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Cognitive-motor interference in people with multiple sclerosis: a kinematic approach to clarify the effect of cognitive load on walking performance

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Cognitive-motor interference in people with multiple sclerosis: a kinematic approach to clarify the effect of cognitive load on walking performance

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Giuseppina Pilloni

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Abstract

The simultaneous performance of cognitive tasks during locomotion (or cognitive-motor dual-task) is known to cause performance deficits in either one of, or both tasks. Furthermore, these performance decrements are exacerbated by the presence of motor impairments and cognitive dysfunctions characteristic of numerous neurological diseases, such as multiple sclerosis (MS). In this regard the assessment of walking while performing a secondary cognitive task may represent a relevant outcome measure, because it allows measuring, in a laboratory setting, individual's ability to cope with walking challenging situations similar to everyday living.

The first aim of this thesis is to provide an experimental setup, based on the use of optoelectronic stereophotogrammetry, for obtaining quantitative evaluation of walking biomechanics and motor strategies during dual-task performance in both healthy adults and patients affected by MS. Then, this experimental dual-task methodology is tested as suitable method not only for detecting, measuring and characterizing disability, but also for testing intervention effectiveness in clinical practice. Specifically, the study was focused on the assessment of spatiotemporal parameters and lower limb angular kinematics during single-task (normal pace walking only) and dual-task (walking while performing a discrimination and decision-making task, the Stroop Color Word Test) performance.

This thesis is composed of four experiments. The first two aimed to measure and characterize the effect of cognitive-motor interference on walking biomechanics in terms of spatiotemporal parameters and lower limb angular joint kinematics. In this regard, a sample of MS patients stratified by disability level (low disability patients, EDSS 1.0-2.5, n=37; mild to moderate disability patients, EDSS 3.0-6.0, n=44) and a sample of age- and gender-matched healthy adults (n=41) underwent a 3D kinematic evaluation of single- and dual-task performance using a motion capture system. Differences between conditions and groups were investigated using a two-way repeated ANOVA. While a prediction method was carried out to discriminate the angular joint kinematics variations due to gait speed changes from those caused by the presence of an additional cognitive load. The results reported that gait speed and stride length were sensitive motor variables in detecting differences from single- to dual-task condition in both MS patients and unaffected individuals, whereas spatiotemporal parameters closely related to balance control (e.g., step width, double support phase duration) were sensitive to changes only in patients with moderate disability. Moreover, those patients showed significant changes in the kinematics of distal joint (shank-foot) and proximal joint (hip), including a reduction in ankle plantarflexion and hip extension peak at the terminal stance phase. These observed changes in more impaired patients are compensatory mechanism to stabilize body posture and allow safe locomotion during complicate dual-task activities.

Finally, the other two experiments were designed to provide a practical application of this dual-task methodology, as a tool for quantitatively assessing biomechanics changes after an innovative therapeutic intervention. In this regard, a sample of MS patients (n=34) with mild to moderate disability participated in a bicentric clinical trial. As per protocol, patients completed a multimodal intervention, consisting of either active or sham multiple sessions of transcranial direct current stimulation (tDCS) combined with standard physical activity, aimed to improve walking performance. Following repeated application of active tDCS, the results obtained from the quantitative gait analysis showed greater improvements in gait velocity, step length and walking endurance. This improvement measured in walking had corresponding effects on walking dual-task performance. In fact, the dual-task cost of gait parameters was significantly reduced after the active tDCS intervention.

In conclusion, the quantitative assessment of walking impairments during the execution of functional task in people with MS can support a deep learning of both movement features and motor strategies, which should have implications for the design and validation of clinical intervention aimed at improving functional walking.

Table of Contents

List of Abbreviations

21-MFIS	21-item Modified form of the Fatigue Impact Scale
AAI	Attention Allocation Index
AI	Ambulation Index
AP	Antero-Posterior
CCD	Charged-Couple Device
CIS	Clinically Isolated Syndrome
CMOS	Complementary Metal-Oxide Semiconductor
CNS	Central Nervous System
CoM	Centre of Mass
CPG	Central Pattern Generators
DGI	Dynamic Gait Index
DLPFC	Dorsolateral Prefrontal Cortex
DT	Dual-Task
DTC	Dual Task Cost
DTE	Dual Task Effect
EDSS	Kurtzkee Expanded Disability State Scale
fNIRS	Functional Near-Infrared Spectroscopy
FSS	Fatigue Severity Scale
IMU	Inertial Measurement Unit
LED	Light-Emitting Diode
LTP	Long Term Potentiation
M1	Primary Motor Cortex
ML	Medio-Lateral

MS	Multiple Sclerosis
MSWS-12	12-item Multiple Sclerosis Walking Scale
NIBS	Non-Invasive Brain Stimulation
PFC	Prefrontal Cortex
PMC	Premotor Cortices
PP	Primary Progressive
PR	Progressive Relapsing
PRP	Psychological Refractory Period
ROM	Range of Motion
RR	Relapsing-Remitting
rTMS	Repetitive Transcranial Magnetic Stimulation
SMA	Supplementary Motor Area
SO	Supra Orbital
SP	Secondary Progressive
ST	Single-Task
tDCS	Transcranial Direct Current Stimulation
TES	Transcranial Electrical Stimulation

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Chapter 1

Introduction

In day-to-day activities, purposeful and safe locomotion requires higher-level cortical processes in order to adapt motor strategy to own individual goals and environment's burdens, and commonly involves also the performance of several concurrent cognitive tasks, such as conversing, phone's texting or dividing attention to external stimulus. The simultaneous assessment of walking while performing secondary cognitive task may represent a more relevant outcome measure than gait analysis alone, because it allows measuring, in a laboratory setting, individual's ability to cope with challenging situations similar to everyday living. The most common methodology adopted to investigate the interaction between walking and cognitive tasks is the dual-task paradigm. People's ability to walk while performing a concurrent cognitive task has been previously investigated for both healthy individuals and people affected by neurological diseases, reporting that biomechanics and dynamic stability could be affected during walking dual-task. Therefore, the presence of cognitive load during walking performance may elicit the so-called *cognitive-motor interference* phenomenon.

Whenever the simultaneous performance of a motor task and a cognitive task results in a deterioration in one or both tasks, compared with the performance of a single task (e.g., walking or cognitive tasks alone), this is likely to indicate the occurrence of *cognitive-motor interference*. Although this phenomenon is

present in healthy individuals, it becomes more evident in people with neurodegenerative disease with system-specific deficits, such as people affected by multiple sclerosis (MS). In this regard deficits in walking and in cognitive functioning are well recognized characteristics of MS people and they could exacerbate limitations in walking dual-task performance. Recently, the use of dual-task methodology to assess the interplay between gait and cognition has been a growing topic of research in MS. The principal detrimental effect of dual-task performance on walking was a significant reduction of gait velocity and stride length.

Despite the increasing interest to assess *cognitive-motor interference* phenomenon in patients with MS, the evidences are still scarce and there are several methodological issues. There is no homogeneity concerning the cognitive task that should generate the appropriate interference in MS population, and the meaningful gait kinematic parameters that should be used for measuring the degree of *cognitive-motor interference*. Moreover, most studies do not compare results with healthy controls and they are focused on a limited set of gait spatiotemporal parameters.

Given the lack of standardized dual-task protocols, this thesis focuses on providing an experimental dual-task paradigm and setup in order to quantitatively assess the effect of *cognitive-motor interference* on walking biomechanics in both healthy individuals and people affected by MS. In fact, the use of advance techniques of 3D gait analysis makes possible a quantitative and multifactorial evaluation of biomechanics changes in a wide set of gait kinematic parameters.

The primary purpose of this thesis is to validate a dual-task paradigm consisting of the concurrent performance of walking and the Stroop Color and Word Test - the discrimination and decision-making task par excellence - by means of 3D motion analysis technique. Moreover, this thesis wants to provide quantitative information regarding the impact of cognitive load during walking performance not only on spatiotemporal parameters, but also on joint angle kinematic patterns of lower limbs. This last aspect allows the identification of the actual gait pattern adopted during walking dual-task performance and a better understanding of the effect of cognitive load on walking biomechanics.

Given the challenges that walking dual-task can pose for individuals with MS in daily living activities, another growing area of research is the possibility to enhance dual-task performance with innovative rehabilitation approach. In this context, the dual-task methodology is tested as suitable method not only for detecting and measuring disability, but also for testing intervention effectiveness.

Finally, this thesis wants to provide a practical application of this experimental setup in clinical practice, as a tool for objective measuring the outcomes of an innovative therapeutic treatment consisting of paired standard physical activity with a relatively new non-invasive brain stimulation technique, transcranial direct

current stimulation (tDCS). Firstly, the aim is to analyze the potential effect of the treatment in improving walking biomechanics in single-task condition and investigate the time course of changes in motor performance following the application of repeated sessions, and then to assess if the improvement measured in walking has corresponding effects on dual-task performance.

1.1 Thesis overview

In the following, the thesis roadmap is briefly described. In the first three chapters context and background are provided, then the research studies and their relative results are outlined in details.

Chapter 2 provides a description of qualitative and quantitative techniques employed generally for assessing walking in clinical and research setting. Particular emphasis is given to terminology and kinematic parameters used in gait analysis, and to the influence of walking speed on kinematic angle joint patterns. This last aspect is crucial to better understand which factors mostly provoke variation in joint angle kinematics of lower limb during dual-task.

Chapter 3 provides an overview of theoretical models of dual-task interference, task prioritization strategies, factors that influenced dual-task performance and the relative brain area involved.

Chapter 4 briefly introduces the key features of MS disease and its impact on motor functions. Furthermore, it reviews the pertinent dual-task gait literature and the possible approach used to enhance walking performance in single- and dual-task conditions.

Chapter 5 describes the common methods used throughout this thesis. Single- and dual-task experimental procedure, the experimental setup including the instrumentations (i.e., 3D gait analysis, wearable inertial sensor) used to quantitatively assess gait performance, the procedure for data acquisition and data analysis are described as well.

Chapter 6 includes the validation of a quantitative methodology to assess the effect of cognitive-motor interference on walking performance in both healthy individuals and people with MS, with focus on examine the impact of disability level on dual-task performance. Some of the results presented in this chapter have been published in an international journal and conference proceedings.

Chapter 7 discusses the effect of *cognitive-motor interference* on gait kinematics, in order to identify the actual biomechanical adaptation strategies used by healthy individuals and patients with MS during dual-task performance.

Chapter 8 examines the effect of multiple sessions of tDCS over the primary motor cortex (M1) paired with aerobic conditioning training on single-task walking biomechanics in those with MS. Some of the results presented in this chapter have been published in conference proceedings.

Chapter 9 examines the possibility to use the experimental dual-task methodology for investigating the effectiveness of tDCS over M1 in enhancing dual-task performance in those with MS. Some of the results presented in this chapter have been published in conference proceedings.

Chapter 10 concludes the thesis by outlining the contributions of this work, illustrates limitations and challenges faced, and discusses future directions.

Chapter 2

Human gait: a window into the biomechanics of the movement

Walking is the first method of locomotion adopted by human, providing independence and used in many activities of daily living (Kirtley, 2006). It is a voluntary movement, resulting from a complicated process involving brain, spinal cord, peripheral nerves, muscles, bones and joints. In fact, walking is realized through a complex and coordinated pattern of nerve signals, sent to the muscles, which in turn move the joints, the limbs and the whole body (Whittle, 2007). In this chapter background information relevant for understanding walking biomechanics and technologies available to support gait analysis are provided. Terminology and kinematic parameters used in gait analysis are described. Particular emphasis is given to the influence of walking speed on kinematic angle joint patterns. This last aspect is crucial to discriminate which factors provoke variation in joint angle kinematics of lower limb during dual-task.

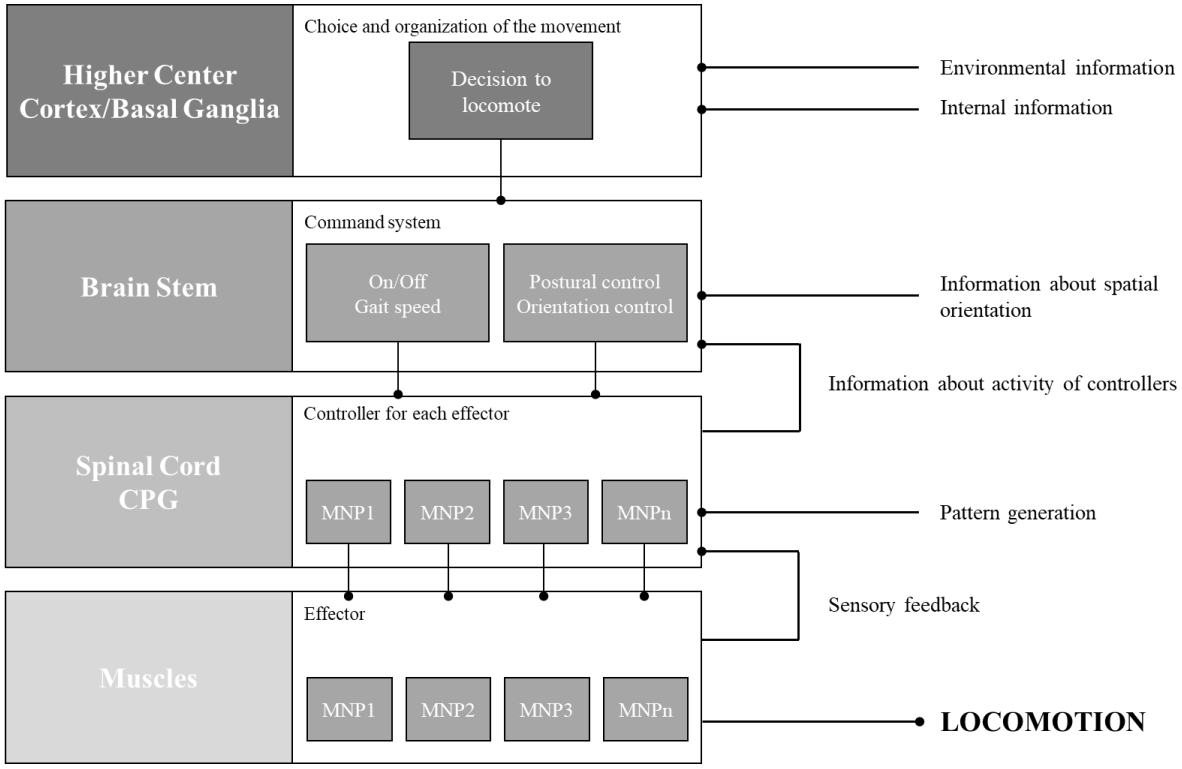
2.1 Neural control of gait

Somehow the central nervous system coordinates which joint has to be moved, how far and at what time. The cyclical and rhythmic movements of the lower limbs can be made properly if a set of biomechanical requirements are met using a pattern of electrical signals sent along the nerves to activate the appropriate set of muscles (Duysensa and Van de Crommert, 1998). Walking was generally considered to be an automatic process not involving higher cognitive resources. Much of the research in the automaticity of gait has been done on experimental animals. Brown (1911) and Brown (1914) demonstrated in the early 1900's that stimulating groups of spinal neuronal networks produced rhythmic motion in the limbs of cats, even if feedback from sensory afferents and high-level brain centers was blocked. Later, this was extended to humans, showing that infants were able to perform step-like movements if stimulated by peripheral stimuli (Patla and Prentice, 1995). Other evidence comes from studies that examined stimulation of spinal structures in patients with spinal cord injury, reporting the generation of rhythmic stepping action in those with low and middle spinal lesion (Dimitrijevic et al., 1998). Thus, basic locomotor pattern is generated by neuronal networks in all vertebral mammal, including humans, which are called as the central pattern generators (CPG) (Grillner and Wallen, 1985). More recent evidences suggest that the CPGs are not located in a single place but consist of networks of neurons in various parts of the brain and spinal cord (Duysensa and Van de Crommert, 1998). Brainstem and sub-cortical supraspinal structures influence CPG activity and locomotion (Takakusaki, 2017). Dedicated neuronal populations in the brainstem carry locomotor instructions, including aspects like initiation, velocity, and termination (Pahapill and Lozano, 2000; Takakusaki, 2013).

However, gait can be considered a goal directed behavior, and as such requires input from high-level cognitive processes which originate from higher cortical center (Takakusaki, 2013). Accordingly, several studies have proposed a model for the neural control of locomotion in vertebrates which integrates cortical, brainstem and spinal inputs (Orlovskiĭ et al., 1999; Takakusaki, 2013). Thus, the cortical regions select and integrate the large amount of sensory inputs from the periphery and incorporate these into the ongoing movement. Locomotion is continuously subject to adjustment when obstacles are encountered, ensuring the smooth progression of the executed movements. In order to cope with unfamiliar environments and situation, subjects require cognitive posture-gait control that depends on cognition of self-body information put together with spatial localization information of objects in the surrounding environment (Takakusaki, 2017). Figure 2.1 reports a schematic representation of locomotor control system. For example, motor cortex and the corticospinal pathway are directly involved in muscle activation during ongoing gait (Petersen et al., 2001). Instead, supplementary motor area is suggested to be involved in internally triggered\self-initiated movement (Takeuchi et al., 2012) and in the initiation of gait via the CPGs'

activation (Nachev et al., 2008; Takakusaki, 2013). Premotor cortex guides adjustments of motor performance based on the sensory information (e.g., visual cues, vestibular information) and in response environmental perturbations (Suzuki et al., 2004; Takakusaki, 2013). In conclusion, these evidences seem to confirm that human and animal quadrupeds locomotion are organized in a similar way: a rhythm-generating system within the spinal cord is controlled by neural input from "higher levels" in the brain and receives feedback from receptors in the muscles, joints and skin of the legs (Duysensa and Van de Crommert, 1998).

Figure 2.1. A schematic representation of locomotor control system. Adapted from Orlovskiĭ (1999).



2.2 Methods of gait analysis

To better understand the complex behavior of locomotion, gait analysis has been introduced as systematic technique to study human walking, using the eyes and the brain of experienced observers, augmented sometimes by the instrumentations for measuring body movements, body mechanics, and the activity of the muscles (Whittle, 1991). Since the later part of the 20th century, quantitative gait analysis has become a useful tool in clinical setting for patients with neurologic and orthopedic conditions, in sports field to improve and optimize athletes' performance, in ergonomics and occupational health to identify posture-related or movement-related problems and in the related research fields to improve our

understanding of gait mechanism. Its application in clinical setting is becoming widespread because it can support clinicians to detailed diagnoses and to plan optimal treatment or surgery intervention (Cimolin and Galli, 2014). Clearly, no single method of analysis is suitable for such a wide range of uses and for all the pathological populations existing. Thus, a number of different methodologies and instrumentations have been developed. In order to allow meaningful evaluation, the measurement tools must demonstrate specific features, such as validity, reliability, and responsiveness to change. Currently, the gold standard in the biomedical field is the computerized multifactorial and integrated 3D analysis of human movement, which provides information concerning both kinematic and kinetic aspects of the movement (Cimolin and Galli, 2014).

The following paragraphs review the main methods and tools to assess walking alterations in clinical field. Firstly, the qualitative methods are presented, including the video, the questionnaire-based scales and the observation-based scales. Secondly, the quantitative methods are outlined, including terminology used to describe gait biomechanics.

2.2.1 Qualitative methods for gait analysis

The management of patients with gait disorders requires identification and understanding of gait deviations. The identification of gait deviations can be performed with different methods according to numerous factors such as level of complexity, the available resources and the desire level of precision. Qualitative gait assessment is the first choice in clinical practice since it allows having an overview of the walking abilities of the patient in a fast manner, without or with minimum equipment. The adopted tools can be divided into the following categories: observational evaluation, observational-based scales and questionnaire-based scales.

The observational evaluation has always been the first step in gait evaluation in clinical setting. This clinical examination can provide information about existing musculoskeletal impairments, and can allow a proper evaluation of the compensatory mechanisms used by the patient to stand upright and walk. Similarly, the observation-based scales aim to evaluate gait pattern of the patient or their walking ability through direct or indirect (i.e., video recorded) observations. The final main result is generally a classification by classifying the patient in a predefined group, or an overall score based on the results. In the observational gait analysis, video recording is an essential tool. The advantages are numerous due to its simplicity and it also allows showing as many times as needed the patient gait and generating still images or slow-motion videos to facilitate interpretation. Second, it can be a support tool to fill observation-based scales.

The timed walking tests are objective assessments with the advantage of providing quickly quantitative measure of walking. Basically, a chronometer is enough to catch a set of parameters and various basic

clinical tests have thus been developed. Gait velocity can be measured through the 10-meter walk test, gait distance covered through the 6-minute walk test and the initiation of walking and change of directions through the Timed Up and Go test. Thus, these tests have high practical value in the clinical setting, requiring a minimum of time and space and providing an objective evaluation of walking. The main drawback of these tests is that they detect only a deviation from normal gait performance, such as a decreased walking speed or walking distance, and its variation over time, without providing direct information about gait patterns and mechanisms underlying gait dysfunctions.

Many questionnaires are available for making a questionnaire-based evaluation. Their focus is to evaluate the patient's capacities when walking or performing a walking-related task. Questionnaires can be self-reported or proxy-reported depending on the cognitive capacities of the patient. Questionnaires can be global, focusing overall on gait, or focal, focusing on a specific gait aspect. Self-report questionnaires sometimes reflect the patients' performance over the course of the day or week in the ecological environment. Although questionnaires, self- or proxy-reported, are the most widespread technique due to their low cost, easiness of use and versatility, but it is noteworthy that such tools suffer from poor reliability and validity, participant recall bias and interpretation of questions (Silfee et al., 2018).

Although clinical test and/or clinical scales are inexpensive, they are prone to evaluator variation, hard to systematize and difficult to compare across multiple measurements.

2.2.2 Quantitative methods in gait analysis

The era of evidence-based medicine promotes nowadays the development and use of instrumentations and methodologies that allow the quantitative assessment of gait. The main goal of quantitative gait analysis is the acquisition of quantitative information about the mechanisms of the musculoskeletal system while executing a motor task. Quantitative gait analysis is becoming a widely used tool during clinical evaluation, allowing to quantify normal and pathological patterns of locomotion and making possible comparison with normative data or between different conditions (e.g., pre versus post rehabilitative treatment).

The development of many kinds of sensors and cutting-edge technologies makes possible the computation of several biomechanical parameters (e.g., kinematics, kinetics, muscular activity, plantar pressure). Typically, data acquired during gait analysis include relative positions and orientations of body segments, patterns of the lower limb joint angles and spatiotemporal parameters. Even if technology is extensively used, since it can find application in supporting the clinical evaluation, fast and reliable clinical tests remain often the first choice. Though both qualitative and quantitative approaches are used, quantitative methods for gait analyses have the advantages of collecting objective and unbiased data. Progress in new technologies has led the development of a series of devices and techniques which allow for objective and

fast evaluation, making measurements more efficient and effective and providing reliable information. For this purpose, different types of devices exist. These technological devices used to study the human gait can be classified according to two different approaches: motion capture systems or non-motion capture system.

Motion capture system

In general, motion capture system (also known as "mocap") is classified into two categories: marker-based techniques and markerless techniques.

Marker-based motion capture: *optoelectronic stereophotogrammetry*

In marker-based techniques, video-based optoelectronic systems are used in order to identify the 3D position in space of a set of cutaneous markers placed on each segment. Stereophotogrammetric methods are used to reconstruct 3D landmark coordinates. In a similar way to how eyes work together to provide 3D binocular vision, the images from two or more 2D cameras are tracked by optical systems and these points are used to reconstruct the original 3D trajectories. These systems, used to track the 3-D position of a set of markers, consist of charged-couple device (CCD) cameras or complementary metal-oxide semiconductor (CMOS). While the markers can be either retroreflective (passive) or light-emitting (active).

Retroreflective passive markers are covered by retroreflective material and they are illuminated at regular time interval by an array of light-emitting diodes (LEDs) mounted coaxially to the lens of each camera. Passive markers reflect the incoming light back into the camera's lens. The 3D coordinates of each marker in a calibrated volume are computed based upon the 2D data from two or more cameras using triangulations techniques. Given that the reflective markers appear as bright dots on a dark background, the thresholds of the cameras can be adjusted in such a way that only bright reflective markers are recognized via image-based methods. Recognition of passive markers in the video frames can be performed either via pattern recognition software (Taylor et al., 1982) or by dedicated hardware circuits (Ferrigno et al., 1990).

Conversely, active markers are powered to emit their own light. They are triggered sequentially at predefined frequencies, so the cameras can detect automatically each marker by virtue of the pulse timing, and marker tracking is easily performed (Davis, 1988; Chiari et al., 2005). Finally, the cameras detect markers correspondence in multiple images and triangulates the relative positions of each point. This methodology allows identifying the marker with higher spatial resolution (often less than 0.1 mm within the calibrated volume). Accuracy of passive marker system is typically around ±0.1% of the calibrated volume (i.e., if the capture volume is around 5 m, this is equivalent to about ±5 mm). Even if the accuracies of passive marker systems are not as good as those for the active marker systems, the absence of wires and batteries on the body of the subject during the analysis is an important advantage (Cappozzo, 1991).

Therefore, passive markers are considered to have minimal effect on the natural walking patterns of the individual.

Although optical motion capture is the gold-standard method (e.g. compared to magnetic or inertial sensor), it has the drawback of marker visibility constrains. This drawback can be partially overcome by using multiple cameras positioned in a task-specific manner. In fact, for the reconstruction of 3D coordinates, each marker must be seen simultaneously by at least two cameras, but in practice more than two are recommended, since markers can be obscured from camera views because of arm swinging, walking aids and subject rotation (Furnée et al., 1997). Six cameras generally provide enough redundancy to successfully track markers on the upper body and both lower limbs simultaneously.

Moreover, other several sources of inaccuracy affected stereophotogrammetry measurements, resulting in an error on marker coordinates can be recognized: instrumental errors, soft tissue artefacts and anatomical landmark misplacement. The instrumental errors derive from both instrumental noise and inaccuracies in the calibration volume. The instrumental noise can be reduced by low pass filtering, while the volume calibration inaccuracies depend on the inadequate number of cameras or/and the volume of calibration algorithm chosen for the specific application (Cappozzo et al., 2005). Nevertheless, the contribution of instrumental errors to the total error is considered to be small, almost negligible (Cappozzo et al., 2005). Soft tissue artefacts result from the use of skin-mounted markers and as a consequence from the relative motion between the markers and the underlying bone (Kadaba et al., 1990). Since this error has the same frequency content as the bone movement, there is no way of distinguishing the artefact from the actual bone movement by using a filter. However, solution to reduce its effect has been proposed (Cappozzo et al., 2005). First of all, marker locations should be chosen so that the relative displacement is minimized. Secondly, mathematical operators can be used to estimate position and orientation of the bone from skin marker positions (Chiari et al., 2005). The third source of error is the anatomical landmark misplacement. The incorrect location of subcutaneous bony anatomical landmark through palpation can derive from three main factors: the anatomical landmarks is not a point but a surface, large and irregular; a soft tissue layer of variable thickness and composition cover the landmark; the identification of the location of the landmark depends on which palpation procedure was used. The aforementioned sources of errors represent the major limitation on accuracy of the marker-based movement analysis.

Markerless motion capture

Another ongoing research area in human motion capture is the development of markerless techniques. The development of markerless motion capture systems originated from the fields of computer vision and machine learning. In the past two decades, the field of registering human body motion using computer vision has grown substantially, and a great variety of vision-based systems have been proposed for tracking

human motion. These systems vary in the number of cameras used (camera configuration), the representation of captured data, types of algorithms, use of various models, and the application to specific body regions and whole body (Mundermann et al., 2006). Traditional markerless optical motion tracking are based on active vision systems, which emit light-information in the visible or infrared light spectrum in the form of laser light, light patterns or modulate light pulses.

Active systems (e.g., laser scanners, structured light patterns) provide accurate 3D measurements, but require a controlled laboratory environment (Mundermann et al., 2006). A greater variety of algorithms has been proposed for estimating human motion (e.g., silhouette-based techniques, statistical models of background and foreground, fuzzy clustering process) and they typically derive features either directly in the single or multiple 2D image planes or, in the case of multiple cameras, utilize a 3D representation for estimating human body kinematics (Bregler et al., 1996; Cheung et al., 2003). These algorithms can be classified into model-based and model-free techniques (Poppe, 2007). The majority of approaches are model-based in which an a priori model with relevant anatomic and kinematic information is tracked or matched to 2D image planes or 3D representations (e.g., stick-figure, cylinders, CAD models). Model-free approaches attempt to capture skeleton features in the absence of an a priori model. Finally, the main advantages of this techniques are the possibility to reconstruct body kinematics without markers or fixtures placed on the body, making markerless system more affordable and flexible than the marker-based one. Eliminating the need for markers greatly expand the applicability of this techniques and reduce also preparation time of the individual, but the accuracy achieved by these methods is still not comparable with the gold standard (i.e., marker based) approaches.

Non-optical motion capture system

Alternatives to optical motion capture systems are non-optical motion capture technologies, in which accuracy is usually sacrificed to reach higher flexibility and usability. In this context, different types of motion sensors and systems are available for various gait analysis applications. Some of these technologies used for gait analysis such as inertial sensor and flexible goniometer, are briefly described in the following section.

Inertial sensors

The using of Inertial Measurement Units (IMU) for body tracking is a relatively new technologies in gait analysis. Single or multiple IMUs are commonly attached to the body segments of the user, through Velcro straps or using specific Lycra suites, for that reason they take also the name of *wearable* sensor. IMUs are generally equipped with accelerometers, gyroscopes, and often magnetometers. These electronic devices,

thus, measure body segment's velocity, acceleration, orientation, and gravitational forces. An accelerometer is a type of inertial sensor that can measure acceleration along its sensitive axis (Tao et al., 2012). Although there are different types of transducers for this purpose (e.g., piezoelectric crystals, piezoresistive sensors), the main theory behind the accelerometers is the spring-mass system. The operation principle of accelerometers is based on the Newton's Laws of Motion (force= mass × acceleration), which say that the acceleration of a body is proportional to the net force acting on the body. If it is known the proportionality quotient (mass of the object), and all the forces (measured with the sensors), it is possible calculate the acceleration. A uniaxial accelerometer records acceleration signal in a single direction, while a triaxial-accelerometer operates on three orthogonal axes and provides the measurements on each axis. By taking the integral of the acceleration, it is possible to obtain the velocity, and by integrating the velocity, the position as refers to the 3 axes is computed. The gyroscope is an angular velocity sensor, consisting of a vibrating element merged with a sensing element. Gyroscope are based on the following property, which implies that all bodies that revolve around an axis develop rotational. This device is thus based on the concept of measuring the Coriolis force, which is an apparent force proportional to the angular rate of rotation in a rotating reference frame (Tao et al., 2012). By detecting the linear motion from the Coriolis force and performing an integration of the gyroscopic signal, the angular rate can be obtained. The gyroscope provides thus angular velocity measurements and the estimation of the joint angles can be derived by the integration of angular velocity. Instead, magnetometer is a device which measures the strength and direction of the magnetic fields. Based on the magnetoresistive effect, these sensors can estimate changes in the orientation of a body segment in relation to the magnetic North or the vertical axis in the gait analysis. Such sensors can provide information that cannot be determined by accelerometers or the integration of gyroscope signals (Tao et al., 2012). In general, magnetometers are combined with accelerometers and gyroscope in biomechanics application to make the definition in the global reference frame possible.

Finally, with 3-axis accelerometers, 3-axis gyroscopes and a magnetometer it is possible to obtain acceleration, angular velocity and orientation of the body segment. In gait analysis application, these devices are commonly attached to the feet or legs or waist of the individual, and the post-processing of the above-mentioned signals (using filtering and classifying algorithms) allows the extraction of spatiotemporal parameters of gait and lower limb joint angles (López-Nava and Munoz-Melendez, 2016).

Inertial-based solutions are becoming the second most popular motion capture technology, after optical systems, because they allow to collect motion data in ecological environment free from range limitations thanks to characteristics, such as small size, cost-effective, portability, and relatively easy-to-use. The main

drawbacks of this approach are related to noise and drift phenomenon, which can affect the accuracy of the measures.

Electromechanical system

To overcome the drawbacks of optical system, electromechanical system can be a valid alternative. This kind of system is classified as well as wearable device and allow real-time, relatively low-cost, free-of-occlusion assessment and with unlimited capture volume. The most employed electromechanical devices are the electrogoniometers. This electronic device that uses sensors, such as potentiometers and strain gauges, measure the angle between two adjacent body segments. These angle sensors are placed in correspondence of the joint of interested. For example, the potentiometers are attached to a joint's rotation point and the variation in the potentiometer's electrical resistance can be used to determine the angle between the body segments. The strain-gauge based electrogoniometer, also known as flexible electrogoniometers, consists of flexible spring (strain gauge) with plastic end blocks on each end. The strain-gauge changes its electrical resistance proportionally to the change in angle between the plastic end blocks' longitudinal axes.

The main drawbacks of the electromechanical system are low-accuracy of the measure due to the presence of soft tissue artefact and restriction of the user's movements. An example of integration of multiple electromechanical devices is the exoskeleton, which can directly provide measurements of various joint angles and relative body motion through rods connected by potentiometers.

Magnetic system

Magnetic motion capture systems utilize sensors placed on the body to measure a low-frequency magnetic field generated by a transmitter source (formed by three orthogonal coils). The sensors measure the strength of the field which is proportional to the distance of each coil from the field emitter assembly. Both sensors and source are connected to a processor that calculates position and orientation of each sensor based on its measured field values. Magnetic systems are not affected by line of sight problems because the human body is transparent for the used magnetic fields. However, the shortcomings of magnetic tracking systems are directly related to the physical characteristics of magnetic fields, magnetic fields decrease in intensity rapidly as the distance from the transmitter source increases and so the measure can be affected by (ferro) magnetic materials in the work volume.

2.3 Terminology and Parameters used in gait analysis

2.3.1 Spatiotemporal parameters

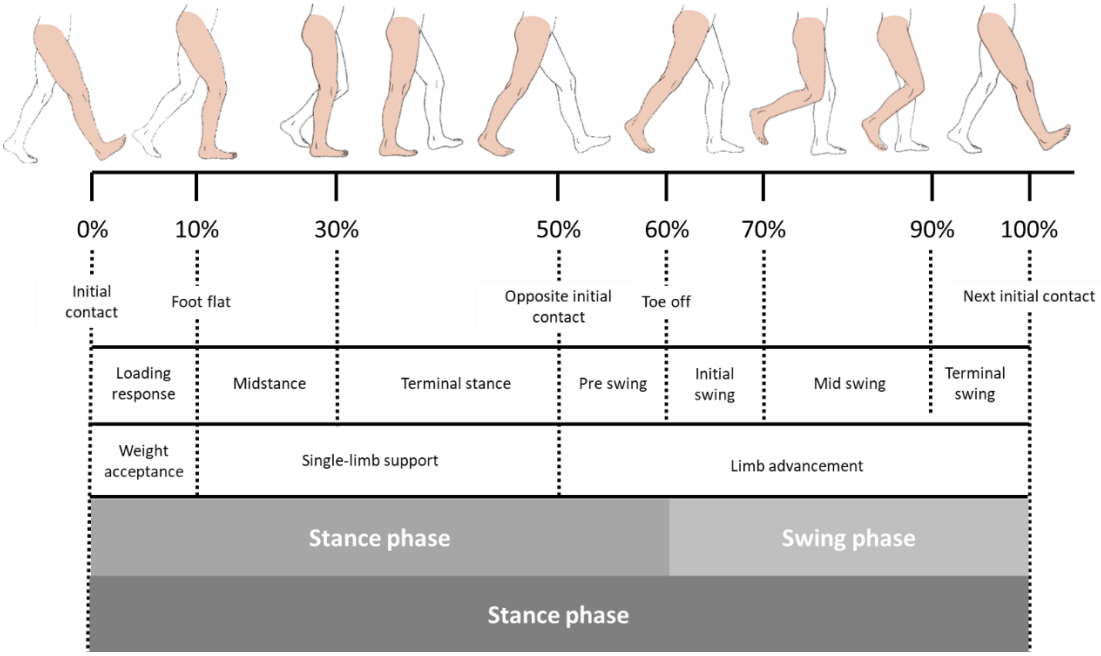
The parameters used in gait analysis can be classified as: spatiotemporal parameters and kinematic parameters. Spatiotemporal parameters are easiest to understand and, with respect to the other, more applicable in clinical practice. The following pages report terminology and definitions of the most common parameters used in gait analysis.

