion/exclusion criteria; informed consent collection; clinical-functional examination; administration of measurement scales; training session and delivery of materials (wearables).
- *T1: the day after the end of an intensive 5-day rehabilitation program*

Visit at the end of the intensive 5-day rehabilitation program T1: history gathering, clinical-functional examination, and administration of measurement scales.

- *T2*: *after 12 weeks (at the end of the self-management plan through a wearable sensor/self-management alone)*

  Visit at the end of 12 weeks of use of the telemonitoring system T2 (duration approximately 60 minutes): history gathering; clinical-functional examination; administration of measurement scales and material return.
- *T3: after 24 weeks (follow-up*)

  Follow-up visit at 24 weeks (T3) from baseline visit (duration approximately 60 minutes): anamnestic reconciliation; clinical-functional examination and administration of measurement scales.

Table 18: Flowchart of information collection

Activity	**Enrollment**	**Visit 1 (T0)**	**During Treatment**	**Visit 2 (T1)**	**Visit 3 (T2)**	**Visit 4 (T3)**
	1st day-enrolment	Before treatment (day before starting rehab)	(5 days/week for 1 week)	The day after the 5-days intensive program	After 12 weeks (at the end of the self-management plan)	Follow-up visit at 24 weeks from baseline visit
Inclusion/ Exclusion Criteria	X	X				
Informed consent	X	X				
Demographics and baseline characteristics	X					
Medical History	X	X		X	X	
Concomitant medications	X					
Randomization mechanism	X					
Clinical-functional examination		X		X	X	X
Measurement scales administration		X		X	X	X
Primary endpoint					X	
Recruitment rate (number of patients who accept/refuse the treatment)					X	

Intervention acceptability (number of dropouts before ending the treatment)					X	
Safety: adverse events during the treatment (falls, events near falling during rehabilitation)					X	
Time to train the patient in using TOMs					X	
Resources feasibility: budget issues using TOMs during the EG intervention					X	
Data management issues in collecting and analyzing data: accuracy, completeness, consistency and timeliness					X	
Secondary endpoint examination:						
S-FMDRS		X		X	X	X
MFI-20		X		X	X	X
EQ-5D		X		X	X	X
BPI		X		X	X	X
SF-12		X		X	X	X
Static balance		X		X	X	X
Spatio-temporal gait parameters		X		X	X	X
BDI-II		X		X	X	X
BAI		X		X	X	X
Health services volume, direct and indirect costs		X		X	X	X
iMTA *Productivity Cost Questionnaire*		X		X	X	X
CGI				X	X	X
CG treatment			X			
EG treatment			X*		X*	
EG monitoring (TOMs)				X*	X*	
Medical Therapy		X			X	X
* additional procedure						

7.2 Primary and Secondary Outcomes

Clinicians with experience in assessing motor and non-motor symptoms in patients with FMD, unaware of group assignment, collected primary results secondary to T0, T1, T2, and T3 (primary and secondary outcomes are summarized in Table 19). This thesis evaluates all patients with T0, T1, and T2. Due to very few patients with T3, these data will be evaluated at the end of the study.

Primary outcomes are related to feasibility measures (collected at T2), including recruitment, acceptability of the intervention regarding the number of withdrawals before the end of treatment, and safety regarding adverse events reported during treatment (falls or near-falls).

Secondary outcomes include the variations from T0 to T2 of the following outcomes investigating motor and non-motor symptoms. The differences between the experimental and the control groups are explored.

Motor symptoms

Motor symptoms are assessed based on the duration and severity of functional motor symptoms, measured by the Simplified Objective Assessment of Functional Movement Disorders (S-FMDRS) scale (range: 0-54; highest = worst).

Non-motor symptoms

Fatigue is assessed with the Multidimensional Fatigue Inventory Scale (MFI-20) [182], differentiating general, physical fatigue from reduced activity, reduced motivation, and mental (sub-scale range: 4-20; higher = worse). Pain, depression, and anxiety will be assessed with the self-assessed Brief Pain Inventory (BPI) divided into intensity (range: 0-40; highest = worst) and interference (range: 0-70; highest = worst), the Beck Depression Inventory (BDI-II) (range: 0-63; highest = worst) [183], the Beck Anxiety Inventory (BAI) (range: 0-63; highest = worst), respectively.

Health-related quality of life (QoL)

Health-related LQ is assessed by the Mental Health and Physical Functioning of the Short Form Health Survey (SF-12) at 12 items (range: 0-100; highest = best). The SF-12 is a patient-reported outcome measure that quantifies health status and measures health-related quality of life. It comprises a 12-item measure divided into eight subscales and two composite domains. The eight subscales are physical functioning, role limitations due to physical problems, general health perceptions, vitality, social functioning, role limitations due to emotional issues, general mental health, and health transition. Then, the EuroQol-5D (EQ-5D) is used to evaluate the generic QoL [184].

Self-assessed perception of change

The productivity iMTA *Productivity Cost Questionnaire* and *t*he self-assessed perception of change are evaluated with the Clinical Global Impression (CGI), from 7 points 20 with scores from 1 (significantly improved) to 7 (very worse) [177].

Evaluation of gait and posture in the laboratory (supervised)

For the postural and gait assessments, both the control and experimental group, a stabilometric platform (Tecnobody, Dalmnine, Italy) and wearable devices (Feetme baropodometry insoles, FeetMe, Paris, France), are respectively used.

The stabilometric platform measures static balance through tasks with open and closed eyes. The stabilometric parameters used as a postural proxy control are the Romberg index (the ratio between the area covered by COP at closed eyes and the area covered by COP at open eyes), the length of the trajectory of the center of pressure (CoP) (mm) and oscillation area (mm2) measured with eyes open (integrating visual, proprioceptive and vestibular contributions) and the with close eye (proprioceptive contribution and visual dependence on postural control). In this study, the Romberg value of sway area and perimeter were analyzed, and also sway area (mm^2) and perimeter (mm) of the COP.

Instead, with wearable insoles, the spatiotemporal gait parameters are evaluated under different dual-task conditions: single task, motor dual, visual, and cognitive dual task. The parameters considered are the stride length (m) and stride time (s), swing and stance time (s), and gait velocity (m/s).

Monitoring of physical activity, metabolic consumption, and sleep in the ecological environment

Axivity AX6 is used to monitor the level of physical activity, metabolic intake, and sleep in an ecological environment, only in the experimental group (EG).

From the sensor data processing, at the end of the 7 days of Monitoring, the following parameters are considered:

- *Physical activity:* type of activity, sedentary or not using the sensor. This parameter directly relates to the outcomes of motor and non-motor symptoms derived from the other evaluations. It especially helps in understanding how patients behave in an ecological environment.
- *Energy expenditure*: MET, PAL, and Average TEE for 24h: the metabolic equivalent (MET-minutes) provides information on physical activity greater than moderate intensity in minutes. It's a significant parameter related to physical activity, as it is known that certain types and quantities of physical activity provide substantial health benefits (as reported by some guidelines on physical activity, such as ACSM and NNGB). Also, the PAL, or the total energy expenditure of a person based on 24 hours and divided by its basal metabolic rate (BMR), helps describe the lifestyle. For example, a sedentary lifestyle, on average, has a PAL value of about 1.2, while a lifestyle of a very active life, on average, has a PAL value between 2.0 and 4.0. Instead, the average TEE per 24h is the total energy one person uses (calculated from the sum of BMR, DIT, and AEE) on average in 24 hours. Once total TEE energy is calculated during the whole week of Monitoring, an average energy estimation in performing the different daily tasks can be calculated. This value, directly related to the amount of activity, is essential for monitoring the appropriate expenditure balance of total energy and energy supply.
- *Sleep quality*: movements performed while resting. The movements performed during sleep are important in assessing nocturnal rest as an indirect sleep quality index. These values are an emerging and relatively underexplored area in this field.

Table 19: Primary and secondary outcomes

Primary Endpoints	**Secondary Endpoints**
Measures of feasibility:	- Functional motor symptoms (severity and duration) between T0 and T2 using S-FMDRS

- recruitment rate (number of patients who accept/refuse the treatment) - acceptability of the intervention in terms of the number of dropouts before the end of therapy (physiotherapy compliance) - safety regarding reported adverse events during the treatment (falls or events near falling occurred during rehabilitation). Time to train the patient in using the sensor and budget issues in the use of the sensor during the EG intervention as a measure of resource feasibility. Human and data and management issues in collecting and analyzing data.	- Fatigue rated using the Multidimensional Fatigue Inventory. Fatigue Scale (MFI-20) [182] - Pain scored using the Brief Pain Inventory. (BPI) - Psychological symptoms with the Beck Anxiety Inventory and Beck Depression Inventory. (BDI-II and the BAI) [183] - Quality of life using the Mental Health and Physical functioning of the 12-item Short-Form Health Survey (SF-12) [183] - The EuroQol-5D (EQ-5D) to evaluate the generic quality of life [184] - The productivity iMTA Productivity Cost Questionnaire, Self-rated perception of change at T1 and T2, was assessed with the 7-point Clinical Global Impression (CGI) [177] - Gait and balance outcomes

7.3 Expected results

The expected results are in terms of recruitment rate, time, and budget to collect the feasibility study, human and data optimization problems such as personnel and data management issues and treatment safety assessment, dose levels and response, and treatment effect estimation.

Acceptability of interventions will be high, and no TOM training-related adverse events will be expected. Medium-term effects will be expected at T2 (12 weeks) in favor of the digital telerehabilitation program combined with TOMs (experimental training) consisting of a significant decrease in the severity of motor (overall function measured by the primary outcome, gait, and balance) and non-motor (fatigue and pain) symptoms more than the control group. Using the accelerometers (Axivity AX6) could promote the creation of cutting-edge solutions to make healthcare systems sustainable and improve FMDs' quality of life.

This feasibility study will provide data for conducting the main confirmatory study on comparing the effects of a digital telerehabilitation program, including TOMs, on motor symptoms severity and duration in patients with FMDs, and then to compare the training effects on non-motor symptoms (pain, fatigue, anxiety, and depression), the self-perception of clinical change and Health-Related Quality of Life, and health care costs.

7.4 Possible limitations, bias, and adverse events

Possible criticisms of the project and mitigation strategies are listed in Table 20.

Table 20: Possible risks

	Risk description	Likelihood	Impact	Mitigation strategies
Wearable devices use	Difficulty in using TOMs in the ecological environment for FMD patients due to usability and wearable skills	Medium	high	Patient training in wearing the device during the in-hospital training. The patient will be in contact with the clinicians in case of any problems
Dropout risks	Presence of dropouts at T2 and T3 (follow-up evaluation)	medium	n.a.	A reminder phone call 1 week before the follow-up appointment
Falls and other environmental risks	Accidental falls in telerehabilitation, particularly for postural alignment skills, freezing coping strategies, and fall prevention	medium	Medium (depends on the fall consequences: if harmful, the patients contact in the first instance their physician and then the study team who can provide counseling).	Ensuring that the area around the user is safe and therefore eliminates architectural barriers in the treatment area; use of non-slip footwear; exercises based on the individual's falling risk, a risk assessed during the screening visit.

Muscle pain and breathlessness	Untrained individuals may report muscle pain and breathlessness	Medium	low	The intensity and complexity of exercise will progressively increase and adapt to each person's ability and clinical condition. Subjects will be advised to stop treatment at any time to rest or withdraw from the study without giving reasons.

Adverse events will be collected through the patient's interview at T2. An adverse event (AE) is an unexpected clinical event that results in unintended and undesirable harm to the subject. A worsening of a preexisting clinical condition or disease is considered an adverse event. The severity of each AE will be regarded as mild (the event is transient and well tolerated by the subject; discontinuation of treatment is not necessary), moderate (the event causes discomfort to the subject by limiting their activities of daily living, discontinuation of therapy is needed) or severe (the event causes severe limitation in activities of daily living and may be life-threatening) by the referring physician. A serious adverse event (SAE) is a life-threatening event. This event requires or prolongs hospitalization, an event that involves significant or persistent disability, or an event that requires medical or surgical therapy to prevent the serious outcomes listed above.

Any adverse event will be monitored during the study, and the following will be recorded in detail: date of onset, possible diagnosis (if known) or signs and symptoms, severity, course (resolution, ongoing event, intermittent), relationship to treatment, and any intervention performed.

7.5 Statistical Analysis

Sample size calculation may not be necessary for pilot studies [184]. However, to ensure the representativeness of the study's target population and based on the recruitment rate at the USD Parkinson's Disease and Movement Disorders in

Verona (Italy), it was planned to enroll 30 patients (15 patients per group) over 2 years. To date, 23 patients have been recruited (14 for the CG group and 9 for the EG group) and reported in this study; moreover, 15 of them completed the evaluation scheduled at time T2. Only three patients completed the assessment scheduled at time T3.

All results will be shown as mean and standard deviation of the mean (SD) or as median and interquartile range according to the type of variable distribution. Categorical variables will be described through contingency tables.

This single-blind, randomized trial described the primary endpoint using descriptive statistics (i.e., percentage, mean, standard deviation, range, and percentages for continuous and ordinal variables). Secondary continuous outcomes are using test parameters, considering the small sample size. The Mann-Whitney is used to analyze the differences between the two groups in primary and secondary outcome measures at time T0 and T1 and to evaluate the differences in primary and secondary outcome measures between times T0 or T1 (depending on the scheduled evaluation time) and T2 in the two groups. The Wilcoxon test evaluates differences between T0 or T1 (depending on the scheduled evaluation time) and T2 time within each group for primary and secondary outcome measures. The level of statistical significance is set at a p-value<0.05. The statistical analysis is performed using JASP software.

The analysis for the primary target is given below.

The eligibility and recruitment rate in terms of patients assessed for eligibility and those respecting the inclusion criteria are considered with the following data:

- *Eligibility rate*: proportion of patients evaluated that meet the criteria
  Eligibility rate = (numbers of eligibility patients) / (numbers of total patients evaluated) x 100
- *Recruitment rate*: proportion of patients included compared to eligible patients
  Recruitment rate = (numbers of total patients enrolled) / (numbers of eligibility patients) x 100

The acceptability of the intervention in terms of the number of discontinuations before the end of the treatment is considered with these data:

- *Total number of initial participants*: the number of patients enrolled at the beginning of the intervention.
- *Number of dropouts*: the number of participants who have dropped out of the intervention before the end of the treatment.
- *Number of participants who have completed the intervention*: necessary for the calculation of acceptability as a percentage of completion concerning the total enrolled.

With this data, acceptability can be expressed as the percentage of participants who completed the intervention compared to the total number enrolled at the beginning:

Acceptability= (number of patients who have completed the intervention) / (number of patients who have been enrolled at the beginning) x 100

To assess the safety of the intervention in terms of adverse events reported during treatment, the rate of adverse events is calculated according to the following steps:

- *Adverse event data collection*: the total count of adverse events reported during treatment, including all reported events (serious and non-serious).
- *The adverse event rate per participant* is calculated as the average rate of adverse events per participant, which is helpful for comparisons between groups or treatments.

The time calculation for training is calculated considering the following factors:

- The average duration of each training session (in minutes or hours).
- Total number of sessions needed to make the patient autonomous with wearable.

The formula applied is the following:

Total time training= average duration of one session x number of total sessions

8. Results of the feasibility 2-arm parallel randomized controlled trial

In this study, 62 patients were assessed for eligibility during the seven-month observation period from May 2024 to December 2024. Of these, 30 patients (48,4 %) met the inclusion criteria (summarized in the previous section). Of these eligible patients, 23 were recruited into the study, with a recruitment rate among eligible patients of 76,67%. The remaining seven patients decided not to participate in the study. Regarding the 32. The reasons for patients who didn't meet the inclusion criteria and who didn't accepted to participate were non-acceptance of the diagnosis (n=2), Mini-Mental State Examination score below 24 (n=3), prominent dissociative crises (n=2), age problems (under 18 years old or too old, over 70 years old) (n=2), functional non-epileptic seizures (PNES) (n=4), unmotivated (n=3), no FMD diagnosis (n=2), doubtful about diagnosis (n=2), request for early discharge (n=4), non-cooperation (n=2), absence of motor symptoms (n=9), and no capability to walk and stand up also with external aid (n=4). The demographic and clinical characteristics of the sample are shown in Table 21; data are reported differentiated between T0-T1 and T2. The sample analyzed consists of 23 patients with a definite diagnosis of FMD with a mean age of 42.91 years (standard deviation 11.53; range: 25-63 years), predominantly female (17/23, 73.91%). The mean age of the control group is 45.61 (standard deviation 12.01; range: 28-63 years); instead, the experimental group's mean age is 39.40 (standard deviation 10.67; range: 25-55 years). The two groups differed in age, but neither was statistically significant ($p = 0.214$). Instead, regarding years of schooling and level of education, the mean was 13.870 years, and specifically, the mean of EG was 14.200 (with a standard deviation of 4.237) and of CG was 13.615 (with a standard deviation of 2.468).

At T0, the sample presented a level of anxiety assessed at the BAI and depression assessed at the BDI-II of 17.82 (standard deviation 10.45; range: 4-38) and 11.52 (standard deviation 8.78; range: 1-33), respectively, showing a moderate level of anxiety and a minimum level of depression according to the normative cut-offs (Guy et al. 1976). In particular, the CG group registered a mean value of 16.07 (standard deviation 8.27; range 4-27) and 7.61 (standard deviation 4.35; range 1-16) at the BAI and BDI-II, respectively. The EG group, instead, registered a mean value of 20.10 (standard deviation 12.87; range 4-38) and 16.60 (standard deviation 10.61; range 3-27) at the BAI and BDI-II, respectively.

At T2, after the same T0 protocol, the sample presented a level of anxiety and depression of 14.06 (standard deviation 7.824; range: 2-30) and 9.13 (standard deviation 8.28; range: 0-28), respectively, showing a moderate decreasing in both non-motor symptoms three months after the hospitalization. In particular, the CG group registered a mean value of 14.875 (standard deviation 7.41; range 4-27) and 9.50 (standard deviation 8.07; range 3-27) at the BAI and BDI-II, respectively. The EG group, instead, registered a mean value of 8.71 (standard deviation 9.16; range 2-28) and 16.60 (standard deviation 10.61; range 3-27) at the BAI and BDI-II, respectively. The experimental group showed an improvement in both symptoms, different from the control group, which worsened depression.

Two groups are homogeneous in sex, age, disease duration, primary and secondary outcomes. In total, 15 patients (CG n=9 and EG n=6) completed clinical evaluations at T0, T1, and T2, and only 3 (CG, n=2, and EG n=1) also completed assessment at T3. Of 23 patients initially enrolled, three patients from the CG group refused or never answered the recruiter to come to the hospital for the T2 evaluations, and other different three patients (2 from the EG group and 1 from the CG group) refused or never answered to the recruiter to come to the hospital for the T3 evaluations.

Table 21: Demographic and clinical characteristics of the sample enrolled at T0 and T1 (n=23) and of the sample with T2 follow-up completed (n=15)

	All patients (n=23)	**EG Group (n=9)**	**CG group (n=14)**	**Between-groups analysis (p-value)**
Mean age (± SD)	42.91 (11.63)	39.4(10.67)	45.61 (12.01)	p=0.214
Women (%)	73.91%	60%	84,6%	p=0.207
Symptoms mean age duration (± SD)	3.06 (3.88)	2.33 (1.67)	3.57 (4.87)	p=0.973
T0-T1 Clinical data (%)				
Motor Symptoms				
Tremor	15 (65.21)	7 (77.78)	8 (57.14)	

Weakness	18 (78.26)	8 (88.89)	10 (71.42)
Dystonia	8 (34.78)	3 (33.33)	5 (35.71)
Facial disorders	4 (17.39)	1 (11.11)	3 (21.42)
Parkinsonisms	2 (8.69)	2 (22.22)	0 (0)
Tics	1 (4.34)	1 (11,11)	0 (0)
Swallowing disorders	4 (17.39)	2 (22.22)	2 (14.28)
Voice disorders	5 (21.74)	1(11.11)	4 (28.57)
Gait disorders	19 (82.61)	9 (100)	10 (71.43)
Non-motor symptoms			
Fatigue	19 (82.61)	8 (88.89)	11 (78.57)
Chronic pain	7 (30.43)	4 (44.44)	3 (21.42)
Insomnia	10 (43.48)	5 (55.55)	5 (55.55)
Anxiety	10 (43.48)	5 (35.71)	5 (35.71)
Depression	6 (26.09)	3 (33.33)	3 (21.43)
PNESS	2 (8.69)	0 (0)	2 (14.28)
Psychiatric comorbidity	1 (4.35)	1(11.11)	0 (0)
Neurological comorbidity	2 (8.69)	0 (0)	2 (14.28)
No neurological comorbidity	12 (52.17)	4 (44.44)	8 (57.14)

T2 **Clinical data (%)**	**All patients (n=15)**	**EG Group (n=6)**	**CG group (n=9)**	**Dropout (EG n=0, CG n=3)**
Motor Symptoms				
Tremor	2 (13.33)	1 (16.67)	1 (11.11)	
Weakness	2 (13.33)	1 (16.67)	1 (11.11)	
Dystonia	6 (40)	2 (33.33)	4 (4.44)	
Facial disorders	5 (33.33)	2 (33.33)	3 (33.33)	
Parkinsonisms	1 (6.67)	0 (0)	1 (11.11)	
Tics	1 (6.67)	0 (0)	1 (11.11)	
Swallowing disorders	0 (0)	0 (0)	0 (0)	
Voice disorders	0 (0)	0 (0)	0 (0)	
Gait disorders	4 (26.67)	2 (33.33)	2 (22.22)	
Non-motor symptoms				
Fatigue	7 (46.67)	2 (33.33)	5 (55.55)	
Chronic pain	2 (13.34)	1 (16.67)	1 (11.11)	
Insomnia	7 (46.67)	3 (50)	4 (4.44)	

Anxiety	2 (13.34)	1 (16.67)	1 (11.11)
Depression	4 (26.67)	1 (16.67)	3 (33.33)
PNESS	3 (20)	1 (16.67)	2 (22,22)
Psychiatric comorbidity	2 (13.34)	0 (0)	2 (22.22)
Neurological comorbidity	2 (13.34)	0 (0)	2 (22.22)
No neurological comorbidity	6 (40)	1 (16.67)	5 (55.55)

Legend: EG= experimental group, CG= control group, SD= standard deviation

8.1 Primary Outcomes Results

The eligibility rate is calculated as the proportion of assessed patients who meet the criteria to participate in the study. In this case, the number of eligible patients (n=30) divided by the total number of evaluated patients (n=62) multiplied by 100, resulting in 48,4%. This result represents a good percentage, considering the small sample available.
The recruitment rate indicates the proportion of included versus eligible patients. To calculate this, the number of recruited patients (n=23) is divided by the number of eligible patients (n=30), then multiplied by 100, resulting in a rate of 76,66%, showing good adherence to the study. In our study, the number of initial patients doesn't match the final number at T2 (n=15). The study is ongoing, so excluding the five patients with the T2 evaluation planned in the following weeks, we count three dropouts, all among the control group. By calculating the number of participants who completed the treatment concerning the initial total and multiplying this by 100, an acceptability rate of 83,33% is obtained, underlying and reinforcing the hypothesis that the experimental study is well tolerated. The safety of the intervention is measured by the presence of adverse events, which were absent in this study: no patients reported critical events or required discontinuation of participation.

The training time for patients is short: patients are briefly explained the experimental design and those who agree to participate receive, in the case of the experimental group, about 10 minutes of training in the application of the sensor and instructions for its use. For the patients in the control group, a single training session takes an average of 10 minutes. Finally, the training in using the TOMs device is quick and simple, based on a brief interview in which the operating principle and usefulness of the device are explained, as well as its correct application and how to apply it again, if necessary, during the 7-day survey. Moreover, a paper with figures and explanations is delivered in case of problems or the necessity to remove and replace the sensor.

8.2 Secondary outcomes result of the T0-T1-T2 subgroup

Despite the trends observed in the various secondary outcome measures, statistical analysis did not show statistically significant differences between or within groups. However, this effect may be justified by the sample size enrolled to date (n=23), which has not reached the sample hypnotized.

The descriptive statistics concerning the motor and non-motor symptom rating scales of the experimental group and the control group (subgroup T0 - T1) are shown in Table 22. No statistically significant differences were observed between and within groups. The experimental group performed significantly better than the control group in these measures. Intra-group analysis showed reduced intensity and interference values in both groups, major in the experimental one. Regarding fatigue, the MFI-20 score registered no statistically significant differences between and within groups, but values decreased from T0 to T1 in both groups.
Then, the descriptive statistics concerning the motor and non-motor symptom rating scales of the experimental and control groups (subgroup T2) are shown in Table 23. No statistically significant differences were observed between and within groups, but the control group performed better than the control group in some measures, such as BPI intensity. While in the control group, it increased at T2 follow-up, in the experimental group, it decreased, underlying possible better improvement in pain symptoms. Regarding fatigue, the MFI-20 score registered no statistically significant differences between and within groups, but values increased from T1 to

T2 in both groups. Due to the limited sample of patients who have concluded T3 evaluation, no analysis has been done on that data.

Table 22: Descriptive statistics of the motor and non-motor scales of the experimental and control groups at T0 and T1.

	Group	Median	Mean	SD	Differences between groups (p-value)
Motor symptoms S-FMDRS					
T0	EG	8.0	11.37	9.39	0.619
	CG	10.5	12.57	7.68	
T1	EG	8.0	8.87	3.2	0.827
	CG	9.0	10.28	8.04	
Pain BPI					
T0 intensity	EG	18.0	15.37	11.71	0.678
	CG	8.5	11.93	12.99	
T1 intensity	EG	5.0	10.62	11.69	0.543
	CG	0.0	8.14	3.78	
T0 interference	EG	25.5	24.87	19.77	0.075
	CG	0.0	7.86	14.31	
T1 interference	EG	3.0	11.37	16.81	0.181
	CG	0	3.78	7.42	
Fatigue MFI 20					
T0 Global	EG	16.0	15.0	4.47	0.143
	CG	13.0	13.0	4.42	
T1 Global	EG	15.0	12.85	5.52	0.224
	CG	10.0	9.23	3.22	
T0 Physical	EG	15.0	14.57	4.12	0.588

	CG	13.0	13.0	4.42	
T1 Physical	EG	12.0	11.43	3.73	0.568
	CG	10.0	9.23	2.68	
T0 Activity	EG	12.0	13.85	4.52	0.391
	CG	13.0	13.0	4.42	
T1 Activity	EG	9.0	10.57	3.91	0.043
	CG	10.0	9.31	3.35	
T0 Motivation	EG	9.0	9.14	3.98	0.333
	CG	8.0	8.31	3.23	
T1 Motivation	EG	5.0	6.43	2.69	0.662
	CG	8.0	7.23	3.01	
T0 Mental	EG	12.0	11.71	4.75	0.371
	CG	12.0	10.85	4.76	
T1 Mental	EG	12.0	12.57	4.47	0.391
	CG	8.0	9.31	4.68	

Legend: BPI = Brief Pain Inventory, MFI = Multidimensional Fatigue Inventory, SFMDRS = Simplified Functional Movement Disorders Rating Scale, CG = Control group, ES = Experimental group, DS = Standard Deviation.

Table 23: Descriptive statistics of the motor and non-motor scales of the experimental and control group at T2.

	Group	Median	Mean	SD	Differences between groups (p-value)
Motor symptoms S-FMDRS					
T2	EG	0.0	3.2	6.09	0.807
	CG	2.0	3.78	4.94	
Pain BPI					

T2 intensity	EG	5.0	9.71	13.32	0.442
	CG	16.5	15.62	14.80	
T2 interference	EG	0.0	9.28	12.28	0.360
	CG	18.0	17.87	18.09	
Fatigue MFI 20					
T2 Global	EG	15.0	13.0	7.21	0.883
	CG	16.0	14.11	12.89	
T2 Physical	EG	16.0	12.67	5.77	0.509
	CG	13.0	12.89	4.57	
T2 Activity	EG	7.0	10.33	6.66	0.239
	CG	10.0	11.56	4.64	
T2 Motivation	EG	8.0	7.67	2.51	0.555
	CG	6.0	8.11	4.26	
T2 Mental	EG	14.0	14.0	2.0	1.000
	CG	12.0	11.67	4.95	

Legend: BPI = Brief Pain Inventory, MFI = Multidimensional Fatigue Inventory, SFMDRS = Simplified Functional Movement Disorders Rating Scale, CG = Control group, ES = Experimental group, DS = Standard Deviation.