The *gait cycle* is defined as the time between two consecutive occurrences of one of the repetitive events of walking. Although any event could be chosen to define the gait cycle, it is generally adopted the instant at which the foot contacts the ground (or initial contact). For example, if it is decided to start with the initial contact of the right foot, then the cycle will end when the right foot contacts the ground again. The left foot goes through the same series of events as the right, but displaced in time by half cycle. The gait cycle can be divided into two main phases, which are generally estimated during normal pace walking as *stance phase* (60% of the gait cycle), when foot is in contact with the ground, and *swing phase* (40% of the gait cycle), when the foot is moving forward not in contact with the ground. The stance phase lasts from the initial contact to the toe off, and it is subdivided into: loading response, mid-stance, terminal stance and pre-swing. Instead, the swing phase lasts from the toe off to the next initial contact, and it is subdivided into: initial swing, mid-swing and terminal swing. The stance phase can be also subdivided into: the double support phase (20% of the cycle) during which both feet are in contact with the ground and the single support phase that corresponds to the swing phase of the contralateral limb. In each gait cycle, there are thus two periods of double support and two periods of single support. The two periods of double support can be termed *initial* (in which weight is being transferred from contralateral to ipsilateral limb) and *terminal* (in which weight is being transferred from ipsilateral to contralateral limb). The duration of a complete gait cycle is known as the *cycle time* (or *stride time*).

The spatial parameters are used to describe the placement of the feet on the ground during walking. The *stride length* is the distance between two successive placements of the same foot. It consists of two *step lengths*, left and right, each of which is the distance from the heel of the trailing limb to the heel of the leading one. The *walking base* (also known as the *stride width* or *base of support*) is the side-to-side distance between the two feet, usually measured as distance between midpoints of the back of the heel or between the centers of the ankle joint. Other two parameters, commonly used in gait analysis, are *cadence* and *speed* of walking. The number of steps taken in a given time is called the cadence, and the usual unit is step per minute. Instead, the speed of walking is the distance covered in a given time. It is measured in meters per seconds. It is important to consider that spatiotemporal parameters are a global expression of gait function and can be directly influenced by several factors (e.g., the subject's sex and age, the measurement method

used, the instructions given to the subject). Figure 2.2 reports a description of the gait cycle considering events of the right limb.

Figure 2.2. Terminology to describe the events of the gait cycle. Adapted from Kirtley (2006).



2.3.2 Kinematic parameters

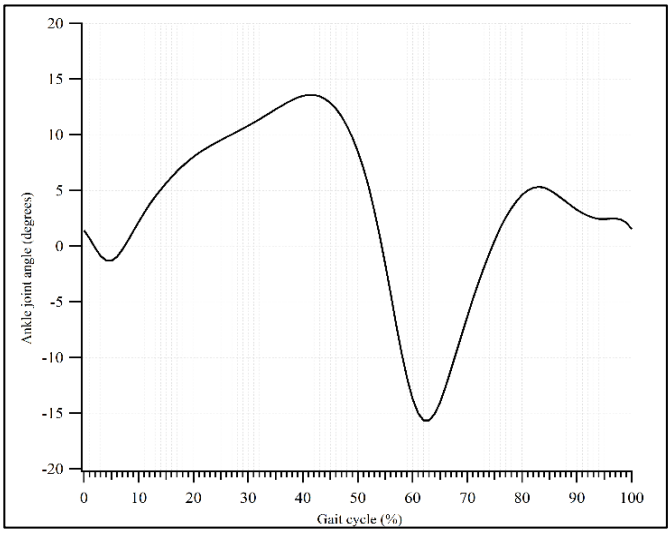
Kinematics is the study of bodies in motion without considering the forces (internal and external forces) that cause the body movement. Thus, the terms *kinematics* means a description of the gait in terms of the angles, positions (displacements), velocities and acceleration of the body segments and joints. The joint angle patterns describe how the angle between two adjacent segments in a specific plane changes across the gait cycle. The three common planes used in the description of the gait kinematics are the sagittal plane (flexion-extension movements), the frontal plane (adduction-abduction movements) and the transversal plane (internal-external rotations). However, the most meaningful variations of lower limb joint kinematics are commonly referred to the sagittal plane. The following lines provide a description of joint kinematics on the sagittal plane for hip, knee and ankle during normal gait.

Ankle angle

The ankle angle on the sagittal is defined as the relative angle between the long axis of the shank and the long axis of the foot (Figure 2.3). The main role of the ankle during the stance phase is guarantee the wheel-like rolling motion under the foot, described in literature also as the *three rockers* (Perry and Burnfield, 2010). The function of the three rockers is the progression of the leg over the support foot. At the initial

contact with the ground, the ankle is in neutral position (first rocker) in order to facilitate the progression of the limb (Kirtley, 2006). After this short period (around 5% of the gait cycle) the ankle starts the plantarflexion. During the mid-stance, the shank advances and the ankle angle moves from plantarflexion to 15 degrees of dorsiflexion, thus the foot is in contact with the ground in foot-flat posture. This period is called the *second rocker*. The last rocker (*third rocker*) occurs during the second double-support phase and corresponds to the heel rise. In this phase only the forefoot is in contact with the ground. The ankle moves from dorsiflexion to around 15-20 degrees of plantarflexion in order to maintain the propulsion of the body during the gait. During the swing phase, the ankle angle moves from plantarflexion to dorsiflexion in order to guarantee the correct foot clearance. Finally, the movements of the ankle on the sagittal plane allows the accommodation of the foot to the ground, provides shock absorption during the first phase of the stance and also has a pivotal role in the propulsion of the body during the second double support. The dynamic range of motion of the ankle joint, defined as the difference between the maximum and minimum excursion of the ankle angle during the gait cycle, is around 35 degrees for a normal gait.

Figure 2.3. Sagittal ankle angle during the gait cycle. Positive value indicates dorsiflexion, while negative value indicates plantarflexion.

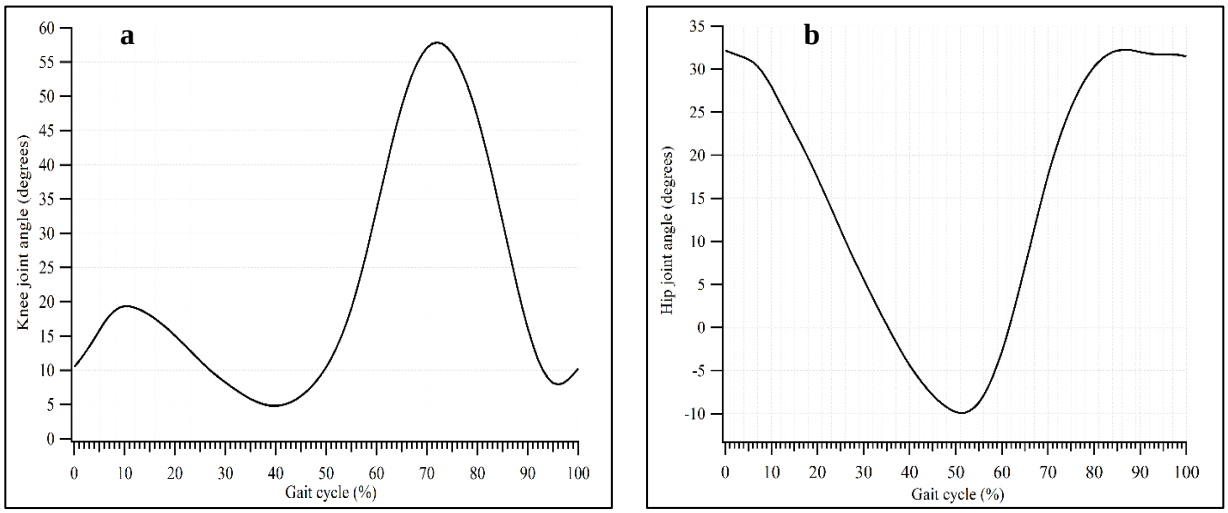


Knee angle

The knee angle on the sagittal plane concerns the relative angle between the long axis of thigh and the long axis of shank (Figure 2.4-a). The knee has several functions during the gait, including limb stability during the stance phase, supporting the body weight, deceleration and flexibility to allow limb movement during the swing phase (Witthle, 1991). At the initial contact the knee is in full extension, but suddenly moves to a flexed position (around 15 degrees of flexion) during the loading response phase in order to absorb the shock of the weight transfer onto the limb and to guarantee stability. During the second double-support

there is an increase of the knee flexion due to the movement in plantarflexion of the ankle. This is a passive movement that prepares the limb to the swing phase. During the first period of the swing phase, the knee is in flexion (around 60 degrees) to allow the correct foot clearance and to allow the limb advancement. While at end of the swing phase, there is a passive extension of the knee to prepare the limb for the initial contact with the ground. In conclusion, the knee angle plays a key role to maintain stability and to allow the shock absorption. The dynamic range of motion of the knee during the gait cycle is around 60 degrees for a normal gait.

Figure 2.4. Sagittal knee angle (a) and sagittal hip angle (b) during the gait cycle. Positive value indicates flexion, while negative value indicates extension.



Hip angle

The hip angle on the sagittal plane is defined as the relative angle between the long axis of the thigh and a perpendicular axis to the pelvic plane (Figure 2.4-b). The hip joint starts in a flexed position (around 35 degrees) to allow a forward progression. During the mid-stance phase, the hip moves from a flexion position to an extension position (around 10 degrees). This angle variation of the hip guarantees the stabilization of the limb during the weight acceptance phase and to maintain the correct position of the pelvis and trunk. During the double-support phase the hip moves from an extension motion to a flexion motion to allow the body advancement. The hip reaches the maximum flexion during the mid-swing phase (around 35 degrees). To conclude, the hip movement on the sagittal plane allows the forward progression of the limb and maintains the pelvis and trunk position. The dynamic range of motion of the hip is around 40 degrees for normal gait.

2.4 Factors that influence joint kinematics

Analysis of kinematic variations during normal gait has received considerable attention over the last years, and studies have shown that factors such as walking speed (Lelas et al., 2003; Fukuchi et al., 2019), age (Öberg et al., 1993; Ko et al., 2011) and gender (Callisaya et al., 2010; Bruening et al., 2015) can influence kinematics of gait. The identification of kinematic deviations in clinical is highly dependent with the characteristics of the normative database used. In particular, a mismatch between patient characteristics and an asymptomatic population database in terms of walking speed, demographic and anthropometric parameters may lead to misinterpretation during the clinical assessment. Some demographic and anthropometric parameters are easily controlled during enrollment and randomization, while it is not the same for factors like walking speed. When comparing the results of gait analysis from patients, with those from healthy individuals, or the results from different trials conditions such as single- and dual-task, it is essential to understand the effects of walking speed on biomechanical variables of interest. The next paragraph reports a brief description of the influence of gait speed on kinematic gait patterns in order to introduce some key concepts, supporting the experimental findings of this thesis.

2.4.1 The influence of gait speed on gait kinematic parameters

It is accepted that gait parameters follow a consistent pattern of change in response to varying gait speed. In this regard, several studies shown that spatiotemporal parameters of gait exhibited characteristic and predictable relationship with gait speed (Kirtley et al., 1985; Öberg et al., 1994), while there are varying conclusions on the existence of the relationship between kinematic gait parameters and gait speed (Lelas et al., 2003; Fukuchi et al., 2019).

As aforementioned, the knee kinematic curve shows two extension peaks during walking, one immediately before the heel-strike and one about at two thirds of the stance phase. Neither extension peak varied significantly with velocity (Kirtley et al., 1985). Instead, knee flexion angle in stance has a significant positive correlation with gait speed (Lelas et al. 2003; Fukuchi et al., 2019). It has been suggested that the increase of the peak knee flexion with walking speed during loading response could be due to the need for greater shock absorption at higher gait speed (Fukuchi et al., 2019). The flexion of the knee during the swing phase appears to have a fairly straightforward relationship with gait speed even if, according to some authors, the change in knee flexion with walking speed is not very great (Lelas et al., 2003; Hanlon et al., 2006), whereas according to Fukuchi et al. (2019) the peak knee flexion in swing phase increased with walking speed. In healthy control contraction of the hamstrings allow maintaining the knee flexion at low walking speed during swing phase, whereas at higher speeds most of the knee flexion is accomplished passively (Oberg et al., 1994; Lelas et al., 2003). The ankle joint plays an important role in changing gait speed, and it has been suggested that plantarflexion is a strong predictor of step length and gait speed (Kwon

et al, 2005). The plantarflexion of the ankle joints has a positive correlation with gait speed (Fukuchi et al., 2019). This increase is related to the need of greater power generation at higher speeds to move the body forward. In young adults, the effects of gait speed on the flexion and extension peak of hip joint angles have also been reported (Lelas et al., 2003; Hanlon et al., 2006; Fukuchi et al., 2019). Specifically, both hip extension in the pre-swing phase and of hip flexion in the late swing phase has a positive correlation with gait speed (Hanlon et al., 2006; Fukuchi et al., 2019).

As shown previously, walking speeds itself affects biomechanical gait variables and thus several methods were proposed to isolating the effect of pathology, aging or different task conditions from the gait speed when comparing kinematic gait patterns. To overcome this challenge of gait variation, a solution is to employ prediction methods for estimating joint kinematics of normative gait data at any given speed. The general approach of these methods is to collect experimental data at different gait speeds (i.e., slow, normal and fast) or allowing participants to walk at their self-selected speeds in order to cover a wide speed range. Then, adjust regression models to the gait data versus speed to determine prediction equations with speed as the predictor variable. The most adopted approach considers minimum and maximum values of joint kinematic curve, and there are two methods in literature to predict these values at a given speed. In one method, referred as *peak methods*, regression equations are adjusted directly to only the experimental minimum and maximum values of gait data versus speed. In the second method, referred as *cycle method*, regression equations are adjusted to the entire gait cycle versus speed (e.g., an equation at every 10% of the gait cycle for a given joint kinematic curve), and then the minimum and maximum values of this predicted gait cycle can be found. Although the *cycle method* might be more advantageous because it can predict data for the entire cycle, it might be less accurate than the *peak method* when the interest is only for the minimum and maximum values of the joint kinematic curve. Recently, Fukuchi et al. (2019) tested these two prediction methods and they found that overall the values predicted by the *peak* and *cycle* method agreed with the experimental one. The prediction methods proposed in literature to account the effect of gait speed on the lower limb angular kinematics are reported in Table 2.1, Table 2.2 and Table 2.3. In general, the peak sagittal plane kinematic parameters have moderately predictive relationship with gait speed (Lelas et al., 2003). Lelas et al. (2003) and Fukuchi et al. (2019) found a moderately predictive quadratic correlation between peak knee flexion during loading response and gait speed ($R^2 = 0.600$, $R^2 = 0.532$). Moreover, these authors found also moderately predictive quadratic correlation for the peak knee flexion during swing phase (Lelas et al., 2003; Fukuchi et al., 2019). Kirtley et al. (1985) reported similar correlation coefficients of $R^2 = 0.600$ and $R^2 = 0.430$ for the peak knee flexion in stance and swing phase, respectively, while they were obtained using a predicting linear relationship. Instead, the relationship between gait speed and peak hip flexion and extension were found poor, as well as for the plantarflexion and dorsiflexion peak of the ankle joint angle (Lelas et al., 2003; Hanlon et al., 2006; Fukuchi et al., 2019). Finally, these previous

results showed that speed affects the kinematic gait patterns in healthy adults. Overall prediction methods, especially for knee joint values, are valid alternative to overcome this challenge of the kinematic variations with gait speed.

Table 2.1. Regression equations to the experimental peak flexion values of the knee joint angle at stance and swing phase as function of gait speed (m/s), considering only studies where a peak prediction method was employed and healthy individuals (range age between 19 and 60) were enrolled.

Peak knee flexion stance phase							
Author (year)	**Sample size**	**Surface conditions**	**Instruments**	**Gait speed range**	**Trendline type**	**Regression equations**	**R^2**
Kirtley et al. (1985)	10	Overground	3D gait analysis	-	Linear correlation	$4.7 + 13.0\ v$	0.600
Oberg et al. (1994)	60	Overground	2 photocells and electrogoniometers	0.91 m/s – 1.54 m/s	Linear correlation	$1.2 + 13.5\ v$	-
Lelas et al. (2003)	64	Overground	3D gait analysis	0.45 m/s – 2.73 m/s	Quadratic correlation	$-2.84\ v^2 + 19.59\ v - 4.00$	0.600
Hanlon et al. (2006)	17	Overground	3D gait analysis	0.93 m/s – 2.11 m/s	Linear correlation	-	0.210
Fukuchi et al. (2019)	24	Treadmill	3D gait analysis	8 different gait speeds	Quadratic correlation	$-17.27\ v^2 + 50.96\ v - 2.24$	0.532
Peak knee flexion swing phase							
Kirtley et al. (1985)	10	Overground	3D gait analysis	-	Linear correlation	$49.6 + 8.6\ v$	0.430
Oberg et al. (1994)	60	Overground	2 photocells and electrogoniometers	0.91 m/s – 1.54 m/s	Linear correlation	$56.5 + 6.8\ v$	-
Lelas et al. (2003)	64	Overground	3D gait analysis	0.45 m/s – 2.73 m/s	Quadratic correlation	$-3.19\ v^2 + 14.92\ v - 44.08$	0.437
Hanlon et al. (2006)	17	Overground	3D gait analysis	0.93 m/s – 2.11 m/s	Linear correlation	-	0.030
Fukuchi et al. (2019)	24	Treadmill	3D gait analysis	8 different gait speeds	Quadratic correlation	$-64.02\ v^2 + 73.88\ v + 43.73$	0.504

Table 2.2. Regression equations to the experimental minimum and maximum values of the ankle joint angle as function of gait speed (m/s), considering only studies where a peak prediction method was employed and healthy individuals (range age between 19 and 60) were enrolled.

Peak ankle plantarflexion							
Author (year)	**Sample size**	**Surface conditions**	**Instruments**	**Gait speed range**	**Trendline type**	**Regression equations**	**R^2**
Lelas et al. (2003)	64	Overground	3D gait analysis	0.45 m/s – 2.73 m/s	Linear correlation	$3.78\ v + 12.88$	0.087
Hanlon et al. (2006)	17	Overground	3D gait analysis	0.93 m/s – 2.11 m/s	Linear correlation	-	0.040
Fukuchi et al. (2019)	24	Treadmill	3D gait analysis	8 different gait speeds	Quadratic correlation	$-59.36\ v^2 + 75.64\ v + 7.07$	0.324
Peak ankle dorsiflexion mid-stance							
Lelas et al. (2003)	64	Overground	3D gait analysis	0.45 m/s – 2.73 m/s	Linear correlation	$-2.4\ v + 13.62$	0.105
Hanlon et al. (2006)	17	Overground	3D gait analysis	0.93 m/s – 2.11 m/s	Linear correlation	-	0.090
Fukuchi et al. (2019)	24	Treadmill	3D gait analysis	8 different gait speeds	Quadratic correlation	$-3.22\ v^2 – 3.30\ v + 15.08$	0.070

Table 2.3. Regression equations to the experimental minimum and maximum values of the hip joint angle as function of gait speed (m/s), considering only studies where a peak prediction method was employed and healthy individuals (range age between 19 and 60) were enrolled.

Peak hip flexion							
Author (year)	**Sample size**	**Surface conditions**	**Instruments**	**Gait speed range**	**Trendline type**	**Regression equations**	**R^2**
Lelas et al. (2003)	64	Overground	3D gait analysis	0.45 m/s – 2.73 m/s	Linear correlation	$7.38\ v + 23.81$	0.240
Hanlon et al. (2006)	17	Overground	3D gait analysis	0.93 m/s – 2.11 m/s	Linear correlation	-	0.240
Fukuchi et al. (2019)	24	Treadmill	3D gait analysis	8 different gait speeds	Quadratic correlation	$8.72\ v^2 + 11.66\ v + 26.87$	0.187
Peak hip extension							
Lelas et al. (2004)	64	Overground	3D gait analysis	0.45 m/s – 2.73 m/s	Linear correlation	$5.11\ v + 3.82$	0.136
Hanlon et al. (2006)	17	Overground	3D gait analysis	0.93 m/s – 2.11 m/s	Linear correlation	-	0.190
Fukuchi et al. (2019)	24	Treadmill	3D gait analysis	8 different gait speeds	Quadratic correlation	$14.11\ v^2 - 28.19\ v + 1.19$	0.134

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Chapter 3

Gait, cognition and dual-task paradigm

In day-to-day activities, purposeful locomotion requires the ability to adapt motor strategy to own individual goals and environment's burdens, and commonly involves the performance of several concurrent cognitive tasks. Gait is no longer considered to be an automatic task, as the role of cognitive function is increasingly acknowledged. In particular, two cognitive domains are recognized to be involved in gait performance: executive function and attention.

At the moment, people's ability to cope with different and concurrent activities, such as walking and talking, or walking while phone's texting, is a topic of increased interest for both healthy individuals and people affected by neurological diseases. The most common instrument adopted to investigate the mutual effect of cognitive and motor tasks (cognitive-motor interference) is the dual-task paradigm. Generally speaking, the term dual-task has been defined as "*the concurrent performance of two tasks that can be performed independently, measured separately and have distinct goals*" (McIsaac et al., 2015). This chapter, thus, provides an overview of theoretical models of dual-task interference, task prioritization strategies, factors that influenced dual-task performance and the relative brain area involved.

3.1 Theoretical models of dual-task interference

Before explaining the experimental findings, it is necessary to begin by considering a few theoretical ideas and concepts that have been widely applied in trying to understand *motor-cognitive interference* phenomenon. The three common theoretical frameworks utilized to explain interference between tasks are the *serial bottleneck model*, the *capacity sharing model* and the *cross-talk model*. The first one refers to the idea that certain critical mental operations are carried out sequentially. When this limitation applies, the interference arises because certain tasks demand simultaneous access to a processor (or processors) that can only complete one task at a time (Pashler, 1994). During the time that one task is occupying the bottleneck process, there is a postponement of the processing of one task on the other one (Pashler and Johnston, 1989). In contrast, the capacity sharing model assumes that individual has a finite attentional capacity (Wickens, 1980) and that both cognitive and motor tasks require a certain amount of attentional resources to be completed successfully. It is supposed that multiple tasks can proceed in parallel, because fewer resources are available to each task under these conditions, and therefore the tasks proceed at a reduced rate (Tombu and Jolicoeur, 2005). If the combined attentional requirements of the tasks are greater than the capacity reserve, there is a decline in one or both tasks. The last model, the cross-talk, assumes that interference might be dependent not on what sort of operation is carried out but on the content of the information actually being processed (e.g., what sensory inputs are present, that thoughts the person is having). The *serial bottleneck, capacity-sharing* and the *cross-talk* models provide very different pictures of our mental machinery; the capacity model assumes that task can be processed simultaneously, whereas bottleneck model assume that some processes can be handled strictly serially and the *cross-talk* model assumes that performing simultaneously similar tasks reduce dual-task interference, because the adoption of the same pathway increases the processing efficiency and less attentional resources are recruited (Pashler, 1994).

3.2 Task prioritization models

Previous studies suggest that when there is a competition between two tasks, one of which involves postural control, the maintenance of stability is the priority (Shumway-Cook et al., 1997; Bloem et al., 2001). Thus, the hypothesis of *posture first* strategy is implicitly applied to guarantee safety when healthy adults walk while performing a secondary cognitive task (Geurts et al., 1991; Lajoie et al., 1993; Shumway-Cook et al., 1997). In contrast to the appropriate prioritization of gait in healthy adults, *secondary posture* strategy seems to be adopted in those with neurological disease (Bloem et al., 2006). However, recent evidences raise the concern that the allocation of attention during the performance of concurrent tasks is

complex and depending on many factors including the nature of both cognitive and motor tasks, the goal of the individual, and the instructions (Shumway-Cook et al., 1997; Plummer and Eskes, 2015). Thus, we cannot make a generalization from the evidences of literature. In fact, even healthy young adults may not always prioritize gait over the cognitive task (Hausdorff et al., 2005; Yogev-Seligmann et al., 2010). As shown in previous studies, healthy adults reduced their gait speed and also increase gait variability, when they completed a cognitive task while walking (Priest et al., 2008; Al-Yahya et al., 2011). The conceptual framework proposed by Yogev-Seligmann et al. (2012) suggesting that two putative constructs may drive task prioritization and dual-task performance costs in paradigms that involve motor and cognitive tasks (Yogev-Seligmann et al., 2012). The model of *task prioritization* suggests that when a competition for attentional resources occurred, the individuals self-select their strategy based on cognitive and motor aspects including functional reserve, compensatory capabilities, and other factors related to individual and personal features (Yogev-Seligmann et al. 2012). The most relevant motor properties involved in the strategy adopted during walking dual-task is the *postural reserve*, defined as the individual's capabilities to respond most effectively to a postural threat (Yogev-Seligmann et al. 2012). In response to a challenging dual-task conditions sensorimotor integration, adaptive adjustments, anticipatory mechanisms, and other higher-level cortical control features enable postural control (Shumway-Cook et al., 1997). Healthy adults have a greater postural reserve, therefore they can successful cope with challenging motor situations, even in presence of limited amounts of attentional resources, as when performing cognitive-motor dual-task (Plummer and Eskes, 2015). In contrast, deteriorations of sensory and motor systems and impairment in high cortical functions, commonly present in neurological patients, cause alteration in motor and balance performances and as consequence also a decrease in postural reserve (Kelly et al., 2012; Leone et al., 2015; Woollacott and Shumway-Cook, 2002). Following this model, during cognitive-motor dual-task healthy young adults with intact postural reserve are focused on the cognitive one as long as the postural request is relatively low. A second key factor is the cognitive status of the individual, defined by Lezak (2001) as the awareness of one toward himself (physically and psychologically) and toward the situations. This aspect takes into account estimation of the potential environmental hazards and self-limitations (e.g. restrictions and impairments resulting from disease state and low postural reserve). According to Yogev-Seligmann et al. (2012), this cognitive aspect (or *hazard estimation*), is conceived as an aspect of executive functions that is concerned with planning, risk estimation and judgment.

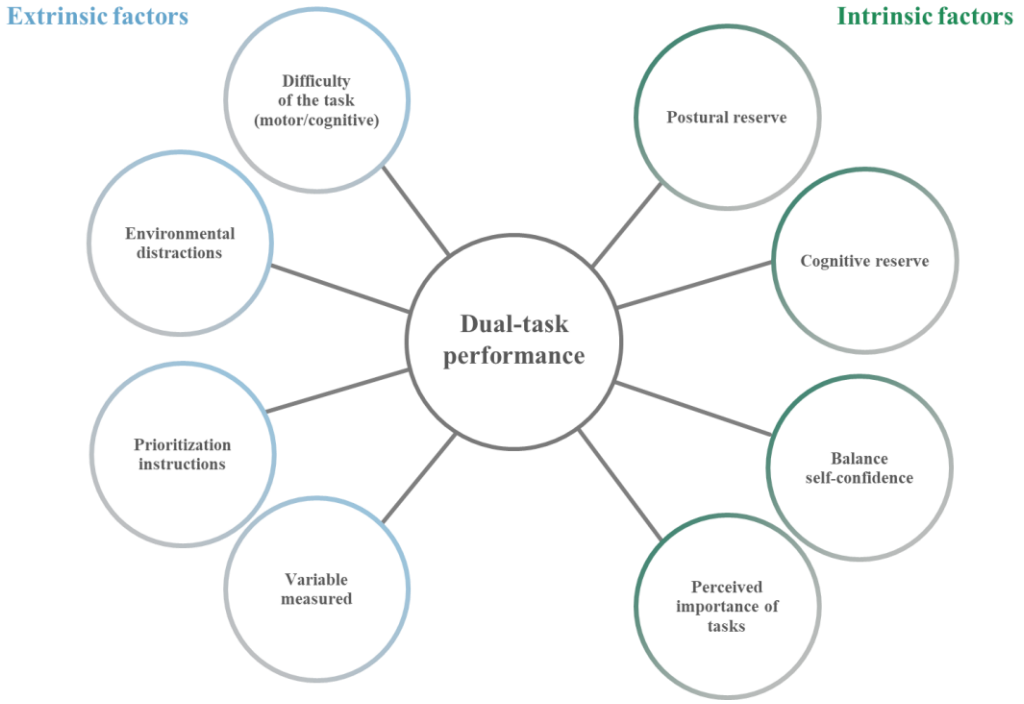
3.2.1 Factors influencing dual-task performance

The frameworks and models presented above help researchers better understand dual-task performance. There are several factors that influence the magnitude and pattern of cognitive-motor interference and these need to be considered when implementing and interpreting dual-task assessments (Figure 3.1). As discussed

previously, when processing capacity is insufficient for task demands, the allocation of attentional resources is generally influenced by subject-related factors and/or by task-related factors (Tombu and Jolicoeur, 2003; Yogev-Seligmann et al., 2012). Task factors (or *extrinsic factors*) include the nature and difficulty of the tasks (cognitive, motor), the presence of the environmental distractions or hazards that may distract the subject's attention (closed or open environment), the instructions given to the subject and the variable measured. Subject-related factors (or *intrinsic factors*) include motor impairments, cognitive reserve, lesion location, balance self-confidence, and perceived importance of each task.

Specifically, for neurological patients, Kelly et al. (2012) identified three reasons that link closely to the theoretical causes of dual-task interference, in order to explain how task interaction plays in creating deterioration in performance for patients. First, pathologies may affect the capacity available for attention to task. In multiple sclerosis (MS) patients, for example, the number and extent of cortical lesions and brain atrophy have been linked to cognitive impairments, including decreased information processing speed and attentional deficits (Honce, 2013; Coghe et al., 2018). Second, pathologies may affect executive functions. This association has been suggested in Parkinson's disease (PD) patients, where changes in the connections between prefrontal cortex and basal ganglia are present in a majority of them and have been linked to problems with executive functions (Dubois and Pillon, 1996). Finally, single-task performance requires greater attention following neurological injury, so that combining tasks creates significant functional compromise. For example, in a person with MS who has difficulty walking due to a recent exacerbation, the walking requires increased physical and mental effort to control the limbs and ensure that balance is maintained. The addition of a secondary task may be more difficult to accomplish for these people with neurological disease than a healthy peer because the cognitive effort that must be given to walking limits resources available for other activities. As shown in previous studies, the presence of motor impairments and, thus the adoption of slow gait speed, is correlated with higher dual-task costs of gait parameters (Plummer-D'Amato et al., 2012). In conclusion, all of these factors have the potential to influence how one patient will select the allocation of attention in the absence of sufficient processing capacity.

Figure 3.1. Schematic representation of intrinsic (green) and extrinsic (blue) factors influencing dual-task performance.

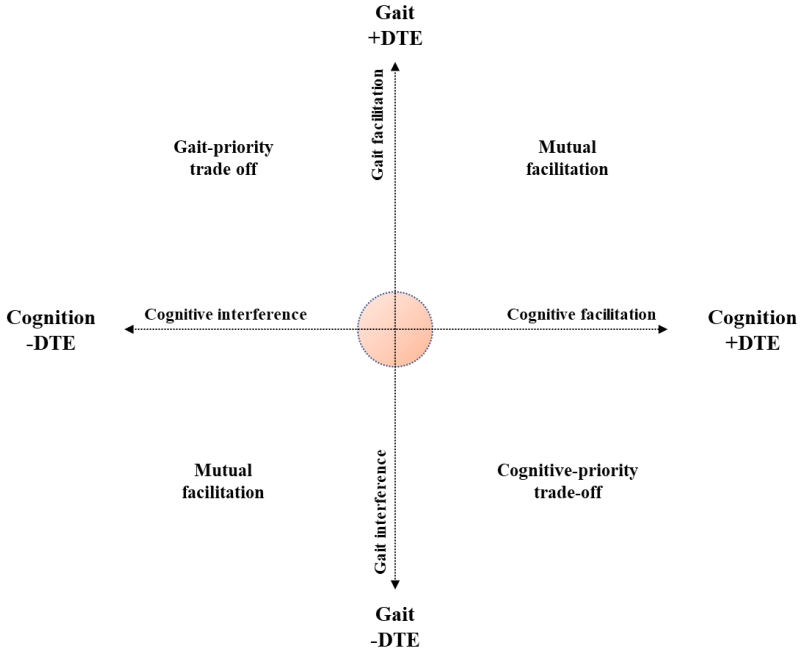


3.3 Measuring dual-task performance

As mentioned in the previous paragraph, it is generally accepted that in the central nervous system the ability to process information is limited (Marois and Ivanoff, 2005). This limitation in availability of central resource influences the ability to prepare and perform multiple tasks. These limitations seem to increase in people affected by neurological diseases. The characterization of dual-task performance is based on the measurement of the interference of one task due to the concurrent performance of a second task resulting in a pattern of performance deterioration of one or both tasks. A possible meaningful outcome, proposed to describe the mutual interaction between cognitive and motor tasks, is the measurement of the interference (Plummer et al., 2013). The measurement of the interference, that one task creates over another, allows understanding cognitive information processing during dual-task activities. Table 3.1 summarizes the four main measurement approaches used in dual-task literature. The first measure is based on the reaction time for a primary task of interest measured alone (baseline) and with a secondary task added to interrupt the information processing of the primary task. The delay in performance has been termed as psychological refractory period (PRP) and represents the sequential processing of information due to interference (Welford et al., 1952; McIsaac et al., 2015). The most common approach is based on measure

the performance of each task in isolation (e.g., walking alone and cognitive task alone) and, then, measure the performance of each task while performed concurrently. The change in performance on the primary task from baseline to dual-task performance is considered the cost of doing a second task simultaneously (Baddeley et al., 1986). Calculating dual-task effect, it is possible to visualize the processing leading to interference using performance operating characteristic plots, as shown in Figure 3.2 (Plummer and Eskes, 2015).

Figure 3.2. Illustration of conceptual model for characterizing patterns of cognitive-motor dual-task interference. Adapted from Plummer and Eskes (2015).