When comparing the groups for anxiety and depression, the experimental group performed better than the control group in both measures (but not significantly). Intra-group analysis for the experimental group showed a reduction in anxiety and depression symptoms in both. Instead, the control group showed an increasing depression at T2 evaluation. The other secondary outcome measures (CGI T1 T2, EQ-5D at T1) showed no statistically significant differences between the groups.

8.2.1 Motor Symptoms Severity

Of 23 patients, 12 (EG, n=6; CG, n=9) performed T0, T1, and T2 assessments. Figure 14 below shows the changes in motor-functional symptom severity before and after the rehabilitation phase and at T2. When comparing the mean S-FMDRS scores between the EG and CG at the various time points (T0, T1, and T2), a general trend is observed in which the experimental group always shows lower mean scores than the control group. At time T0, the control group has an average S-FMDRS score of around 13, while the experimental group has a lower average of around 12. This trend persists at time T1, where the control group's scores remain higher than the experimental group. Finally, at time T2, both groups show a high reduction in average scores, with the experimental group continuing to maintain lower values. Statistical analysis, however, doesn't reveal any significant differences between the two groups and intra-groups, suggesting that although there is a visible difference in the scores, this doesn't reach the statistical significance threshold.

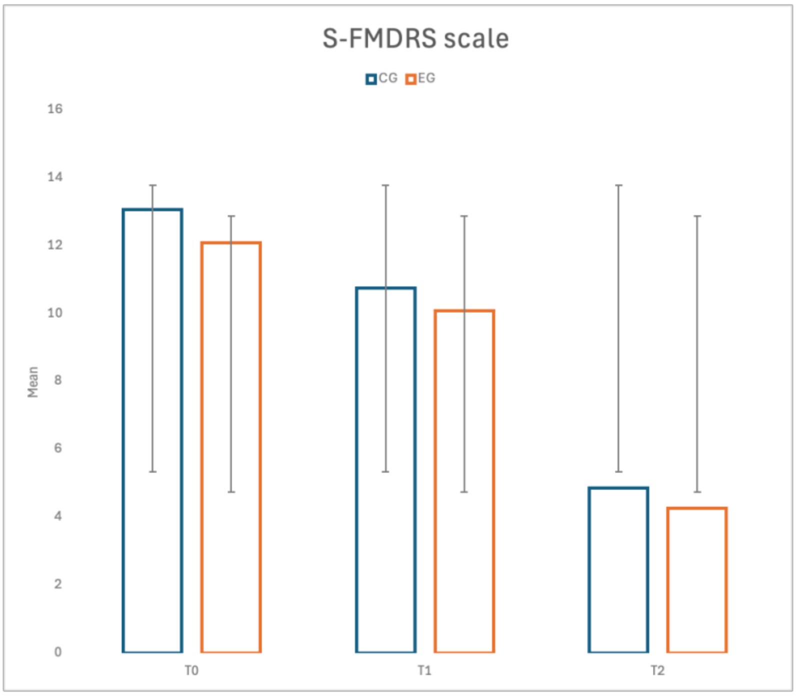


Figure 14: Trend in the severity of motor symptoms assessed by the S-FMDRS scale.

8.2.2 Non-motor symptoms

Analysis of the data reveals no significant differences between the two groups. The scores collected at times T0 and T2 show no statistically significant variations for all measures considered. However, there is a trend toward symptom reduction in some measures in the EG, although these variations don't reach statistical significance.

In pain, they show moderate variation between the initial and later assessment. As measured by the BPI, pain intensity showed no significant difference between T0 and T2 in the experimental group (W=6.000, z=0.000, p=1.000). The comparison also showed no significant variation for pain interference as assessed by the same scale (W=6.000, z=0-135, p=1.000). In the control group, pain intensity remained stable between T0 and T2 (W=2.000, z=-1.782, p=0.093), with a slight downward trend, but it didn't reach significance. Pain interference was non-significant in either group (W=0.000, z=-2.023 p=0.059), but the control group reported a variation close to statistical significance (Figure 15).

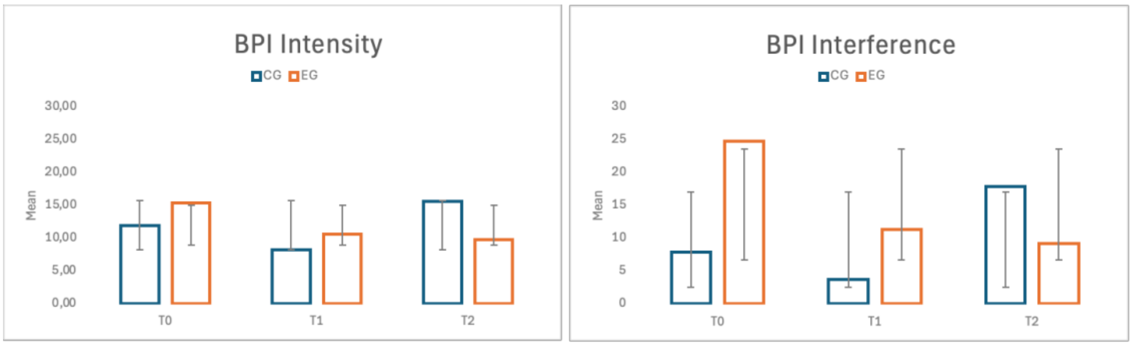


Figure 15: The trend of pain severity assessed on the BPI scale. On the left side, the subscore related to the pain intensity; on the right side, the subscore related to the pain interference

In the experimental group, anxiety, as measured by the BAI, shows a slight trend toward symptom reduction between the initial time (T0) and the final time (T2), with W=15.000, z=2.023, and p=0.059. Although an improvement is present, this change didn't reach statistical significance. Conversely, anxiety is stable between T0 and T2 in the control group, with W=19.500, z=0.210, and p=0.889. A similar situation to the experimental group can also be observed here, in which a tendency towards improvement is not statistically significant. A tendency towards a reduction in symptoms between T0 and T2 can also be observed in the experimental group for depression, as measured by the BDI-II, with W=14.000, z=1.753, and p=0.125. However, this variation wasn't statistically significant. A similar situation was found in the control group, with a non-significant change in depressive symptoms (W=9.500, z=-1.154, p=0.138). In the control group, different from the control group, the condition between T0 and T2 worsened. The data suggest a slight trend in favor of the experimental group, supporting the acceptability of the intervention and its ability to intervene on non-motor aspects significant for the motor condition. Anxiety and depression trends are reported in Figure 16.

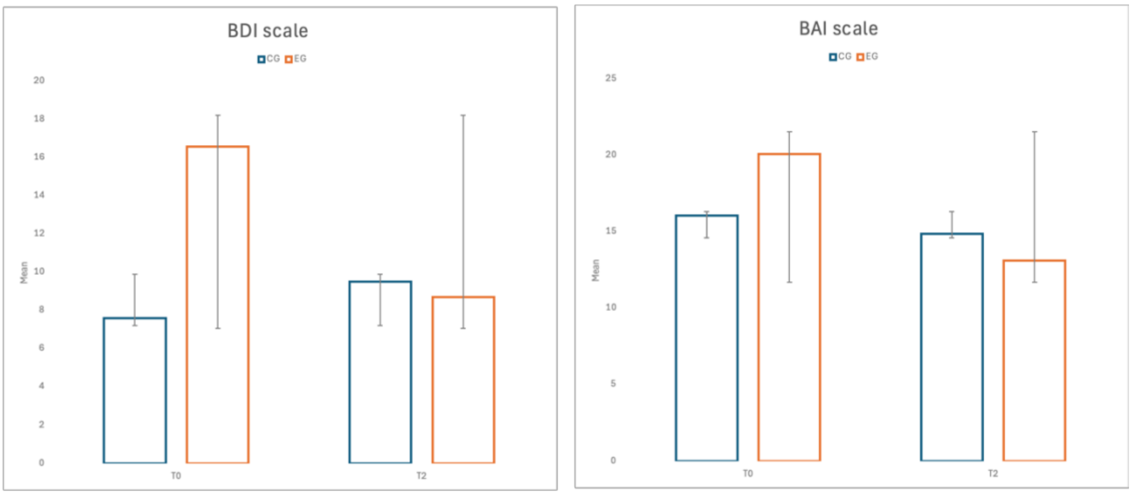


Figure 16: BAI and BDI scale results. On the left, the trend of depression severity observed on the BDI-II scale; on the right, the trend of anxiety severity observed on the BAI scale.

The MFI-20 scales (physical, activity, motivation, and mental) show group differentiation according to the subscore. In particular, the control group shows the stability of scores, with values slightly above the significance threshold in intensity and interference and a statistically significant variation in MFI-global (p=0.035), activity (p=0.042), and physical (p=0.029) comparing T0 and T2, differently from the experimental group, where the measures didn't show significant changes over time. The fatigue trend is reported in Figure 17.

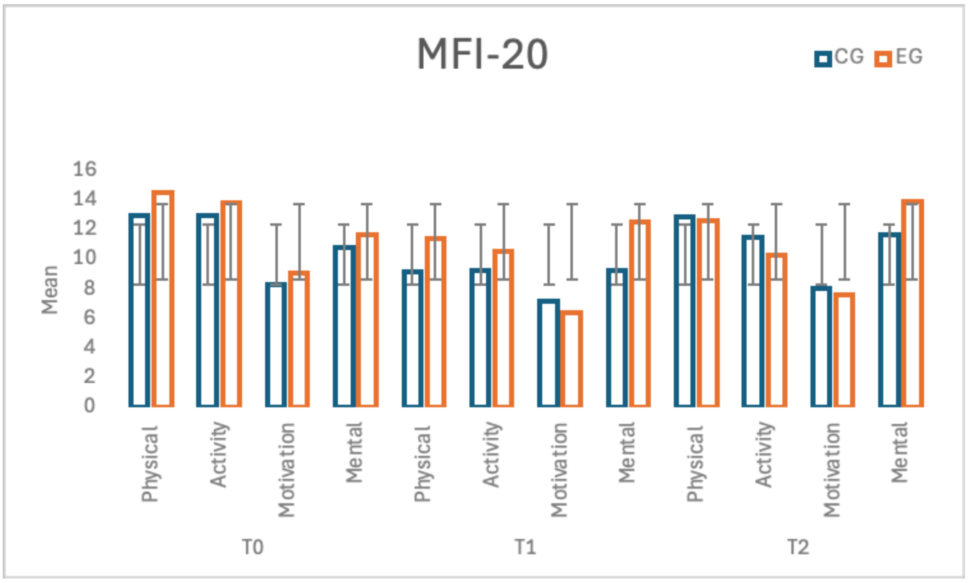


Figure 17:Trend of fatigue assessed on the MFI-20 scale. The other subscores (physical, activity, motivation, and mental) are reported.

8.2.3 Quality of life (QoL)

The graph (Figure 18) illustrates the quality-of-life results, measured with the SF-12 scale, for the control group (in blue) and the experimental group (in orange). The experimental group has higher average scores than the control group on all variables, indicating a possible trend toward improving the physical and mental quality of life associated with the intervention. However, it is important to note that this difference is not statistically significant, suggesting that although there is an apparent benefit, the results don't reach the significance threshold required to confirm an intervention effect.

In the experimental group, the physical and mental components of the SF-12 questionnaire (PCS and MCS) show no significant changes between T0 and T2. Measures show W=2.000, z=-1.753, and p=0.125 for PCS and W=1.000, z=-1.483, and p=0.188 for MCS, indicating a stability of the scores over time. Also, in the control group, the physical and mental components of SF-12 remained stable between T0 and T2, with values of W=15.000, z=-0.889, p=0.426 for PCS and W=30.000, z=0.889, p=0.426 for MCS. These results mirror what was observed in the experimental group, where the scores for the two components show no significant variation.

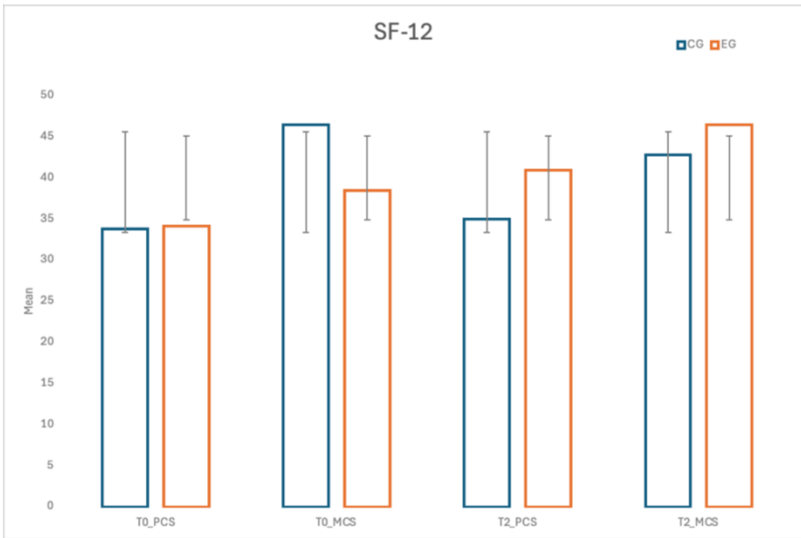


Figure 18: Quality of life trends assessed by the SF-12 scale, comparing EG and CG group at T0, T1 and T2

8.2.4 Monitoring self-assessment perception of change

When comparing the frequency distributions of the CGI scores between the CG and the EG groups (Figure 19), some distinctive observations emerge at both T0 and T2. At T0, the CGI scores in the two groups are distributed mainly between the categories of 'Better' ('Moderate', 'Marked', 'Minimal' changes) and 'No Change'. Both groups show a similar frequency of cases falling into these categories without showing significant variations. The occurrence of 'Better' cases is comparable between CG (n=9) and EG (n=6), indicating a certain homogeneity in the levels of perceived improvement or clinical stability of both groups at T0.

At time T2, however, there is a change in the score with greater variability, especially in the EG group, which shows some cases in the 'Better' ('Moderate,' 'Marked,' 'Minimal' changes) categories. This suggests that compared to the CG group, the EG group reported an increase in cases showing a perceived improvement of the clinical condition, with a reduction in the frequency of scores associated with worsening. On the contrary, the CG group registered a more concentrated distribution in the 'Worse' categories, suggesting a more persistent instability than the EG group. These results indicate a difference in the perceived clinical course between the two groups, with a favorable trend in the EG group compared to the CG group at the end of the observed period. This may be a consequence of the two treatments (with or without sensor).

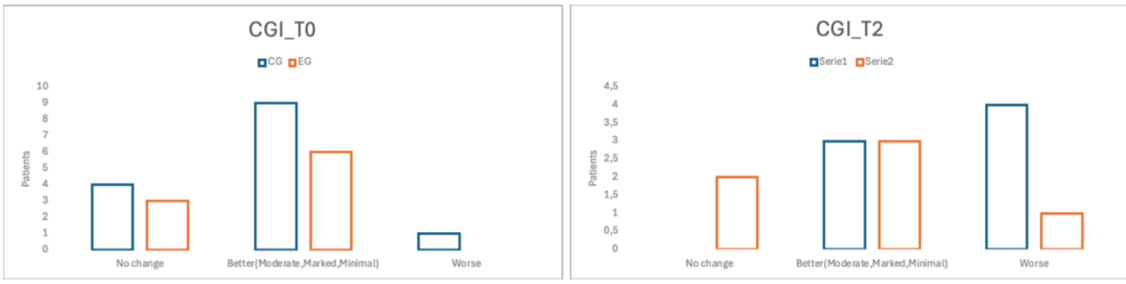


Figure 19: Trend in the self-assessed perception of change assessed using the CGI scale at T0 (on the left) and T2 (on the right).

When considering self-perception according to EQ-5D score, the questionnaire used to evaluate the generic QoL, patients had to indicate a value between 0 (the worst) to 100 (the best) according to their perceived state of health. It was found that the CG registered a mean value of 68.21 (with a standard deviation of 13.673) at T1 instead of a mean value of 63.33 (with a standard deviation of 14.57) at T2. The EG group registered a mean value of 73.87 (with a standard deviation of 15.779) at T1 instead of a mean value of 64.0 (with a standard deviation of 20.125) at T2. Both groups show improved health perception, but the scores for the two components show no significant variation.

Moreover, the iMTA Productivity Cost Questionnaire, completed at T1, T2, and T3, is under analysis, so no results are available to date.

8.2.5 Balance in single, cognitive, and motor dual tasks

Stabilometric evaluations, aimed at investigating balance performance and the possible positive effect of dual-task distraction, are executed with three different tasks: single, motor, and cognitive dual tasks. During the cognitive dual task, patients execute subtractions with the number seven, focusing view on a red cross on the screen in the case of the open-eyes situation or with closed eyes. Figure 20 reported the mean value of error and total subtractions done (comprised of operations wrong and right). EG has a higher level of schooling in the mean than CG; this is reflected by the general attitude of the minor numbers of errors and most subtractions done. The main result is that at T2, EG made fewer mistakes than CG.

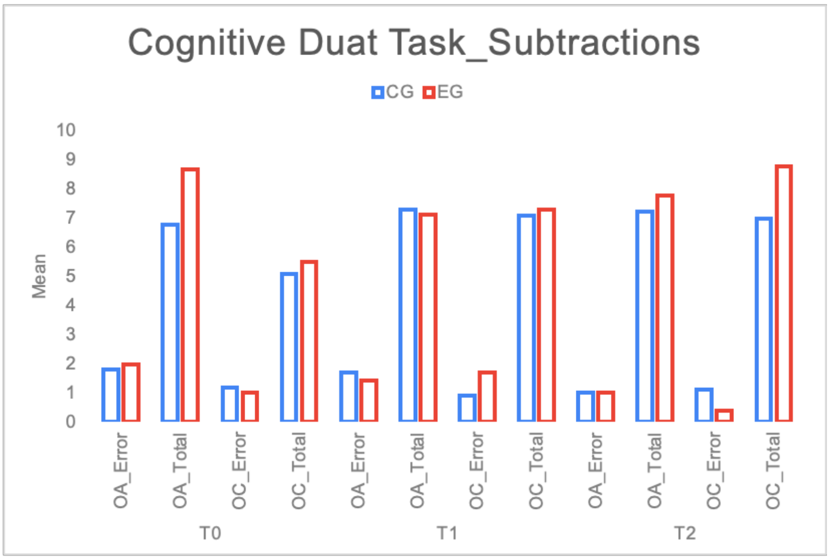


Figure 20: Error and total subtractions during cognitive dual tasks at open and closed eyes at T0, T1, and T2 balance evaluations.

The stabilometric evaluations (Romberg area and perimeter) under single, motor, and cognitive dual-task conditions are shown in Figure 21. The experimental group shows greater stability in all conditions, suggesting a potential positive effect of the treatment on balance and postural control, even during complex tasks. However, these differences are not statistically significant, nor between groups nor intra-group, and can't be considered conclusive. Statistical analysis comprised performance comparison between T0 and T1 evaluations and between T1 and T2 evaluations Romberg area and perimeter in all tasks (single, motor, and cognitive).

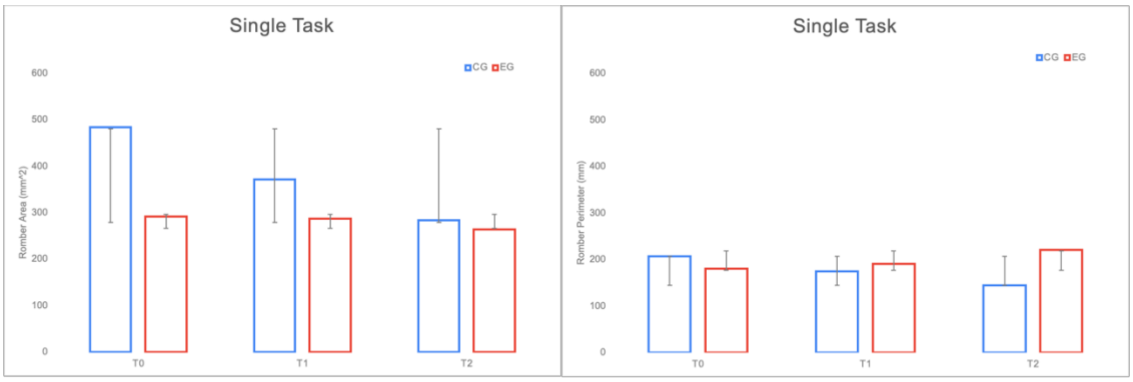
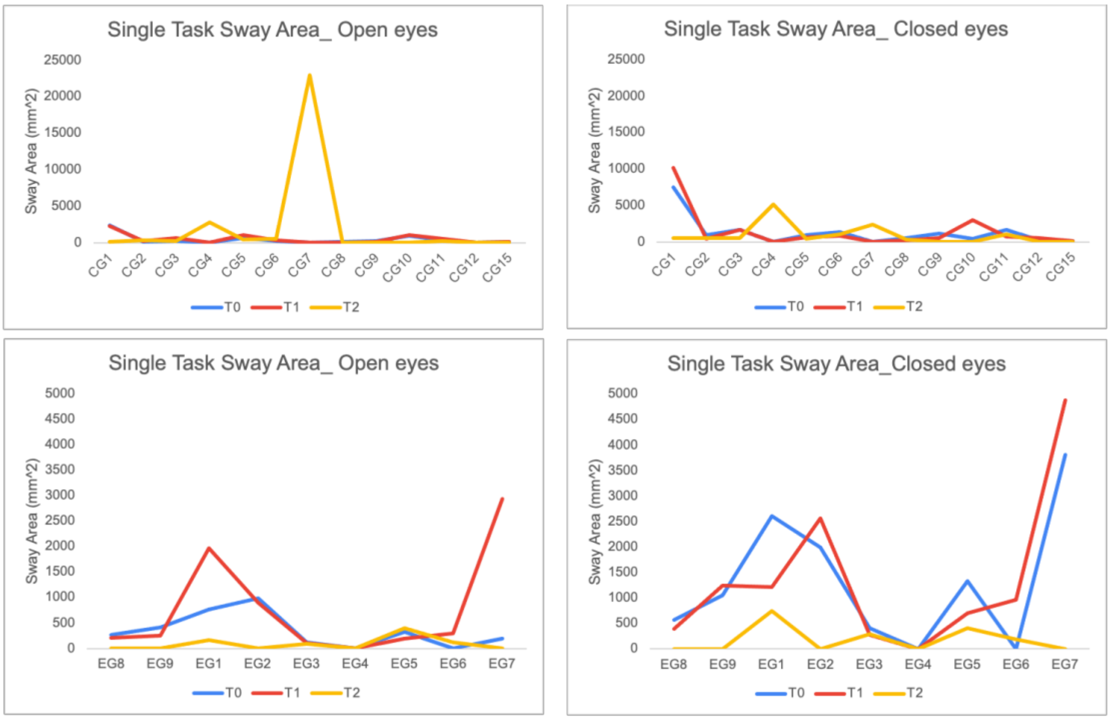


Figure 21: Development of stabilometric platform assessment values in the single task (first figure), motor (second figure), and cognitive (third figure) dual tasks at T0, T1, and T2 assessments.

In Figure 22, changes in COP sway area in T0, T1, and T2 evaluations with open and closed eyes are reported separately for EG and CG. Statistical analysis included the comparison performance between T0 and T1 evaluations as well as between T1 and T2 on the sway area (at open and closed eyes) in all tasks (single, motor, and cognitive) didn't result statistically significant, nor between groups nor intra-group. In Figure 23, changes in COP perimeter in T0, T1, and T2 evaluations with open and closed eyes are reported separately for EG and CG. Statistical analysis comprised performance comparison between T0 and T1 evaluations and between T1 and T2 evaluations on the perimeter (at open and closed eyes) in all tasks (single, motor, and cognitive) didn't result statistically significant, nor between groups nor intra-group.



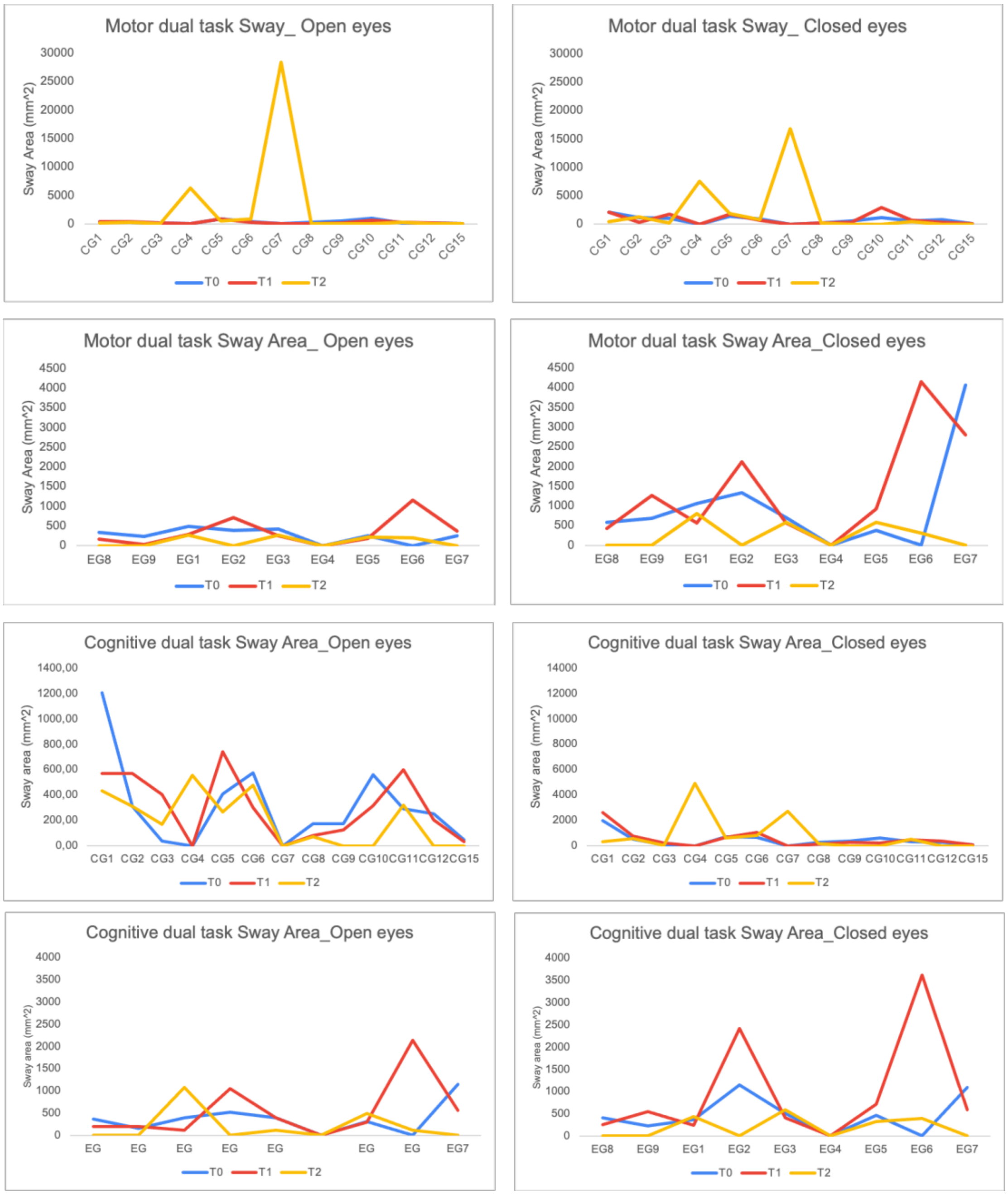
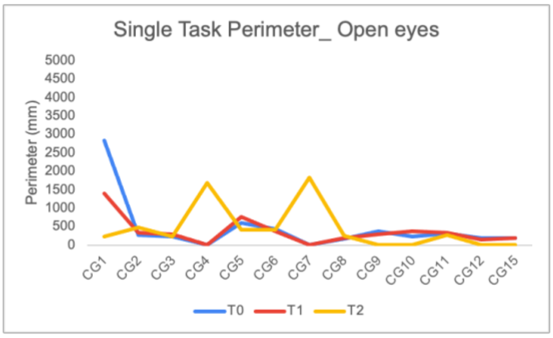
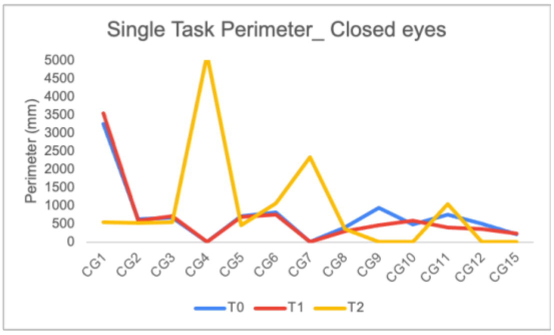


Figure 22: COP sway area changes at T0, T1, and T2 evaluations in single, motor, and cognitive dual tasks. Each patient's progression or regression in performance is reported, and the EG and CG groups are compared. On the left side, it displayed the test executed with open eyes, and on the right, with closed eyes.