These plots represent how two processes, or tasks, interact and indicate either if one task is prioritized over another, indicating a between task trade-off, or a better performance of both tasks, indicating mutual facilitation. The Attention Allocation Index (AAI) is another measurement proposed by Siu and Woollacott (2007). It can quantify the attentional focus placed on one task over another in response to an instruction or condition indicating a within task trade-off. During dual-task performance participants are focused on one of the two tasks, either explicitly instructed or constrained by task conditions, the AAI reveals the amount of attention shifted toward or away from the focus task due to the occurrence of interference from the secondary task. A perfect focus on the primary task results in a value of 1 and a complete shift away from the primary task is a value of −1. Since the interaction of two tasks does not always result in a decay of the

performance, a more suitable measurement might be the *effect* due to dual-task. Dual-task effect (DTE) is a bidirectional measure, taking into account the result in cost or benefit of dual-task performance (Kelly et al., 2010). A positive multiplier is used for variables where the relationship is positive. For example, when trying to improve impaired gait an increase in speed represents an improved performance. The same calculation can be performed for measures where a decrease in value represents improved performance. Thus, a negative multiplier is used to indicate the negative relationship. Double support phase would be an example of a variable with a negative relationship; the less is the duration of double support phase the better the performance. Finally, by convention, negative DTE values indicate that performance deteriorated in the dual-task condition compared to the single-task (dual-task cost, DTC), whereas positive DTE values indicate a relative improvement in dual-task performance (dual-task benefit).

Table 3.1. Three common measures commonly used in the dual-task literature to quantify differences in task performance when two tasks are executed simultaneously.

Authors (year)	Parameter	Formula	Description
Welford (1952)	Psychological Refractory Period (PRP)	$PRP = T(DT) - T(ST)$ T(DT): mean response time to answer at the X task during dual-task execution T(ST): mean response time to answer at the X task during single task execution	The delay (beyond the normal reaction time) in responding to a second stimulus which closely follows the presentation of another simultaneous stimulus.
Plummer and Eskes (2015)	Performance-resource operating characteristic	Graphic displays dual-task effect of the performance of each individual task when performed in conjunction with a second task $DTE = \frac{(Dual\ task - Single\ task)}{Single\ task} \cdot 100$	*Between task trade-off or mutual facilitation* It is plot in which the distribution of attention for the two tasks is shown; the influence of one task on another is visualized.
Siu and Woollacott (2007)	Attention Allocation Index (AAI)	$AAI = \frac{(P - S)}{N}$ P: prioritized task S: secondary task N: task of interest when priorities are equal	*Within task trade-off* 1 indicates total allocation of attention to the prioritized task, while −1 indicates a complete shift away from the prioritized task.
Kelly et al. (2010)	Dual-task effect (DTE)	$DTE = \frac{(Dual\ task - Single\ task)}{Single\ task} \cdot 100$	A decrement is represented by a (−) result and an improvement by a (+) result.

3.4 Cognitive task classification

Cognitive tasks are classified according to their demands and the mental processes required to execute them. Al-Yahya and colleagues (2011) identified the following five general domains, where each one is different from every other one at behavioral and/or cognitive level:

- Reaction time tasks: refer to a task that involves the measure of the elapsed time between a stimulus (e.g. sensory, visual stimulus) and a behavioral response. This kind of cognitive task has been usually used to measure processing speed where a slowed processing could be related to an attentional deficit (Lezak et al., 2004).
- Mental tracking tasks: refer to a task that require keeping an information in the mind while performing a mental process (Lezak et al., 2004). This kind of task has been usually used to examine sustained attention and information processing speed.
- Discrimination and decision-making tasks: refer to task that require selective attention to a specific stimulus and respond accordingly. This kind of task has been usually used to evaluate attention and response inhibition, such as the Stroop Color and Word Test (Stroop, 1935; MacLeod, 1991).
- Working memory tasks: refer to a task that require only keeping an information in the mind (Baddeley, 1986). The difference between working memory task and mental tracking task is that the first one requires holding information only, while the second one requires holding information plus manipulation belong to the mental tracking category (Barde and Thompson-Schill, 2002).
- Verbal fluency tasks: refer to a task that requires word production either spontaneously or under pre-specified search conditions. This kind of task has been recently used to examine semantic and executive functions (Lezak et al., 2004).

3.4.1 Discrimination and decision-making task: Stroop Color and Word Test

The Stroop Color and Word Test is a neuropsychological test widely adopted in clinical practice and research field to assess the ability to inhibit cognitive interference that occurs when the processing of a specific stimulus feature obstructs the simultaneous processing of a second stimulus attribute, also well-known as the Stroop Effect (Stroop, 1935). The most common version required that individuals read three different tables as fast as possible. The test consists of three tables, two of them are defines as the *congruous condition*, in which participants are required to read the names of colors printed in black ink (W) and name different color patches (C). By contrast, in the third table, named color-word (CW) condition, color-words are printed in an inconsistent color ink, for instance the word “red” is printed in green ink. In this last condition, participants name the color of the ink instead of reading the word. Thus, participants are required to cope with a less automated task (i.e., naming ink color) while inhibiting the interference arising from a

more automated task (i.e., reading the word). The inhibition of the more automated task process is named the Stroop effect (Stroop, 1935). The Stroop Color and Word Test is extensively used to measure the ability to inhibit cognitive interference, as well as to assess other related cognitive functions such as attention, processing speed and cognitive flexibility. Given that the Stroop interference effect is robust and consistent involving different cognitive domains, the present study will adopt it as cognitive test to pair with walking during dual-task condition.

3.5 Pattern of brain activity during walking dual-task

A large body of the literature is focused on the identification of the neural circuits that are engaged during walking dual-task performance. Based on the principle of neural overlap (capacity sharing and bottleneck model), dual-task interference should occur when the cognitive and motor tasks engage the same neural circuits (Li et al., 2018). In this respect, several neuroimaging studies have been carried out to identify patterns of brain activity during single- and dual-task walking. The most employed neuroimaging technique is the functional near-infrared spectroscopy (fNIRS), which allowed measuring in real time a robust signal from cerebral hemodynamic while participants are actively engaged in movements under unrestricted conditions, such as walking under single- and dual-task conditions.

Given that executive functions and attentional resources play a key role during walking (Yogev-Seligmann et al., 2008), numerous studies investigated the neural substrates involved in specific aspects such as walking alone and dual-task coordination (Holtzer et al., 2011; Hamacher et al., 2015). These findings revealed that the networks linked to dual-task executive functions cover anterior and posterior cerebral areas and are not only localized to the frontal cortex (Collette et al., 2005; Hamacher et al., 2015; Stuart et al., 2019). Several studies outlined that prefrontal cortex (PFC) activity was elevated during walking dual-task in healthy individuals (Mirelman et al., 2014; Lu et al., 2015), while abnormal patterns of activation were observed in neurological patients (Hernandez et al., 2016; Doi et al., 2013; Chaparro et al., 2017) compared to walking alone. However, more recent evidences have supported that in addition to the PFC, premotor cortices (PMC) and supplementary motor area (SMA), or also defined as premotor areas, play an important role in executive functioning (Harding et al., 2015; Ptak et al., 2017), cortical control of walking (Koenraadt et al., 2014) and guidance of the movement (Saleh et al., 2018) during walking dual-task performance.

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Chapter 4

Dual-task performance in the context of multiple sclerosis management

In activities of daily living, successful walking performance depends on the ability to divide attention between motor and cognitive tasks. As mentioned in the previous chapter, people with neurological disorders are particularly susceptible to dual-task interference, which can also significantly impact recovery of functional walking. In this chapter background notions relevant for understanding the context of this research are provided. The first section gives an overview of the typical motor deficit in MS patients and the clinical instruments commonly used to evaluate gait. The second section outlines a synopsis of the literature pertaining to dual-task gait in MS patients and the available techniques to improve motor functions.

4.1 Multiple sclerosis: epidemiology, causes and predisposing factors

Multiple Sclerosis (MS) is a chronic, neurological and progressive disease of the Central Nervous System (CNS). It is characterized by inflammation, demyelination and axonal degeneration, leading to cumulative and heterogeneous disability during the course of the disease. MS is mainly diagnosed in the young adults during their most productive years and it affects twice as many women as it does men (Compston and Coles, 2008). Disease etiology is still unknown; however, interaction between genes and the environment is involved in its pathogenesis (Dendrou et al., 2015; Leray et al., 2016). The disease is more prevalent in temperate zones than in tropical areas, and it is predominant in population residing at high latitude (i.e., North Europe, North America). In this context, Sardinia is an exception and represents a high-risk area for MS (Cocco et al., 2011; Monti et al., 2016). The pathology course appears rather unpredictable and, four MS subtypes are recognized: relapsing-remitting (RR), secondary progressive (SP), progressive relapsing (PR) and primary progressive (PP). Accordingly, the first three subtypes are initially characterized by a pattern of relapses and remission over the time, with the appearance of new symptoms or the worsening of previously present symptoms; whereas, the PPMS is characterized by a gradual but continual worsening over the time (Shevil and Finlayson, 2010). Through the disease process, MS patients may report a panel of motor, cognitive and behavioral symptoms. Globally, MS symptoms are defined disabling and affect many activities of daily living, compromising independence of the person and the overall quality of life (Cattaneo et al., 2017). Among the wide spectrum of MS symptoms, the most common is walking impairment, which has been reported in up to 90% of people with MS (Bethoux et al., 2011). Other reported symptoms in MS include: fatigue, defined as feeling of exhaustion with physical, cognitive and psychosocial dimension; slowed reaction time; visual problems; muscle dysfunctions, such as muscle weakness and spasticity (Kister et al., 2013).

4.1.1 Ambulation deficits in patients with multiple sclerosis

Although a wide range of factors can contribute to gait dysfunction in people with MS, sensory changes and resulting balance deficit, lower extremity weakness or spasticity, and cerebellar ataxia are thought to mainly contribute to gait abnormalities observed in MS. Definition, related symptoms and signs of the factors that contributed to walking dysfunction, are shown in Table 4.1. Several studies have reported that people with MS, also in early stage of the disease, present gait abnormalities including decreased step length, decreased cadence, reduced joint motion, and more variability of most gait parameters compared with healthy controls (Martin et al., 2006; LaRocca, 2011). These abnormalities result in a reduced walking endurance, an increased metabolic cost of walking, and reduced community mobility (LaRocca et al., 2011). Furthermore, people with MS reduce their walking speed and increase the variability of their gait when they walk while performing a cognitive task more than healthy controls,

suggesting that they need to devote greater cognitive reserve to ensure dynamic stability during walking than do unaffected individuals.

Table 4.1. Description of common impairments related to gait and balance dysfunctions in MS patients.

Impairment	Definition	Signs and symptoms
Muscle weakness	Deconditioning of muscles results from lack of use or damage to the nerve fibers that stimulate the muscles	Dropped foot, loss of balance, limited mobility of the affected leg
Spasticity	Motor disorder marked by a velocity-dependent increase in muscle tone or tonic stretch reflexes associated with hypertonia	Stiff and heavy muscles, spasm, difficulty in moving the leg, pain
Cerebellar ataxia	Impaired coordination of voluntary muscle movement caused by cerebellar lesions	Tremor, incoordination, dysmetria, loss of balance, unsteady gait
Sensory deficit	Sensory loss occurs due to a dysfunctional sensation process, whether it be ineffective receptors, nerve damage, or cerebral impairment	Absent or reduced sensitivity to cutaneous stimuli, paresthesia, loss of balance, numbness

4.2 Evaluation of gait dysfunction in MS

Gait dysfunction in people with MS can be evaluated using standardized clinician-assessed rating scales (ordinal measures), performance tests (usually continuous measures), self-report questionnaires (usually ordinal measures), observational gait analysis or 3D gait analysis. The ideal method for the evaluation depends on the examiner's expertise, the time, the equipment available, and the goals of the assessment. In the following session, the most common clinical measures for the evaluation of gait alterations in MS patients are briefly described, while advantages and disadvantages are reported in Table 4.2.

Rating scale

Kurtzkee Expanded Disability State Scale (EDSS) is the most common rating scale to evaluate level of disability in MS patients (Kurtzke et al., 1983). The EDSS is a disease-specific instrument that has become the gold-standard for characterizing disability levels and determining disability progression in patients with MS. A numerical score from 0 to 10 is generated, but each step on the ordinal scale does not reflect an equal change in disability. The assessment of walking is based on maximum distance walked up to 500 m and the use of an assistive device. However, wide variability was observed in maximum distance walked within each EDSS level, with patients with high level of disability that often walking the same maximum distance as those with low level of disability (Bethoux et al., 2011). Two studies evaluated the properties of this tool, and suggested that EDSS may be less optimal, generally demonstrating low sensitivity, poor reliability, and, most important, suboptimal responsiveness to

change (Sharrack et al., 1999; Hobart et al., 2000). In summary, EDSS is only marginally useful instrument for assessing walking performance in those with MS.

Hauser Ambulation Index (AI) is another scale, consisting of a single-item, ordinal scale that was developed specifically for MS patients (Hauser et al., 1983). The AI scale is a 10-point scale (0-9), with 0 representing no impairment (fully active) and 9 representing confinement to a wheelchair. Scoring of AI is dependent on the need for an assistive mobility device and on the ability and time need to walk 25 feet.

The Dynamic Gait Index (DGI) is another clinical scale consisting of 8-item assessment tool. The final score depending on the rater's observation of the degree of limitation during a patient's performance of specific tasks (Shumway-Cook and Woollacott, 1995). Although this instrument was originally designed to evaluate the likelihood of falling in older adults, it provides an overall assessment of ambulation also for MS patients, thanks to the items of walking, stair climbing and balance.

Timed walking tests

Timed walking tests are objective assessments which are integral part of MS clinical evaluation. The inherent advantage is to provide a quantitative measure of walking performance. Although these tests are not disease-specific, they have demonstrated good reliability and reproducibility in patients with MS (Nilsagard et al., 2007). Among the timed tests, the timed 10-meter walk and the 6-minute walk test are the most widely employed and has been also validated in MS. Although the timed 25-foot walk was not developed as a disease-specific instrument for MS, it correlates with the EDSS across disability severity and MS subtypes (Kalkers et al., 2000). Instead, the 6-minute walk test records the maximum distance travelled by the patients in 6 minutes. The 6-minute walking test is considered a reliable measure of walking endurance. This test, as well as the 25-foot walk test, correlated strongly with overall measures of disability, including the EDSS and with a patient-reported measure of walking, such as the 12-item Multiple Sclerosis walking scale (MSWS-12) (Goldaman et al., 2007). An alternative is the 2-minute walk test. This shorter version of the test, with a greater feasibility and reduced patient burden, has been previously validate in patients with MS (van den Berg et al., 2006).

Patient-reported outcomes

The MSWS-12 was designed as a disease-specific, patient-based tool in clinical trials and clinical practice, to capture the complex impact of MS on walking abilities (Hobart et al., 2003). It consists of 12 questions with Likert-type responses and has a recall period of two weeks. Many studies investigated the properties of the MSWS-12, demonstrating high reliability and validity, and good generalizability (Motl et al., 2007). It has also shown to be strong correlated with the EDSS and with several objective measures of mobility (i.e., number of step count performed in a given time period, gait speed) (Hobart et al., 2003; Motl et al., 2008). One of the most relevant attributes is its responsiveness to change (Hobart et al., 2003).

Observational gait analysis

Observational gait analysis is the clinical tool most commonly used to assess gait quality. As mentioned in the *Chapter 1*, it involves observing a person walk and analyzing their gait pattern in terms of kinematic and spatiotemporal parameters. This analysis can be conducted during a routine clinic visit or during standardized clinical test of gait such as the timed 10-meter walk test, or under walking conditions that best match the patient's complaints. Given that particular impairments such as weakness or spasticity, lack of coordination, or sensory loss cause identifiable alteration of the gait pattern, observational gait analysis can be used to determine the mechanisms underlying gait dysfunction and thus help with the selection of the best treatment to reduce walking dysfunction.

Table 4.2. Methods of gait evaluation in MS: advantages and disadvantages.

Measure	Advantages	Disadvantages
Standardized clinical measures	EDSS: directly related to neurological examination AI: simple and quick DGI: assessment of various tasks involving gait	Required a skilled examiner Limited precision and responsiveness Do not identify mechanism underlying gait dysfunction
Timed measures	Simple and readily quantified Required limited training Normative data has been published	Do not identify mechanism underlying gait dysfunction
Patient-based measures	Document the patient's perspective Require little time to complete	Do not identify mechanism underlying gait dysfunction Recall bias
Observational gait analysis	Identify mechanism underlying gait dysfunction Require little time and equipment	Limited validity, reliability and precision Required skilled examiner
3D gait analysis	Identify mechanism underlying gait dysfunction Provide precise estimation of kinematic and spatiotemporal data	Required expensive equipment Long patient preparation Skilled examiner

Note. EDSS: Expanded Disability State Scale; **AI:** Ambulation Index; **DGI:** Dynamic Gait Index.

3D gait analysis

To overcome the subjective nature of the aforementioned evaluations, objective methods which use advanced technologies and sensors have been introduced in the in the clinical evaluation process of the MS patients. In this regard, 3D gait analysis using motion capture systems can provide accuracy, repeatability and reproducibility of the measurements and a better insight into the neuromechanical factors leading to alter gait in patients with MS (see *Chapter 2 – Paragraph 2.2.2* for further explanations on motion capture technique). A growing number of studies have been using this technique not only to characterized gait abnormalities and underlying mechanisms of walking disability, but also

to better target preventive and rehabilitation strategies (Pau et al., 2014; Lizama et al., 2016). Since 3D gait analysis allow detecting minimum changes in gait kinematics, the measures of gait can be also used as biomarkers of disease progression or to test the effectiveness of intervention (pharmacological and non-pharmacological).

4.3 Impact of multiple sclerosis in walking dual-task

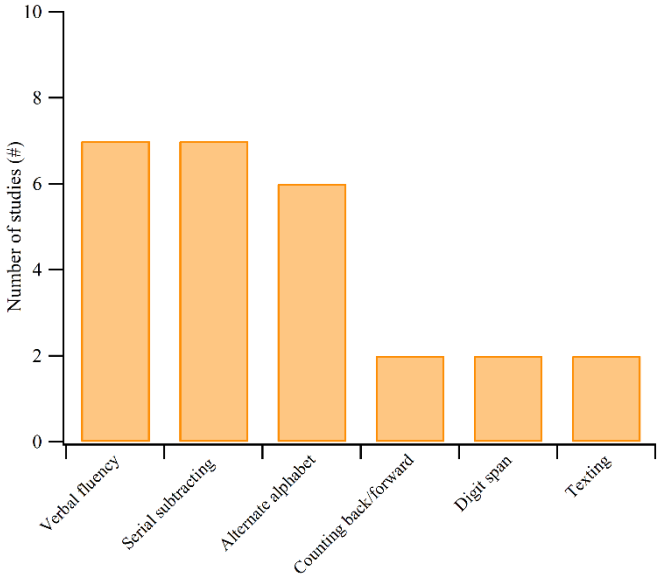
This section will provide a synopsis of the literature pertaining to walking dual-task in those with MS. The relevance of dual-task walking to everyday activities is widely acknowledged, and literature has demonstrated that gait dysfunctions are exacerbated due to the presence of *cognitive-motor interference*. When assessing the influence of a secondary cognitive task on walking in patients with neurological disorders, it is important to consider individual characteristics (*intrinsic factors)* such as, physical and cognitive constrains, age and other symptoms, as well as task-related factors and the complexity of both walking and cognitive tasks. It is generally accepted that functional walking required an involvement of higher-order cognitive functions for its correct execution (Whitman et al., 2001; Rosano et al., 2008), and people with MS need to a more cognitive and voluntary control during walking as a consequence of the presence of damage at the CNS (Cattaneo and Jonsdottir, 2012). This increase of cognitive control requires adequate levels of attention, memory, and problem-solving skills (Cattaneo and Jonsdottir, 2012). Biomechanical constrains and sensory-motor deficits, in addition to the presence of cognitive deficits in the areas of information-processing speed and executive functions (Chiaravalloti and DeLuca, 2008), have been identified as an influence factors in dual-task performance for MS patients (Benedict and Zivadinov, 2011; Sosnoff et al., 2014). Overall, this framework leads a reduction of *postural reserve*, provoking greater demands for attention to the task's performance.

The main observation across walking dual-task studies is the presence of great motor interference, quantified principally in term of gait speed reduction (Hamilton et al., 2009; Kalron et al., 2010; Nogueira et al., 2013; Wajda et al., 2013; Learmonth et al., 2014). In a few other studies, it was also measured by using spatiotemporal parameters such as stride length (Sosnoff et al., 2011; Motl et al., 2014), double support time as percentage of the gait cycle (Kalron et al., 2010; Sosnoff et al., 2011; Wadja et al., 2013; Nogueira et al., 2013; Pau et al., 2018; Coghe et al., 2018), and cadence (Wadja et al., 2013; Motl et al., 2014; Learmonth et al., 2014). The percentage decline in gait speed during dual-task performance was estimated by Wajda and Sosnoff (2015) between around 6% and 27%. This reduction in gait speed had been attributed to the presence of deficits in sensory-motor functions and attention. According to Wajda and Sosnoff (2015), in walking single-task the presence of sensory-motor dysfunctions lead to a shift of great amount of the attention resources to the control of the motor tasks, but during dual-task performance the amount of attention resources devoted to the motor control is necessarily reduces, resulting at the end in worsening of the motor performance.

Even if walking dual-task performance has been widely explored in MS literature, the role of disability level during dual-task performance is not clearly defined, mixed results have been found about the relationship between dual-task cost and disability level. Sosnoff and colleagues (2011) reported a greater dual-task cost in patients with moderate and severe disability, which might be caused either to a higher prevalence of cognitive dysfunction with the progression of the disease or to the increased of walking impairments, requiring the availability of more cognitive resources (Sosnoff et al., 2011; Leone et al., 2015). Learmonth et al. (2017) in their meta-analysis performed an explanatory analysis based on studies that considered MS patients with mild and moderate disability. The final results reported that the dual-task cost decrease in those with less neurologic disability (Learmonth et al., 2017). However, the presence of dual-task cost also in Clinically Isolated Syndrome (CIS) and MS patients with relative low disability suggests that is still not clear if (and how) the physical status can explain the cognitive-motor interference phenomenon (Kalron et al., 2010; Allali et al., 2014).

As of today, there is not a methodology recommendation about the cognitive task that should be employed to identify cognitive-motor interference. A large variety of cognitive tasks (e.g. Alternate Alphabet task, Digit Span task, Counting Backward, Phonemic or Semantic Verbal Fluency tests) addressing specific cognitive domains were used to evaluate motor-cognitive interference across the studies (Figure 4.1).

Figure 4.1. The bar chart reported the number of studies presented in MS dual-task literature per cognitive domains



The recent review of Learmonth et al. (2017) indicates that the effect of cognitive-motor interference on motor performance significantly differs between MS and healthy individuals when decision-making tasks were adopted. Even if the verbal fluency tasks resulted in a significant deterioration in motor performance compared to mental tracking tasks, neither of them resulted in a significant difference

between MS patients and healthy individuals (Learmonth et al., 2017). Additionally, only few works took into account the effect of walking on the cognitive performance (Hamilton et al., 2009; Allali et al., 2014; Downer et al., 2016; Mofateh et al., 2017). Mixed results are reported by Hamilton et al. (2009), Allali et al. (2014), Downer et al (2016), and Mofateh et al. (2017). The first author revealed a deterioration in cognitive performance only when cognitive task difficulty was elevated (Hamilton et al., 2009), whereas the second and third authors did not find any alterations in cognitive performance during dual-task (Allali et al., 2014; Mofateh et al., 2017). Instead, Downer et al. (2016) showed recently that walking impaired mental tracking performance among people with MS but not controls. The works of Allali et al. (2014) and Mofateh et al. (2017) considered minimally disabled MS patients and their findings may reflect successful adaptation of a motor strategy that preserved cognitive performance.

In a recent meta-analysis, Leone et al. (2015) generalized that the findings across the walking dual-task studies should support the capacity-sharing model. As explained in the *Chapter 2*, this model sustains that the simultaneous performance of two attention-demanding tasks decreased if central capacity limits are exceeded. At the same time, the presence of cognitive and motor deficits in people with MS could lead a greater limitation in the central capacity and, as a consequence, they would be easily overloaded during walking while performing a secondary cognitive task (Leone et al., 2015). Thus, both walking and cognitive performance are strictly connected to dual-task cost of walking in people with MS (Sosnoff et al., 2014). This implied that the dual-task cost could be reduced with an improvement of either mobility or cognition.

4.4 Interventions for gait dysfunction

In the last decades, great improvements have been done in terms of disease-modifying treatments, which are able to reduce the number of the relapses and slow down the progression of the disease. However, interventions to ameliorate MS related symptoms remains a significant clinical goal. Various pharmacologic and non-pharmacologic interventions have been proposed to ameliorate gait dysfunction in people with MS. Theoretically, these interventions address the specific impairments underlying the gait dysfunction, and are generally chosen based on the result of the clinical neurologic examination and gait analysis. Among the pharmacological treatment, the most adopted are oral medications (i.e., Baclofen, tizanidine, and benzodiazepines) and intrathecal and intramuscular medications (i.e., intrathecal baclofen, intramuscular botulinum toxin) for the treatment of spasticity (Cameron and Wagner, 2011). This treatment has generally shown their effectiveness in the reduction of pain, but there is still a lack of evidences of their efficacy in restoring totally or partially the compromised motor function (Cameron and Wagner, 2011). Instead, several experimental studies have reported positive results of physical intervention, such as passive or active exercises, in improving various aspect of mobility and balance in those with MS (Cattaneo et al., 2007; Sandroff et al., 2014). Regarding exercise programs, including aerobics, flexibility, strengthening exercise, and yoga, there

are significant evidences reporting beneficial effect on both disease symptoms and general fitness in MS patients with mild and moderate disability, as well as with positive effect on quality of life (Snook and Motl, 2009). A relative new tendency in the management of walking impairment is the adoption of multimodal approach model that should provide stronger and long-lasting gain in the maximization of the target range of motor functions. In fact, there is also emerging support that a combination of different modalities, rather than the individual components, may produce additive or synergistic effects on brain plasticity phenomenon. Multimodal interventions are thus designed to engage concurrently different components, such as physical, sensory, and cognitive, or to combine standard interventional protocol with technologies (i.e., functional electrical stimulation, non-invasive brain stimulation) which are able to work as a priming and/or boosting (Bisht et al., 2017; Jonsdottir et al., 2018).

4.4.1 Non-invasive brain stimulation techniques

As mentioned in the previous paragraph, the purpose of any kind of rehabilitation is to ameliorate clinical symptoms by modulating neuronal activity, inducing long-lasting effects over the time (Leocani et al., 2019). Recently for achieving this aims, non-invasive brain stimulation (NIBS) techniques, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial electrical stimulation (TES), have been proposed as valid tools to treat symptoms related to neurological conditions, mainly for the potential synergy with neurorehabilitation and as add-on treatment for the common neurological symptoms, from fatigue to cognitive deficits (Kobayashi and Pascual-Leone, 2003; Woods et al., 2016). Both rTMS and TES involve the application of electric fields capable of modulating the dynamics of cortical networks (Priori et al., 2009). rTMS consists in the application of brief magnetic pulses that easily cross the skull and induce electrical potentials in the brain, inducing depolarization of a neuron population and trigger action potentials (Fitzgerald and Daskalakis, 2013). Whereas, TES is a term that refers to different techniques based on the application of weak currents by means of a pair of electrodes placed on the scalp, with one or both over the target area (Paulus, 2011). In contrast to rTMS, TES induces small subthreshold current flows unable to trigger neuron action potentials; their effects on brain function are mainly based on a polarizing effect on the resting membrane potential, provoking a reduction or increase of spontaneous neuronal firing rates depending on the polarity of stimulation (Peterchev et al., 2012).

4.4.2 Neuromodulation in MS

The most common form of TES techniques is transcranial direct current stimulation (tDCS), mainly because it is a non-invasive, ease of use, low cost and portable option for a wide range of clinical application (Brunoni et al., 2012). tDCS involves the application of a constant low amplitude electric current (ranged from 1.0 mA to 2.5 mA) through scalp electrodes (Woods et al., 2016). During standard tDCS, with a pair of pad electrodes, direction of the current flow differentially modulates the resting membrane potential in both cortical and sub-cortical brain areas (Nitsche and Paulus, 2000), with anodal

tDCS leading to neuron's depolarization, increasing the probability of action potentials occurring, whereas cathodal stimulation leading to neuron's hyperpolarization, decreasing the probability of action potential occurring. tDCS can also modulate blood flow (Zengh et al., 2011), neuronal synapsis strength, triggering plasticity process (Polania et al., 2011). Although its mechanisms to improve behavioral functions are not fully understood, this technique has been suggested as an add-on therapeutic method in MS rehabilitation addressed to manage pain, fatigue and cognitive symptoms. Even if several studies had investigated the effect of tDCS on boosting motor rehabilitation outcomes in various neurological diseases, none of them had addressed the question to individuals affected by MS. Table 4.3 summarizes the most relevant experimental applications of tDCS to treat the most relevant MS symptoms.

Table 4.3. Application of tDCS for the management of the most relevant MS symptoms.

Author (year)	Patients	Protocol Design	Stimulation/ Target	Number of sessions	Training	Results	Follow-up
Fatigue							
Ferrucci et al. (2014)	22 RRMS	Sham controlled/ cross-over	Anodal tDCS/ Bilateral M1	5 daily sessions	-	Significant fatigue reduction after real treatment	Up to 3 weeks
Saiote et al. (2014)	25 RRMS	Sham controlled/ cross-over	Anodal tDCS/ left DLPFC	5 daily sessions	-	No significant changes	No effects at 30 days
Tecchio et al. (2014)	10 RRMS	Sham controlled/ cross-over	Bilateral whole body	5 daily sessions	-	Significant fatigue reduction after real treatment	Up to 2 months
Chalah et al. (2017)	10 MS	Sham controlled/ cross-over	Left vs. Right DLPFC	5 daily sessions	-	Significant fatigue reduction only after real treatment Left DLPFC	-
Charvet et al. (2018)	27 MS	Sham controlled	Anodal tDCS/ left DLPFC	5 daily sessions	-	Significant fatigue reduction after real treatment	-
Cognitive functions							
Mattioli et al. (2016)	21 RRMS	Sham controlled	Anodal tDCS/ left DLPFC	10 sessions	Cognitive training	Improvement in attention and executive function after real treatment	Up to 6 months
Charvet et al. (2018)	45 MS	Open label study	Anodal tDCS/ left DLPFC	10 sessions	Adaptive cognitive training	Improvement in complex attention and response variability after real treatment	-
Pain							
Mori et al. (2010)	19 RRMS	Sham controlled	Anodal tDCS/ Motor cortex	5 daily sessions	-	Pain improvement after real treatment	Up to 3 weeks
Berra et al. (2019)	33 MS	Sham controlled	Anodal tDCS/ Spinal cord	10 sessions	-	Pain improvement after real treatment	Up to 1 month
Spasticity/Motor impairment							
Iodice et al. (2015)	20 RRMS	Sham controlled	Anodal tDCS/ M1	5 consecutive days	-	No differences between active and sham	-
Oveisgharan et al. (2019)	13 MS	Sham controlled	Anodal tDCS/ M1	7 sessions	-	Significant increase in walking speed after real treatment	-

Note. M1: Primary Motor Cortex; **DLPFC:** Dorsolateral Prefrontal Cortex.

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Chapter 5

General methods: from the intervention paradigms to the quantitative assessment

The focus of this chapter is to describe the assessment procedure for single- and dual-task walking conditions. In particular, the task procedure and the technologies used for the acquisition of the trials are presented in detail. Then, the biomechanical model and the data processing procedures are described. Moreover, the movement features and the kinematic parameters are summarize in order to provide an overview of the measures used to characterize first the impact of dual-task activities on walking biomechanics in healthy individuals and in presence of neurological disease, and then to investigate the effect of a relative new treatment aimed to improve both single- and dual-task performance in those affected by neurological disease.

5.1 Participants

In this thesis, individuals affected by multiple sclerosis (MS) and healthy age- and gender-matched volunteers were recruited for cross-sectional studies. Before each study, experimental procedures were outlined to the participants, and each participant gave written informed consent in accordance with Helsinki's Declaration.

For the studies in which transcranial electric stimulation were adopted (*Chapter 7*, *Chapter 8*), medical contra-indication were identified according previously recommendations (Fregni et al., 2005; Lefaucheur et al., 2017) and included: pregnancy, history of cardiovascular disease, chronic migraines and headaches, history of neurosurgical procedures, epilepsy, hearing or vision issues, history of psychiatric disorders and surgically implanted metal in the head or neck. All brain stimulation experiments were preceded by a 60 seconds tolerability test in order to establish the current intensity for the intervention.

Groups' characteristics, study design as well as clinical assessment tools used to assess gait impairments will be extensively described in the following chapters.

5.2 Experimental design: dual-task gait assessment

In the studies that explored the cognitive-motor interference (*Chapter 5*, *Chapter 6* and *Chapter 8*), participants were tested under two conditions: they were first requested to walk along 10-meter walkway at self-selected speed (single task condition); then, to perform a second trial during which they had to complete a secondary cognitive task the Stroop Color Word Test while walking (dual-task condition). The setup, used to administer the Stroop Color Word Test, consisted of a 48" LCD TV screen located perpendicularly to the gait direction. During dual-task performance, participants completed the incongruent color words test. In the incongruent condition participants had to name the word's font color and to inhibit reading the word (e.g., the word ''red" presented in blue font color). Each dual-task trial differed in the sequences of the color words. The time interval between two consecutive words occurrences was varied to avoid rhythm. The words (46–96 cm in width and 15–19 cm in height) were displayed at a distance in the range of 200–750 cm between the participant and the screen.

5.2.1 3D gait analysis

Gait analysis has been implemented using a marker-based motion capture system for the evaluation of single- and dual-task walking performance. The following paragraphs will explain in detailed features of the biomechanical models, instrumentation and data processing.

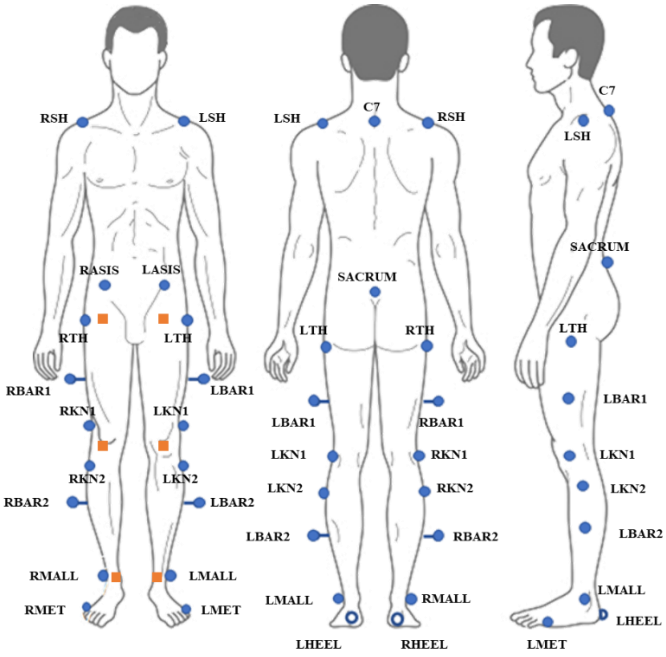
5.2.2 Model and marker position

In order to define angular variations of the lower limb joints, it is required to define the position and orientation of each bony segment during the gait cycle. First step is thus the choice of an appropriate biomechanical models, which define the hierarchy of the bony segments, their anthropometry and the type and number of degrees of freedom of the joints linking them (Moissenet and Armand, 2015). In the following sections, 3D gait analysis procedure will refer to Davis' biomechanical model (Davis et al., 1991), which is the most used in clinical setting. According to this model, the segments are defined as rigid body where are not taken into account the deformations due to the different type of structures composing these segments (i.e., muscles, ligaments). Each bony segment is defined through the position of at least three markers, representing a proximal and distal point of the segment and a third non-collinear marker to allow rotational orientation. The segments are assumed to be linked by joints with three rotational degrees of freedom. According to Davis' model (1991) the human body is defined by eight rigid segments (trunk, pelvis, left and right thigh, left and right shank, left and right foot), which are defined from the position of 22 retro-reflective markers (14 mm diameter) placed with medical adhesive tape on superficial body landmarks (Figure 5.1). During data collection, individuals are asked to wear minimal clothing (i.e., bathing suit or underwear) so that the reflective markers can be placed directly to the skin in specific anatomical locations. The position of body landmarks is defined in correspondence of superficial bony landmarks in order to reduce soft tissue artefacts and allow greater test retest placement of the markers.

The trunk and pelvis positions were estimated by placing markers respectively on: the acromion (RSH and LSH) and seventh cervical vertebra (C7) (trunk segment); the pelvic anterior superior iliac spine (RASIS and LASIS) and the second sacral vertebra (SACRUM) (pelvis segment). Markers were placed bilaterally on the greater trochanter (RTH and LTH), the lateral femoral condyle (RKN1 and LKN1) and another marker fixed on a lateral bar must be attached to the tight using an adaptable strap (RBAR1 and LBAR1) in order to identify the position and orientation of tight segments. The shank positions were estimated by placing markers bilaterally on the head of the fibula (RKN2 and LKN2), the lateral malleolus (RMALL and LMALL) and another marker fixed on a lateral bar must be attached to the shank. To define the position of foot segments, the markers were positioned bilaterally on the fifth metatarsal head (RMET and LMET) and the heel (RHEEL and LHEEL). The marker on the heel was removed after the acquisition of the rest trial.

Anthropometry of the model must be defined from physical measurements (i.e., weight, height, leg length), including also data used in the estimation of the joint center locations (i.e., knee and ankle width on the coronal plane, distance between right and left pelvic anterior superior iliac spine (ASIS), the vertical distance on the sagittal plane of the supine subject between the ASIS and the greater trochanter).

Figure 5.1. Marker placement according to Davis' protocol in anterior, posterior and lateral view. Calibration markers (unfilled circle), tracking markers (filled circles) and joint center locations (orange square).

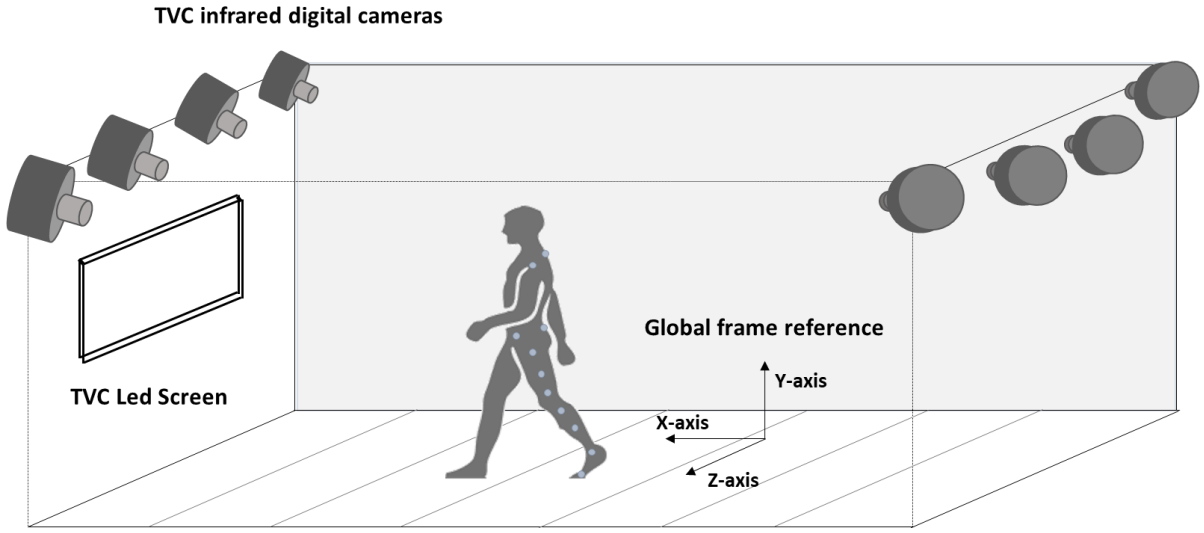


5.2.3 Experimental set-up

An 8-camera SMART-D stereophotrogrammetric optoelectronic system (BTS Bioengineering, Italy) based on passive markers was employed to acquire experimental data in both single- and dual-task condition. Acquisition rate was set to 120 Hz and resolution of the CCD digital cameras was 640×480 pixels. Two digital video-cameras (BTS Vixta, Bioengineering, Italy), integrated with the motion capture system, recorded the movement in the sagittal and frontal planes. Prior to data collection, calibration was performed following manufacturer's recommendations: a three-axes calibration grid was placed on the ground and acquired for determination of the global frame of reference, while a rigid wand on which three markers are mounted at predetermined distance is swept through the volume of interest, in a dynamic acquisition, for simultaneous calibration of intrinsic parameters, and relative position, of the infrared cameras.

The global frame of reference was defined with X-axis directed along the direction of the path, Z-axis directed forward (laterally) and Y-axis directed upward (superiorly). The cameras were calibrated to a measurement volume of almost 2×12×2 m in order to ensure marker visibility throughout the task. The 8-cameras and the global frame of reference positions are illustrated in Figure 5.2.

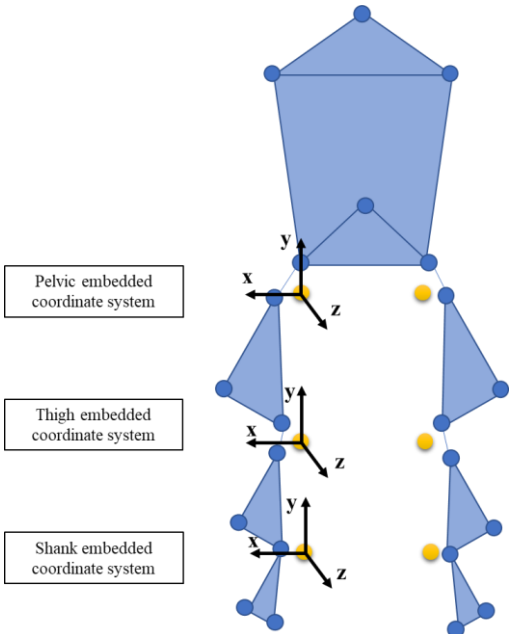
Figure 5.2. Arrangement of cameras in a typical 3D gait analysis. The cameras are positioned that at least two see each marker at any given time. Infra-red sources around each camera reflect from the passive markers result in a bright spot in each image, and this spot are then combined to generate the 3D trajectories.



5.2.4 Data processing

After data collection, the static trial and the walking trials were checked in the Smart Tracker environment (BTS Bioengineering, Italy). The marker labelling process begins by the static trial in which the individual is standing still in the center of the calibrated volume. Once the individual markers on this static capture are identified and labelled according to the biomechanical model, the software automatically labels the markers in the proceeding dynamic trials. The raw data was processed by means of a code implemented in the Smart Analyzer environment (BTS Bioengineering, Italy). Three dimensional coordinates of each marker are computed stereometrically from data collected by at least two 2D cameras. Then, the entire 3D trajectory of the markers was reconstructed as a function of time. In case of marker occlusion from the camera, the 3D trajectories were interpolated by a cubic-spline and data were low-pass filtered before further calculations (4th order zero-lag Butterworth filter, cut-off frequency of 6 Hz). Then velocity and acceleration of each marker were also computed through numerical differentiation. The three markers used to determine each bony segment allowing also the definition of the instantaneous orientation of an orthogonal, marker-based, embedded coordinate system for each thigh, shank and foot segment. The lower limb coordinate systems were established at each joint on the basis of the method proposed by Davis et al. (1991). The marker-based embedded coordinate system of thigh, shank and foot are then realigned with the joint center-based embedded coordinate systems (Figure 5.3).

Figure 5.3. Biomechanical model of trunk and lower limbs used to compute kinematics: embedded coordinate systems are displayed for the right lower limb.



The next step was the estimation of the location of hip, knee and ankle joint centers. They are calculated with respect to the associated embedded coordinate system origin, for example the knee center location is relative to the origin of the marker-based thigh embedded coordinate system (located at knee marker). Finally, the limb rotation algorithm is based on the determination of Euler angles (Greenwood, 1965; Kadaba et al., 1990) with a Y-X-Z axis rotation sequence. These joint angles correspond to:

- flexion – extension was measured as rotation around the medio-lateral axis: positive value represents the flexion, while negative value the extension;
- abduction – adduction was measured as rotation around the anterior-posterior axis: positive value represents the adduction, while negative value the abduction;
- internal – external rotation was measured as rotation around longitudinal axis: positive value represents the internal rotation, while negative value the external rotation.

The joint angles that are routinely determined are trunk and pelvic obliquity-tilt-rotation, hip ad/abduction and flexion/ extension, knee flexion/extension, ankle plantar/dorsi- flexion, and foot rotation. The trunk, pelvic and foot angles are referred to the coordinate system of the laboratory, while hip, knee and ankle are all relative angles. The knee ad/abduction and rotation angles are not utilized clinically because their poor signal-to-noise ratio associated with these data. The following analysis are only focused on kinematic measures of hip, knee and ankle joints and mainly in the sagittal plane (Cofré Lizama et al., 2016).

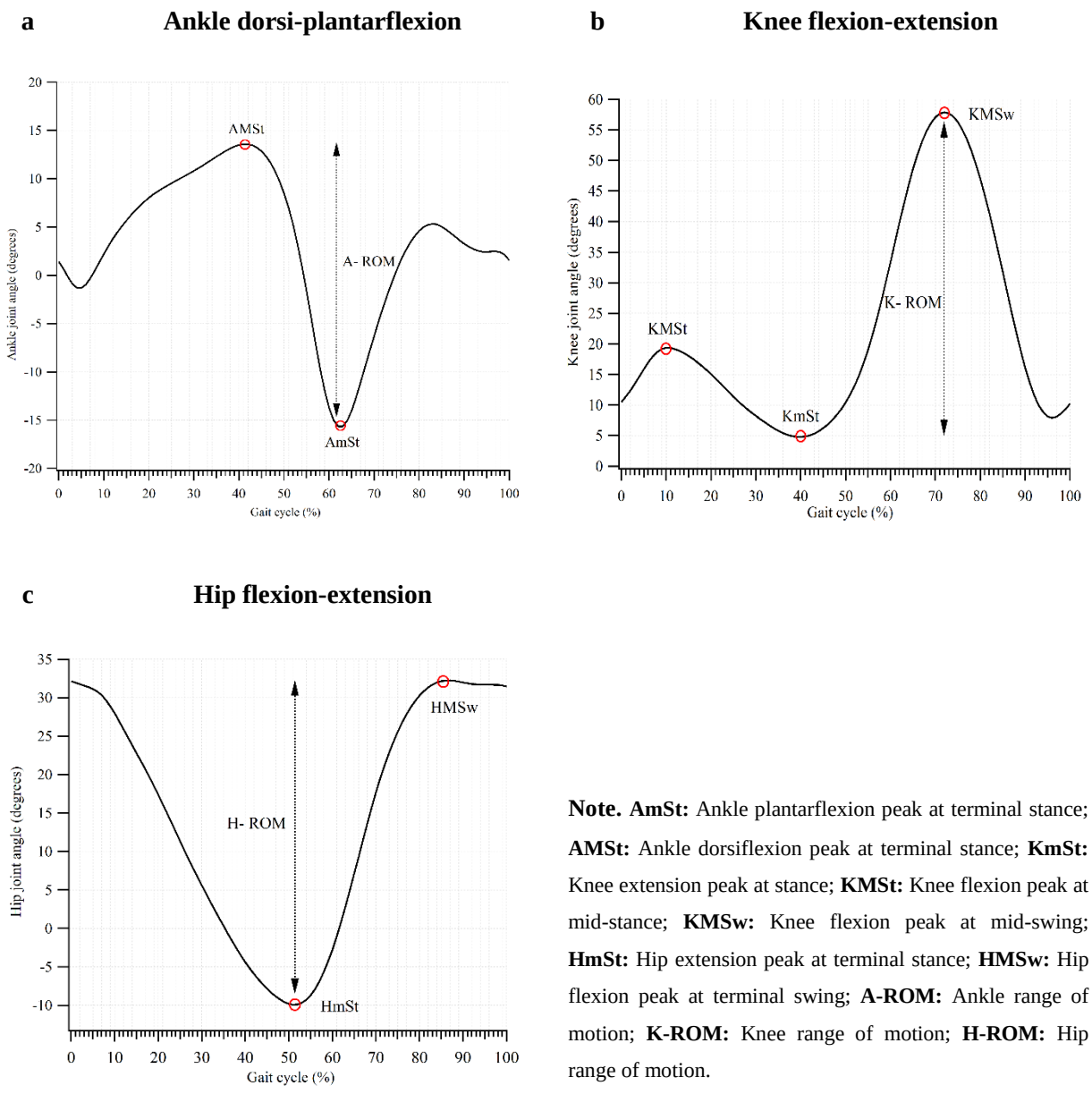
Then in the elaboration phase, the gait cycle was segmented into two main phases according to previously literature: the stance phase and the swing phase (Davis et al., 1991). The starting and ending time of the two phases were manually selected by the identification of the following events for right and left side, respectively:

- Heel strike- foot initial ground contact (at least two events must be defined);
- Toe off- toes are lifted off the ground (one event between each of the two previously defined strikes).

5.2.5 Kinematic features of movement

Spatiotemporal parameters used to evaluate the walking task under single- and dual-task performance are summarized and briefly described in Table 5.1, while kinematic graphs are shown in Figure 5.4. Moreover, punctual parameters (i.e. angle joint values in specific gait cycle instant) were also identified and quantified, in order to define gait strategy of main lower limb joints (Table 5.2).

Figure 5.4. Lower limb kinematic patterns on the sagittal plane during gait cycle: a) ankle joint; b) knee joint; c) hip joint.



Note. AmSt: Ankle plantarflexion peak at terminal stance; **AMSt:** Ankle dorsiflexion peak at terminal stance; **KmSt:** Knee extension peak at stance; **KMSt:** Knee flexion peak at mid-stance; **KMSw:** Knee flexion peak at mid-swing; **HmSt:** Hip extension peak at terminal stance; **HMSw:** Hip flexion peak at terminal swing; **A-ROM:** Ankle range of motion; **K-ROM:** Knee range of motion; **H-ROM:** Hip range of motion.

Table 5.1. Description of spatiotemporal parameters of gait.

Parameter	Unit	Description
Gait cycle duration	s	Time between two consecutive ground contacts of the same foot
Stance phase	% gait cycle	Duration of the phase during which the foot remains in contact with the ground
Swing phase	% gait cycle	Duration of the phase during which the foot is not in contact with the ground
Double support	% gait cycle	Duration of the phase during which both feet are in contact with the ground
Gait speed	m/s	Mean velocity of progression
Stride length	m	Longitudinal distance between two consecutive heel contacts of the same foot
Cadence	steps/min	Rate at which a person walks
Step width	m	Side-to-side distance between the line of the two feet

Table 5.2. Description of kinematic parameters of gait.

Parameter	Unit	Description
Hip extension peak at terminal stance (HmSt)	Deg	Minimum value of hip flex-extension angle during stance
Hip flexion peak at terminal swing (HMSw)	Deg	Maximum value of hip flex-extension angle during swing
Knee flexion peak at mid-stance (KMSt)	Deg	Maximum value of knee flex-extension angle during stance phase
Knee extension peak at stance (KmST)	Deg	Minimum value of knee flex-extension angle during stance phase
Knee flexion peak at mid-swing (KMSw)	Deg	Maximum value of knee flex-extension angle during swing phase
Ankle plantarflexion peak at terminal stance (AmSt)	Deg	Minimum value of ankle dorsi-plantarflexion during stance phase
Ankle dorsiflexion peak at terminal stance (AMSt)	Deg	Maximum value of ankle dorsi-plantarflexion during stance phase
Hip range of motion (H-ROM)	Deg	Hip excursion, defined as | HMSw – HmSt |
Knee range of motion (K-ROM)	Deg	Knee excursion, defined as | KMSw – KmSt |
Ankle range of motion (A-ROM)	Deg	Ankle excursion, defined as | AMSt – AmSt |

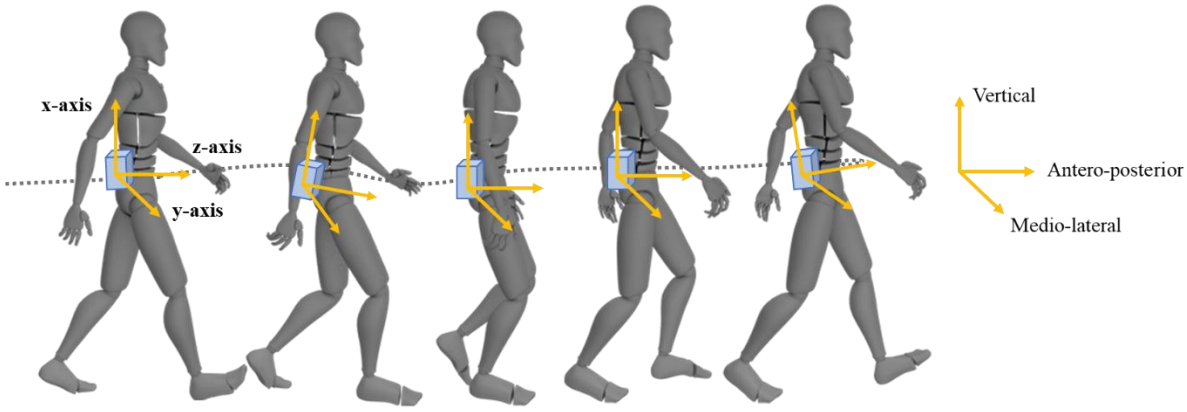
5.3 Experimental design: gait analysis with a single wearable inertial sensor

As mentioned in *Chapter 2* (see *Chapter 2, paragraph 2.2.2*), the wearable inertial systems based on miniaturized sensors and wireless communication systems have made it possible to obtain measurements of the different aspects of gait in real time, allowing an evaluation of gait outside the laboratory (i.e., clinical settings). In order to track day-by-day progress in gait performance during the stimulation intervention (*Chapter 8*), gait analysis was carried out using a single inertial sensor. The following section will describe in detailed the experimental set-up and the data processing procedure.

5.3.1 Data acquisition

Gait analysis has been implemented using a single wearable inertial sensor (G-sensor, BTS Bioengineering, Italy) controlled by BTS G-walk environment via Bluetooth communication. The sensor is sized 70 × 40 × 18 mm, has a weight of 37 g, and includes a 3-axis accelerometer (max range ±16 g), 3-axis gyroscope (full scale ± 2000 deg) and a 3-axis magnetometer (full scale ± 1200 μT). However, in the present study only data from the accelerometer was used. Several studies (Zijlstra and Hof, 1997; Zijlstra and Hof, 2003; Buganè et al., 2014) have shown that during walking a consistent pattern of trunk acceleration occurs with fixed relationships to spatiotemporal parameters. In fact, the 3D trajectories of the trunk are well predicted by an inverted pendulum model of the body's center of mass (CoM) trajectories and in agreement with this the amplitude and timing of pelvic displacements depended on spatiotemporal parameters of the stride length.

Figure 5.5. Device placement during experiments and reference anatomical direction. In particular, antero-posterior direction is aligned with the direction of motion during gait.



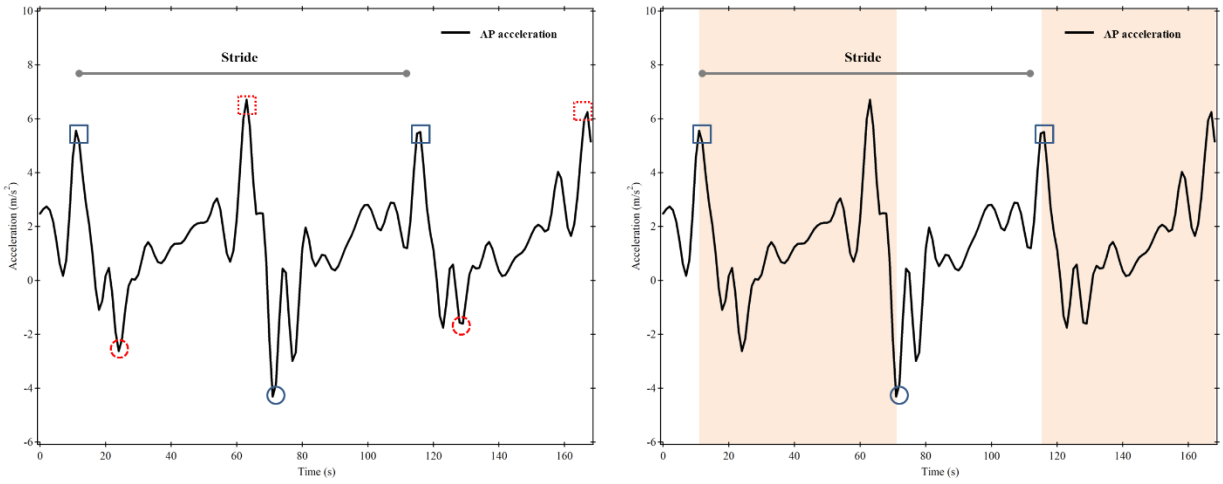
Thus, the walk protocol required that the sensor was attached to the subject's waist with a semi-elastic belt covering the 5th lumbar vertebrae (L5), in a way that acceleration of the trunk is collected at 100 Hz frequency along the three orthogonal anatomical axes (i.e., anterior-posterior, medio-lateral and vertical

axes). With the subject standing in anatomical position the positive X values correspond to upward acceleration (vertical direction), positive Y values to an acceleration to the right (medio-lateral direction), and positive Z values to an anterior acceleration (antero-posterior direction). During the acquisition, participants had to walk at their normal speed along a straight path. Figure 4.5 reports a schematic representation of the device placement during the test. To ensure a correct execution of the test, it was recommended to record at least five steps for each side.

5.3.2 Features extraction

Signals from the accelerometers were transmitted wirelessly to a computer running G-walk environment, where they were low pass filtered (4th order zero-lag Butterworth filter at 2 Hz). Accelerometric data was subsequently processed with a custom routine to calculate spatiotemporal parameters of gait using an established approach proposed by Zijlstra and Hof (2003). This approach is based on the detection of gait events like heel strike and toe-off using an acceleration magnitude analysis. In particular, both heel strike and toe-off are associated to specific features of the lower trunk accelerations along the antero-posterior (AP), medio-lateral (ML) and vertical directions.

Figure 5.6. Detection of gait parameters with single inertial sensor placed at L5. Squares indicate heel strike event, circles indicate toe-off event; red color is used for the events of one leg, blue dashed for the other one.



As shown in Figure 4.6, the antero-posterior acceleration local maximum preceding the change of sign (from positive to negative) was taken as the left or right initial contact, whereas toe-off event corresponded to the local minimum. The anterior-posterior (z-axis) accelerometer signal was thus used to detect mean stride duration, calculated as between two acceleration local peaks of the same foot, and to determine the length of stance and swing phase duration. To determine whether a foot contact was left or right, medio-lateral acceleration (y-axis) were analyzed. According to the pendulum model, the CoM accelerate to the

left side during a right support and vice versa. Mean stride length and mean walking speed were estimated using the upward and downward accelerations along the vertical direction (x-axis). In the adopted inverted pendulum model, changes in height of the CoM during the gait cycle is related to stride length (Zijlstra and Hof, 1997). Thus, changes in vertical position are known by computing double integration of the vertical acceleration signal (to avoid integration drift position data were high-pass filtered at 0.1 Hz), stride length can be predicted from the relationship as follows:

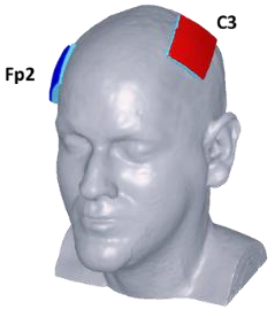
$$stride\ length = 2\sqrt{2lh - h^2},$$

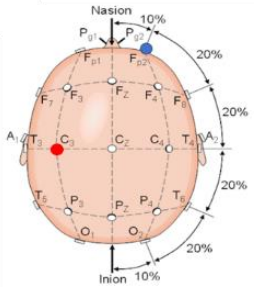
where *l* is equals to the leg length and *h* is the change in height of the CoM. Leg length was estimated from the subject height using the proportion reported in the anthropometric dimensional data by Winter (2009). The first and the last stride were removed from any analysis in order to avoid transitional phases. For the definition of spatiotemporal parameters of gait see Table 5.1.

5.4 Transcranial Direct Current Stimulation

In *Chapter 8* and *Chapter 9*, transcranial stimulation was delivered via programmable battery driven stimulators (1x1 tDCS mini-clinical trial device, Soterix Medical Inc., USA; Starstim system, Neuroelectrics Inc., Spain) comparable as performance. Both devices were programmed before the intervention and, they guaranteed blindness of the study technician not displaying whether the stimulation was active or sham. tDCS was delivered via two rubber electrodes placed in saline soaked sponge covers. The electrodes were held in place using either the Soterix EasyStrap customized to allow M1-SO electrode montage with anodal electrode over C3 and cathodal electrode over Fp2 according to the 10–20 EEG system, or the Neuroelectrics wireless hybrid headset consisted of a neoprene headcap with electrode positions based on the 10–20 EEG system (Figure 5.7). Both active electrode and reference electrodes was 25 cm^2 in size. For the active condition, current intensity was set up to 2.5 mA based on the tolerance of the individual and delivered for 20 minutes. For the sham condition, the device delivered a 60 second ramping up/down electrical current for the first and last minute of the stimulation period, following conventional blinding protocol (Gandiga et al., 2006).

Figure 5.7. Electrode positioning according to the 10-20 EEG system. M1-SO electrode montage: anodal electrode (red) over C3 and cathodal electrode (blue) over Fp2.





5.5 Statistical analysis

All data were analyzed using the Statistical Package for Social Sciences (SPSS Statistics, IBM). Demographic and clinical features and kinematic parameters were described with descriptive statistics, using mean and standard deviation for continuous and discrete variables. Data were firstly checked for normality using the Kolmogorov-Smirnov test. Differences between groups and/or study time points in the investigated parameters as well as relationships between gait speed and joint kinematic were assessed with parametric or non-parametric tests, according to data distribution. Data analysis will be described in detailed in each chapter, in accordance with the characteristics of the study design. The level of significance was set at $p < 0.05$. Based on the recommendations of Lakens (2013), partial eta squared (η^2) was used as a measure of effect size for analysis of variance (ANOVA) main and interaction effect size.

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Chapter 6

Exploring cognitive-motor interference in multiple sclerosis: a quantitative study

Measurements of the motor impairments during walking dual-task activities could give further information about disability level of people with MS with respect to clinical outcomes and contribute to better planning patient-based rehabilitation treatments. Given the lack of standardized dual-task protocols, this thesis focuses on providing an experimental setup to assess cognitive-motor interference in both healthy individuals and people with MS. In this chapter, a quantitative methodology to assess walking dual-task is presented in order to outline the most relevant gait parameters in detecting gait alterations provoked by cognitive-motor interference and to examine the impact of disability level on dual-task performance.

6.1 Context

Gait dysfunction in people with MS has a wide impact on independence, quality of life and functional status. More than 85% of the patients exhibited deficits in walking, and 70% of them define gait disturbances as the major limitations encountered in their life (LaRocca, 2011). Among the many factors that can contribute to gait deterioration, such as spasticity, muscle weakness and impaired balance, cognition has been recently subject to the most extensive research (Bethoux, 2003). The everyday act of walking requires continuous high-level cognitive control when navigating in a complex environment. It involves planning movements and calculating obstacles. These skills pertain to executive functions, which are strictly related to walking performance (Yogev-Seligmann et al., 2008). Indeed, executive functions, together with information processing speed and episodic memory problems, are the cognitive domains mainly impaired in those with MS (Amato et al., 2010). A recent meta-analysis of Leone et al. (2015) suggests to move beyond the habit to assess cognitive and motor abilities separately, because a large body of literature has shown that, especially gait impairments, appear or get worse under dual-task conditions.

In fact, the new trend in the laboratory setting is to evaluated walking impairments adopting dual-task paradigm, which consists of the concurrent performance of motor and cognitive tasks. Indeed, the dual-task paradigms allow exploring cognitive-motor interference, giving directly information of how cognition impacts on motor abilities (Leone et al., 2017). Accordingly, cognitive-motor interference arises when a detrimental effect on one or both tasks concurrently tested occurred, and it is generally measured in terms of dual-task cost (Baddeley et al., 1997; Wajda et al., 2013). Although cognition's dual-task cost has been only explored by few studies and showed mixed results (Hamilton et al., 2009; Allali et al., 2014), the detrimental effect of dual-task on walking is well recognize, and overall characterized by gait speed reduction. Digit span, talking, word list generation, backward or forward counting, serial subtraction and answering questions are the most common cognitive tasks that have been used in MS dual-task paradigm (Leone et al., 2015; Wajda et al., 2013). However, no studies have focused on walking in combination with the Stroop Color and Word Test.

Stroop Color and Word Test is defined as the discrimination and decision-making task par excellence. It assesses the ability to inhibit cognitive interference due to the simultaneous processing of two features of the same stimulus (Stroop, 1935). This cognitive task is able to evaluate attention, processing speed, cognitive flexibility and working memory (Jensen and Rohwer, 1966; Kane and Engle, 2003). Accordingly, the Stroop Color and Word Test should be the most useful cognitive task during walking dual-task in patients with MS for the following reasons: it is related to processing speed, which is the most relevant cognitive deficit in those with MS; it is an interference task; it can quantify executive functions (Langdon et al., 2011). Moreover, a recent meta-analysis by Learmonth et al. (2017) suggests that the Stroop Color

and Word Test is a good candidate for cognitive-motor interference assessment. Until now, the Stroop Color and Word Test was adopted only in two studies, aimed to measure in MS patients the effect of this cognitive task on static balance abilities and not on walking performance (Kalron et al., 2011; Prosperini et al., 2015). Moreover, it is still unclear whether different levels of disability can influence the dual-task cost (Leone et al., 2015). Even if this aspect was taking into account by some authors (Kalron et al., 2010; Sosnoff et al., 2011), they don't fully clarify if (and how) gait patterns is differently altered in MS patients with different level of disability under dual-task conditions.

Starting from the previous considerations, the aim of the present study was to find an appropriate and standardized instrument to evaluate cognitive-motor interference in those with MS, bearing the following points: to consider the Stroop Color and Word Test as a cognitive task suitable for the mechanisms of cognitive-motor interference in patients with MS; to evaluate a wide range of spatiotemporal gait parameters by means of the gold-standard technology for gait analysis; to assess which are the most relevant gait parameters in detecting gait alterations provoked by dual-task condition; to assess the impact of disability level on dual-task performance.

6.2 Methods

6.2.1 Participants

Eighty-one patients suffering from MS (54 females, 27 males, and mean age 45.10 ± 12.04 years) were enrolled in the study. All patients are being followed at the Regional Multiple Sclerosis Center of Sardinia (Cagliari, Italy). The inclusion criteria were a confirmed diagnosis of MS according to the 2010 McDonald criteria (Polman et al., 2011), being 18 years or older, being able to independently ambulate without an assisting device (i.e. cane, crutches or walking frames) for at least 100 m, and being free of any other disease potentially able to severely affect gait or balance. In this study two subgroups based on their disability level, assessed through the Expanded Disability Status Scale (EDSS) score, were defined as follow:

- Low disability patients (EDSS 1.0-2.5, n=37)
- Mild to moderate disability patients (EDSS 3.0-6.0, n=44)

Forty-one age- and gender-matched unaffected individuals, who were free of any musculoskeletal and neurological diseases, were recruited (27 females, 14 males, mean age 44.93 years) from friends or family members of the MS patients or members of the university and hospital. All tests were performed at Biomechanics and Industrial Ergonomics Laboratory (University of Cagliari, Italy) in a single visit that lasted less than one hour. The main demographic and clinical features of the participants are reported in

Table 6.1. The local ethics committee approved the study, and all participants signed an informed consent form before their participation.

Table 6.1. Demographic, anthropometric and clinical features of the participants. Values are expressed as mean ± sd.

Variable	Healthy group	Entire MS sample	Low disability EDSS 1.0-2.5	Mild to moderate disability EDSS 3.0-6.0
Participants	41 (27F, 14M)	81 (54F, 27M)	37 (25F, 12M)	44 (29F, 15M)
Age (years)	44.93±14.00	45.10±12.04	41.08±10.39	48.48±10.42
Height (cm)	167.89±8.96	165.77±9.03	165.92±9.24	165.64±8.94
Weight (kg)	68.44±9.98	66.33±10.45	68.33±11.05	67.99±9.23
EDSS	-	3.48±1.56	1.94±0.52	4.19±0.97

Note. EDSS: Expanded Disability Status Scale.

6.2.2 Experimental protocol

The experimental protocol included two different test conditions: the single-task motor performance (walking only) and the dual-task performance (walking while performing a cognitive task).

The cognitive task adopted was the Stroop Color and Word Test, which belongs to the discrimination and decision-making category. Specifically, the third table of the test, named color-word condition, was used during the dual-task trials. The test consisted only of incongruent stimulus, where the color-words are printed in an inconsistent color ink (i.e. the word “red” is printed in green ink). Participants had to name only the word's font colour and not to read the word. The test was administered via a 48” LCD TV screen located perpendicularly to the gait direction (Wollesen et al., 2016; Coghe et al., 2018). The time interval between two consecutive word occurrences was varied to avoid rhythm. The words (46–96 cm in width and 15–19 cm in height) were displayed at a distance in the range of 200–750 cm between the participant and the screen. For each task condition, at least six trials were performed to collect sufficient spatiotemporal data.