Single Task Perimeter_ Open eyes
Perimeter (mm)
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
CG1 CG2 CG3 CG4 CG5 CG6 CG7 CG8 CG9 CG10 CG11 CG12 CG15
T0 T1 T2


Single Task Perimeter_ Closed eyes
Perimeter (mm)
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4500
4000
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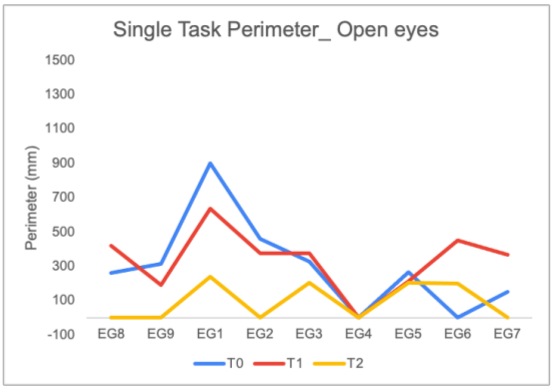
CG1 CG2 CG3 CG4 CG5 CG6 CG7 CG8 CG9 CG10 CG11 CG12 CG15
T0 T1 T2


Single Task Perimeter_ Open eyes
Perimeter (mm)
1500
1300
1100
900
700
500
300
100
-100
EG8 EG9 EG1 EG2 EG3 EG4 EG5 EG6 EG7
T0 T1 T2


Single Task Perimeter_ Closed eyes
Perimeter (mm)
1500
1300
1100
900
700
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300
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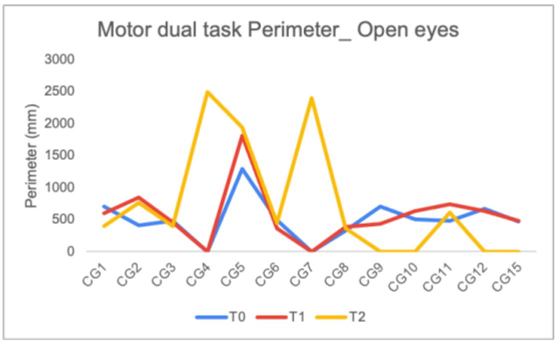
-100
EG8 EG9 EG1 EG2 EG3 EG4 EG5 EG6 EG7
T0 T1 T2


Motor dual task Perimeter_ Open eyes
Perimeter (mm)
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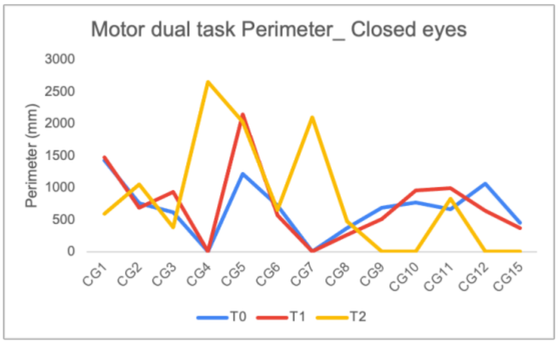
CG1 CG2 CG3 CG4 CG5 CG6 CG7 CG8 CG9 CG10 CG11 CG12 CG15
T0 T1 T2


Motor dual task Perimeter_ Closed eyes
Perimeter (mm)
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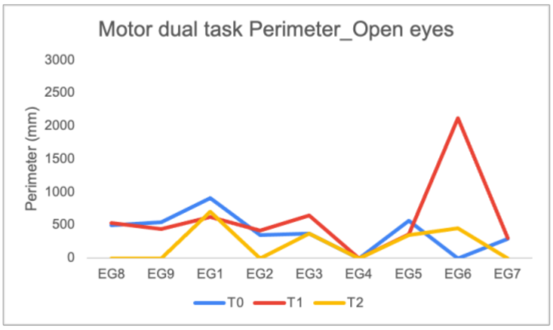
CG1 CG2 CG3 CG4 CG5 CG6 CG7 CG8 CG9 CG10 CG11 CG12 CG15
T0 T1 T2


Motor dual task Perimeter_Open eyes
Perimeter (mm)
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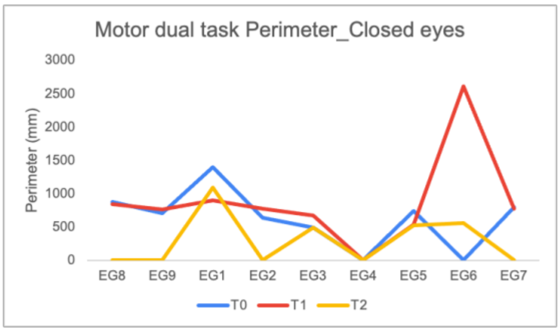
EG8 EG9 EG1 EG2 EG3 EG4 EG5 EG6 EG7
T0 T1 T2


Motor dual task Perimeter_Closed eyes
Perimeter (mm)
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EG8 EG9 EG1 EG2 EG3 EG4 EG5 EG6 EG7
T0 T1 T2

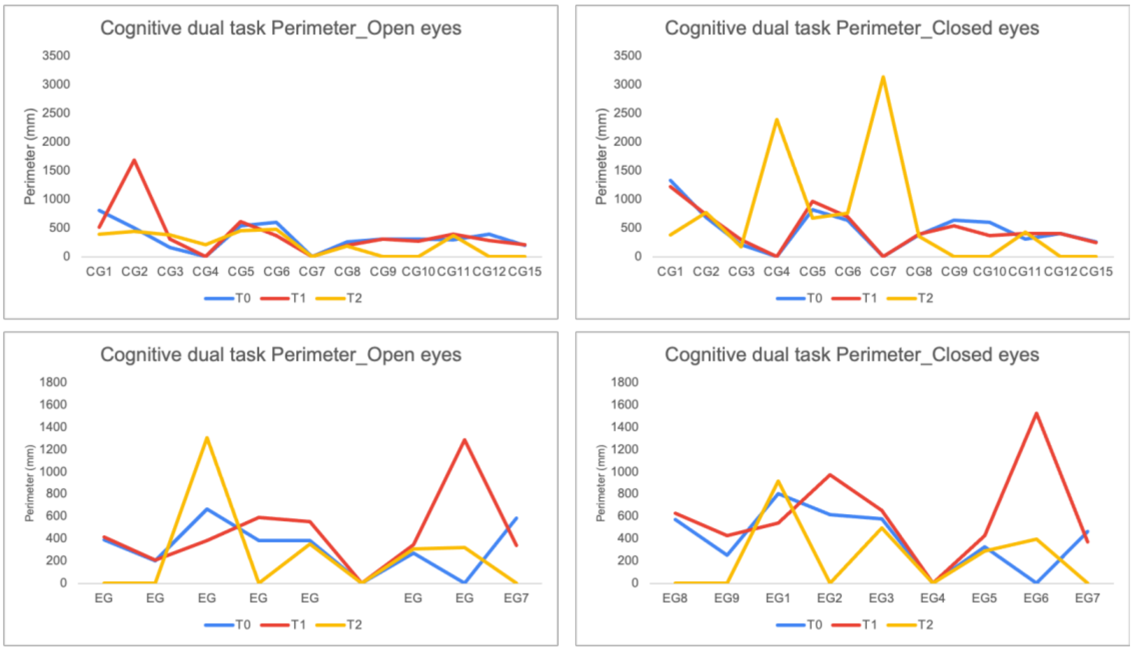

Figure 23: COP perimeter changes at T0, T1, and T2 evaluations in single, motor, and cognitive dual tasks. Each patient's progression or regression in performance is reported, and the EG and CG groups are compared. On the left side, it displayed the test executed with open eyes, and on the right, with closed eyes.

8.2.6 gait in single, cognitive, motor, and visual-fixation tasks

The gait evaluation under single-task, motor, cognitive, and visual-fixation dual-task conditions at T1 and T2 are shown in Figure 24. Due to some problems with the wearable company, some patient data are not yet available, so the sample of available data is reduced, and descriptive analysis was computed.

During the cognitive dual task, patients execute subtractions with the number seven, focusing the view straight on the hospital corridor. Figure 25 reported the mean value of error and total subtractions done (comprised of operations wrong and right). EG group has a higher level of schooling in the mean than CG; this isn't reflected by the general attitude of the minor numbers of errors and most subtractions done. The main result is that at T2, EG made major subtractions compared to CG, but the mean error was the same. This underlines that those cognitive implications while walking are unrelated to the level of schooling, which is different from results obtained in balance evaluations regarding errors and total subtractions.

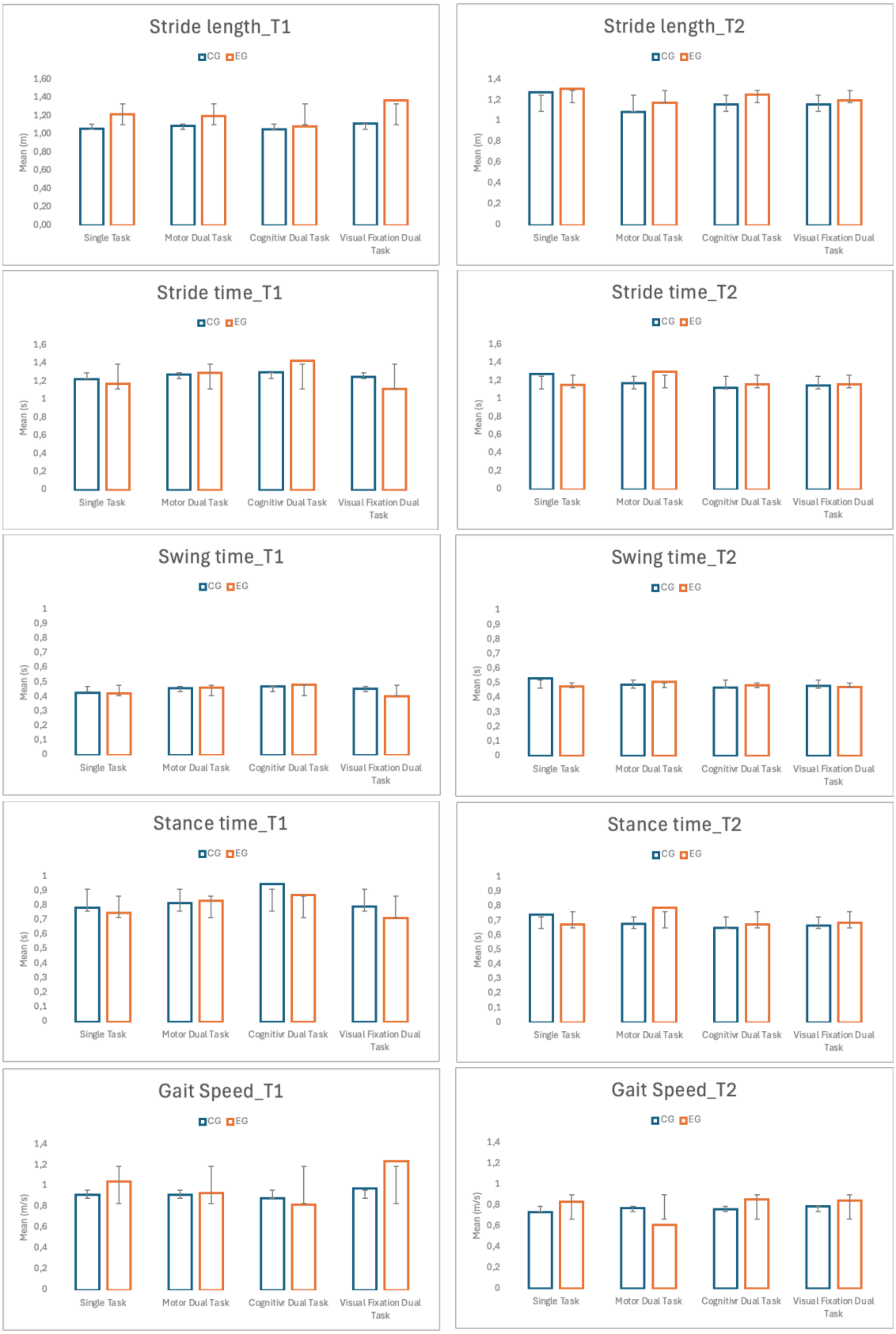

Figure 24: Gait performance in the single task, motor, cognitive, and visual-fixation dual tasks at T1 (on the left) and T2 (on the right), comparing the two groups, CG in orange and EG in blue.

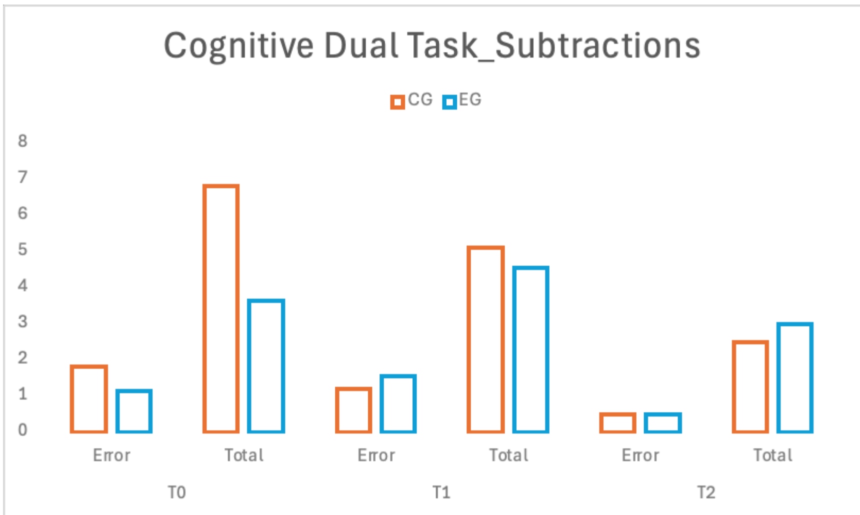

Figure 25: Error and total subtractions during gait cognitive dual tasks at T1 and T2

8.2.7 Monitoring of use and physical activity by wearable devices

Figure 26 shows seven patients' daily steps and sensors, comparing acquisition post T1 and T2. The percentage of the time (%) the sensor was not worn can be seen on the right. The highest value appears at EG44, with approximately 3.5 % time without the sensor at T2, followed by patients EG5 at T1, around 2.5 %. Patient EG4 also registered a high value at T1, with a value of around 3%. Patients EG2 and EG8 have lower values, with patient EG8 around 0.5%. The total number of steps per day is shown on the left, with patient EG4 having the highest value at around 120.000 steps at T1, followed by patient 3 with around 60.000 steps at T1, and patient EG2 with around 60.000 steps at T2. Patient 1 has the lowest number of steps, around 10.000 at T1, followed by EG6 with around 20.000 steps, and Patient EG5 with around 15.000 steps at T2. Patients who spent less time without the sensor do not necessarily have more steps, indicating variability in use and recorded activity.