6.2.3 Gait evaluation

The spatiotemporal parameters of gait were acquired using a motion-capture system composed of eight infrared cameras (Smart-D, BTS Bioengineering, Italy) set at a frequency of 120 Hz. Prior to the tests, participants’ anthropometric data such as height, weight, anterior superior iliac spine (ASIS) distance, pelvis thickness, knee and ankle width, and leg length (distance between ASIS and medial malleolus) were

collected using the following instrumentations: digital scale, pelvimeter, and flexible meter. Then, 22 spherical retro-reflective passive markers (14 mm diameter) were placed on the subjects' skin following the protocol described by Davis et al. (1991). Participants were asked to walk up and down a 10 m walkway at least six times at a self-selected speed in the most natural manner for both single- and dual-task conditions. The raw data were processed using Smart Analyzer software (BTS Bioengineering, Italy) to calculate stride time, gait speed, cadence, stride length, step width, stance, swing, and double support phase duration (expressed as a percentage of the gait cycle). The gait parameters were calculated as an average of the six trials for each tested condition. The cognitive-motor interference was quantified by the dual-task cost, which was calculated as the percent change from single-task to dual-task performance for each spatiotemporal parameters of gait (Baddeley et al., 1997):

$$DTC = \frac{(ST-DT)}{DT} \cdot 100,$$

where ST is the single-task performance and DT is the dual-task performance. A positive dual-task cost indicates for gait speed, stride length, cadence and swing phase duration a decrease in walking performance when a concurrent cognitive task is performed. Instead, a negative dual-task cost indicates a decrease in walking performance for stride time, step width, stance and double-support phase duration.

6.2.4 Statistical analysis

All statistical analyses were performed using Statistical Package for Social Sciences (SPSS Statistics, IBM). Normal distribution of the data was assessed by the Kolmogorov-Smirnov test. This analysis indicated that all variables of the study met the criteria of normality. Because of all variables (spatiotemporal parameters of gait and dual-task cost) were normally distributed, all statistical analyses applied were parametric tests. Descriptive analyses were generated for all demographic and clinical variables of the three groups. Results were expressed as a mean ± standard deviation for the spatiotemporal parameters of gait and as mean ± standard error for the dual-task cost. Stride time, stance phase duration, swing phase duration and stride length data were screened to evaluate whether the gait parameters differed bilaterally. One-way Analysis of Variance (ANOVA) revealed no significant differences between the left and right sides for any gait measure. Thus, the mean value of the two sides was considered as representative of each participant in the analysis. The presence of possible alterations introduced in gait patterns by the concurrent cognitive task were explored using two-way ANOVA for repeated measures (RM-ANOVA), where the participant's group (healthy controls, low disability MS patients, mild to moderate MS patients) and the task condition (walking, walking while performing the Stroop Color and Word Test) were considered as independent variables and as dependent variables the abovementioned spatiotemporal parameters. In case of a significant effect of group or task condition, a *post-hoc* test for pairwise comparison with Holm-Sidak correction was

carried out to assess intragroup and intergroup differences. The level of significance was set at p=0.05 and effect sizes were assessed using the eta-squared coefficient (η2). One-way multivariate analysis of variance (MANOVA) was carried out to verify the possible effect of the level of disability (healthy controls, low disability MS patients, mild to moderate MS patients) on the dual-task cost calculated for the 7 spatiotemporal parameters of gait. The level of significance was set at p = 0.05 and the effect sizes were assessed using the eta-squared coefficient (η2). Univariate ANOVA was carried out as a *post-hoc* test by reducing the level of significance to *p*=0.007 (0.05/7) after Bonferroni correction for multiple comparison.

6.3 Results

Table 6.1 shows the demographic and clinical characteristics of the participants by group. None of the demographic variables were significantly different among the groups. Mean age was similar in the three groups, and women were twice than man in both healthy individuals and MS subgroups.

6.3.1 Gait parameters in single- and dual-task condition

Spatiotemporal parameters of gait, as a function of the disability level, in single-task and dual-task condition are reported in Table 6.2 and in Figure 6.1.

ANOVA revealed a significant effect of task condition on the following spatiotemporal parameters of gait: gait speed ($F_{1, 120} = 71.90$, $p<0.001$, $\eta^2= 0.56$), stride length ($F_{1, 120} = 53.73$, $p<0.001$, $\eta^2= 0.52$), step width ($F_{1, 120} = 5.16$, $p=0.025$, $\eta^2= 0.13$), cadence ($F_{1, 120} = 25.24$, $p<0.001$, $\eta^2= 0.45$), stride time ($F_{1, 120} = 16.41$, $p<0.001$, $\eta^2= 0.15$), stance phase duration ($F_{1, 120} = 14.74$, $p<0.001$, $\eta^2= 0.12$), and double support phase duration ($F_{1, 120} = 31.78$, $p<0.001$, $\eta^2= 0.57$). The *post-hoc* analysis revealed that in mild to moderate patients with MS all parameters, with the exception of swing phase duration, were significantly affected by the Stroop Color and Word Test. Gait speed, cadence and stride length were reduced under dual-task conditions, while step width, stance and double support phase duration increased. In contrast, unaffected individuals and low disability MS patients exhibited significant decrease only in gait speed and stride length. The two-way RM-ANOVA also accounted a significant main effect of group variables for the following spatiotemporal parameters: gait speed ($F_{2, 119} = 50.41$, $p<0.001$, $\eta^2= 0.88$), stride length ($F_{2, 119} = 40.89$, $p<0.001$, $\eta^2= 0.87$), step width ($F_{2, 119} = 5.16$, $p<0.001$, $\eta^2= 0.67$), cadence ($F_{2, 119} = 34.66$, $p<0.001$, $\eta^2= 0.85$), stride time ($F_{2, 119}=25.31$, $p<0.001$, $\eta^2= 0.80$), stance phase duration ($F_{2, 119} = 28.63$, $p<0.001$, $\eta^2= 0.42$), swing phase duration ($F_{2, 119} = 5.69$, $p=0.004$, $\eta^2= 0.31$), and double support duration ($F_{2, 119} = 44.44$, $p<0.001$, $\eta^2= 0.71$). This mean, as expected, that the mild to moderate disability group had a significantly lower speed (-38.3%, p<0.001), shorter stride length (-31.0%, p<0.001), wider base of support (13.6%, p=0.010), longer stride time (21.7%, p<0.001), and a greater percentage of the gait cycle

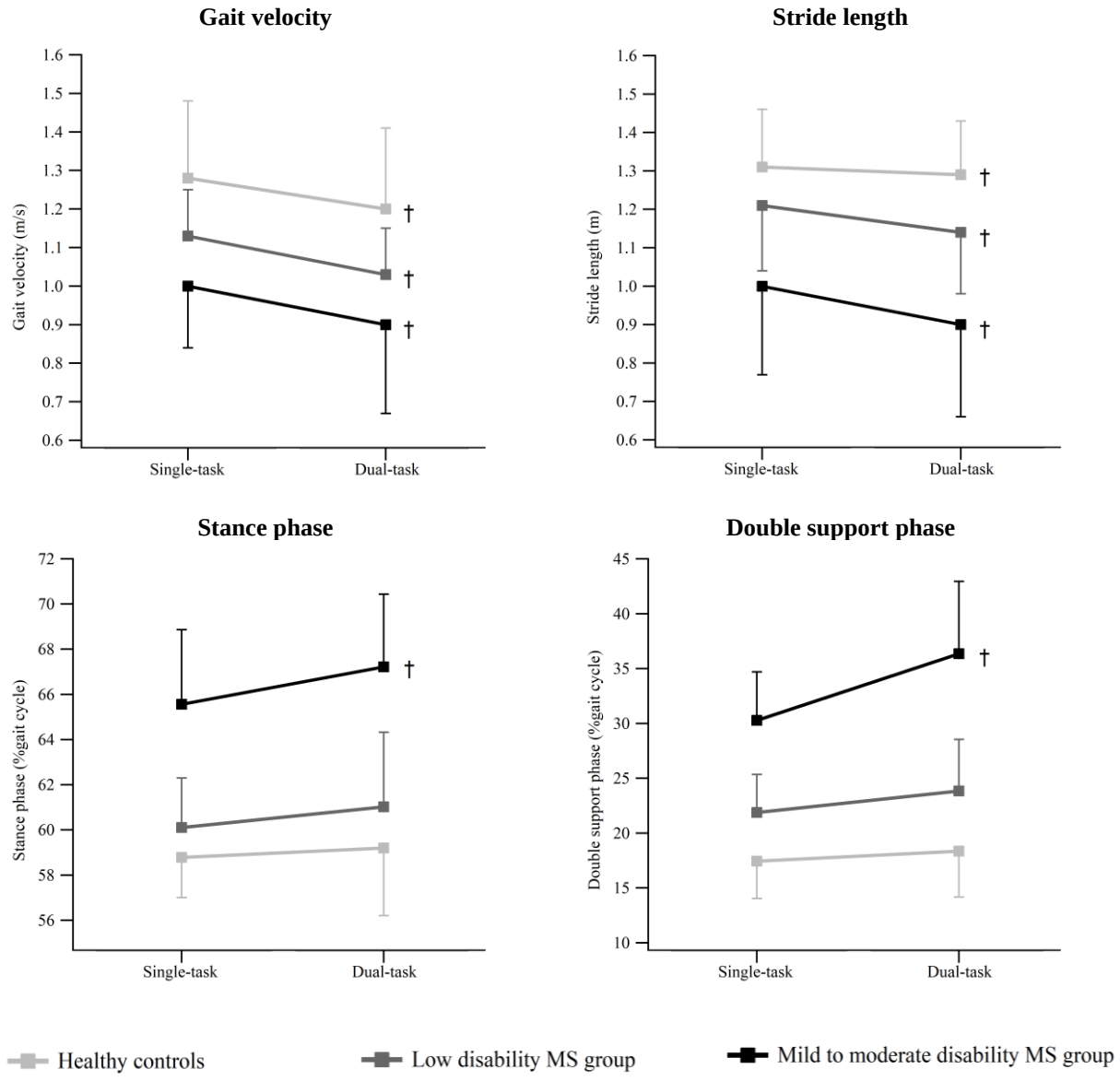
in stance (10.3%, $p<0.001$) and double support phase (42.4%, $p<0.001$) with respect to healthy individuals. Instead, patients with low disability exhibited lower gait speed (-13.2%, $p=0.016$) and shorter stride length (-8.2%, $p=0.010$). Finally, significant group × task interactions were found for stride length ($F_{2, 119} = 3.12$, $p=0.048$, $\eta^2= 0.10$), cadence ($F_{2, 119} = 3.83$, $p=0.025$, $\eta^2= 0.12$), stride time ($F_{2, 119} = 4.40$, $p=0.012$, $\eta^2= 0.13$), stance phase duration ($F_{2, 119} = 5.96$, $p=0.002$, $\eta^2= 0.03$), and double support phase duration ($F_{2, 119} = 9.59$, $p<0.001$, $\eta^2= 0.11$).

Table 6.2. Spatiotemporal parameters of gait in healthy controls and MS patients with low and mild to severe disability under single- and dual-task conditions. Values are expressed as mean ± sd.

	Healthy controls		**Low disability – MS group**		**Mild to moderate disability- MS group**		***p*- value**		
	ST	**DT**	**ST**	**DT**	**ST**	**DT**	**Group**	**Task**	**Group×Task**
Stride time (s)	1.08 ± 0.13	1.08 ± 0.11	1.07 ± 0.11	1.14 ± 0.14	1.38 ± 0.15	1.48 ± 0.24†	<0.001	<0.001	0.014
Stance phase (% gait cycle)	58.78 ± 1.72	59.20 ± 3.98	60.11 ± 2.19	61.02 ± 3.30	65.56 ± 5.30	67.22 ± 3.32†	<0.001	<0.001	0.002
Swing phase (% gait cycle)	40.81 ± 1.71	39.55 ± 2.91	39.90 ± 2.22	38.18 ± 2.83	34.40 ± 5.33	32.33 ± 5.71	0.004	0.392	0.188
Double support phase (% gait cycle)	17.45 ± 3.40	18.36 ± 4.19	21.88 ± 3.47	23.84 ± 4.70	30.28 ± 4.41	36.36 ± 6.59†	<0.001	<0.001	<0.001
Gait velocity (m/s)	1.28 ± 0.19	1.20 ± 0.20†	1.13 ± 0.21	1.03 ± 0.21†	0.79 ± 0.31	0.68 ± 0.30†	<0.001	<0.001	0.528
Cadence (steps/min)	112.90 ± 10.52	112.04 ± 10.80	112.25 ± 9.95	110.68 ± 11.26	91.32 ± 18.72	86.99 ± 15.86†	<0.001	<0.001	0.025
Stride length (m)	1.31 ± 0.15	1.29 ± 0.14†	1.21± 0.17	1.14 ± 0.16†	1.00 ± 0.23	0.91 ± 0.24†	<0.001	<0.001	0.048
Step width (m)	0.20 ± 0.03	0.20 ± 0.04	0.20 ± 0.03	0.20 ± 0.04	0.22 ± 0.03	0.25 ± 0.04†	<0.001	0.025	0.205

The symbol † denotes a significant difference between single-task and dual-task task (p<0.05). **Note. ST**: single-task; **DT**: dual-task.

Figure 6.1. Trends in spatiotemporal parameters of gait for the 3 groups under single- and dual-task conditions. The symbol † denotes a significant difference between single- and dual-task conditions ($p < 0.05$).



6.3.2 Motor dual-task cost

In Table 6.3, the dual-task cost of the investigated spatiotemporal parameters are reported. The one-way ANOVA revealed a significant main effect of the group on the dual-task cost variables ($F_{7, 119} = 30.47$, $p=0.002$, Wilks $\Lambda = 0.75$, $\eta^2 = 0.135$). The *post-hoc* analysis showed that mild to moderate MS patients had a higher dual-task cost of stance phase duration ($p=0.006$), double support phase duration ($p<0.001$), gait speed ($p<0.001$), and stride length ($p=0.002$). Instead, the *post-hoc* test failed to detect significant

differences in dual-task cost of the investigated spatiotemporal parameters between MS patients with low disability and healthy individuals.

Table 6.3. Dual-task cost of the gait spatiotemporal parameters in healthy controls, low disability and mild to moderate disability MS patients. Values are expressed as mean ± se.

		Healthy controls	Low disability EDSS 1.0-2.5	Mild to moderate disability EDSS 3.0-6.0
DTC (%)	**Stride time**	-1.60 ± 0.98	-3.76 ± 1.14	-6.20 ± 1.18
	Stance phase	-1.40 ± 1.02	-1.54 ± 0.75	-4.59 ± 0.91†
	Swing phase	3.03 ± 1.08	4.31 ± 1.34	6.11 ± 1.04
	Double support phase	-3.45 ± 1.98	-5.95 ± 2.44	-19.69 ± 4.40†
	Gait velocity	7.04 ± 1.10	9.21 ± 1.35	14.76 ± 1.46†
	Stride length	1.67 ± 0.82	4.78 ± 0.89	7.04 ± 1.07†
	Cadence	1.28 ± 1.01	4.95 ± 1.11	6.16 ± 1.63

The symbol indicates a significant difference vs. healthy controls after Bonferroni correction ($p < 0.007$). **Note. DTC:** dual-task cost.

6.4 Discussion

Despite the growing number of papers exploring the effect of cognitive task on walking abilities in unaffected individuals and people with MS, there is a lack of standardized data. In particular, there is no indication about which are the most sensitive gait parameters and the cognitive tasks able to generate cognitive-motor interference in those with MS (Learmonth et al., 2017; Postigo-Alonso et al., 2018). These are important aspects considering that walking dual-task is becoming not only an accepted protocol in MS research, but also rehabilitation protocols are sometimes based on the results of dual-task performance (Learmonth et al., 2017). Starting from the previous consideration, the use of validated measures is relevant not only for research but also for clinical purposes. The aim of this study was to test the clinical usefulness of the dual-task paradigm consisting of walking while concurrently performing the Stroop Color and Word Test for the cognitive-motor interference evaluation and to explore the effect of this cognitive task on gait performance in healthy individuals and in people with MS across varying levels of disability. Thanks to the motion capture technology – the gold standard for identify ambulatory impairment (Cofré Lizama et al., 2016) - a wide range of gait parameters were evaluated compared to other studies available in literature for this topic. The Stroop Color and Word Test was selected as a cognitive task because its performance is related to discrimination, executive functions, information processing, decision-making, and processing speed (Macniven et al., 2008), proving to be suitable in eliciting cognitive-motor interference. This is also

due to the fact that executive functions, information processing and processing speed are the most compromise cognitive domains in MS patients (Chiaravalloti and DeLuca, 2008).

The analysis of the gait spatiotemporal parameters, collected in single-task condition, showed a decrease in gait speed, cadence and stride length, and an increase in stride time, step width, stance and double support phase duration for mild to moderate MS patients in comparison with unaffected individuals. This result was both expected and well proven by other studies (Benedetti et al., 1999; Martin et al., 2006; Givon et al., 2009; Cameron and Lord, 2010). MS patients with low disability exhibited a decrease in gait speed and stride length compered to healthy individuals. Other studies, in minimally disabled (EDSS ranged between 1.0 and 2.0) and no disabled (EDSS 1.0) MS patients, or failed to detect any differences with respect to healthy individuals or found alterations in only few parameters (Kalron et al., 2010; Pau et al., 2017; Morel et al., 2017; Liparoti et al., 2019). The results of this study, regarding patients with low disability, are consistent with previous studies performed on individuals with similar levels of disability (Kalron et al., 2011; Liparoti et al., 2019).

As expected, the simultaneous performance of the Stroop Color and Word Test while walking originates significant alterations of gait, even though they are expressed differently among the three groups tested. In unaffected individuals, significant reductions in gait speed and stride length were found and such changes are in agreement with those reported in a previous similar study (Wollesen et al., 2016). In contrast to our results, these studies that explored the effect of the Stroop Color and Word Test on walking performance in young and older adults found also a significant increase in step width (Grabiner and Troy, 2005; Wollesen et al., 2018). This disparate result could be explained by the difference in the experimental methodologies adopted (overground vs. treadmill walking). Similar effect of the cognitive load on walking performance were found in MS patients with low disability, where only a reduction in gait speed and stride length were found compered to single-task. This is consistent with other authors who have shown either no differences or only marginal difference between minimally impaired MS patients and healthy controls in walking dual-task performance, even if different cognitive tasks were adopted (Sosnoff et al., 2011; Allali et al., 2014; Kirkland et al., 2015; Liparoti et al., 2019).

Although no significant differences were found in dual-task cost between unaffected individuals and low disability patients. The dual-task cost of double support phase duration and stride length showed a trend toward an increase in minimally disable patients, indicating a slightly worse gait performance. In contrast, MS patients with mild to moderate disability exhibited a significant deterioration in all investigated spatiotemporal parameters in dual-task condition. In this regard, gait speed and stride length variations were more than two times higher in MS patients with mild to moderate disability than the healthy controls (stride length: 7% vs. 2%; gait speed: 15% vs. 7%). Step width, stance phase duration and the percentage of time

spent in double support, which are closely related to perceived dynamic stability during walking, worsen only in patients with mild to moderate disability. It may thus be that severe impaired MS patients, having more serious balance impairments, tend to modify their gait pattern seeking for more stability with respect to those unaffected. The increase in double-support time could be a strategy to preserve stability at the expense of speed.

Our results found that the strategy to cope with motor-cognitive dual-task did not significantly differ between healthy adults and minimally disabled MS patients. Even if gait speed and stride length decreased in all three groups when performing dual-task, patients with mild to moderate disability were the most affected, suggesting that dividing attention between two tasks was most challenging for them. Moreover, this is also confirmed by worsening of balance-related parameters that occurs only in those with mild to moderate disability. This phenomenon could be not only caused by the less "*posture reserve*" of this severe disable patients but also to the presence of cognitive disability that are more common in the advance stage of the disease.

Having discussed the biomechanical strategies adopted during the concurrent performance of motor and cognitive task, it is possible to conclude that the slowing down during dual-tasking activity is a direct consequence of the application of the strategy "control of velocity" postulated by Harris and Wolpert (Harris and Wolpert, 1998). In fact, moving at lower speed requires a less set of motor commands compared to the motor-pattern associated with higher speed. Moreover, the changes in gait pattern confirm that coping with the Stroop Color and Word Test provoked a need of further resources at central level. The adoption of shorter stride length and decrease in gait speed might allow healthy and low disability individuals to continuing to prioritize the cognitive task during dual-task task performance. Instead, patients with mild to moderate disability might adopted a compensatory strategy aimed at reducing the risk of falling, consisting in increasing base of support and the time spent in double support (Wajda et al., 2013; Cameron and Lord, 2010; Nogueira et al., 2013).

Most previous studies evaluating the cognitive-motor interference have only considered gait speed as a motor parameter (Kirkland et al., 2015; Nogueira et al., 2013). Furthermore, this finding indicated that speed does not discriminate between MS patients or healthy individuals because all three studied groups significantly reduced their gait speed during dual-task condition. This is in line with the result from the meta-analysis conducted by Al-Yahya et al. (2011), which showed that the principal effect of dual-task performance, independently from the cognitive task adopted, was a detrimental effect on gait speed in both individuals with neurological disorders and unaffected individuals. However, we found that the dual-task cost values for stride time, stance phase, double support phase and stride length are significantly higher in those with MS compared to HC. Thus, the reduced ability to elaborate cognitive and motor load impacts

also the full spectrum of parameters associated with ambulation. Specifically, double support could distinguish MS patients with high disability, but not those with low disability, from healthy individuals. In summary, the analysis revealed that gait speed and stride length were sensitive motor variables in detecting significant differences from the single- to dual-task in both patients with MS and unaffected individuals, whereas balance-related spatiotemporal parameters of gait (step width, stance and double-support phase duration) were sensitive to changes only in patients with high disability.

Nevertheless, a limitation of the study has to be acknowledged. This study did not explore the influence of walking on the cognitive performance. Although the focus of the study was to analyze the changes in gait pattern induced by the Stroop Color and Word Test, the assessment of the reciprocal influence of the cognitive task on the motor task and vice versa could have provided a more complete view of the dual-task interference model and the task prioritization adopted, as stated by Plummer and Eskes (2015).

6.5 Conclusion

The present work provides a useful and validated basis for future studies about walking dual-task in patients with MS. The data shows that the combination of walking and the Stroop Color and Word Test test is a dual-task paradigm able to elicit cognitive-motor interference. Walking while performing a secondary cognitive task originates a significant alteration of gait patterns in both MS patients and healthy individuals, even though the presence of the disease and the level of disability influences the strategy adopted to cope with. In fact, not only patients with mild to moderate disability presented a larger set of spatiotemporal parameters affected, but the percent of change in stride length and gait speed was found to be in a larger magnitude with respect to unaffected individuals and minimally impaired patients. Thus, it is probably due to the difference in terms of the ability to respond most effectively to a postural threat (*postural reserve*) and the presence of cognitive deficits. The present work highlighted also to investigate all set of gait spatiotemporal parameters because, especially balance-related parameters, are able to discriminate disabled MS patients from those minimally impaired and healthy individuals.

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Chapter 7

Using kinematic parameters to explain changes in gait due to cognitive-motor interference

It is well-documented that challenging situations of daily activities, such as walking while performing a cognitive task, caused higher motor and attentional demands affecting coordination and kinematic adaptations. In this session the biomechanical adaptation strategies adopted during the simultaneous performance of a cognitive and motor task are investigated. Along with traditional gait parameters (e.g., stride length, stride width, gait speed), evaluation of joint kinematics, through advance 3D motion capture technology, is used to provide a detailed objective evaluation of dual-task motor strategy. In fact, observing joint kinematic patterns allows for a more complete description and a better understanding of the effects of cognitive-motor interference in healthy controls and individuals with MS.

7.1 Context

Walking is a dynamic, rhythmic and essential component of daily activities and the correct execution is determined by a combination of neural and mechanical parameters such as cortical activity, muscular contraction and joint kinematic. As complex motor task, it requires the central nervous system to use high levels of information processing and control strategies to coordinate and maintain efficiency and smoothness of walking (Yogev et al., 2008). Walking has been widely studied from a biomechanical perspective across healthy life span as well as in neurological disease, such as multiple sclerosis (MS). In everyday activity, walking is defined as goal-oriented task and for a significant period of time concurrent tasks, such as conversing, interacting with the mobile phone, watching street signals, are undertaken. For this reason, growing research studies have been adopted dual-task walking paradigms to investigate the interaction between cognitive and motor tasks and their mutual impact. As shown in the previous chapter, dual-task walking provokes cognitive-motor interference phenomenon, which seems to occur when the total demand of attention and the executive function exceed the individual's information processing capacity, provoking a negative effect on one or both tasks. Decreased in gait speed under dual-tasking was reported as common detrimental effect in both healthy controls and MS patients (see *Chapter 6 – paragraph 6.4.1*). On the other hand, gait changes in lower limb joint angular kinematics have received little attention in dual-task studies. The influences of cognitive load on joint kinematics have been examined in few previous studies, but still little is known about the adaptive strategies used to cope with walking dual-task activities in both healthy adults and minimally disabled MS patients (Agostini et al., 2015; Lin and Lin, 2016; Liparoti et al., 2019). Globally, it seems that cognitive load on motor tasks such as walking would affect motor coordination and lead to kinematic adaptations (Chiu, 2013). In fact, healthy young adult during challenging dual-task performance used a strategy consisting of adopting a more in-phase dynamic behavior of the lower extremities, in order to better control walking performance (Harbourne and Stergious, 2009; Longo et al., 2018). Angular kinematics variations in terms of reduction in lower limb range of motion were also detected in neurological disease such as Parkinson's disease, frontotemporal dementia and Alzheimer's disease (Speciali et al., 2014; Rucco et al., 2017). However, other factors can be recognized to influence lower limb angular joint kinematics, such as walking speed, age and sex differences (Winter et al., 1991; Bruening et al., 2015; Pau et al., 2018; Fukuchi et al., 2019). Some demographic and anthropometric parameters can be easily controlled during enrollment and randomization, while it is not the same for factors like walking speed. With regard to this, numerous authors explored changes in lower extremities kinematics during walking at different speed (Lelas et al, 2003; Hanlon and Anderson, 2006). Overall, these studies revealed that gait parameters follow a pattern of change in response to varying gait speed (Kirtley et al., 1985; Oberg et al., 1993; Lelas et al, 2003). Since during walking dual-task there are a decrease in gait

speed compared to the single-task performance, it appears crucial to take into account this aspect in the analysis of lower limb joint kinematics during walking dual-task.

Finally, it is still unclear whether the addition of a secondary cognitive task causes changes on lower limbs kinematics in healthy young adults and patients with MS. Thus, this study aims to investigate the effect of cognitive-motor interference on gait kinematics, taking into account also the effect of gait speed variation from single- to dual-task condition, in healthy young adults and in patients affected by MS ranged from minimally to moderate impaired.

7.2 Methods

7.2.1 Participants

In the period October 2017- May 2019, 81 patients with MS (54 females, 27 males; age: 45.10±12.04 years) were recruited at the Regional Multiple Sclerosis Center of Sardinia (Cagliari, Italy). To be included in the research study, participants had to have a confirmed diagnosis of MS according to the 2010 McDonald criteria (Polman et al., 2011). Only patients able to ambulate without an assisting device (i.e. cane, crutches or walking frame) for at least 100 meters and without of any other potential condition able to severely compromise gait or balance were considered in the final analysis. In this way all confounding factors lead to gait kinematic alterations, not related to the disease, were disregarded (Crosbie et al., 1993; Bachschmidt et al., 2001). Then MS patients were divided into two groups based on their disability level assessed through the Expanded Disability Status Scale (EDSS) score as follows:

- Low disability patients (EDSS 1.0-2.5, n = 37)
- Mild to moderate disability patients (EDSS 3.0-6.0, n = 44)

Forty-one age-matched healthy individuals (27 females, 14 males; age: 44.93 ± 14.00 years) free of any musculoskeletal and neurological disease were also recruited in the study. Main demographic and clinical features of MS patients and healthy control are reported in Table 7.1.

As shown in the *Chapter 5*, both healthy control and patients with MS walk significantly slower when performing dual-task. As it is generally accepted, gait kinematic parameters follow a consistent pattern of change in response to varying gait speed (Kirtley et al., 1985; Oberg et al., 1994; Lelas et al., 2003; Hanlon and Anderson, 2006). Thus, when comparing the results from dual-task condition with those from single-task condition, it is essential to account for the effects of walking speed on the kinematic parameters of interest. In order to explore the relationship between gait speed and kinematic parameters, it was used a dataset with gait data of 109 healthy individuals (58 females, 51 males; age: 34.81±14.21 years; height:

168.61±9.08 cm; BMI: 22.28±2.83 kg/m^2) and 81 MS patients (47 females, 34 males; age: 45.10±12.03 years; height: 165.77±9.03 cm; BMI: 28.75±6.87 kg/m^2).

Table 7.1. Demographic, anthropometric and clinical features of the participants. Values are expressed as mean±sd.

Variable	Healthy group	Entire MS sample	Low disability EDSS 1.0-2.5	Mild to moderate disability EDSS 3.0-6.0
Participants	41 (27F, 14M)	81 (54F, 27M)	37 (25F, 12M)	44 (29F, 15M)
Age (years)	44.93±14.00	45.10±12.04	41.08±10.39	48.48±10.42
Height (cm)	167.89±8.96	165.77±9.03	165.92±9.24	165.64±8.94
Weight (kg)	68.44±9.98	66.33±10.45	68.33±11.05	67.99±9.23
EDSS	-	3.48±1.56	1.94±0.52	4.19±0.97

Note. EDSS: Expanded Disability Status Scale

7.2.2 Dual-task experimental procedure

Participants were tested under two conditions: they were first requested to walk along a straight path in a 10-meter walkway at self-selected speed (single-task condition); then, to perform a second trial during which they had to complete a secondary cognitive task the Stroop Color and Word Test while walking (dual-task condition). As shown in the *Chapter 5*, the setup consisted of a 48" LCD TV screen located perpendicularly to the gait direction, used to administer the Stroop Color and Word Test. During dual-task performance, participants completed the third table of the test, also named the incongruent color words test. In the incongruent condition participants had to name the word's font color and to inhibit reading the word (e.g., the word "red" presented in a different color, e.g., blue font color). Each dual-task trial differed in the sequences of the color words. The time interval between two consecutive words occurrences was varied to avoid rhythm. The words (46–96 cm in width and 15–19 cm in height) were displayed at a distance in the range of 200–750 cm between the participant and the screen.

7.2.3 Kinematic data collection

Kinematic data were collected performing a 3D gait analysis, using a motion-capture system composed of eight infrared cameras (Smart-D, BTS Bioengineering, ITALY), set at a frequency of 120 Hz. Preliminarily, data of height, weight, anterior superior iliac spine (ASIS) distance, pelvis thickness, knee and ankle width, leg length (distance between ASIS and medial malleolus) were acquired using a digital scale, an ultrasonic height measurement device, a pelvimeter and a flexible meter. Then, 22 spherical retro-reflective passive markers (14 mm diameter) were placed on the skin of participant's lower limbs and trunk at specific

landmarks as described by the Davis' protocol (Davis et al., 1991). Afterwards, participants walked barefoot along a 10-meter straight walkway at their comfortable speed. Each participant completed at least six trials for each condition. The raw data were processed with the dedicated software SmartAnalyzer (BTS Bioengineering, Italy) to calculate the following parameters (McGinley et al., 2009):

- Kinematic pattern on the sagittal plane: hip and knee flexion-extension and ankle dorsi-plantarflexion angle variations during the gait cycle. The sagittal plane joint angle data of the hip, knee and ankle of each gait cycle were normalized to 0-100% with a step of 1%. An average across the six trials for single- and dual-task condition was calculated for each individual.
- Peak values of the average curves of hip, knee and ankle on the sagittal plane included knee flexion at mid-stance and mid-swing phase, ankle plantarflexion at terminal stance phase and, hip extension and flexion at terminal stance/early swing and mid-swing phase respectively (see *Chapter 5- Paragraph 5.2.5*).
- Dynamic range of motion (ROM) calculated during the whole gait cycle as the difference between the maximum and minimum value recorded for the angle during each trial condition (see *Chapter 5- Paragraph 5.2.5*).

7.2.4 Statistical analysis

Descriptive analyses were generated for all demographic and clinical variables of the groups. Results were expressed as a mean ± standard deviation. Normal distribution of the data was assessed by the Kolmogorov-Smirnov test. This analysis indicated that all variables of the study met the criteria of normality. Because of all the variables (gait speed, dynamic ROMs and peak sagittal plane kinematic parameters) were normally distributed, parametric tests were performed for the following analyses. The issue of between-limb dependence in statistical analysis has been identified in several research studies (Menz, 2005; Stewart et al., 2018). In order to avoid misleading significant conclusion due to the inclusion of both limbs for each individual when kinematic data are highly correlated, a Pearson product-moment correlation analysis was accounted between right and left kinematic curves. First of all, the possible differences introduced in gait patterns by the cognitive load was explored for hip, knee and ankle joint angles on the sagittal plane using a whole curve analysis (Park et al., 2017; Bruening et al., 2015). Two-way repeated measure of variance (RM-ANOVA) was calculated at each point of the gait cycle to detect differences between task condition (single-task and dual-task conditions) and among groups (healthy adults, low disability and mild to moderate disability MS patients). Thus, it was possible to define in which interval of the gait cycle differences associated with task conditions occurred. When a significant main effect was reached, *post-hoc* with Holm-Sidak test for pairwise comparison was carried out to assess intra- and intergroup differences. Two-way repeated measure analysis of variance (RM-ANOVA) was further performed to compare the

dependent variables (dynamic ROMs and peak sagittal plane kinematic parameters) between task condition (single-task and dual-task conditions) and participant's level of disability (healthy adults, low disability and mild to moderate disability MS patients).When a significant main effect was reached, *post-hoc* tests with Holm-Sidak correction for multiple comparisons were conducted to assess task condition or level of disability differences. The effect of gait speed was assessed for each peak kinematic parameter and dynamic ROM, using the data recorded during normal walking trials of healthy individuals and patients with MS, separately. The correlation between gait speed and the selected kinematic parameters was assessed with Pearson's product-moment correlation analysis. A significant correlation was assumed for $p<0.05$. A significant correlation indicates a reliable positive or negative relationship between kinematic parameters and gait speed. Then, a linear regression was fit for each parameter and the goodness of the fit was verified with the coefficient of determination (R^2). In order to define if the kinematic variation assessed between normal and dual-task walking was due to a gait speed changing, the linear regression equations were further used to predict changes in the kinematic parameters accounting only the effect of velocity variation that occurred between the single- and dual-task performances. Differences between the predicted kinematic variation due to only a gait speed variation and the experimental variation, accounted also the presence of the cognitive load, were compared performing a Students t-test. Significant level was set at 0.05 and the effect size was assessed with the eta-squared (η^2) for all the analysis.

7.3 Results

Table 7.1 shows the demographic and clinical characteristics of the participants by group. None of the demographic variables were significantly different among the groups ($p>0.05$). Mean age was similar in the three groups, and women were twice than man in both healthy individuals and MS subgroups.

Results from Pearson product-moment analysis showed that left and right kinematic curves were highly correlate for both healthy control (hip: $r=0.983$ $p<0.001$; knee: $r=0.910$ $p<0.001$; ankle $r=0.899$ $p<0.001$) and the entire sample of MS patients (hip: $r=0.993$ $p<0.001$; knee: $r=0.824$ $p<0.001$; ankle $r=0.738$ $p<0.001$). Thus, only one limb randomly selected was used in the subsequent analysis.

7.3.1 Joint angle curves and discrete points

The angle variations in the sagittal plane along the gait cycle for hip, knee and ankle joints are reported in Figure 7.1. The two-way RM-ANOVA accounted at each time point for the hip, knee, and ankle kinematics in the sagittal plane for the three groups revealed the existence of significant differences between single- and dual-task conditions ($p<0.05$). In particular, *post hoc* analysis revealed similar pattern of decrease plantarflexion at pre-swing phase during dual-task condition for healthy adults (46% -65% of the gait cycle,

p<0.05), low disability (46%-66% of the gait cycle, p<0.05) and mild to moderate disability MS patients (52%-72% of the gait cycle, p<0.05). Healthy adults and low disability patients showed reduction in knee flexion at mid-stance (HC: 0%-12% of the gait cycle, p<0.05; LD: 0%-20% of the gait cycle, p<0.05) and mid-swing phases (HC: 50%-72% of the gait cycle, p<0.05; LD: 46%-73% of the gait cycle, p<0.05). Instead, mild to moderate disability MS patients presented a significant reduction in knee flexion only at mid-swing phase (50%-81% of the gait cycle, p<0.05). As regards hip joint, patients with mild to moderate disability exhibited a reduction in hip flexion at initial phase of the stance (0%-13% of the gait cycle, p<0.05) and during the swing phase (78%-100% of the gait cycle, p<0.05), and also a reduction of the extension at the terminal stance and pre-swing phase (35%-55% of the gait cycle, p<0.05). Healthy adults and MS patients with low disability showed only a reduction flexion from the heel strike to the early mid-stance (for both groups 0%-10% of the gait cycle, p<0.05) and at end of the swing phase (HC: 80%-100% of the gait cycle, p<0.05; LD: 77%-100% of the gait cycle, p<0.05).

7.3.2 Dynamic range of motion

The average data for dynamic ROMs of hip, knee and ankle are reported in Table 7.2. The RM-ANOVA analysis detected a significant main effect of task condition ($F_{1,120}$ = 20.63, p<0.001, η^2= 0.51) on hip dynamic ROM, but not task × group interaction ($F_{2,119}$ = 1.404, p=0.669, η^2= 0.03). Specifically, *post-hoc* analysis revealed a significant reduction of hip ROM between single- and dual-task within each group (for all groups p<0.001). Comparable reduction trend was found also for knee and ankle dynamic ROMs. In fact, RM-ANOVA revealed a significant main effect of task ($F_{1,120}$ = 28.12, p<0.001, η^2= 0.56) on knee ROM. Moreover, a significant interaction task × group was detected ($F_{2,119}$ = 7.58, p<0.001, η^2=0.13). The subsequent *post-hoc* analysis revealed for the three groups a significant reduction of the knee ROM during dual tasking. A pattern of results similar to that of previous analyses was found also for the ankle dynamic ROM with a significant reduction between single- and dual-task. In particular RM-ANOVA analysis showed a significant mean effect of task condition ($F_{1,120}$ = 29.19, p<0.001, η^2=0.25), but no significant interaction task × group was found ($F_{2,119}$ = 1.67, p=0.542, η^2=0.02).

The two-way RM-ANOVA also accounted a significant main effect of group variables for the following parameters: hip ROM ($F_{2,119}$ = 9.72, p<0.001, η^2=0.69), knee ROM ($F_{2,119}$ = 30.23, p<0.001, η^2= 0.29) and ankle ROM ($F_{2,119}$ = 21.44, p<0.001, η^2=0.37). This mean, as expected, that the mild to moderate disability group had a significantly decreased in the dynamic ROM of hip (-11.81%, p<0.001), knee (-25.49%, p<0.001) and ankle (-33.94%, p<0.001) with respect to healthy individuals. While, low disability MS individuals had a significantly decreased in the dynamic ROM of knee (-6.87%, p<0.05) and ankle (-19.61%, p<0.001) compared to healthy controls. No significant difference was detected for the dynamic hip ROM.

7.3.3 Peak sagittal kinematic curves

The results of peak sagittal kinematic curves are summarized in Table 7.3. The RM-ANOVA analysis revealed main effect of task condition as regard the ankle plantarflexion peak ($F_{1,120}$ = 29.26, $p<0.001$, $\eta^2=0.37$), the flexion peak of the knee at mid-stance phase ($F_{1,120}$ = 65.95, $p<0.001$, $\eta^2=0.36$), the flexion peak of the knee at swing phase ($F_{1,120}$ = 65.95, $p<0.001$, $\eta^2=0.20$), the flexion peak of the hip ($F_{1,120}$ = 30.66, $p<0.001$, $\eta^2=0.26$) and the peak hip extension ($F_{1,120}$ = 32.80, $p<0.001$, $\eta^2=0.21$). A significant interaction between task × group was found only for the knee flexion at mid-stance phase ($F_{2,119}$ = 4.95, $p<0.05$, $\eta^2=0.02$), for the peak hip extension ($F_{2,\ 119}$ = 21.06, $p<0.001$, $\eta^2=0.29$) and for the peak hip flexion (($F_{2,\ 119}$ = 3.49, $p<0.05$, $\eta^2=0.29$). The follow *post-hoc* analysis revealed a significant decrease of ankle plantarflexion, knee flexion at swing phase and hip flexion at mid-swing phase for all the three groups ($p<0.001$) during dual-task performance. Instead, *post-hoc* analysis detected a significant reduction of the knee flexion during the load response phase for the healthy control ($p<0.001$) and for MS patients with low disability ($p<0.001$), while a significant reduction of the peak hip extension was revealed for mild to moderate disability group ($p<0.001$) during dual-task. The two-way RM-ANOVA also accounted a significant main effect of group variables for the following parameters: peak knee flexion at swing phase ($F_{2,\ 119}$ = 13.62, $p<0.001$, $\eta^2=0.89$), peak ankle plantarflexion ($F_{2,\ 119}$ = 28.83, $p<0.001$, $\eta^2=0.92$), peak hip extension ($F_{2,\ 119}$ = 18.40, $p<0.001$, $\eta^2=0.93$) and peak hip flexion at swing phase ($F_{2,\ 119}$ = 3.65, $p<0.05$, $\eta^2=0.15$). This mean, as expected, that the mild to moderate disability group in single-task performance had a significantly decreased in knee flexion during swing phase ($p<0.001$), in ankle plantarflexion at push-off event ($p<0.001$) and in hip extension ($p<0.001$), as well as at the terminal stance phase, with respect to healthy individuals. While, low disability MS individuals showed in single-task performance a decrease in peak knee flexion during swing phase ($p<0.001$) compared to healthy controls.

Table 7.2. Dynamic ROMs in healthy controls and MS patients with low and mild to severe disability under single- and dual-task conditions. Values are expressed as mean ± sd.

		Healthy control		Low disability – MS group		Mild to moderate disability- MS group	
		ST	**DT**	**ST**	**DT**	**ST**	**DT**
ROM (degrees)	**Hip**	46.58 ± 4.05	44.83 ± 4.32†	43.88 ± 4.06	41.66 ± 5.99†	41.57 ± 6.10	38.04 ± 6.17†
	Knee	61.10 ± 3.86	59.31 ± 4.40†	57.17 ± 6.02	54.84 ± 6.00†	48.69 ± 6.98	45.07 ± 6.74†
	Ankle	31.23 ± 4.92	29.31 ± 4.91†	26.11 ± 5.76	23.84 ± 6.07†	23.31 ± 5.53	21.37 ± 5.86†

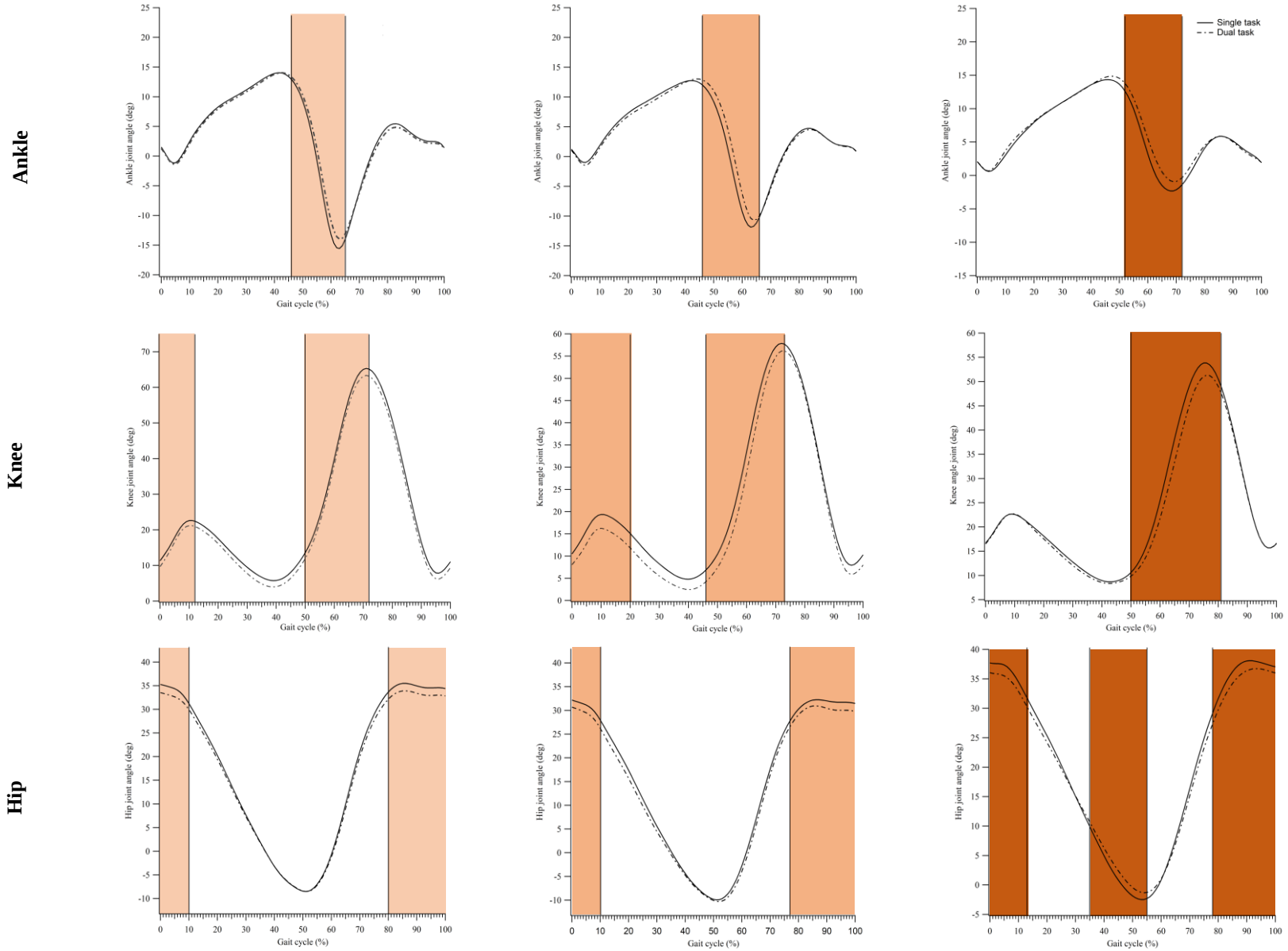
The symbol † denotes a significant difference between single-task and dual-task task ($p < 0.05$). **Note**. **ROM**: range of motion; **ST**: single-task; **DT**: dual-task.

Table 7.3. Peak calculated from the sagittal kinematic curves of hip, knee and ankle in healthy controls and MS patients with low and mild to severe disability under single- and dual-task conditions. Values are expressed as mean ± sd.

		Healthy control		Low disability – MS group		Mild to moderate disability- MS group	
		ST	**DT**	**ST**	**DT**	**ST**	**DT**
Hip	**Peak extension**	-10.13 ± 5.87	-9.90 ± 6.20	-9.90 ± 7.36	-9.58 ± 6.61	-2.99 ± 8.71	0.40 ± 8.57†
	Peak flexion swing	35.85 ± 4.80	33.71 ± 5.03†	35.94 ± 6.47	33.31 ± 6.59†	32.01 ± 7.21	30.37 ± 7.38†
Knee	**Peak flexion mid-stance**	22.66 ± 6.38	20.06 ± 6.82†	20.73 ± 6.62	16.38 ± 6.36†	23.73 ± 6.74	22.50 ± 7.49
	Peak flexion swing	65.31 ± 5.36	62.26 ± 5.43†	59.12 ± 5.79†	56.77 ± 5.24†	56.08 ± 6.05	52.07 ± 6.43†
Ankle	**Peak plantarflexion**	-16.45 ± 6.30	-14.01 ± 6.52†	-13.77 ± 6.92	-10.19 ± 6.45†	-5.68 ± 6.06	-2.02 ± 5.79†

The symbol † denotes a significant difference between single-task and dual-task task ($p < 0.05$). **Note**. **ST**: single-task; **DT**: dual-task.

Figure 7.1. Lower limb kinematic graphs during single- (solid line) and dual-task (dashed line) condition. Kinematic curves of healthy individuals, low disability and mild to severe disability MS patients are reported in column from the left to right. Shaded areas denote the periods of the gait cycle in which a significant difference between single- and dual-task conditions exists ($p < 0.05$).



7.3.4 Influences of gait speed on kinematic changes

From the dataset used for exploring correlation between gait speed and kinematic parameters, healthy individuals' walking speeds were ranged from 0.84 m/s to 1.66 m/s and MS patients' walking speeds from 0.29 m/s to 1.51 m/s. Results from Pearson's bivariate correlation analysis are reported in Table 7.5 and Figure 7.2. In particular, the analysis showed that gait speed was moderately correlate with hip dynamic ROM for both healthy ($r=0.570$, $p<0.001$) and MS patients ($r=0.693$, $p<0.001$). A moderate correlation between gait speed and knee dynamic ROM was found for both healthy individuals ($r=0.368$, $p<0.001$) and MS patients ($r=0.769$, $p<0.001$). Instead, a low correlation between gait speed and ankle dynamic ROM for healthy control ($r=0.268$, $p<0.001$), while MS patients showed a moderate correlation ($r=0.532$, $p<0.001$). From the analysis of peak sagittal plane kinematic parameters, we found a moderate significant correlation in the healthy control group for the peak knee flexion at mid-stance phase ($r=0.458$, $p<0.001$) and for the peak ankle plantarflexion ($r= -0.349$, $p<0.001$). Whereas, MS patients showed a moderate correlation between gait speed and peak hip extension ($r= -0.588$, $p<0.001$), peak knee flexion at swing phase ($r=0.566$, $p<0.001$) and peak ankle plantarflexion ($r= -0.584$, $p<0.001$). For the above kinematic parameters, significantly correlated with gait speed, the linear regression equation was fitted as shown in Figure 7.2, the regression equations are summarized in Table 7.4. In Table 7.6 and Table 7.7 are reported the results of predicted and measured variation of peak sagittal plane kinematic points and dynamic ROMs. The predicted variation of hip, knee and ankle ROMs was significantly different from the experimental variation measured in all the three groups ($p<0.05$). The Students t-test revealed that the predicted variation of peak knee flexion at mid-stance phase and of the peak ankle plantarflexion was significant smaller than the experimental one for healthy individuals, with $p=0.001$ and $p=0.002$, respectively. For comparison with the literature, the predicted variation estimated with our linear regression model for the peak knee flexion at mid-stance phase is compared with the ones assessed with Lelas et al., Oberg et al., Kirstley et al. and Fukuchi's equations (Kirstley et al., 1985; Oberg et al., 1993; Lelas et al., 2003; Fukuchi et al., 2019), and reported in Table 7.8. Regarding MS patients, in both subgroups a significant difference between predicted and experimental variation was found for the peak knee flexion at swing phase and peak ankle plantarflexion ($p<0.05$). The predicted variation of peak hip extension was significant different to the experimental one only for patients with mild to moderate disability ($p<0.001$).

Table 7.4. Correlations between gait speed and dynamic ROMs of hip, knee and ankle, and relative regression equations (v = velocity [m/s]).

Group	Parameter	Unit	Equation	R^2	*r*
Healthy individuals (n=109)	ROM hip flexion-extension	Degrees	23.70 + 17.47 *v*	0.325	0.570*
	ROM knee flexion-extension	Degrees	48.26 + 9.80 *v*	0.135	0.368*
	ROM ankle plantarflexion	Degrees	19.17 + 9.12 *v*	0.072	0.268*
MS individuals (n=80)	ROM hip flexion-extension	Degrees	29.53 + 13.86 *v*	0.474	0.693*
	ROM knee flexion-extension	Degrees	28.42 + 25.57 *v*	0.592	0.769*
	ROM ankle plantarflexion	Degrees	14.51 + 10.61 *v*	0.283	0.532*

The symbol * denotes a significant correlation at p<0.001. **Note. ROM:** range of motion.

Table 7.5. Correlations between gait speed and peak sagittal plane kinematic parameters, and relative regression equations (v = velocity [m/s]).

Group	Parameter	Unit	Equation	R^2	*r*
Healthy individuals (n=109)	Peak hip flexion	Degrees	30.63 + 3.65 *v*	0.016	0.124
	Peak hip extension	Degrees	5.42 – 4.08 *v*	0.013	-0.114
	Peak knee flexion mid-stance	Degrees	1.65 + 13.73 *v*	0.210	0.458*
	Peak knee flexion swing	Degrees	59.07 + 4.32 *v*	0.019	0.139
	Peak ankle plantarflexion	Degrees	-0.37 – 12.62 *v*	0.122	-0.349*
MS individuals (n=80)	Peak hip flexion	Degrees	33.53 + 0.10 *v*	0.025	0.004
	Peak hip extension	Degrees	8.53 – 15.86 *v*	0.340	-0.588*
	Peak knee flexion mid-stance	Degrees	14.55 + 6.78 *v*	0.067	0.258
	Peak knee flexion swing	Degrees	37.33 + 20.59 *v*	0.408	0.566*
	Peak ankle plantarflexion	Degrees	4.29 – 14.63 *v*	0.341	-0.584*

The symbol * denotes a significant correlation at p<0.001.

Figure 7.2. Scatterplots of the correlation between dynamics ROMs of hip, knee and ankle, peak knee flexion at stance and swing phase, and peak ankle plantarflexion. Red and black circles represent MS and healthy control group, respectively; while solid lines represent regression lines.

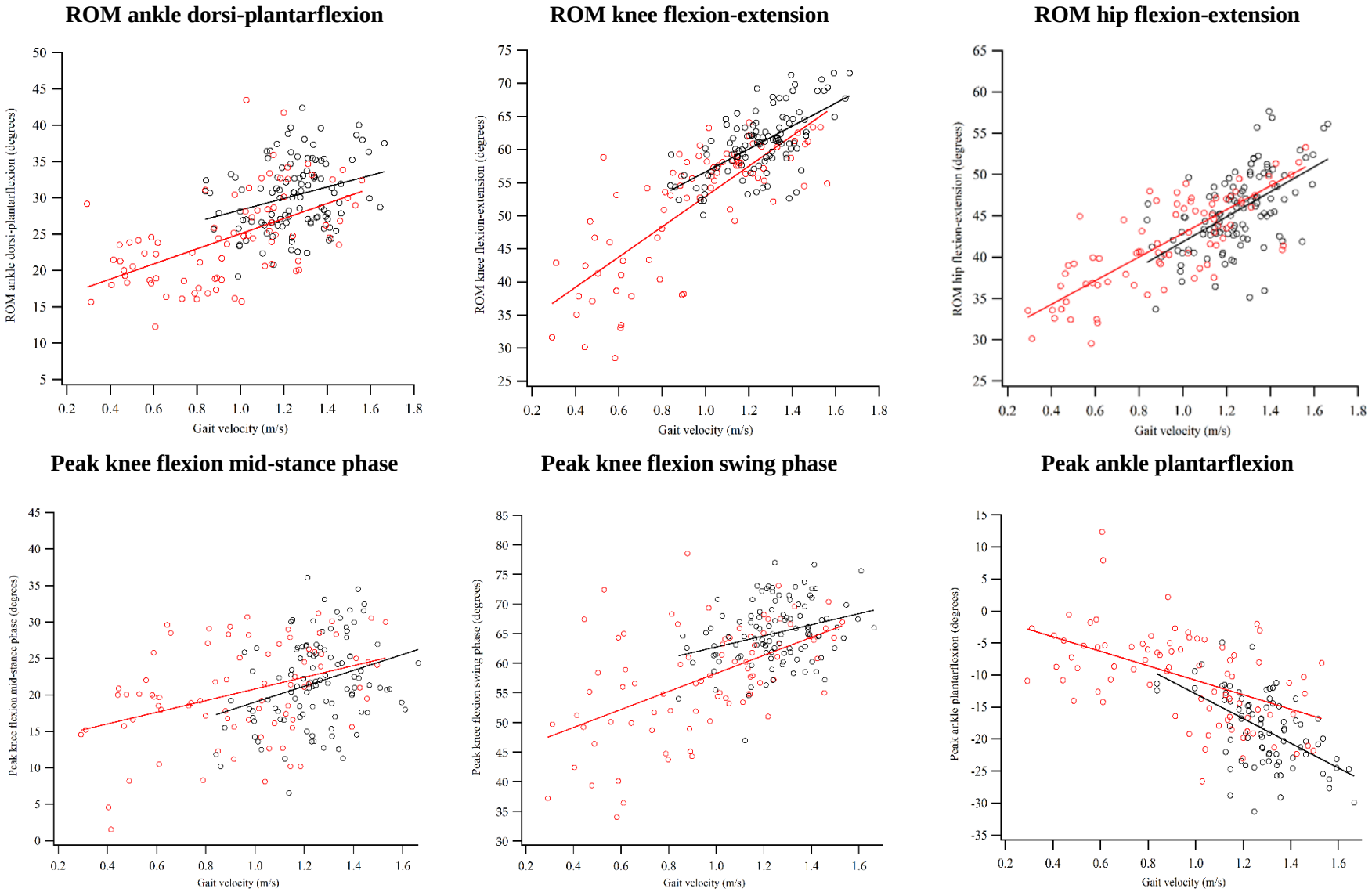


Table 7.6. Predicted and experimental variation measured for the dynamic ROMs of hip, knee and ankle in the three groups. Values are reported as mean ± sd.

		Healthy control		Low disability – MS group		Mild to moderate disability- MS group	
		Predicted variation	**Experimental variation**	**Predicted variation**	**Experimental variation**	**Predicted variation**	**Experimental variation**
ROM mean variation (degrees)	**Hip**	1.07 ± 0.84	2.15 ± 0.68†	1.04 ± 0.58	2.45 ± 0.59†	1.17 ± 0.69	2.53 ± 0.59†
	Knee	0.70 ± 0.33	1.82 ± 0.64†	1.27 ± 0.50	3.38 ± 0.49†	1.52 ± 0.68	3.62 ± 0.733†
	Ankle	0.72 ± 0.34	1.92 ± 0.70†	1.08 ± 0.47	2.24 ± 0.45†	1.02 ± 0.76	2.00 ± 0.55†

The symbol † denotes a significant difference between predicted variation and experimental variation ($p<0.05$). **Note. ROM:** range of motion.

Table 7.7. Predicted and experimental variation measured for the peak kinematic curve values. Values are reported as mean ± sd.

	Group	**Parameter**	**Unit**	**Predicted variation**	**Experimental variation**
Healthy individuals	**-**	Peak knee flexion mid-stance	Degrees	1.09 ± 0.80	2.60 ± 0.81†
		Peak ankle plantarflexion	Degrees	1.18 ± 0.59	2.55 ± 0.75†
MS individuals	**Low disability**	Peak hip extension	Degrees	1.56 ± 0.76	1.03 ± 0.56
		Peak knee flexion swing	Degrees	1.18 ± 0.79	2.39 ± 0.89†
		Peak ankle plantarflexion	Degrees	1.17 ± 0.75	2.76 ± 0.91†
	Mild to moderate disability	Peak hip extension	Degrees	1.59 ± 0.78	2.59 ± 0.74†
		Peak knee flexion swing	Degrees	1.44 ± 0.71	2.71 ± 0.53†
		Peak ankle plantarflexion	Degrees	1.21 ± 0.82	2.91 ± 0.61†

The symbol † denotes a significant difference between predicted variation and experimental variation ($p<0.05$).

Table 7.8. Comparison with the literature, variation of the peak knee flexion at mid-stance was predicted with the regression equations presented by other authors.

Author (year)		Regression equation	R^2	Predicted kinematic variation ($\Delta v = 1.28 - 1.20$)	Experimental kinematic variation from ST to DT
Present study	Linear correlation	1.65 + 13.73 *v*	0.210	1.10	2.60
Kirtley et al. (1985)	Linear correlation	4.7 + 13.0 *v*	0.601	1.04	
Lelas et al. (2003)	Quadratic correlation	-2.84 v^2 + 19.59 *v* – 4.00	0.600	1.01	
Oberg et al. (1993)	Linear correlation	1.2 + 13.5 *v*	0.437	1.08	
Fukuchi et al. (2019)	Quadratic correlation	-17.27 v^2 + 50.96 *v* – 2.24	0.532*	0.60	
Hanlon and Anderson (2006)	Linear correlation	-	0.210	-	

The symbol * indicates that the authors used adjusted R^2. **Note. ST:** single-task; **DT:** dual-task.

7.4 Discussion

Coordination of limb movements is known to be affected by the cognitive load imposed during walking dual-task (Yogev-Seligmann et al., 2013). The impact of dual-task on locomotion has been widely quantified in terms of changes in spatiotemporal parameters by several authors in both healthy and MS individuals (Al-Yahya et al., 2011; Leone et al., 2015). However, these measures do not reveal which specific kinematic adaptations individuals use to maintain a satisfactory motor performance and dynamic balance when they walk and perform a concurrent cognitive task. The identification of the actual gait pattern requires a more detailed gait analysis, including analysis of joint kinematics.

As shown in the previous chapter, and according also to the results of other authors (Al-Yahya et al., 2011; Leone et al., 2015), the main effect of walking dual-task is a decrease in gait speed for both healthy individuals and patients with MS. On the other hand, several studies have been explored the effects of gait speed on joint kinematics, reporting increase in hip flexion, hip extension, knee flexion, and ankle plantarflexion angles with higher gait speed (Lelas et al., 2003; Fukuchi et al., 2019). In the present study, the influence of gait speed changes has been excluded using a prediction method, which allows quantifying the expected angle variations related to the measured speed change. Therefore, we can conclude that one part of the lower limb joint angular kinematic variation detected during dual-task performance was accounted for the presence of the cognitive load.

The results of the present study suggest that both healthy individuals and patients with MS altered their joint kinematics to cope with the motor-cognitive interference that resulted from walking dual-task. The influences of cognitive task on gait kinematics have been previously examined, but still little is known about the motor strategies adopted during walking dual-task activities in both healthy individuals and patients affected by neurological disorders.

The dynamic ROMs of hip, knee and ankle joints were significantly smaller during dual-task condition for both healthy controls and MS patients. Previous studies have shown similar results, where ROMs of hip, knee and ankle joint along the sagittal plane significantly decrease during dual-task condition in both healthy adults and neurological patients (Speciali et al., 2014; Lin et al., 2016; Rucco et al., 2017; Ko et al., 2018; Liparoti et al., 2019).

Consistent changes in ankle kinematic were found for both healthy controls and the overall MS group. In fact, beyond the disease, both healthy adults and patients with MS showed a decrease in peak ankle plantarflexion during pre-swing phase. This reduction may lead to a not adequate active push-off during terminal stance and, consequently, the generation of less energy required to move the limbs forward. A reduced push-off is linked, especially in mild to moderate disable patients, to absent heel-rise in terminal stance and foot clearance at initial swing. On the basis of this consideration, dual-task condition might contribute to increased risk of falls in those patients with an increase level of disability.

Mixed results have been reported regarding this aspect. Lin et al. (2016) observed similar results of reduced ankle plantarflexion in healthy adults when walked and concurrently performed the *n-back* working memory test; while, Agostini et al. (2015) reported a trend forward a reduction of the peak ankle plantarflexion in a group of healthy adults during the simultaneous performance of walking and texting tasks.

Liparoti et al. (2019) did not detect any changes in ankle joint kinematics in both healthy controls and MS individuals minimally impaired when they walked and concurrently performed the serial subtraction test. An increase stiffness of the ankle joint at the push-off event during walking dual-task was instead detected by Hallal et al. (2013) in healthy older adults. This author postulated that ankle stiffness was a result of muscular co-contractions adopted by old adults in order to maintain dynamic balance during challenging dual-task conditions. Finally, these results suggested the adoption of a neuromuscular mechanism that stiffens ankle joint in order to maintain stability during walking dual-task. However, an increase in stiffness is not always a good response because it might contribute to increase risk of falls (Cenciarini, et al., 2010).

According to the results of this study, both healthy individuals and MS patients with low disability showed a reduction of the peak knee flexion at mid-stance during dual-task performance. The extended knee may

be a strategy to achieve joint stabilization, however this could reduce lower limb musculature's ability to absorb the impact force produced during weight acceptance at stance phase (Shamaei and Dollar, 2011).

All three groups commonly reported a reduction of peak knee flexion angle at swing phase. Since in early swing phase knee flexion is a passive movement, resulting from the active plantarflexion, the decrease of the peak knee flexion could be attributed to the reduction detected in the peak ankle plantarflexion.

The decrease of the peak knee flexion angle during the weight acceptance phase of the gait cycle and the swing phase observed in this study for the healthy controls is consistent with literatures (Lin and Lin, 2016; Seymore et al., 2017; Grindle et al., 2018).

Regarding to changes in hip biomechanics during dual-task performance, all three groups presented a reduction of hip flexion angle at mid-swing phases. However, only patients with mild to moderate disability showed a significant reduction of the peak hip extension at the end of the stance phase. Overall, during single-task performance MS patients with mild to moderate disability tended to walk with less hip extension at pre-swing phase compared to unaffected subjects and minimally disabled MS patients. The reduction of the peak hip extension in patients with mild to moderate disability could be caused by a significant hip tightness or hip flexion contractures or weakness of hip flexor-extensor muscle, preventing the hip from achieving full extension during walking (Filli et al., 2018). Moreover, hip extension at toe-off was found to be further reduced in dual-task condition compared to single-task. The increase of hip flexion at terminal stance may be a compensatory strategy associated with reduced push-off ability. As also previously reported, they may increase the hip flexion to achieve greater power at hip joint level to move forward the leg (Kelleher et al., 2010).

Thus, the kinematic patterns of gait in mild to moderate disability patients appear quite similar to those observed in unaffected subjects and MS patients with low disability for ankle joint, but opposite at the proximal level.

According to these results, changes in kinematic parameters due to the simultaneous performance of cognitive and walking task occurred both in healthy adults and in patients with MS, although the kinematics gait adaptation strategy employed to maintain dynamic balance was different and dependent on level of disability. The strategy unconsciously adopted by healthy controls and patients with low disability seems to be similar. These two groups adopted in dual-task condition a stiffening strategy of the knee during loading acceptance phase. Instead, the dual-task strategy adopted by mild to moderate MS patients differed from that of healthy and low disabled individuals. Under dual-task condition MS patients with mild to moderate disability walked with reduced joint excursions including a reduced hip extension during terminal stance. Thus, patients with mild to moderate disability seems to use a different strategy specifically during

push-off to ensure forward progression of the limb. In fact, patients with mild to moderate disability adopted a *hip strategy* consisting in increasing hip flexion at late stance/pre-swing phase of the gait cycle to compensate decreased plantarflexion.

The results showed that the kinematic of the distal segment (e.g., shank-foot) was significantly different in both healthy individuals and MS patients during dual-task performance compare to single-task. This implies that although proximal joints play a greater role in balance and walking control in comparison to distal joints (Chiu et al., 2013), the correct adjustment of distal segments may also be important during late stance and swing phase for accommodating more complicated walking task. Thus, these findings indicate the importance of controlling also distal segment movement, especially, during terminal stance and swing phase, which could be critical for safe foot clearance and forward progression of the limb (Chiu et al., 2013). This is relevant because the lack of ability to adjust distal joint, typically showed by mild to moderate MS patients, may result in stumbling and falling during walking dual-task.

These preliminary results may need to be integrated in future studies with kinetic information and EMG analysis in order to have better understanding of lower extremity kinetics and muscle activation during functional activities, such as dual-tasking. The kinetic analysis can give more insight in terms of power generated and absorbed at interested joints during the various phases of the gait cycle; while EMG analysis can provide high levels information of lower extremity muscle co-contraction in order to detect differences between single- and dual-task conditions.

7.5 Conclusion

Healthy controls and patients affected by MS adopted different strategies to cope with more cognitively demanding task conditions. These differences could be influenced by multifactorial reasons. The *postural reserve* might be one factor that contributes to the strategy selected. Healthy controls and MS patients with low disability, having higher *postural reserve*, allocated attentional resources toward the secondary cognitive task, compromising distal segment kinematics. Contrary, patients with mild to moderate disability applied a stiffness regulation at ankle and hip joints to deal with the uncertainties introduced by the cognitive load, either to maintain at satisfactory level of dynamic balance during walking or to a decrease ability to respond most effectively to a postural threat (reduction in *postural reserve*).

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Chapter 8

Towards the use of transcranial direct current stimulation to improve walking: a quantitative study.

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique, which has the potential to modulate cortical excitability. The effects of tDCS are known to outlast the stimulation period, and in some cases, repeated applications have been found to produce long lasting clinically relevant effects. The primary aim of this chapter is to explore the reliability and therapeutic potential of this technique in improving walking in MS patients, when it is paired with a physical activity training. Thanks to advanced wearable sensor technologies, it was possible obtained objective and quantitative measures of walking day-by-day across the intervention period.

8.1 Context

Multiple sclerosis (MS) is the leading cause of progressive functional impairments such as motor, sensory and cognitive dysfunctions in younger adults (Cameron and Wagner, 2011). Among the wide spectrum of potential symptoms, gait dysfunction is one of the most troublesome due to its association with disability, compromising functional independence in several activities of daily living and overall quality of life (LaRocca, 2011). Gait alterations, which typically result in reduced speed, walking endurance, step length and alteration of the stance/swing phase duration (Givon et al., 2009; Pau et al., 2016), are reported by around the 70% patients with MS as the most challenging aspects of the disease (LaRocca, 2011).

Disease-modifying and symptomatic pharmacological treatments are designed to slow down the course of the disease and are only partially effective in the treatment of the motor symptoms (Motl et al., 2010). In fact, the most common approach to manage walking impairment and improve ambulation is motor rehabilitation (Beer et al., 2012). Among the motor rehabilitation techniques, physical activity has been considered the most effective non-pharmacological treatment in MS with robust evidence for improvements in walking outcomes (Motl et al., 2017). Several scientific evidences have shown that physical activity and exercise training have also promising beneficial effects in people with MS on other outcomes, such as fitness, mood, cognitive functions and quality of life (Motl et al., 2009; Jonsdottir et al., 2018). Physical training may also lead to changes at the functional and structural level of brain organization both in healthy people and MS patients (Prosperini and Filippo, 2019). Given that MS is a chronic, long-lasting and disabling disease, ideally rehabilitative interventions should minimize functional disability and maximize walking ability, while simultaneously facilitating plasticity of neural pathways that execute walking in order to achieve long-term restoration of function (Devasahayanah et al., 2017; Pearson et al., 2015).