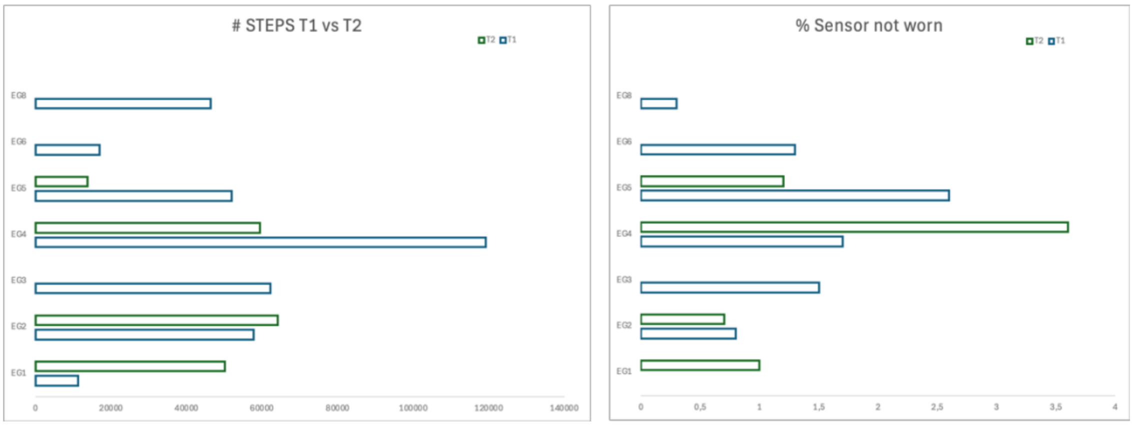

Figure 26: Percentage trend of the time of wearable sensor use and total steps walked

The analysis of the physical activity monitoring graph (Figure 27) in seven patients shows that the distribution scores of the activities monitored by the TOMs system vary, highlighting differences in movement habits and time spent in different postures. Most patients spend more than 40% of their time lying down at T1, except patient EG1 and patient EG3, who show a lower percentage of time spent in this position, suggesting that for them, the time spent resting is more limited than for the others, who require more extended periods of rest. At T2, instead, all four patients reported more than 40% of their time lying down. This suggests that, despite individual differences, there is a common tendency to spend a portion of time sitting, probably due to rest and daily activities. However, patient EG1 presents a higher percentage, while patients EG5 and EG6 spend less time in this position than the others.

All patients, except patient EG5 and patient EG6, spend more than 10% of their time in active physical activity. This suggests that patients EG5 and EG6 show lower activity levels, perhaps due to physical, motivational, or special health conditions that lead them to be more sedentary. The distribution of total time between activities shows some patient variability, evidenced by the different color compositions in each bar, as reported in Figure 28. This suggests heterogeneity in the sample population, with possible differences in each patient's movement needs, rehabilitation goals, and functional abilities.

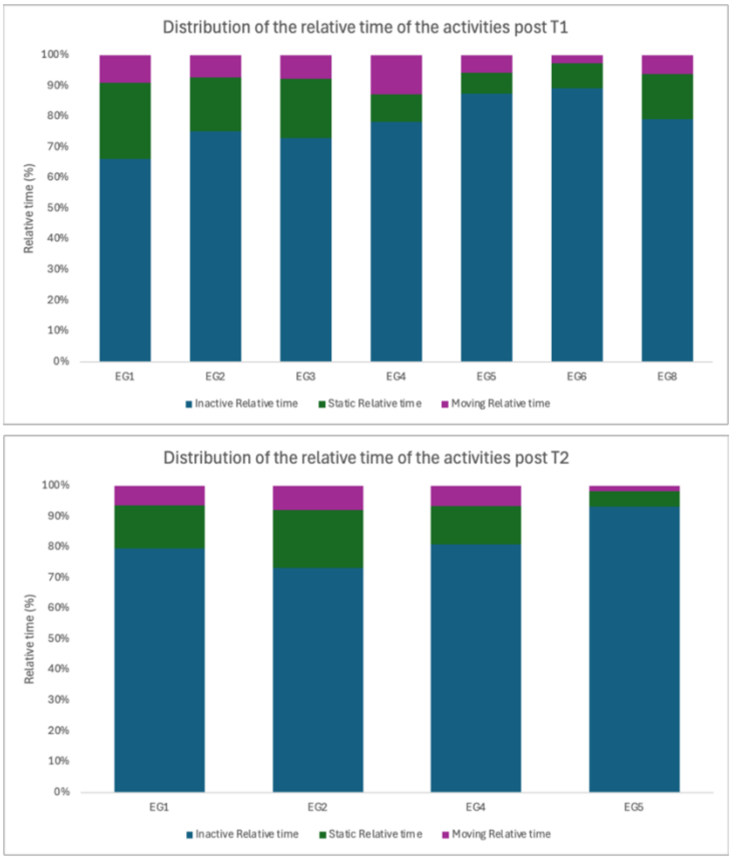

Figure 27: Physical activity monitoring trend comparing T1 and T2. The relative time (in percentage) per activity is summarized, distinguishing into active, static, and moving time

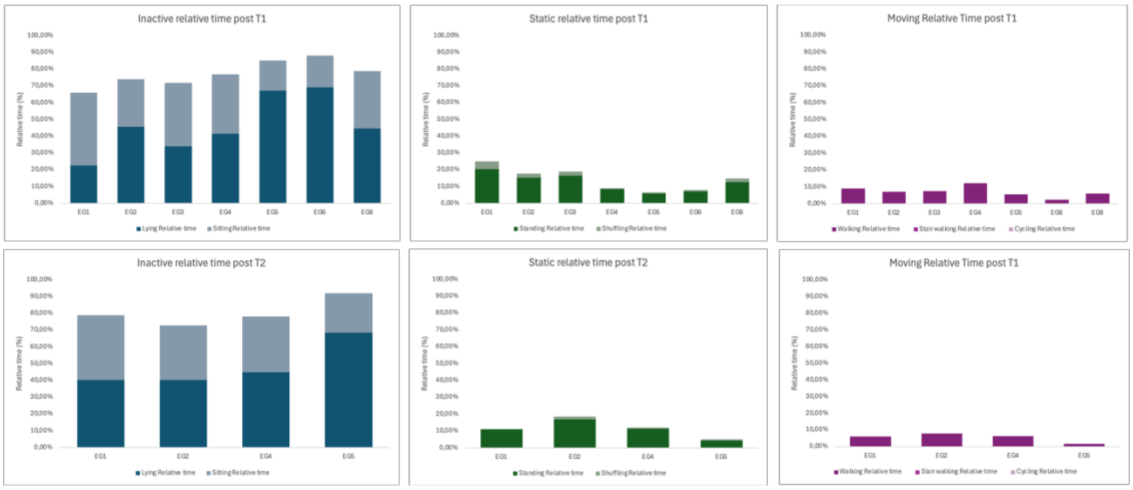

Figure 28: Physical activity monitoring trend measured with wearable sensors comparing T1 and T2. Static, moving, and inactive relative times are reported according to different activities for each group.

8.2.8 Energy expenditure monitoring using TOMs devices

The analysis of the graph of energy expenditure (Figure 29) monitoring in the seven EG patients (n=7) at T1 and four (n=4) at T2 shows that the data extrapolated from the TOMs system varies between the patients, highlighting differences in movement habits. The BMR, i.e., the minimum amount of energy a body requires during physiological and mental rest, represents the largest percentage of energy expenditure for all patients. Generally, in healthy subjects, the BMR represents about 60-75% of the total energy expenditure, so the values we find seem to reflect this trend; only in patient EG6 it seems to have a higher percentage, underlining a greater sedentariness, as found in the results of physical activity.

DIT, i.e., the amount used for digestion, absorption, and transport of nutrients, also shows a similar amplitude in all patients, occupying a similar media temporal range. The DIT is generally about 10% of the total energy intake for a Western diet. At T1, only patients EG1, EG2, and EG8 seem to have larger values, probably related to a greater tendency to ingest food and substances. At T2, patients EG1 and EG2 maintain larger values.

Finally, the AEE, the energy expenditure related to physical activity, is the most variable component of total energy expenditure in subjects, and after BMR, is the most important component of daily energy expenditure. The AEE includes expenditure related to muscular activity and increased cardiorespiratory function. It's a parameter that is, therefore, directly related to physical activity; in fact, it confirms the results found with the previous parameters: the subjects who do more activity, i.e., patients EG1, EG 2, EG3, EG4, and EG8, have a higher average daily range, while patients EG5 and EG6, who are more sedentary, have smaller ranges.

Figure 29 shows that the same patients had different daily activities and energy consumption in T1 and T2 acquisition. It's a good signal regarding the acceptance of Monitoring in an ecological setting and not influencing some daily and usual activities.

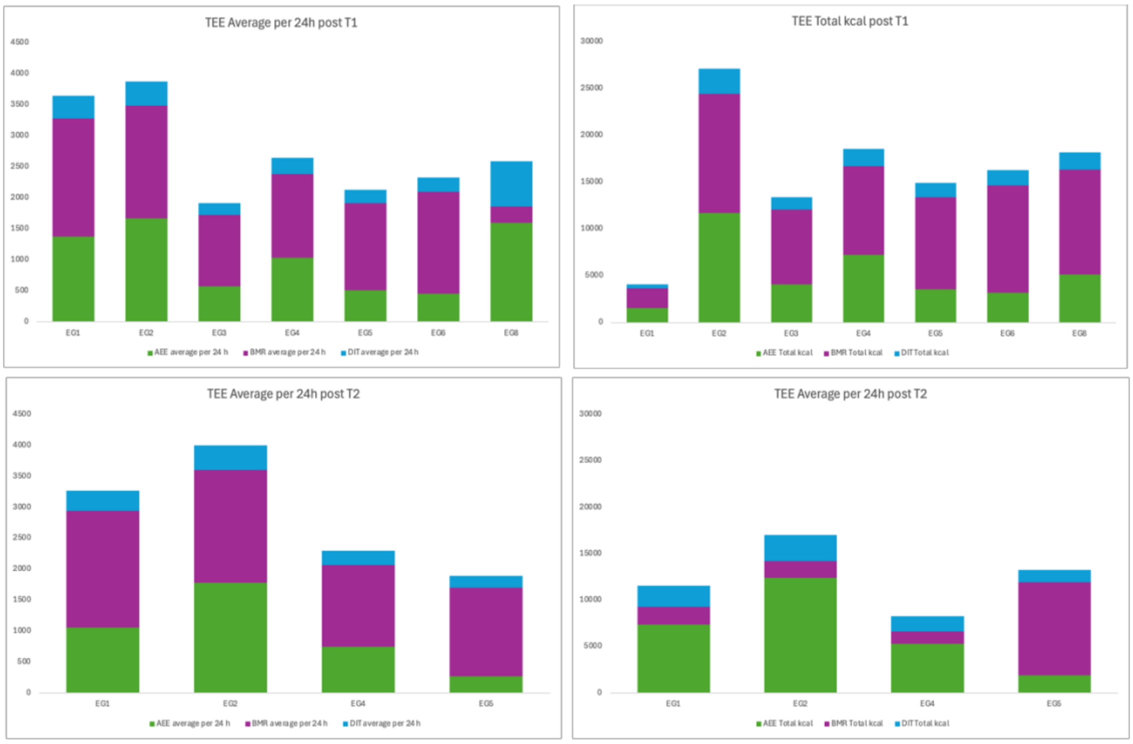

Figure 29: Trend in energy expenditure measured by wearable sensors, TEE average per 24, and TEE-total Kcal at T1 and T2

PAL (Figure 30), i.e., a person's total energy expenditure based on 24 hours, divided by his or her basal metabolic rate (BMR), is an estimate of the (physical) activities performed daily. A value around 1.2 is related to a sedentary lifestyle, while a value between 2.0 and 4.0 is typical of individuals with a very active lifestyle. The graph shows that patients EG1, EG2, EG3, and EG4 lead active or otherwise active lives, while patients EG5 and EG6 lead sedentary lives. These results further confirm the results provided by other parameters analyzed previously.

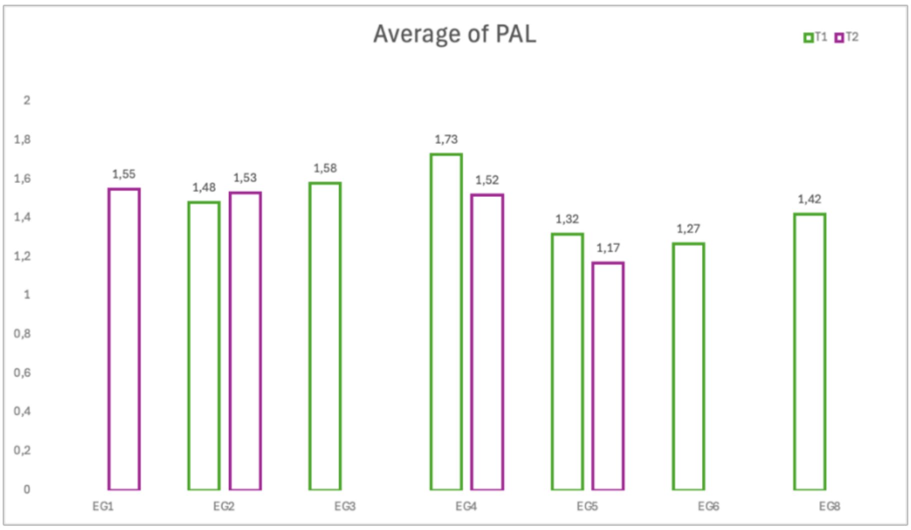

Figure 30: Trend of PAL of the EG during the 7 days of home monitoring using sensors.