Non-invasive brain stimulation (NIBS) techniques are emerging for adjunctive use in rehabilitation (Sanchez-Kuhn et al., 2017). Among NIBS therapies, transcranial direct current stimulation (tDCS) has shown several advantages over the other methods, including a favorable safety and tolerability profile, easiness of application, affordability and portability of devices, with the possibility of remote delivery (Charvet et al., 2015; Bikson et al., 2016). tDCS delivers weak (range between 1 and 2.5 mA) electrical current passed through sponge electrodes placed on the scalp to target brain regions of interest. Depending on the polarity of the stimulation cortical excitability can be increase (under the anode) or reduce (under the cathode) in the underlying cortex. Thus, the stimulation alters brain functions according to the direction of the current flow that differently modulates the resting membrane potential of the stimulated neurons (Lang et al., 2004a). The effect of tDCS are cumulative, with multiple repeated stimulation sessions (i.e. daily across weeks) seems to generate significant long-lasting neuroplasticity changes and a superior persisting modulating effect on the cerebral cortex (Woods et al., 2017). Substantially, anodal tDCS may

interact with long term potentiation (LTP) phenomena causing changes in synaptic efficacy and promoting synergistic effects when paired with a training activity (Nitsche et al., 2005). In the last decade, the growing number of interventional trials based on the use of tDCS proves the interest in the application of this technique for use in neurological disorders.

Preliminary studies of tDCS use in MS have reported efficacy for the management of symptoms such as pain, fatigue, spasticity, anxiety or depression, muscle strength, and manual dexterity (Mori et al., 2010; Ferrucci et al., 2014; Chalah et al., 2017; Charvet et al., 2018;). Sham-controlled trials have found that tDCS improves symptoms of fatigue in people with MS, when compared to sham stimulation with lingering benefits for several weeks following stimulation (Ferrucci et al., 2014; Saiote et al., 2014; Charvet et al., 2018). Beyond symptom management, tDCS has been theorized to be a neuromodulation tool able to provoke synergetic effects when paired with cognitive or physical rehabilitation program with the chance to have superior effects compare to the single technique application (Roche et al., 2015; Steinberg et al., 2019).

Several cross-sectional studies have begun in people with MS to investigate the feasibility and the effectiveness of a combined treatment tDCS and cognitive rehabilitation (Charvet et al., 2015; Mattioli et al., 2016), but no studies have been conducted pairing tDCS with physical training to improve gait functions in MS. In particular, it has recently been reported that the use of tDCS in conjunction with physical activity such as gait and balance training, resulted in significant improvements in motor functions in healthy older adults and individuals with Parkinson's disease, cerebral palsy, stroke and cerebellar ataxia (Grecco et al., 2014; Kaski et al., 2014; Pozzi et al., 2014). Given that the important role of the primary motor (M1) cortex in motor learning, most of the previous mentioned studies placed the active electrode (anode) over this region. The combination of tDCS over M1 and physical activity program has been shown to induce positive changes in gait performance, specifically regarding stride length, stride length variability, and gait velocity in both healthy and neurological patients (Kaski et al., 2014; Satow et al., 2016; Yotnuengnit et al., 2018).

In this study we tested whether tDCS is also a suitable and favorable adjuvant treatment for motor rehabilitation in MS. In this sham-controlled design, multiple tDCS sessions paired with aerobic exercise were evaluated for enhancing the improvements in walking and endurance. To our knowledge, this is the first clinical research study aims to measure the effects of the combination of tDCS addressed to M1 and the simultaneous performance of aerobic physical activity in those with MS.

8.2 Methods

8.2.1 Study design

The study was a two-parallel arm, double-blind, randomized, sham-controlled design to assess the effect of anodal tDCS paired with a physical activity training on gait performance and walking endurance. This study was approved by Review Board Committee and followed the Ethical Principles for Medical Research Involving Human Subjects outlined in the Declaration of Helsinki.

8.2.2 Participants

Individuals with MS aged 18–70 years were recruited through the MS Comprehensive Care Center, NYU Langone Health (New York City, USA) and the Regional Multiple Sclerosis Center of Sardinia (Cagliari, Italy) from May 2018 to March 2019.

Eligible participants met MS diagnostic criteria (Polman et al., 2011), with either relapsing remitting (RR) or secondary progressive (SP) subtype, and an Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) score ranging from 1.0 to 6.5. Participants were excluded if they had history of brain trauma, seizures, skin disorders, uncontrolled migraine headaches, and if they were not physically able to independently walk with or without an assisting device (i.e. cane, crutches or walking frames) for medium-long distance. All participants were evaluated by a study clinician to ensure the exclusion of any major health concern as requested by exclusion criteria (i.e. cardiorespiratory and severe osteoarticular disorders).

Participants were specifically asked to maintain the same level of physical activity and not to engage in any supplemental physical routine program throughout the entire study period. Before starting the trial, participants were informed about all experimental procedures and signed a written informed consent form. Once consented, participants were randomized into one of two study arms (active, sham) in a 1:1 allocation using random block sizes of 4 and 6 to control for age and level of neurologic disability (stratified factors: EDSS score 0-3.5 and 4.0-6.5, age 18-45 and 46-65). Randomization was completed by an independent study technician who took no part in baseline, follow-up, or daily sessions to maintain the double-blind nature of the study). The stimulation device was fully programmable and it ensured the blinded of the study technician who supervised the treatment session.

8.2.3 Interventional protocol

The interventional protocol was structured in two weeks, five daily physical training sessions per week (10 sessions in total) of 20 minutes duration. The aerobic exercise-conditioning program was performed simultaneously with active or sham tDCS.

Transcranial direct current stimulation

The equipment employed to deliver the constant direct current was the 1x1 tDCS mini-clinical trial device (mini-CT; Soterix Medical Inc., USA) at NYU Langone Health, while the Starstim system (Neuroelectrics Inc., Spain) at the Regional Multiple Sclerosis Center of Sardinia. The Soterix EasyStrap was customized to allow M1-SO electrode montage with anodal electrode over Cz and cathodal electrode over Fp2 according to the 10–20 EEG system. The Neuroelectrics wireless hybrid tDCS headset consisted of a neoprene headcap with 39 positions based on the 10–10 system, where the electrodes were inserted in the same position. Rubber electrodes with sponge pad insert (square shape, 5x5 cm^2) were pre-saturated with saline solution before use to augment the conduction of the electrical current across the scalp. For the active condition, current intensity was set up to 2.5 mA based on the tolerance of the individual and delivered for 20 minutes. For the sham condition, the device delivered a 60 second ramping up/down electrical current for the first and last minute of the stimulation period, following conventional blinding protocol (Gandiga et al., 2006).

Physical training

The physical training program consisted of 20 minutes of aerobic exercise using a recumbent combination arm/leg elliptical ergometer (PhysioStep LTX-700). According to the recommendation of physical exercise in MS (Dalgas et al., 2008), participants performed the training at moderate intensity corresponding to 60-80% of age-predicted maximum heart rate (HR_{max}). Thus, the heart rate signal was monitored during the entire session by means of heart rate monitor wristband and transmitted in real-time in telemetry mode for continuous monitoring during the entire session. Age-predicted maximum heart rate was derived from the equation proposed by Tanaka et al. (2001):

$$HR_{max} = 208 - (0.7 \cdot age)$$’

8.2.4 Motor and clinical assessments

Study schedule. Eligible participants attended a baseline visits scheduled approximately one week before the first treatment session. Individuals completed motor assessments (10-meter walking test, 2-minute walking test) and questionnaires as describes in the following paragraph. Baseline procedures included familiarization with equipment used for the physical training, as well as, one minute of tDCS tolerability test. The same motor assessments and questionnaires were administered during the 10^{th} session and at follow-up visit scheduled after around four weeks from treatment end. In order to assess the potential acute and cumulative effect of the intervention, the 10-meter walking test was performed after each tDCS session. The assessment was performed only after that participant’s heart rate return to the resting value.

Instrumented 10-meter walking test. Objective and quantitative gait analysis was performed using a previously validated wearable inertial sensor (Pau et al., 2016). Spatiotemporal parameters of gait were computed from raw accelerations collected by a wireless inertial sensor (GSensor, BTS Bioengineering S.p.A., Italy) that was attached around the subject's waist with a semi-elastic belt (lower lumbar level, centred on L4–L5 inter-vertebral disc). As requested by the test, the participants were instructed to walk along a 10-meter hallway at their self-selected speed and as naturally as possible. The sensor including a tri-axial accelerometer, a gyroscope, and a magnetometer collects acceleration signals along three orthogonal axes, which are transmitted via Bluetooth to a PC. Post-processing of these signals allowed obtaining a set of spatial-temporal parameters (Pau et al., 2016; Bugane et al., 2012) and the following were considered in the analysis:

- Gait speed: the mean velocity of progression (m/s);
- Stride length: the longitudinal distance between two consecutive heel contacts of the same foot (m);
- Gait cycle duration: the time between two consecutive ground contacts of the same foot (s);
- Stance and swing duration: expressed as a percentage of the gait cycle, representing the duration of the phase during which the foot remains in contact with the ground (stance) and not in contact with the ground (% gait cycle);
- Double support duration: the duration of the phase during which both feet are in contact with the ground (% gait cycle).

Instrumented 2-minute walking test. This test assesses participants' physical endurance - with the same reliability of the six minutes walking test in people with MS (Gijbels et al., 2011). The objective of this test is to walk as far as possible in 2 minutes, without running or jogging. The participants were instructed to walk, at maximal gait speed, back and forth in 30-meter hallway for 2 minutes and the use of habitual assistive devices were permitted. Spatiotemporal parameters of gait were computed from raw accelerations collected using a wireless inertial sensor (GSensor, BTS Bioengineering S.p.A., Italy) that was attached around the subject's waist with a semi-elastic belt (lower lumbar level, centred on L4–L5 inter-vertebral disc), as in the 10-meter walking test. Post-processing of raw accelerations allowed obtaining a set of spatial-temporal parameters and the following were considered in the analysis:

- Gait speed: the mean velocity of progression during the 2-minute test (m/s);
- Stride length: the longitudinal distance between two consecutive heel contacts of the same foot (m);
- Distance covered: the distance travelled during the 2-minute test (m).

Self-reported questionnaires. MS-related fatigue was self-reported using the Fatigue Severity Scale (FSS) to score the general impact of fatigue at the baseline (Krupp et al., 1989) and the 21-item Modified form of

the Fatigue Impact Scale (21-item MFIS) to evaluate changes in the physical, cognitive and psychosocial aspects of fatigue (Fisk et al., 1994). To assess the effect of the treatment in reducing the impact of MS on walking ability, participants completed the 12-item MS Walking Scale (MSWS-12) (Hobart et al., 2003).

8.2.5 Statistical analysis

The data were analyzed using the statistical package SPSS version 2 (SPSS, Inc., Chicago, IL). The normal distribution of the variables was assessed by the Kolmogorov-Smirnov test. This analysis indicated that all variables of the study met the criteria of normality. Descriptive analyses were generated for all demographic and clinical variables of the groups. Because of all the variables (spatiotemporal parameters of gait and scores of the self-reported questionnaires) were normally distributed a general mixed model ANOVA 2×3 (treatment × time) were performed to examine the effect of the between-subjects factor *treatment* (active, sham) and the within-subjects factor *time* (baseline, 10^{th} daily session and follow-up). Changes in gait velocity and stride length over 10 tDCS sessions were submitted to a general mixed model ANOVA 2×10 (treatment × time point) with *treatment* (active, sham) as between-subjects factor and *time point* (from baseline to session 10) as within-subjects factor. For these assessments, the type I error (α) was set at 0.05 and the effect sizes were assessed using the eta-squared coefficient (η^2). When a significant main effect was reached, *post-hoc* tests with Sidak correction for multiple comparisons were conducted to assess treatment or time point differences.

8.3 Results

A total of 53 participants were screened between the two study centers, 38 were enrolled in the study to receive the intervention (Figure 8.1). Four participants discontinued from the study due to personal reasons unrelated to the treatment, with n=34 completing all study procedures. Twenty-two participants (8 males, 14 females; age: 52.12 ± 12.85 years; EDSS: 4.67 ± 1.53) were allocated to the active group, while 12 to the sham group (4 males, 8 females; age: 53.52 ± 9.84 years; EDSS: 4.34 ± 1.18).

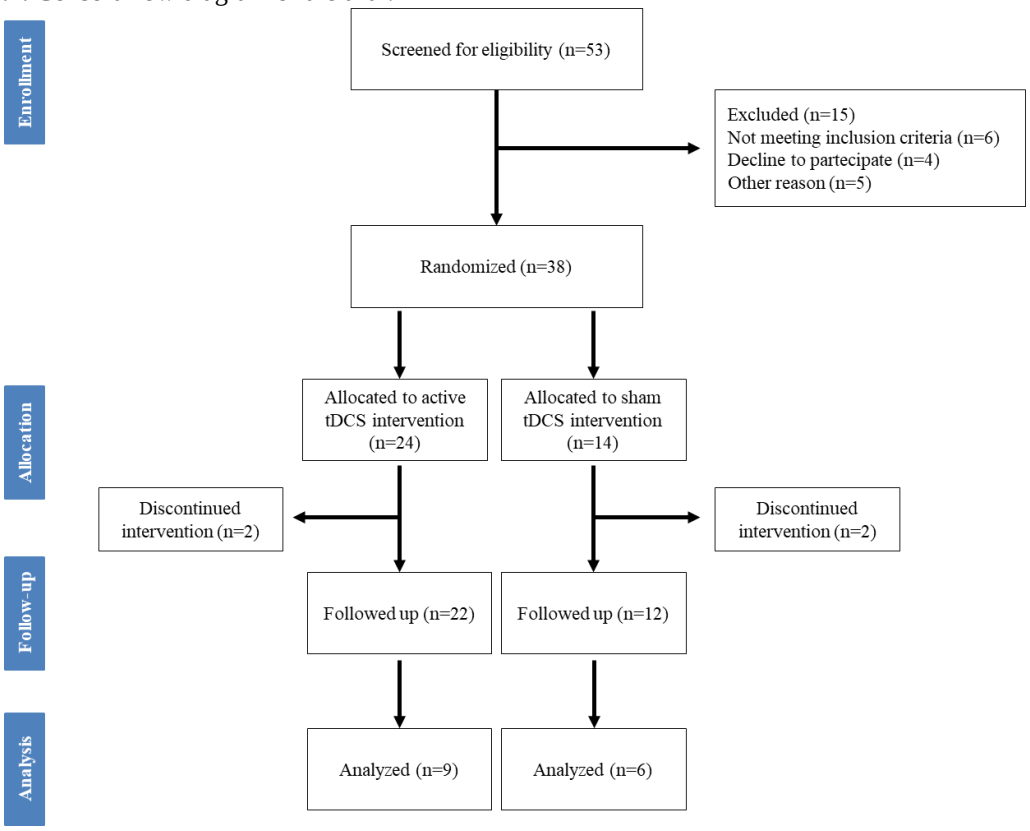
Participants' demographic and clinical features are summarized in Table 8.1. At baseline, no significant differences were found between the active and sham groups in demographic and clinical features, and perceived fatigue (Table 8.1). Stimulation was well-tolerated across participants. The most common side effects were sensations of tingling, itching and warm. Side effects resolved with the end of the stimulation period, and no side effect was associated with treatment limitation or discontinuation.

Table 8.1. Baseline demographic, anthropometric and clinical characteristics of participants enrolled in active and sham groups. Values are expressed as mean ± sd.

	Active treatment	Sham treatment	*p*-value
Participants # (M/F)	22 (8/14)	12 (4/8)	-
Age (years)	52.12 ± 12.85	53.52 ± 9.84	0.263
Weight (kg)	61.41 ± 12.23	66.32 ± 12.68	0.284
Height (cm)	166.00 ± 12.12	166.32 ± 9.24	0.932
EDSS	4.67 ± 1.53	4.34 ± 1.18	0.493
FSS	4.75 ± 1.35	4.25 ± 1.54	0.332

Note. EDSS: Expanded Disability Status Scale; **FSS**: Fatigue Severity Scale.

Figure 8.1. Consort flow diagram of the trial.



8.3.1 Instrumented 10-meter walking test

Table 8.2 reports the results obtained for the spatiotemporal parameters of gait at baseline, after 10 daily sessions and at follow-up. ANOVA revealed a significant effect of the time on stride length ($F_{2, 32}$ =12.916, p<0.001, η^2 =0.112), gait speed ($F_{2, 32}$ =20.615, p<0.001, η^2 =0.169), gait cycle duration ($F_{2, 32}$ =8.221, p=0.006, η^2 =0.128), stance phase duration ($F_{2, 32}$ =13.961, p<0.001, η^2 =0.122) and cadence ($F_{2, 32}$ =9.517, p<0.001, η^2 =0.165). No significant effect of the time was found for swing phase and double-

support duration. ANOVA also revealed a significant effect of the treatment on the following spatiotemporal parameters of gait: stride length ($F_{1, 32}$ =9.981, p=0.003, η^2 =0.113), gait speed ($F_{1, 32}$ =5.064, p=0.031, η^2 =0.151) and stance phase duration ($F_{1, 32}$ =5.311, p=0.028, η^2 =0.262). Significant time × condition interactions were found as regard stride length ($F_{2, 32}$=19.682, p<0.001, η^2 =0.), gait speed ($F_{2, 32}$ =21.693, p<0.001, η^2 =0.140), gait cycle duration ($F_{2, 32}$ =12.814, p=0.004, η^2 =0.299), stance phase duration ($F_{2, 32}$ =11.256, p<0.001, η^2 =0.142) and cadence ($F_{2, 32}$ = 3.415, p=0.002, η^2 =0.101). *Post-hoc* analysis demonstrated a significant increase in gait velocity, stride length and cadence and a reduction of the gait cycle time and the stance phase duration at the end of the treatment compared to baseline and it persisted at follow-up visit (all p<0.001). Regarding changes in gait velocity and stride length over the 10 daily tDCS sessions compared to the baseline assessment, the ANOVA revealed a significant main effect of time point for gait speed ($F_{10, 32}$=3.81, p<0.001, η^2 =0.100) and stride length ($F_{10, 32}$=2.113, p=0.003, η^2 =0.106). A significant effect of treatment condition was found for stride length ($F_{1, 32}$=4.549, p=0.006, η^2 =0.215), but no for gait speed ($F_{1, 32}$= 3.073, p=0.052, η^2 =0.041). A significant interaction treatment × time point was also found for gait speed ($F_{10, 32}$= 6.356, p<0.001, η^2 =0.198) and stride length ($F_{10, 32}$=5.852, p<0.001, η^2 =0.197). Moreover, *post-hoc* analysis showed that gait velocity and stride length significantly increase compared to baseline assessment from the 4th to 10th tDCS session (Figure 8.2).

8.3.2 Instrumented 2-minutes walking test

The descriptive data for the spatial-temporal parameters are reported in Table 8.3. ANOVA performed on the distance covered during the 2-minutes walking test revealed a significant effect of the time ($F_{2,32}$ =16.493, p<0.001, η^2 =0.154) and time × treatment interaction ($F_{2,32}$ = 14.693, p<0.001, η^2 =0.138). Accordingly, the *post-hoc* analysis indicated that compared to the sham group, a significant improvement in the distance covered occurred in the active group (baseline vs. 10th daily session, p < 0.001; baseline vs. follow-up, p<0.05). Analysis reported also a significant effect of the time for gait speed ($F_{2,32}$ =13.069, p<0.001, η^2 =0.131), stride length ($F_{2, 32}$ =6.580, p=0.003, η^2 =0.160) and cadence ($F_{2, 32}$ =9.050, p<0.001, η^2 =0.177). Moreover, significant interaction time × treatment was found for gait speed ($F_{2,32}$ = 15.440, p<0.001, η^2 =0.354) and stride length ($F_{2, 32}$=10.960, p<0.001, η^2 =0.267), but no for cadence ($F_{2, 32}$=2.182, p=0.121, η^2 =0.032). The *post-hoc* test showed for gait speed, stride length and cadence a significant difference in the active tDCS group at 10th daily session and follow-up visit compared to baseline (all p<0.05), but not in the sham group (all p>0.05).

8.3.3 Self-report questionnaires

Table 8.4 reported the descriptive data for the scores of the self-report questionnaires. ANOVA performed on the total score of MSWS-12 revealed a significant effect of the time ($F_{2, 32}$ =7.801, p=0.001, η^2 =0.146)

and treatment condition ($F_{1, 32}$ =4.873, p=0.033, η^2 =0.085). Moreover, the ANOVA analysis detected also a significant time × treatment interaction in MSWS-12 total score ($F_{2, 32}$ =6.781, p=0.008, η^2 =0.103). The *post-hoc* test revealed a significant reduction of the MSWS-12 total score within the active tDCS group at the end of the treatment (10^{th} daily session, p<0.001) and follow-up visit (p<0.05) compared to baseline. The ANOVA analysis showed for the MFIS total score a significant effect of the time ($F_{2, 32}$ =5.277, p=0.007, η^2 =0.113) and a significant interaction time × treatment ($F_{2, 32}$ =6.994, p=0.003, η^2 =0.111). Following *post-hoc* analysis revealed a significant reduction of the perceived fatigue in the active group at end of the treatment (p<0.05) and it persisted also during the follow-up period (p<0.05). Moreover, there was a significant positive change in the physical fatigue subscale after the active treatment. In fact, a significant effect of the time ($F_{2, 32}$=5.198, p=0.008, η^2 =0.094) and a significant interaction time × treatment for the physical subscale ($F_{2, 32}$=6.152, p=0.003, η^2 =0.104) were found. Following *post-hoc* analysis reported significant reduction of the 21-MFIS physical subscale in the active tDCS group after 10 daily sessions (p<0.001) and at follow-up visit compared to baseline (p<0.05).

Table 8.2. Spatiotemporal parameters calculated from the 10-meters walking test at baseline, after 10 daily sessions and follow-up visit. Values are expressed as mean ± sd.

	Active treatment (n=22)			Sham treatment (n=12)			*p*-value		
	Baseline	**10th day**	**Follow-up**	**Baseline**	**10th day**	**Follow-up**	**Time**	**Treatment**	**Time x Treatment**
Gait speed (m/s)	0.96 ± 0.93	1.24 ± 0.11[a]	1.26 ± 0.12[a]	0.92 ± 0.13	1.00 ± 0.12	0.99 ± 0.13	<0.001	0.031	<0.001
Stride length (m)	1.12 ± 0.13	1.33 ± 0.11[a]	1.36 ± 0.14[a]	1.06 ± 0.17	1.13 ± 0.19	1.04 ± 0.17	0.015	0.003	<0.001
Gait cycle duration (s)	1.27 ± 0.10	1.09 ± 0.11[a]	1.12 ± 0.14[a]	1.24 ± 0.11	1.23 ± 0.13	1.25 ± 0.14	0.006	0.182	0.004
Cadence (steps/min)	104.35 ± 5.51	112.00 ± 5.98[a]	109.53 ± 5.67	98.62 ± 5.50	103.73 ± 5.51	103.58 ± 5.99	<0.001	0.255	0.002
Stance phase (%gait cycle)	65.93 ± 2.41	61.17 ± 5.34[a]	60.15 ± 5.98[a]	63.28 ± 7.06	63.81 ± 7.24	64.04 ± 7.04	0.065	0.054	0.104
Swing phase (%gait cycle)	35.48 ± 1.25	40.08 ± 1.27	39.79 ± 1.55	37.35 ± 1.25	38.99 ± 1.38	39.12 ± 1.26	0.537	0.806	0.867
Double support phase (%gait cycle)	14.45 ± 3.31	10.15 ± 2.31	10.74 ± 1.45	14.70 ± 2.32	13.43 ± 2.65	13.64 ± 2.38	0.019	0.788	0.894

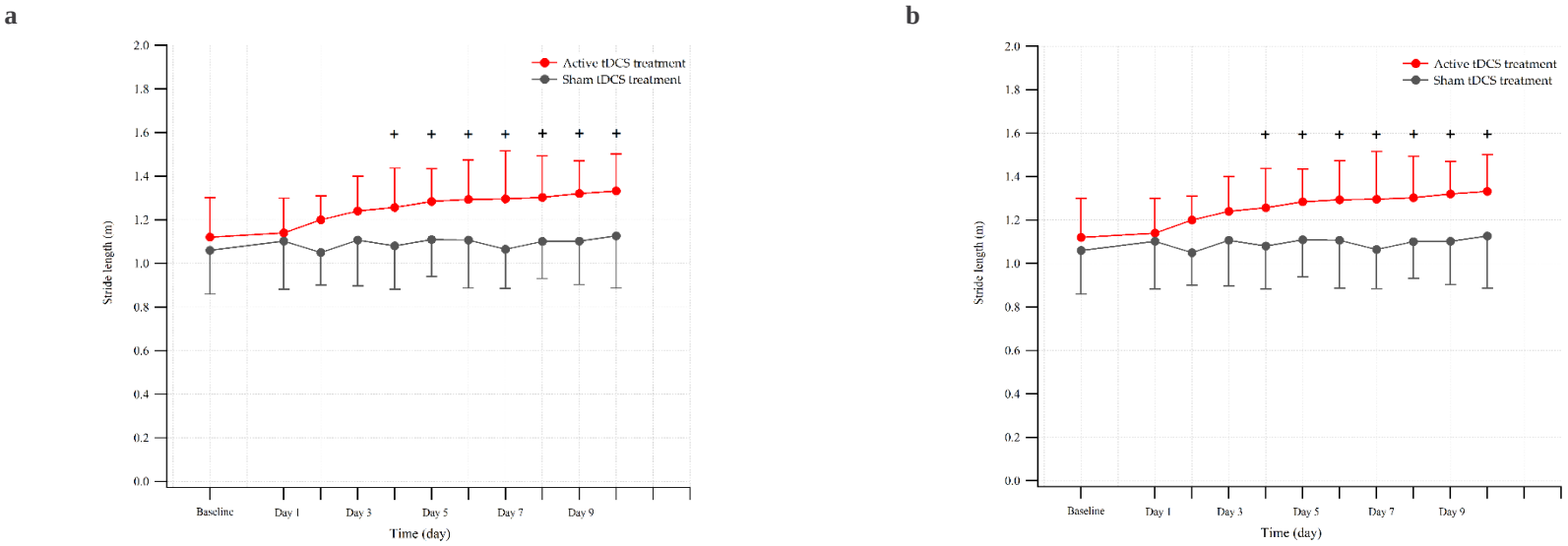
The letter **a** indicates a significant within group difference at $p<0.05$, when compared with baseline.

Table 8.3. Results of RM-ANOVA for spatiotemporal parameters calculated from the 2-minutes walking test. Values are expressed as mean ± sd.

	Active treatment (n=22)			Sham treatment (n=12)			*p*-value		
	Baseline	**10th day**	**Follow-up**	**Baseline**	**10th day**	**Follow-up**	**Time**	**Treatment**	**Time x Treatment**
Distance covered (m)	111.46 ± 27.37	129.78 ± 41.20[a]	135.77 ± 44.27[a]	104.68 ± 20.91	104.52 ± 43.45	105. 67 ± 47.46	<0.001	0.199	<0.001
Gait speed (m/s)	1.10 ± 0.30	1.29 ± 0.30[a]	1.30 ± 0.36[a]	1.08 ± 0.45	1.05 ± 0.45	1.09 ± 0.31	<0.001	0.219	<0.001
Stride length (m)	1.20 ± 0.24	1.35 ± 0.27[a]	1.36 ± 0.29[a]	1.21 ± 0.26	1.18 ± 0.35	1.20 ± 0.23	0.003	0.254	<0.001
Cadence (steps/min)	107.38 ± 16.75	112.44 ± 17.19[a]	113.27 ± 15.95[a]	102.73 ± 16.75	103.96 ± 43.91	105.13 ± 21.08	< 0.001	0.303	0.121

The letter **a** indicates a significant within group difference at $p<0.05$, when compared with baseline.

Figure 8.2. Trend of gait velocity and stride length over 10 tDCS sessions. Active stimulation is represented in red solid line, while sham stimulation is represented in grey.



Changes in gait velocity and stride length over 10 treatment sessions in both stimulation group (active and sham). Values at baseline represent gait velocity/stride length measured before the beginning of stimulation treatment. The symbol + indicates a significant difference compared to the baseline ($p<0.05$).

Table 8.4. Results of RM-ANOVA analysis for the self-report questionnaires. Values are expressed as mean ± sd.

	Active treatment (n=22)			**Sham treatment (n=12)**			***p*-value**		
	Baseline	**10th day**	**Follow-up**	**Baseline**	**10th day**	**Follow-up**	**Time**	**Treatment**	**Time x Treatment**
12-MSWS	57.58 ± 6.51	48.91 ± 5.01[a]	50.88 ± 4.98[a]	60.47 ± 5.13	62.69 ± 5.98	61.19 ± 5.99	0.001	0.033	0.008
21-MFIS	40.36 ± 3.69	30.41 ± 4.01[a]	31.55 ± 5.49[a]	42.67 ± 6.78	39.67 ± 6.09	37.17 ± 6.47	0.008	0.272	0.003
• **Physical subscale**	21.27 ± 3.45	16.18 ± 2.95[a]	17.46 ± 3.06[a]	22.25 ± 3.65	21.58 ± 5.01	19.42 ± 4.56	0.008	0.281	0.003
• **Cognitive subscale**	14.32 ± 5.46	11.27 ± 4.56	10.86 ± 4.01	15.92 ± 5.55	15.00 ± 4.56	14.42 ± 5.03	0.081	0.323	0.590
• **Psychosocial subscale**	3.77 ± 1.32	2.96 ± 1.83	3.23 ± 2.08	4.25 ± 3.45	3.92 ± 2.45	4.17 ± 2.34	0.145	0.280	0.641

The letter **a** indicates a significant within group difference at $p<0.05$, when compared with baseline. **Note. 12-MSWS:** 12-item MS Walking Scale; **21-MFIS:** 21-item Modified form of the Fatigue Impact Scale.

8.4 Discussion

Impaired gait constitutes an important functional limitation in patients with MS. Physical activity can reduced motor related symptoms and consequentially improve walking, balance, fatigue and the overall quality of life in MS and other conditions. Several recent works provide first evidence that NIBS, and tDCS specifically, can serve to augment or potentiate the benefits induced by physical activity (Gosh, 2019). Thus, the aim of this study was to explore the effectiveness of a combined treatment anodal tDCS over the M1 cortex and physical activity program on enhancing gait recovery.

In this study, we found ten sessions of aerobic exercise combined with anodal tDCS over the M1 cortex enhances the acute and long-lasting effects obtained with the physical activity in people with MS. Walking spatiotemporal parameters and endurance significantly improved in the active group after tDCS paired with aerobic physical activity. By the 4^{th} treatment session, the active group showed significantly greater improvements in velocity and stride length. As shown by the trend of increase in gait speed and stride length over ten treatment sessions in the active tDCS group (figure 8.2-a and figure 8.2-b), prolonged stimulation treatment confirms that anodal tDCS leads to cumulative benefits. Remarkably, there was also a parallel improvement on the self-report questionnaire aimed to evaluate the perception of the participants on their walking ability. Self-perceived limitation in walking measured by MSWS-12 decreased significantly after the active treatment, especially for the aspects of the distance travelled and the smoothness of walking. The self-report improvement seems to be in accordance with the results from the quantitative analysis performed. In terms of change in walking performance, a variation between the 12% and 20% is generally indicative of a clinically meaningful difference in those with MS (Kieser et al., 2013; Learmonth et al., 2013). In line with this, we found at the end of the treatment compared to the baseline an improvement of 29.17% in gait velocity measured in the 10-meter walking test and an increase of 16.44% in the distance covered during the 2-minute walking test.

Our findings are consistent with previous studies, which reported functional improvement of gait after anodal tDCS paired with exercise training in other neurological conditions, such as Parkinson's disease (Kaski et al., 2014), cerebellar ataxia (Benussi et al., 2018; Pilloni et al., 2019), cerebral palsy (Grecco et al., 2014; Grecco et al., 2016) and stroke (Sohn et al., 2013; Seo et al., 2017). Recently, few studies investigated the potential effect of anodal tDCS over M1 on endurance walking performance in both healthy adults and people with neurological disease (Kaski et al., 2014; Angius et al., 2018; Grecco et al., 2016). These studies indicated mixed results but point toward a tendency to improve performance following tDCS application.

Two other previous studies investigated the effects of anodal tDCS to treat walking impairment in patients with MS (Oveisgharan et al., 2019; Iodice et al., 2015). However, both used tDCS alone rather than in

combination with aerobic exercise or other physical rehabilitation program, and administered fewer treatment sessions than in this study. In Iodice et al. (2015) the primary outcome was lower limb spasticity without any observed improvement after five days of treatment, and standard measures of walking ability were not included. Oveisgharan et al. (2019) recently found an increase in gait velocity in the active group after seven tDCS sessions but, no effectiveness of the stimulation in improving MSWS-12. Therefore, these two previous studies suggested both that tDCS should be paired with simultaneous exercise and include extended treatment schedules with multiple sessions to lead to measurable benefit (Iodice et al., 2015; Oveisgharan et al., 2019).

In the present study we also showed that cycling training combined with the active stimulation in MS individuals not only improved gait and endurance, but importantly lead to a significant reduction in MS-related fatigue. Similarly, Ferrucci et al. (2014) reported long-term after effects in MS fatigue after anodal tDCS applied over M1, persisting around more than three weeks after the last tDCS session. The results of this study are also in line with those of previous tDCS studies in patients with MS that used different protocols and electrodes montages (Tecchio et al., 2014; Chalah et al., 2017; Charvet et al., 2018). Finally, our protocol proves to be also effective on the treatment of fatigue, in particular in its physical aspect.

Moreover, another main result of this study is that the improvement of the active group in gait velocity, stride length, cadence and the ability to walk for further distance was maintained over a period of up to 4 weeks after treatment end. Of note, patients still reported a notable, and significant, benefit at the follow-up visit. To the best of our knowledge, this pilot study represents the first attempt at demonstrating long-term beneficial aftereffect of multiple sessions of tDCS in MS patients with ambulation impairments. This demonstrates that multiple sessions seem to have a cumulative effect and are needed to induce reliable and long-lasting repercussions. Surprisingly, the duration of aftereffects resulted by anodal tDCS are not widely reported in literature. We found similar evidences in only few studies that indicated potential long-lasting effects of tDCS on motor functions in patients with stroke (Boggio et al., 2007), cerebellar ataxia (Benussi et al., 2018), cerebral palsy (Grecco et al., 2014) and Parkinson's disease (Kaski et al., 2014; Costa-Ribeiro et al., 2017).

The reason behind the lack of significant improvement after the sham treatment could be the length of the physical exercise program, which is about 6 times shorter than the suggested length by literature (Dalgas et al., 2008; Snook et al., 2009). In this regard, a recent meta-analysis suggested that interventions of 3 months resulted in a statistically significant improvement in walking mobility (White and Dressendorfer, 2004; Snook et al., 2009).

This was a pilot study with some limitations including a small sample size. In addition, as dosing parameters for tDCS still remain largely undefined, there is a general lack of standardization of the stimulation methodologies concerning electrode montages and proper length of the treatment. Future studies are required to confirm the observed benefits and explore both individual differences in treatment response and comparison on dosing approaches.

8.5 Conclusion

Although preliminary and on a limited sample of patients, the present results show greater improvements in gait velocity, step length, endurance walking test and MS-related fatigue symptoms. Finally, advance quantitative method for gait analysis indicates that multiple sessions of tDCS coupled with physical activity generated cumulative, with a strong effect across repeated treatment sessions, functional motor benefits superior to those associated with physical treatment alone. Anodal tDCS over M1 can be a useful tool to increase the efficacy of aerobic physical activity addressed to improve gait functions and endurance in MS patients.

8.6 References

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Chapter 9

Effects of transcranial direct current stimulation on walking dual-task: a quantitative study.

Having widely discussed the effects of cognitive-motor interference on walking in terms of spatiotemporal and kinematic parameters, this research study examines the possibility to use the experimental dual-task methodology, previously outlined, for investigating the effectiveness of tDCS over M1 in enhancing dual-task performance in those with MS. Finally, this chapter aims to explore the possibility of enhancing dual-task performance using multiple sessions of transcranial direct current stimulation (tDCS) paired with an aerobic conditioning program. Thus, it is hypothesized that the positive effects detected on walking performance after repeated sessions of anodal tDCS can be appreciable also during walking dual-task.

9.1 Context

In people with multiple sclerosis (MS), the typical clinical hallmarks are impairments of motor and cognitive functions (LaRocca, 2011; Kister et al., 2013). Common motor symptoms include muscle weakness, spasticity, ataxia, balance impairment, and sensory disturbance (Givon et al., 2009). Gait in MS is characterized by a decrease in gait speed, shortened stride length, and postural instability that led to an increase of step width and the duration of double support phase (Cameron and Wagner, 2011). Since real life demands walking while performing concurrent cognitive tasks, research has shown an increasing interest on dual-task methodology as a valid approach for investigating cognitive-motor interference and measuring gait deficits. Recent evidence suggests that motor impairments are compounded when the motor and cognitive tasks are performed simultaneously, reporting as a principal detrimental effect reduction in gait speed and increase in double support phase duration (Learmonth et al., 2014; Coghe et al., 2018). Recent evidences have suggested that individuals with MS can improve their ability to cope with dual-task situations with training (Peruzzi et al., 2017; Sosnoff et al., 2017; Jonsdottir et al., 2018). Although these studies differed from each other in terms of training features, gait and stride length showed progressive improvements throughout dual-task evaluation (Kramer et al., 2014; Peruzzi et al., 2017; Sosnoff et al., 2017), and these were further maintained at 1-month follow-up (Peruzzi et al., 2017).

In this regard, several authors showed that different shared brain areas are involved during dual-task activity (Fritz et al., 2019). In general, literature suggests that the dorsolateral prefrontal cortex (DLPC), especially the left area, has a pivotal role in walking dual-task may be due to its role in executive functions (Fraser et al., 2016). Recently, evidences from literature have shown that also supplementary motor area (SMA), premotor cortex (PMC) and primary motor cortex (M1) are involved in regulation of walking dual-task (Adcock et al., 2000; Johansen-Berg and Adcock, 2002; Fritz et al., 2019). Moreover, some of these studies reported the existence of different pattern of activation between healthy controls and MS individuals (Saleh et al., 2018; Fritz et al., 2019). These findings suggest strategies aimed to modulate neural activity within these networks may optimize dual-task performance and maximize functional capacity. Transcranial direct current stimulation (tDCS) is a relative recent non-invasive brain stimulation technique being considered as a valuable neurological rehabilitation tool. The use of tDCS alone or in combination with behavioral training (motor or cognitive) has demonstrated to facilitate cognitive and motor process separately in MS individuals (Mattioli et al., 2016; Oveisgharan et al., 2019). Despite promising effects were previously reported in healthy elders and in individuals affected by other neurological disease for this multimodal approach tDCS paired with motor training (Zhou et al., 2014; Manor et al., 2016; Swank et al., 2016), no study has investigated its effect in those with MS. Therefore, the objective of this study is to use quantitative

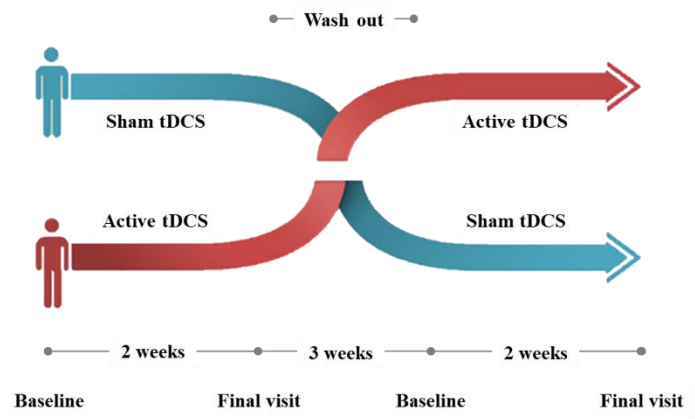
gait analysis to identify if multiple sessions of anodal tDCS combine with aerobic physical activity can reduce dual-task cost in a cohort of patients with MS.

9.2 Materials and methods

9.2.1 Participants

To be included in the study participants had to fulfill the following inclusion criteria: confirmed diagnosis of MS according to the 2010 McDonald criteria (Polman et al., 2011), aged between18–75 years, without history of brain trauma, seizures, or epilepsy. Conversely, patients were excluded if they fulfilled the following criteria: severe cognitive difficulties that could interfere with comprehension of instructions, concomitant progressive disease, severe ataxia, orthopedic surgery in the last 6 months, or other motor disorders not related to MS affecting gait and balance. Participants were recruited from the Regional Multiple Sclerosis Center of Sardinia (Cagliari, Italy). The study was approved by the local ethics committee and conducted in accordance to the Declaration of Helsinki.

Figure 9.1. Study design: crossover study. The study participants were switched throughout to all the treatment groups (active and sham stimulation) after a washout period. Each tDCS treatment lasted 2 weeks (20 min per day, 5 days per week from Monday to Friday).



9.2.2 Study design

The design was a double-blind, cross-over, randomized, and sham-controlled with 3 weeks wash-out period. All subjects underwent a preliminary clinical assessment before randomization to either active (anodal tDCS) or sham treatments. Both anodal and sham tDCS stimulations were delivered simultaneously to a physical activity program for 10 consecutive days. Participants who underwent anodal tDCS as first

treatment were then switched after wash-out period to sham stimulation, and vice versa. Participants completed four separate study visits, occurred during the week pre and post the treatments (Figure 9.1). During each visit, only walking (single-task condition) and walking while performing a cognitive task (dual-task condition) were assessed as describe in the following section. Participants were blinded to the intervention groups, as well as the study technician who performed the evaluation.

9.2.3 Intervention

The physical activity program was taken in 10 x 20 minutes sessions across 2 weeks (5 days per week) for both active and sham treatments. Physical activity program was carried on by a trained physiotherapist in one-on-one training visit. An independent bi-directional upper body ergometer and recumbent bike (Bike Forma, Technogym, Italy) was employed for the aerobic exercised, which allows working on upper and lower body independently from each other. The supervised physical activity program consisted of 20 minutes of aerobic exercise where participants completed in randomly sequence 10 minutes of unloaded pedaling and arm-cranking.

Transcranial direct current stimulation

A battery driven multi-channel direct current stimulator device (Starstim, Neuroelectrics, Barcelona, SPAIN) was used to deliver the direct current over the scalp through two sponge electrodes (circular shape, area: 25 cm^2), soaked in a saline solution to minimize the risk of skin irritation (Palm et al., 2014). The anodal electrode was placed over M1 cortex, according to the International 10-20 EEG system at point Cz, while the cathode was placed over the contralateral supraorbital region (Fp2). In the active group, 2.0 mA current was applied for 20 minutes while the participants performed the physical activity training. For the active stimulation, the current was gradually ramped up during the first 30 seconds to the maximum intensity of 2 mA, which was maintained throughout the 20-min stimulation session. The current was gradually ramped down during the last 30 seconds of the session. In the sham stimulation, the current intensity was set to 2 mA as well, but it was turned off after the first 30 seconds of stimulation and again switched on for the last 30 seconds of the stimulation period.

9.2.4 Quantitative gait analysis

Four assessment visits were performed within one week before and after the active and sham treatments. During each visit, normal walking (single-task condition) and walking while performing a cognitive task (dual-task condition) were assessed. During both single- and dual-task performance, participants were instructed to walk at their preferred speed and no instructions were given regarding task prioritization during dual-task trials. Gait spatiotemporal parameters were acquired using a motion-capture system composed of eight infrared cameras (Smart-D, BTS Bioengineering, Italy) set at a frequency of 120 Hz. Twenty-two

spherical passive markers (14 mm diameter) were placed on individuals' lower limbs and trunk at specific landmarks following the protocol described by Davis et al. (1991).

The cognitive task adopted was the Stroop Color and Word test, which belongs to the discrimination and decision-making category. Specifically, the third table of the Stroop Color and Word test, or named color-word condition, was used during the dual-task trials. The test consisted only of incongruent stimulus, where the color-words are printed in an inconsistent color ink (i.e. the word "red" is printed in green ink). In the incongruent condition participants had to name the word's font color and to inhibit reading the word. The time interval between word insertions was varied to avoid rhythm. For each dual-task trial, the tests differed in the sequences of the color words. The test was administered via a 48" LCD TV screen located perpendicularly to the gait direction as previously validated for patients with MS by Coghe et al. (2018).

Data analysis

The raw data were processed using Smart Analyzer software (BTS Bioengineering, Italy) to calculate gait speed and cadence, stride length, step width, stance, swing, and double-support phase duration (expressed as a percentage of the gait cycle). All these parameters have been previously described (see *Chapter 5 – paragraph 5.2.2*). The gait parameters were calculated as an average of the six trials for each tested condition. Dual-task cost was calculated as a percentage change for each gait parameter between the two conditions, as follows (Baddeley et al., 1997):

$$DTC = \frac{(ST-DT)}{DT} \cdot 100 \,,$$

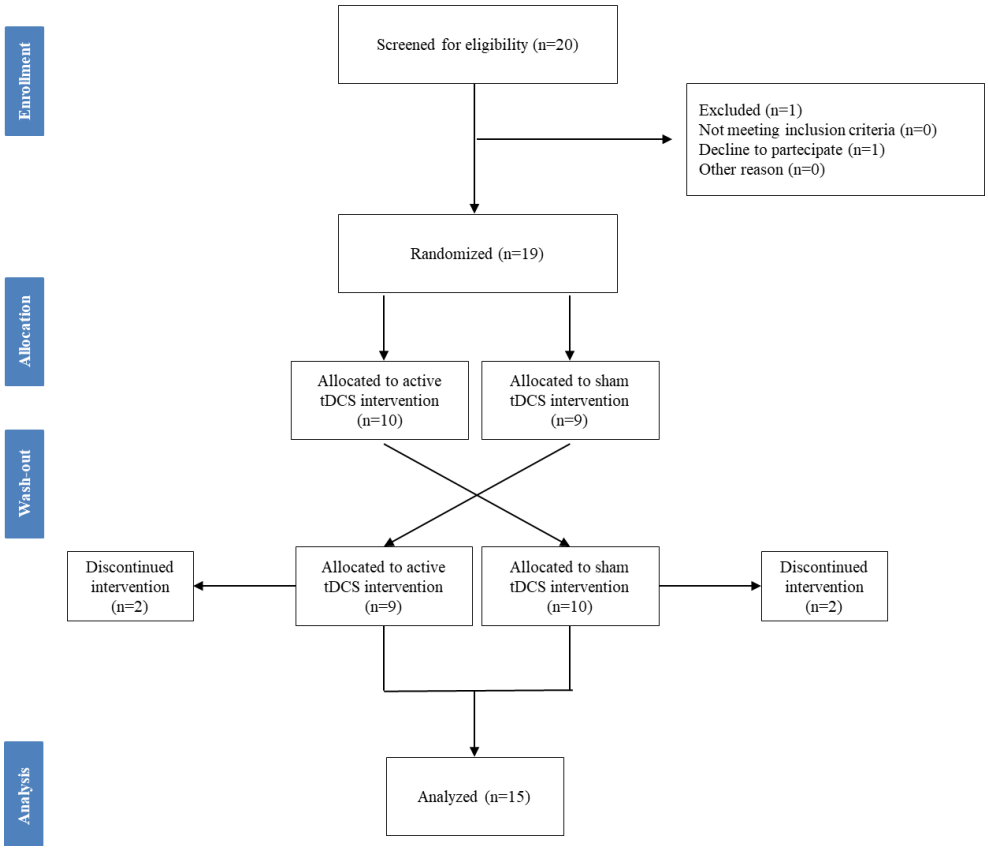
where ST is the single-task performance and DT is the dual-task performance. A positive dual-task cost indicates for gait speed, stride length, cadence and swing phase duration a decrease in walking performance when a secondary cognitive task is performed. Instead, a negative dual-task cost indicates a decrease in walking performance for stride time, step width, stance and double-support phase duration.

9.2.5 Statistical analysis

Descriptive statistics were used to summarize anthropometric measures, demographic and clinical features of the study participants. Distribution normality for the tested variables was assessed by Kolmogorov-Smirnov test. This test showed a normal distribution for all considered variables. A preliminary independent sample t-test was carried out to assess possible differences between left and right limb, and no significant differences were found for any of the investigated gait parameters. The mean value calculated across the two limbs was thus considered representative of each participant. The effect of the treatment on dual-task cost of each gait parameter over the time was assessed by a 2×2 repeated-measure ANOVA (RM-ANOVA), with *time* (baseline, final visit) as within-subject factor and *treatment* (active, sham) as between-subject

factor. The effect of the treatment on spatiotemporal parameters of gait was assessed separately in single- and dual-task condition, with a 2×2 (time, treatment) RM-ANOVA model as well. When a significant main effect was reached, *post-hoc* tests with Holm-Sidak correction for multiple comparisons were carried out to analyze differences. The significance level was set at $\alpha = 0.05$ for all the analysis. Partial eta squared (η^2) was used as a measure of the effect size for main effects and interactions.

Figure 9.2. Consort flow diagram of the trial.



9.3 Results

Twenty patients were screened, and 19 were enrolled in the study (one decline to participate). Four participants discontinued from the study because of personal reason not related with the study procedure. Finally, 15 patients (8 males and 7 females; age: 53.87 ± 11.59 years; EDSS: 3.80 ± 0.89) were taken into account in the final analysis (Figure 9.2), and demographic and clinical features are reported in Table 9.1. The stimulation treatment was well tolerated by all participants and common tDCS-related side effects were observed during the stimulation (e.g., tingling sensation, itching sensation).

Table 9.2 illustrates the dual-task costs of each spatiotemporal parameters considered in the analysis. RM-

Table 9.1. Demographic, anthropometric and clinical characteristics of participants enrolled in the study. Values are expressed as mean ± sd.

Variable	
Participants # (M/F)	15 (8/7)
Age (years)	53.87 ± 11.59
Weight (kg)	64.47 ± 10.07
Height (cm)	164.33 ± 9.72
EDSS	3.80 ± 0.89

Note. EDSS: Expanded Disability Status Scale.

ANOVA exhibited a significant main effect of the time on the following dual-task cost: gait speed ($F_{1, 14}$ =5.463, p=0.035, η^2 =0.279), stride length ($F_{1, 14}$ =6.106, p=0.027, η^2 =0.270), gait cycle duration ($F_{1, 14}$ =5.909, p=0.029, η^2 =0.281) and double-support duration ($F_{1, 14}$ =4.180, p=0.022, η^2 =0.270). Moreover, RM-ANOVA revealed a significant interactions between treatment (active, sham) and time (baseline, final visit) for the following dual-task cost: gait speed ($F_{1, 14}$ =59.773, p<0.001, η^2 =0.579), stride length ($F_{1, 14}$ =16.560, p=0.001, η^2 =0.571) and double-support duration ($F_{1, 14}$ =9.388, p=0.008, η^2 =0.523). *Post-hoc* analysis indicated that after active tDCS treatment the dual-task cost for gait speed (p<0.001), step length (p<0.001), gait cycle duration (p=0.014) and double-support duration (p=0.005) improved. No effects were observed after sham stimulation.

To further understand the effect of tDCS on the dual-task performance, the effects of tDCS were subsequently examined for the spatiotemporal parameters of gait within single- and dual-task conditions separately. Changes in single-task performance across active and sham treatment are shown in Table 9.3, while changes in dual-task performance in Table 9.4.

Within single-task condition RM-ANOVA revealed significant main effect of the time for the following spatiotemporal parameters: gait speed ($F_{1,14}$ =13.887, p=0.002, η^2 =0.187), stride length ($F_{1,14}$ =16.792, p=0.001, η^2 =0.224), cadence ($F_{1,14}$ =10.990, p=0.005, η^2 =0.434), gait cycle duration ($F_{1,14}$ =14.528, p=0.002, η^2 =0.307) and double support duration ($F_{1,14}$ =4.723, p=0.039, η^2 =0.038). Furthermore, RM-ANOVA showed also a significant interaction treatment × time for gait speed ($F_{1,14}$ =36.926, p<0.001, η^2 =0.189), stride length ($F_{1,14}$ =21.860, p<0.001, η^2 =0.300), cadence ($F_{1,14}$ =18.629, p<0.001, η^2 =0.483), gait cycle ($F_{1,14}$ =5.804, p=0.030, η^2 =0.172) and double-support duration ($F_{1,14}$ =8.395, p=0.012, η^2 =0.553). *Post-hoc* analysis revealed after the active treatment a 19.05% increase in gait speed, a 15.38% increase in stride length and a 10.50% increase in cadence, as compared with baseline. Moreover,

post-hoc test showed after active tDCS a 7.86% reduction in double-support phase duration and a 15.39% reduction in gait cycle duration compared to baseline.

Within dual-task condition, RM-ANOVA revealed a significant main effects of time on gait speed ($F_{1,14}$ =37.498, p<0.001, η^2 =0.304), stride length ($F_{1,14}$ =20.000, p<0.001, η^2 =0.297), gait cycle duration ($F_{1,14}$ =14.780, p=0.002, η^2 =0.404), cadence ($F_{1,14}$ =18.211, p<0.001, η^2 =0.393) and stance phase ($F_{1,14}$ =8.159, p=0.002, η^2 =0.312). A significant interaction treatment × time was also detected for the following spatiotemporal parameters: gait speed ($F_{1,14}$ =42.380, p<0.001, η^2 =0.362), stride length ($F_{1,14}$ =24.390, p<0.001, η^2 =0.434), gait cycle duration ($F_{1,14}$ =6.442, p=0.024, η^2 =0.179), cadence ($F_{1,14}$ =11.171, p=0.005, η^2 =0.269), stance phase duration ($F_{1,14}$ =13.983, p=0.002, η^2 =0.340) and double-support phase duration ($F_{1,14}$ =21.640, p<0.001, η^2 =0.476). *Post-hoc* analysis revealed a significant 34.78% increase in gait speed, a 9.37% increase in stride length and a 13.22% increase in cadence, after active treatment as compared with sham tDCS as well as compared with baseline condition. Furthermore, a significant 11.97% reduction in gait cycle duration and a 13.15% reduction in double-support phase was also detected after active tDCS treatment compared with sham tDCS.

9.4 Discussion

As shown in the previous chapters, MS patients with mild to moderate disability demonstrate increased difficulty with gait during dual-task performance because of disease related deficits and the subsequent presence of motor-cognitive interference. Thus, the purpose of this study is to quantitatively examine the impact of a multimodal rehabilitative approach in improving walking dual-task performance, using gait analysis methodology to study biomechanics changes. To the best of the knowledge, this study is also the first that explored whether tDCS can boost the effect of two-week conditioning physical activity program in improving walking in single- and dual-task condition in patients with MS.

The present findings support that this multimodal approach improve some aspects of walking biomechanics under both single- and dual-task conditions. Furthermore, a significant reduction of the dual-task cost of gait was detected after active stimulation.

The magnitude of dual-task cost at baseline visit (before active and sham stimulation treatment) is consistent with those found in *Chapter 6* for MS patients with mild to moderate disability. These findings confirm that patients with MS have a deterioration in gait while a secondary cognitive task is simultaneously performed. Following the active tDCS treatment, MS patients reported an improvement in gait speed, stride length and cadence, and a reduction of the gait cycle time and double-support phase duration during single-task performance. These findings are in agreement with those of the *Chapter 8*, further confirming that

active tDCS coupled with a conditioning physical activity program alters walking biomechanics. In addition, our results report a significant reduction of dual-task cost for gait speed, stride length, double-support phase duration and stance phase duration. The improvement of balance-related gait parameters (double-support and stance phase duration) during dual-task performance may indicate a better control of stability after the active stimulation treatment. Similar improvement in walking dual-task performance was previously reported by other authors, who investigated possible interventions to reduce cognitive-motor interference in MS patients (Kramer et al., 2014; Peruzzi et al., 2017; Sosnoff et al., 2017). These studies utilized as paradigm of intervention or the simple addition of cognitive task during motor training, or exergaming or exercise training based on virtual reality (Kramer et al., 2014; Peruzzi et al., 2017; Sosnoff et al., 2017).

Moreover, the potential effectiveness of anodal tDCS in reducing cognitive-motor interference was described by other recent studies based on the use of active tDCS either alone or coupled with a behavioral task in healthy older adults and patients affected by neurodegenerative diseases (Zhou et al., 2014; Manor et al., 2016; Schabrun et al., 2016). Even if different electrode montages (i.e. DLFC, M1-SO) and behavioral tasks were adopted in these studies, all of them reported promising results (Zhou et al., 2014; Manor et al., 2016; Schabrun et al., 2016).

In the present study, it is not fully clear if the observed tDCS-related reduction in dual-task cost of gait arises either from a specific neuronal change in brain excitability of the M1 cortex or from an overall change in brain excitability. Given that electrical current is delivered to the scalp by a relatively large electrodes, the effect of tDCS on cortical excitability is relatively spread to the neighboring cortical areas and not only limited to the area under the anodal electrode (Datta, 2012). Based on the previous consideration, it is possible that tDCS may promote a more efficient recruitment of the brain networks adjacent to the M1 cortex which are involved in walking dual-task performance (i.e., SMA, PMC). Specifically, a recent study of Saleh et al. (2018) reported a decrease in PMC activation during walking dual-task in those with MS compared to healthy individuals, and thus the tDCS-related reduction in dual-task cost should be related to the possible effect of tDCS on this area, facilitating its activation. However, the present study does not directly investigate if active tDCS can provoke cortical modulation within other brain regions linked with the M1 cortex, thus no certain conclusion can be made.

There are multiple neurological mechanisms may have also contributed to lead an improvement in adapting walking dual-task performance after active tDCS treatment. To date several theoretical frameworks have been utilized to explain cognitive-motor interference phenomenon. The *capacity sharing* theory suggests cognitive resources are limited at central level and, as a consequence, performing two tasks that share the same cognitive resources will deteriorate the performance of at least one of the tasks (Tombu and Jolicoeur,

2003). In this study, the simultaneous performance of the Word and Color Stroop test negatively affects gait spatiotemporal parameters, suggesting may be the two tasks required shared cognitive resources. A similar conclusion was also supported by Wollesen et al. (2016) in a group of healthy individuals, exhibiting a reduction of walking speed when concurrently performing the Word and Color Stroop test. A possible explanation could be active tDCS may have increased the availability of cognitive resources or/and improved the allocation of them between the two tasks (Zhou et al., 2014). On the other side, the *bottleneck* theory states if two tasks are processed by the same neural processor that can handle one task at the time, there will be a postponement in the processing of one task on the other one (Pashler and Johnston, 1989). Within this theoretical model, the reduction of the dual-task cost occurred because tDCS may induce an increase in processing speed and, as a result, reduce the delay between the two tasks (Zhou et al., 2014).

The result of this study should be considered in light of some limitations. First, the findings are based on a small sample of MS individuals. Second, the assessment of cognitive performance was not carried out in both single- and dual-task conditions. This last aspect partially limits the conclusion on tDCS-related effect in changing dual-task neuronal mechanism. Although additional researches are needed, these results provide a preliminary evidence that modulation of the M1 cortex combined with aerobic physical activity may be one strategy to enhance the ability to walk while simultaneously performing a cognitive task in those with MS.

9.5 Conclusion

Overall the results of this study support that anodal tDCS combined with physical activity program has a beneficial effect in ambulation not only during single-task performance but also during walking dual-task. These findings support that a multimodal approach consisting of multiple sessions of tDCS combined with aerobic exercise can reduce the dual-task cost in MS patients with mild to moderate disability. The diffuse effect of tDCS may promote a more efficient recruitment of the brain networks involved in walking dual-task performance (i.e., PMC, SMA). Collectively, these current observations suggest that dual-task performance in persons with MS is amendable with targeted interventions. These findings further promote the development of gait training programs to improve dual-task walking in those with MS and also the potentiality of non-invasive brain stimulation, in this case tDCS, as an adjunctive method to enhance the result of rehabilitation programs.

Table 9.2. Dual-task cost of the gait spatiotemporal parameters. Values are expressed as mean ± sd.

		Active group (n=15)		Sham group (n=15)		*p*-value		
		Baseline	**Final visit**	**Baseline**	**Final visit**	**Time**	**Treatment**	**Time x Treatment**
DTC (%)	**Stride time**	-8.79 ± 1.99	-4.72 ± 1.80†	-8.37 ± 1.91	-6.66 ± 1.99	0.029	0.584	0.255
	Stance phase	-3.32 ± 0.42	-1.73 ± 0.58	-2.29 ± 0.48	-2.05 ± 0.41	0.090	0.584	0.130
	Swing phase	4.12 ± 1.39	3.06 ± 1.41	3.48 ± 1.38	3.29 ± 1.37	0.266	0.151	0.257
	Double support phase	-17.49 ± 0.88	-11.15 ± 0.85†	-13.43 ± 0.88	-14.96 ± 0.86	0.022	0.949	0.008
	Gait velocity	15.66 ± 1.10	6.95 ± 1.25†	15.15 ± 1.35	17.27 ± 1.38	0.035	0.011	<0.001
	Stride length	8.11 ± 0.51	5.09 ± 0.71†	6.42 ± 0.83	6.70 ± 0.80	0.027	0.473	0.001
	Cadence	8.23 ± 1.01	5.90 ± 1.21	5.57 ± 1.11	4.25 ± 1.23	0.069	0.059	0.550

The symbol † indicates a significant difference vs. Baseline ($p < 0.05$). **Note. DTC**: dual-task cost.

Table 9.3. Spatiotemporal parameters calculated from single-task trials at baseline and final visit, respectively. Values are expressed as mean ± sd.

	Active treatment (n=15)		Sham treatment (n=15)		*p*-value		
	Baseline	**Final visit**	**Baseline**	**Final visit**	**Time**	**Treatment**	**Time x Treatment**
Gait speed (m/s)	0.84 ± 0.29	1.00 ± 0.29†	0.84 ± 0.22	0.85 ± 0.23	0.002	0.020	<0.001
Stride length (m)	1.04 ± 0.25	1.20 ± 0.23†	1.04 ± 0.22	1.04 ± 0.22	0.001	0.102	<0.001
Gait cycle duration (s)	1.30 ± 0.22	1.09 ± 0.10†	1.22 ± 0.19	1.20 ± 0.17	0.002	0.205	0.030
Cadence (steps/min)	96.54 ± 17.59	106.68 ± 19.02†	99.64 ± 12.98	99.37 ± 14.01	0.005	0.387	<0.001
Stance phase (% gait cycle)	64.30 ± 3.24	62.84 ± 3.21†	63.80 ± 2.94	64.00 ± 2.82	0.438	0.438	0.042
Swing phase (% gait cycle)	35.70 ± 2.79	36.69 ± 2.92	36.20 ± 2.92	36.26 ± 2.94	0.227	0.840	0.216
Double support phase (% gait cycle)	27.96 ± 6.05	25.76 ± 5.37 †	27.64 ± 5.52	28.83 ± 4.91	0.039	0.034	0.012

The symbol † indicates a significant difference vs. Baseline ($p<0.05$).

Table 9.4. Spatiotemporal parameters calculated from dual-task trials at baseline and final visit, respectively. Values are expressed as mean ± sd.

	Active treatment (n=15)		Sham treatment (n=15)		*p*-value		
	Baseline	**Final visit**	**Baseline**	**Final visit**	**Time**	**Treatment**	**Time x Treatment**
Gait speed (m/s)	0.69 ± 0.28	0.93 ± 0.27†	0.71 ± 0.20	0.70 ± 0.27	<0.001	0.005	<0.001
Stride length (m)	0.96 ± 0.25	1.05 ± 0.23†	0.98 ± 0.23	0.97 ± 0.24	<0.001	0.113	<0.001
Gait cycle duration (s)	1.42 ± 0.28	1.25 ± 0.18†	1.32 ± 0.18	1.29 ± 0.18	0.002	0.369	0.024
Cadence (steps/min)	88.47 ± 16.62	100.17 ± 17.40†	94.02 ± 12.71	95.13 ± 17.39	<0.001	0.411	0.005
Stance phase (% gait cycle)	66.43 ± 3.52	63.88 ± 2.68†	65.28 ± 3.80	65.33 ± 2.68	0.013	0.744	0.002
Swing phase (% gait cycle)	34.27 ± 3.40	34.04 ± 4.48	35.30 ± 3.11	35.42 ± 4.48	0.352	0.175	0.488
Double support phase (% gait cycle)	32. 62 ± 6.25	28.33 ± 4.76†	31.23 ± 6.04	33.06 ± 4.76	0.087	0.028	<0.001

The symbol † indicates a significant difference vs. Baseline ($p < 0.05$).

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Chapter 10

Conclusion

Interference between cognitive and motor tasks, such as gait, is a relevant aspect that needs to be addressed in neurological rehabilitation settings. The research topic described in this thesis has been focused on the application of quantitative analysis techniques to assess walking kinematics during single- and dual-task performance in healthy adults and in people with MS.

The first aim was to validate a dual-task paradigm feasible to be performed by people with motor deficits but, at the same time, difficult enough to elicit cognitive-motor interference. Thanks to the use of 3D motion capture system, a larger set of spatiotemporal and kinematic parameters were investigated in order to explain changes in gait due to the concurrent performance of the cognitive task, providing better understanding of the dual-task strategy adopted by healthy individuals and MS patients with different disability level. The result reports that walking while performing the Stroop Color and Word Test originates a significant alteration of gait patterns in both MS patients and healthy individuals, even though the presence of the disease and the level of disability influences the strategy adopted to cope with. The analysis revealed

that gait speed and stride length were sensitive motor variables in detecting significant differences from single- to dual-task condition in both patients with MS and unaffected individuals, whereas spatiotemporal parameters of gait closely related to balance control (i.e., step width, stance and double-support phase duration) were sensitive to changes only in patients with moderate disability. Thus, patients with mild to moderate disability presented a larger set of affected spatiotemporal parameters and the percent of change was found to be in a larger magnitude with respect to unaffected individuals and minimally impaired patients. Moreover, the results showed that patients with mild to moderate disability reported significant changes in the kinematics of the distal segment (shank-foot) and proximal joint (hip), including a significant reduction in ankle plantarflexion and hip extension during terminal stance and early stage of swing phase. If on the one hand this strategy was adopted for accommodating more complicate walking dual-task activity, on the other may be critical for safe foot clearance and forward progression of the limb. This aspect is relevant because the lack of ability to adjust distal joint, typically showed by mild to moderate MS patients, may increase the probability to stumbling and falling during walking dual-task. These kinematic differences detected in more disabled MS patients are probably due to a decrease ability to respond most effectively to a postural threat (reduction in *postural reserve*).

Finally, this dual-task paradigm appears sensitive enough to differentiate between healthy individuals and patients with different level of disability and, also, able to quantitatively assess subtle dysfunctions in joint kinematics that would not have been possible to detect with standard clinical tests, including those associated with mild disability levels.

After proving that interference between cognitive and motor tasks negatively affected neurological patients' ability to function independently, the second step was to provide a practical application of this experimental setup in clinical practice, as a tool for quantitatively assessing biomechanics changes after an innovative therapeutic treatment. In this context, this thesis proposed to evaluate kinematic changes in walking when standard physical rehabilitation and tDCS are combined in a multimodal intervention, which could have beneficial effects in the context of "motor enhancement".

Accordingly, the studies reported in *Chapter 7* and *Chapter 8* were aimed to quantitatively examine the added-value for coupling a physical activity program to tDCS application over repeated sessions in walking single- and dual-task performance. The results described in *Chapter 7* showed greater improvements in gait velocity, step length and endurance following repeated applications of anodal tDCS. Moreover, advanced quantitative method for gait analysis indicates that multiple sessions of tDCS coupled with physical activity generated cumulative, with a strong effect across repeated treatment sessions, motor function benefits superior to those associated with physical treatment alone. Multiple sessions of anodal tDCS over M1 can

be a useful to increase benefits of aerobic physical activity addressed to improve gait functions and endurance in MS patients.

Consistent with aforementioned results, walking dual-task performance can be facilitated by tDCS. Thanks to the use of quantitative motion analysis technique, it was possible to objectively monitor changes in walking biomechanics during dual-task performance after the intervention. The dual-task cost of gait parameters was significantly reduced after the active treatment. This result could be due to a spread effect of tDCS to neighboring cortical areas, that may promote a more efficient recruitment of the brain networks involved in walking dual-task performance (i.e., PMC, SMA), increasing either the availability of cognitive resources or the processing speed of the processors. Collectively, these observations suggest that dual-task performance in persons with MS is amendable with targeted interventions, supporting the potentiality of non-invasive brain stimulation, in this case tDCS, as an adjunctive method to enhance the result of rehabilitation programs.

The result of this study should be considered in light of some limitations. The findings are based on a small sample of MS individuals and thus further analyses should be done to confirm these preliminary results. Although the focus of the study was to analyze the kinematic change in gait pattern induced by a secondary task, the assessment of cognitive performance in both single- and dual-task conditions could have led information of the influence of walking on the cognitive performance. The understanding of the reciprocal influence of the cognitive task on the motor task and vice versa could have provided a more complete view of the dual-task interference model. Moreover, in order confirm the results concerning the motor strategies employed by unaffected individuals and patients with MS to perform walking dual-task, it would be interesting to integrate walking kinematic assessment with the analysis of joint synergies and with lower limb kinetic and EMG analysis. In particular, it could better clarify dual-task constraints on inter-joint coordination and give an insight into muscle co-contraction and power generated and absorbed during single- and dual-task conditions.

Future research might focus on implementing ecological validity of dual-task test. A characterization of gait disorders during activity of daily living in ecological environment will improve the monitoring of the deficit progression as well as the planning of suitable and tailored rehabilitation intervention. In this context, it appears noteworthy to integrate kinematic analysis with the concurrent assessment of brain activation in order to define which brain areas are involved during single- and dual-task performance and to identify possible differences in brain activation between unaffected individuals and patients with MS. This further knowledge could be used to optimize potential applications of tDCS to enhance motor and cognitive performance. In fact, this line of research is furtherly important for the design and the implementation of specific electrode montages addressed to improve walking kinematics during dual-task performance.