The MET (figure 31), the metabolic equivalent (MET-minutes), provides information on physical activity of greater than moderate intensity in minutes. The graph represents how many METs the patients consumed while using the sensor. The graph shows that patients EG4 and EG5 consume a lot of METs in one week. Compared to the results provided by the other energy expenditure parameters, this parameter confirms the tendency of patient EG4 to lead an active life full of high-intensity activities. Although patients EG1 and EG2 remain active throughout the day, the graph shows they perform medium to low-intensity activities. On the other hand, patient EG5, who had shown a sedentary lifestyle in the results analyzed above, shows in this graph that the few activities performed during the day are at high intensity. The ideal exercise intensity indicated by the guideline for obtaining substantial positive health effects is 500-1000 METs (metabolic equivalents) min/week (Blair et al. 1992). Notably, half of the patients (EG2, EG3, EG4, EG5 at T1 and EG1, EG2, EG4 at T2) exceeded the 500 METs used during the week.

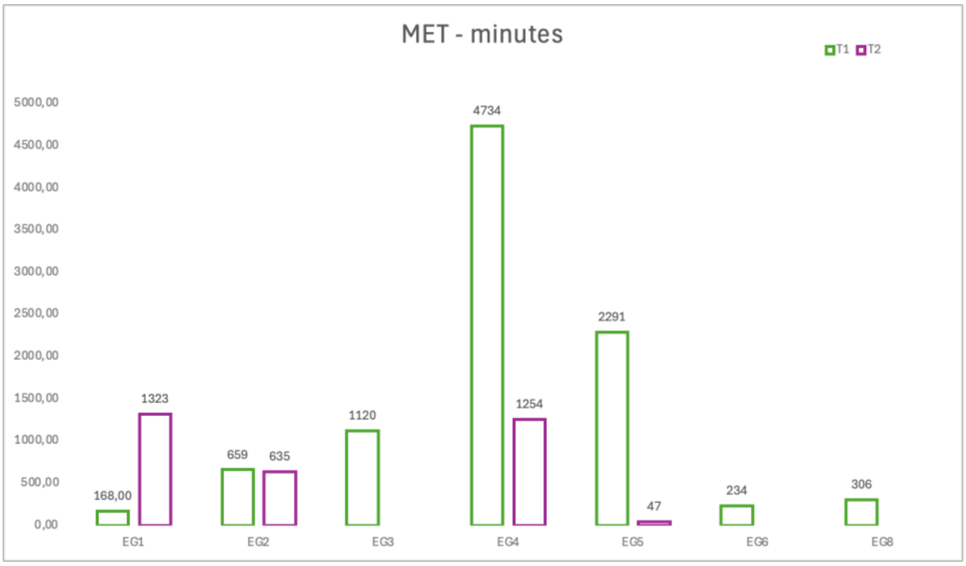

Figure 31: Trend of PAL of the EG during the 7 days of home monitoring using sensors

8.2.9 Sleep quality monitoring using TOMs

The sleep activity monitoring graph analysis in seven patients reveals considerable patient variability. The numbers of transitions during the sleep period, classified as small, medium, large, and extra-large transitions, are reported in Figure 26. The graph (Figure 32), after T1, shows that patients who lead very sedentary or active lives but with low-intensity activities have more transitions defined as extra-large during night rest (patients EG1, EG2, and EG6). On the other hand, patients who lead a very active life are characterized by high-intensity activity report very few extra-large transitions (patients EG4 and EG5).

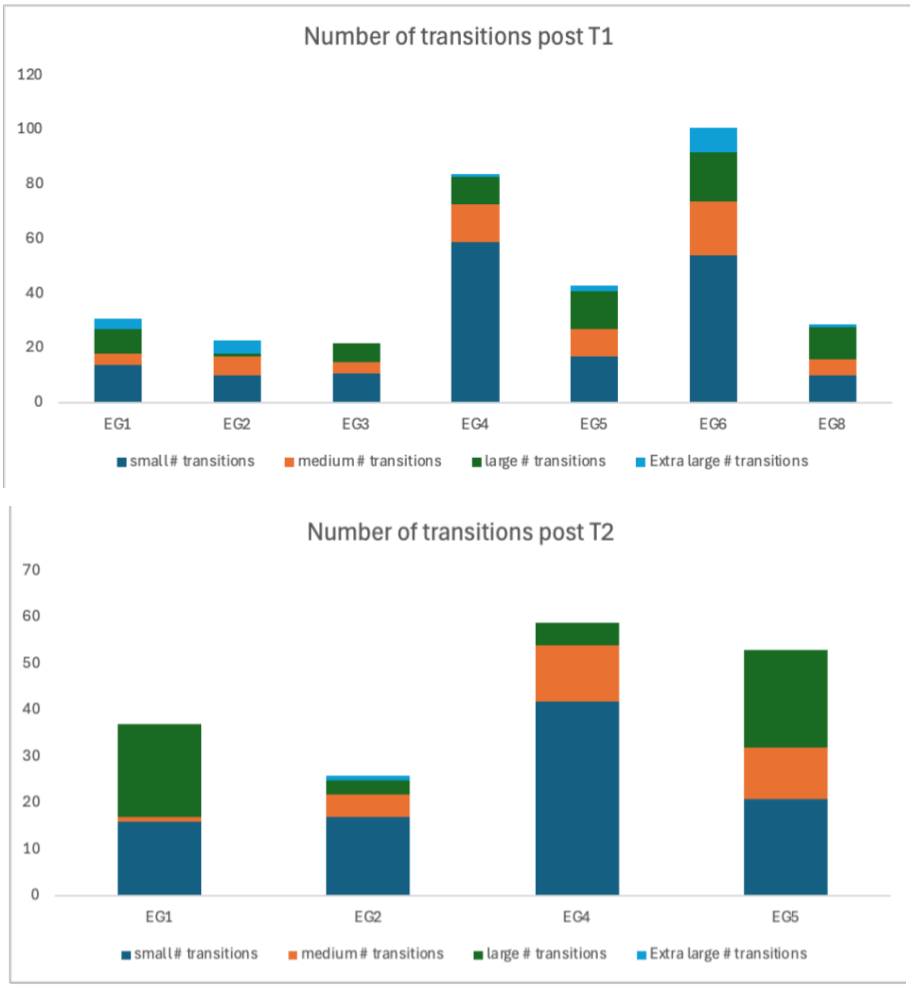

Figure 32: Trend of sleep quality through wearables. Mean number and type of transitions (small, medium, large, and extra-large) are reported for 7-day home monitoring at T1 and T2.

The graph also shows a higher total number of transitions during nighttime rest for those with a very sedentary life (patients EG5 and EG6) or a very active and intense life (patient EG4), compared to those who lead an active but not intense life (patients EG1, EG2, and EG3). These results may indicate, on the one hand, that a higher number of transitions (small) is related to fatigue after intense activity (patient EG4); on the other hand, a high number of transitions may reflect daily activity and non-predisposition to "quiet" rest (patients EG5 and EG6).

At T2, the results remain unchanged, but for all patients, the total number of transitions diminished, indicating an improvement in the patient's health and quality of night rest; at T2, no one of EG reported insomnia symptoms.

In terms of frequencies and numbers of transitions, patient EG4, the most high-intensity active, and patient EG6, one of the most inactive, reported higher numbers of transitions per night with the highest frequency of transition (calculated as the number of transitions per hour). Total frequency, as transitions - hour ratio, and total transitions are reported in Figure 33.

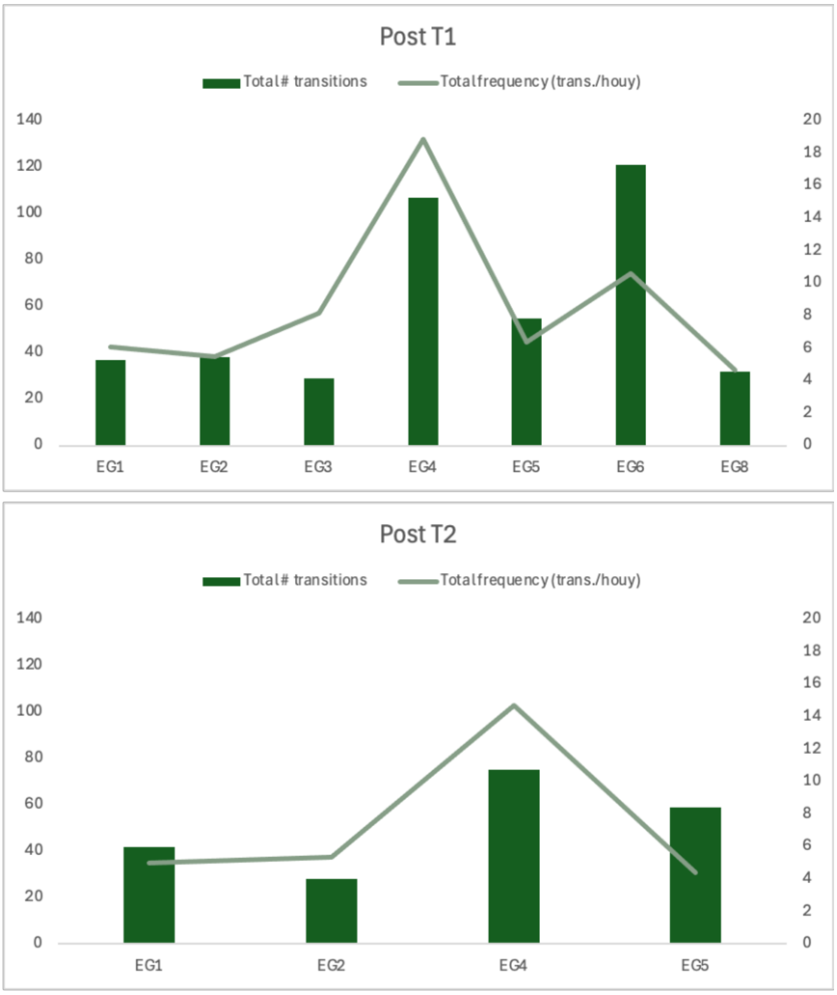

Figure 33: Trend of sleep quality through wearables. Total frequency and number of transitions are reported for 7-day home monitoring at T1 and T2.

8.2.10 Tele-healthcare Satisfaction Questionnaire – Wearable Technology

At follow-up evaluations, all EG patients answer a Tele-healthcare satisfaction questionnaire about wearable technology experience (Figure 34). This questionnaire comprises six areas (benefit, usability, self-concept, privacy, and loss of control, quality of life, and wearing comfort) that evaluate subjects' satisfaction with wearables. Each area includes five statements rated by the user on a 5-point Likert scale between 0, meaning strongly disagree, and 4, meaning strongly agree with the statement. At T2, five patients answered this questionnaire, and the result was that half of them think the wearable helps achieve their goals and they can benefit from it (mean average 2.5). Regarding usability, as feeling safe and good, and the easy use of technology, most patients agree with the wearable use at home (mean average 3.2). Moreover, the wearable sensor is well accepted and not perceived as dangerous in terms of loss of privacy; most patients agree that data are stored or processed appropriately (mean average 1.2). Conversely, wearable use does not create problems such as embarrassment, feeling older, or reminding of losing independence. All patients strongly disagree with all statements about self-concept. Regarding QoL, patients were discordant; some sustained that this technology helps maintain or increase independence, helping improve their physical well-being, while others strongly disagree with this statement (mean average 0.4). Finally, most of all found it comfortable in terms of design, size, weight, and the body-worn part (mean average 3.6).

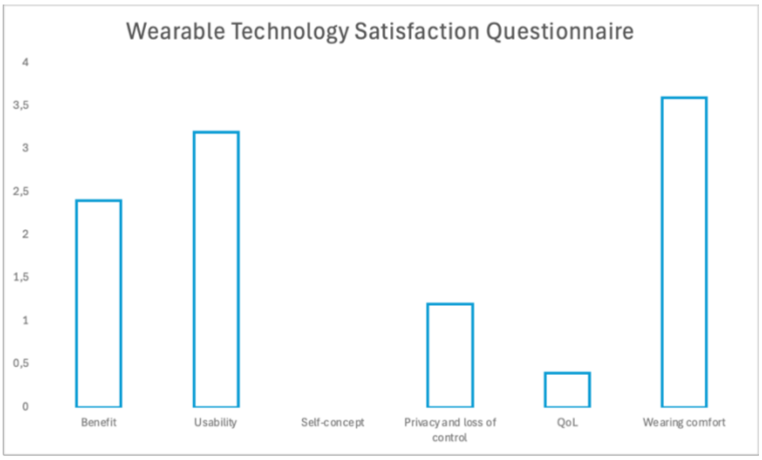

Figure 34: Tele-healthcare satisfaction Questionnaire about wearable technology (benefit, usability, self-concept, privacy and loss of control, quality of life, and wearing comfort). Value from 0 (strongly disagree with the statement) and 4 (strongly agree with the statement)

9. Discussion

Functional motor disorders that affect gait, balance, and posture are profoundly incapacitating [42,63]. FMD patients are affected by motor symptoms as well as non-motor symptoms. Recognizing these conditions is paramount, as they can provide valuable insights into the underlying pathology, particularly in patients with uncertain clinical diagnoses, especially in the early stages of neurological disorders. Traditional medical education typically starts with classic clinical presentations, which may not always align with real-world cases.

Regarding motor symptoms, patients may show isolated gait, balance, or posture abnormalities, making it challenging to diagnose a specific disorder. A new diagnostic approach has been proposed to address this, focusing on observed signs for a tailored exploration of the underlying neurological syndrome. Using tools like portable biomechanical analysis, wearable sensors, or instrumented gait analysis, baropodrometic insoles can quantitatively assess gait impairments, potentially revealing abnormalities not immediately apparent to clinicians [52,57].

However, integrating these tools into routine clinical practice, especially into ecological unsupervised Monitoring, is limited, primarily due to the need for further validation to ensure their reliability in identifying specific gait disturbances associated with neurological disorders and specific technology systems.

Previous studies have attempted to identify spatial-temporal features that could distinguish different patient categories from healthy subjects in a controlled setting, such as the hospital [19,62,185]. However, this is the first study to observe and describe patients' attitudes during their daily activities and possible improvements or worsening between the experimental and control groups (the first monitored with a wearable sensor, the second without the sensor).

So, this study explores the effects of wearable devices (Axivity AX6) in patients with FMD for the first time. Currently, no studies analyze the impact of such devices, or other accelerometers, on this specific population. However, studies have been conducted on wearable devices in an ecological setting in patients with Parkinson's disease and other degenerative neurological disorders, as Langer et al., 2009 and Dijkstra et al., 2010. Wearables and the software platform (McRoberts) provide a broad overview of the patient's motor activity, energy expenditure for 24 hours a week, and sleep quality. The Axivity assessment was supported by both motor and non-motor rating scales administered in the presence, lending additional validity to the results obtained. In this study, the primary objective was the analysis of eligibility and recruitment of FMD patients over a five-month observation period.

Of the 62 patients evaluated, only 30 (38.4%) fulfilled the inclusion criteria, but the recruitment rate among the eligible patients was remarkable, with 23 patients enrolled, corresponding to 76.67%. These results suggest the intervention attracted good interest among eligible patients despite a relatively low eligibility rate.

Regarding the secondary aims, an improvement in the severity of motor symptoms was observed in the experimental group compared to the control group, as evidenced by the ratings using the S-FMDRS scale. This improvement is particularly relevant, as it suggests that the intervention has a tangible impact on the patient's condition. A crucial aspect of this improvement could be attributed to the increased motivation of the patients to engage in daily physical activity using the sensor, as confirmed by the tele-healthcare satisfaction questionnaire on the experience of wearable use. There was a very good response regarding the usability, benefit, and wearable comfort of almost all experimental groups of patients.

Wearing the wearable device can stimulate patients to feel more empowered and aware of their physical activities. The presence of the sensor and its ability to monitor performance may induce patients to engage more in active behavior. In addition, the fact that examiners are aware of patients' activities during evaluations can create a kind of "observation effect," in which patients feel pressured to show progress and engage more. Being observed by the specialist is also viewed positively by the patients, as confirmed by the tele-healthcare satisfaction questionnaire on the experience of wearable use, in which almost nobody expressed doubt about the possible compromise of privacy and loss of control.

This positive feedback mechanism may be particularly effective in rehabilitation, where motivation plays a key role in treatment success, as reported in some studies of post-stroke patients, such as by Nieboer et al. (2023). The hypothesis that sensor use increases motivation is further supported by the results of usability tests, in which patients gave high scores for their overall experience with the device. These high scores indicate a good acceptance of the device and a positive perception of its impact on daily life. When patients feel comfortable and satisfied with the intervention, they are more likely to engage in physical activities actively, thus improving motor symptoms.

In addition, the improvement found in the experimental group at T2 in the stabilometric tests provides further evidence to support this theory. The experimental group patients presented an improvement, in most of them, in the COP sway area in all tasks (single task, motor, and cognitive dual task) at T2, different from the control group.

The stabilometric balance board is useful for assessing balance and stability, which are often compromised in patients with movement disorders. The experimental group's results at time T2 in this context suggest that the intervention improved motor symptoms and positively affected the ability to maintain balance, a crucial aspect of mobility and quality of life. The data suggest a slight improvement for the experimental group, highlighting the acceptability of the intervention and its ability to influence significant secondary aspects. This trend could result from the expectation of a new experimental treatment, especially considering there is currently no proper national guideline for treating FMD patients. The positive trend in non-motor symptoms could be attributed to several factors, such as the expectation of a new experimental treatment, which plays a crucial role.

The novelty of the intervention may have generated an increase in motivation and commitment on the part of the patients, contributing to a more favorable perception of their condition. It is important to emphasize that in the absence of established national guidelines for treating FMD patients, participants may have seen the intervention as a rare opportunity for improvement. Furthermore, the perceived improvement in non-motor symptoms could reflect a placebo effect, whereby the expectation of a positive change influences the perception of pain and fatigue. Other studies have already considered the importance of the placebo effect in neurological diseases, demonstrating its effectiveness in certain case series, such as Murray et al. (2013) and De la Fuente-Fernández et al. (2002).

In this way, there is promising potential for integrating digital telerehabilitation with cognitive digital training in managing FMD patients. Combining motor and cognitive interventions through digital platforms could address the complex interaction between attention, emotion, and motor control, characterizing FMD. Digital coaching, such as real-time feedback, motivational prompts, and personalized goal setting, could improve patient engagement, adherence, and self-efficacy throughout rehabilitation. This integration may support more holistic, patient-centered care and facilitate sustained behavioral and functional improvements over time.

The results on quality of life show a slight improvement, which is particularly evident in the experimental group. This finding is significant, as it suggests that the intervention not only positively influences the physical symptoms but also significantly impacts the psychological aspects and the overall well-being of the patients. Quality of life is a multidimensional concept that includes physical health and emotional, social, and psychological well-being. Therefore, improving this area is a crucial indicator of intervention effectiveness.

Increased patient care, facilitated by using wearable devices and taking advantage of the evolution of technology, contributes to greater confidence in abilities and daily resources. When patients feel actively involved in managing their condition, they tend to develop a more positive view of their situation. This sense of empowerment may translate into increased motivation to participate in daily activities, thus improving their physical and mental states. In addition, the intervention may have stimulated a change in the perception of one's own body and abilities. Patients who monitor their physical activity may become more aware of their progress, however small, which may increase self-efficacy. Awareness of one's improvements, even in non-motor symptoms, can generate a virtuous cycle of motivation and engagement, further contributing to improved quality of life. It’s important to note that the scientific literature supports the idea that regular physical activity is a key factor in enhancing quality of life. According to Biagini et al. (2022), patients who engage in consistent physical activity tend to notice significant benefits in physical health and psychological well-being.

The practice of physical exercise is known to reduce symptoms of anxiety and depression, improve mood, and increase self-esteem, suggesting that the intervention not only improves the physical condition of the patients but also has positive effects on their emotional state. This data may suggest higher rest needs in patients with greater retention but also a lack of physical activity, which, if not compensated for, may have adverse long-term effects. The time spent sitting and in physical activity also varies without critically analyzing the differences in the patients' clinical profiles or health conditions. These elements, if integrated, could strengthen the understanding of the causes behind the data and support targeted optimization of interventions.

Energy expenditure varies significantly between patients, with BMR representing the largest percentage of energy consumption for all patients as healthy subjects. However, in the EG6 patient, the high percentage suggests a lack of energy expenditure consistent with physical activity data. The AEE, closely related to muscle activity, is particularly low for less active patients (patients EG5 and EG6), confirming limited physical activity.

However, the comparison between patients doesn't sufficiently consider possible confounding factors, such as variability in individual metabolism rates or other health conditions. The few pieces of information the platform asks to register patients are age, sex, weight, and height. Without these data, the interpretation of "normal" or "abnormal" energy expenditure remains partial and inconclusive.

The MET analysis shows that almost all patients reach the recommended threshold for weekly physical activity. Instead, sleep quality, monitored by night postures, shows variability among patients, but the frequency of postural transitions does not necessarily correlate with perceived sleep quality. The limited interpretation of these data points to the need to add further sleep assessment tools (such as subjective perception of rest or REM/NREM cycle data) to provide a more comprehensive picture. In the study, the number of transitions during the nocturnal rest period is analyzed and classified as small, medium, large, and extra-large transitions, and consideration of the relationship between daily-life activities and sleep in terms of the number of transitions and frequency was made.

The results showed that patients with a very sedentary or active life with low activity intensity had a higher number of transitions defined as extra-large during sleep, which could be attributed to the fact that they do not have enough activity during the day to be tired at bedtime, which leads to worse sleep quality. On the other hand, patients who lead very active lives have very few extra-large transitions during sleep, which could suggest that being active during the day makes them tired enough to arrive at bedtime sufficiently tired.
The relationship between sleep and FMDs is an emerging and relatively underexplored area in the current literature, so it needs to be studied more. While sleep disturbances are well-documented in other disorders, such as fibromyalgia and irritable bowel syndrome (using actigraphy or polysomnography), their specific characterization in FMDs has only recently gained attention. The potential interaction between impaired sleep quality and motor symptom severity and daytime activities is exciting, as poor sleep may exacerbate attentional dysregulation and emotional distress, potentially amplifying functional symptoms and increasing sleep transitions. Further studies are needed to clarify whether sleep disturbances contribute to the onset and maintenance of FMD symptoms or are a secondary consequence of the disorder.

The self-assessed perception by CGI shows differences between the EG and CG groups. Still, the presence of variability in the EG group at time T2, as opposed to relative variability in the GC group, is not further investigated concerning psychological or social factors that may influence the perceived improvement or worsening. The lack of homogeneity between groups and the variability in CGI scores may suggest that the intervention or treatment didn’t have consistent and repeatable effects on both groups. Still, these considerations would require more extensive data collection and specific follow-up to confirm these hypotheses.

These preliminary analyses are part of an ongoing study of telemonitoring patients through wearable sensors. Therefore, the lack of statistical significance can be attributed to not reaching the sample size established by the initial sample size calculation. However, one of the study's main strengths is its methodological rigor and the in-depth collection of outcomes from a biopsychosocial perspective, which provides a comprehensive and multidimensional view of the patients. In addition, the study stands out for its innovativeness, as there is currently no other similar research. Through this study, we want to discuss and analyze the feasibility of the intervention (use of accelerometers at home) to implement a tele-rehabilitation protocol in the future.

The interdisciplinary approach, in which clinicians and engineers collaborate, is an additional valuable element aimed at improving the care and treatment of people with FMD.

9.1 Limits

This study presents several limitations that warrant consideration.

First, the number of patients to recruit is 30 (15 patients for each group), so it is not a large sample, but the recruitment is strictly related to the two patients weekly recovered at the Neurorehabilitation Unit and the Parkinson's Disease and Movement Disorders Unit of the Integrated University Hospital (AOUI) of Verona. Directly connected, other limits are different, and multiple symptoms could manifest in these patients. In our study, for example, patients without motor symptoms in gait and balance can't be recruited. Then, regarding non-motor symptoms, such as self-perception changes of disease, problems were presented at follow-up evaluations three and six months after hospitalization, as confirmed by the acceptability rate of 83.33%.

Regarding home-based rehabilitation, due to the high complexity, high heterogeneity in symptoms, and lack of digital biomarkers to capture the characteristics of context-dependent motor symptoms, shifting from group-level to individual-level assessment and digital refinement will be significant. However, technical challenges such as sensor accuracy, data reliability, and the need for individualized baseline calibration have to be improved, and more studies are needed to allow this. Moreover, most algorithms and assessment protocols are developed for group-level analysis, making it challenging to interpret progress or treatment response at the single-patient level with sufficient clinical relevance.

These limitations highlight this population's need for more personalized, robust, and clinically validated digital assessment frameworks.
Another limit is related to wearables in unsupervised evaluations for experimental use. Once the patients return home with the sensor, it is impossible to know if it works correctly or if the acquisition has any problems. The researcher can only obtain this information once the data are extracted. Moreover, the sensor in our study, Axivity AX6, acquired a lot of data during the seven days of continuous Monitoring, and all results extracted depended on specific software and algorithms developed. Each movement not recognized by algorithms can't be analyzed and extracted. Thanks to technologies and artificial intelligence development, future studies are needed to better discriminate activities executed in an unsupervised setting.

10. Conclusion

This thesis provides an overview of the Functional Motor Disorder patient's primary symptoms, rehabilitation treatments, and health care system limits in the first section. Then, the current technological solutions for PD, MS, and Huntington applications to monitor gait and balance in the ecological setting are presented. Positive aspects of digital technologies include the possibility of objectively, frequently, and remotely assessing multiple sides of movement disorders in an ecological environment. Wearable devices may enable the earlier identification of individuals at risk for or with disease and may be more sensitive to disease progression, both of which may facilitate the identification of disease-modifying treatments. Devices can provide new insights into disability and progression to integrate the standard clinical assessments and enable deep clinical phenotyping of neurodegenerative diseases. Moreover, wearables may enable more personalized treatment and improved clinical management. However, better validation of new digital outcomes and tools is needed. Appropriate digital and technological solutions hold enormous potential for improving the management of motor disorder patients, enhancing the QoL, and monitoring the effects and the outcomes of the therapy and rehabilitation during the disease progression.

Identifying specific gait biomarkers tailored to different neurological diseases remains an unmet need in clinical and research landscapes, pivotal for enhancing diagnostic precision and therapeutic strategies. A multidimensional approach involving immersive virtual reality in gait assessment in patients with functional motor disorders through protocols developed specifically on the pathophysiology of the disorders helped in understanding deeply biomarkers specific to this disease population. The effect of virtual reality, rather than reducing performance differences between FMD and HC, allows the identification of specific gait parameters not detectable by clinical observation alone that could facilitate early and correct diagnosis of FMD. These results do not exclude the fact that virtual reality may also be helpful in rehabilitation (Brouwer et al., 2023; Bullock et al., 2020). However, the perspectives and critical issues of VR underline the need for further studies to understand VR's effectiveness better and develop specific assessment and treatment protocols for FMD patients.

Advancing the assessment of gait disturbances among patients with functional neurological disorders by incorporating efficient, economical, and non-time-consuming devices can change the future rehabilitation of these patients. Utilizing these innovative tools facilitates a nuanced and enriched examination, enabling clinicians to discern and characterize intricate patterns of gait disturbances specific to various patient populations. Integrating such technologies nurtures a deeper understanding of the multifaceted pathophysiological nuances underpinning neurological diseases, offering rich insights that foster a comprehensive appreciation of disease heterogeneity and progression.

For this reason, the thesis project suggests that a specific protocol based on wearables (Axivity AX6) may effectively monitor motor disorders' progress in the long term. The results support the feasibility and accessibility of this approach, demonstrating 83,33% acceptability, indicating that this method may represent a valid tool for specific and home rehabilitation programs.
Preliminary data suggest that the use of wearable devices can promote improvements in patients' symptoms on several fronts. The use of such devices also seems to contribute to enhancing patients' motivation, facilitating greater adherence and continuity in the rehabilitation program, with positive effects on the perception of change in their state of health, anxiety, depression, and quality of life. However, it is important to emphasize that these preliminary results will have to be confirmed with the expansion of the sample, as envisaged by the study design, to consolidate the evidence of the positive effects observed.

In conclusion, future research should prioritize a larger sample of this new population (as FMD) sizes with more extended remote monitoring periods and longer follow-up; digital device data standardization and the development of data sharing platforms to enable real-time results and cross-study comparisons; the assessment of more non-motor features towards the development of more holistic disease characterization; and clinical trials to monitor structured therapeutic rehabilitation programs over the medium to long term in home settings in comparison with the same in clinical settings to assess differences in terms of outcomes, efficacy, adherence, and sustainability.

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