# COGNITIVE AND MOTOR NEUROBEHAVIORAL RELATIONSHIPS IN PEOPLE WITH MULTIPLE SCLEROSIS AND HEALTHY INDIVIDUALS

Doctoral Thesis

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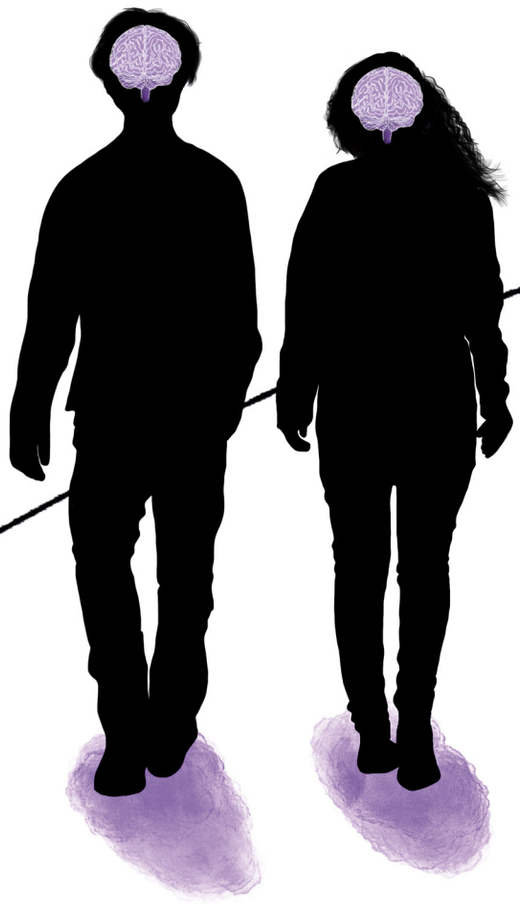

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DOCTORAL THESIS

# Cognitive and Motor Neurobehavioral Relationships in People with Multiple Sclerosis and Healthy Individuals

Submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy and presented by:

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*"No basta examinar; hay que contemplar:*
*impregnemos de emoción y simpatía las cosas observadas;*
*hagámoslas nuestras, tanto por el corazón*
*como por la inteligencia."*
— Santiago Ramón y Cajal

*"In examining disease, we gain wisdom about*
*anatomy and physiology and biology.*
*In examining the person with disease,*
*we gain wisdom about life."*
— Oliver Sacks, *The Man Who Mistook His Wife for a Hat (1985)*

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¡Gracias!

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# List of Abbreviations

| | |
|---|---|
| **MS** | Multiple Sclerosis |
| **CNS** | Central Nervous System |
| **MRI** | Magnetic Resonance Imaging |
| **PwMS** | People with Multiple Sclerosis |
| **EDSS** | Expanded Disability Status Scale |
| **CIS** | Clinically Isolated Syndrome |
| **RRMS** | Relapsing-Remitting Multiple Sclerosis |
| **SPMS** | Secondary Progressive Multiple Sclerosis |
| **PPMS** | Primary Progressive Multiple Sclerosis |
| **RIS** | Radiologically Isolated Syndrome |
| **SDMT** | Symbol Digit Modalities Test |
| **DKEFS** | Delis Kaplan Executive Function System |
| **CVLT** | California Verbal Learning Test |
| **TAVEC** | Test de Aprendizaje Verbal España-Complutense |
| **MACFIMS** | Minimal Assessment of Cognitive Function in Multiple Sclerosis |
| **BRNB** | Brief Repeatable Neuropsychological Battery |
| **BICAMS** | Brief International Cognitive Assessment for Multiple Sclerosis |
| **ERPs** | Event-Related Potentials |
| **BDI-II** | Beck Depression Inventory |
| **D-FIS** | Fatigue Impact Scale for Daily Use |
| **MSQOL-54** | Multiple Sclerosis Quality of Life- 54 |
| **DT** | Dual Task |
| **ST** | Single Task |
| **CMI** | Cognitive-Motor Interference |
| **DTC** | Dual-Task Cost |
| **DT-DP** | Dual Task with Double Priority |
| **DT-CP** | Dual Task with Cognitive Priority |
| **fNIRS** | Functional Near-Infrared Spectroscopy |
| **MoBI** | Mobile Brain/Body Imaging |

| | |
|---|---|
| **EEG** | Electroencephalography |
| **M1** | Primary motor cortex |
| **rIFG** | Right Inferior Frontal Gyrus |
| **SMA** | Supplementary Motor Area |
| **Pre-SMA** | Pre-Supplementary Motor Area |
| **STN** | Subthalamic Nucleus |
| **ERD** | Event-Related Desynchronization |
| **ERS** | Event-Related Synchronization |
| **LCMV** | Linearly Constrained Minimum Variance |
| **FDR** | False Discovery Rate |
| **au** | arbitrary unit |

# *General Abstract*

Even though cognition and motor behavior have been traditionally conceived as independent processes, a growing body of literature supports that motor and cognitive processes are highly interrelated (Hommel et al., 2016; Mirelman et al., 2018). The relative contribution of cognition -or executive control- to motor behavior has been evidenced by means of a behavioral approach (e.g. dual task) and/or a neurophysiological approach (Clark, 2015). In this context, a deeper understanding of the cognitive-motor interference that arises from the dual task performance of a motor and cognitive task is needed, as well as the characterization of cognitive demand in neural oscillatory activity in motor-related cortical regions of the brain. The general aim of this thesis is to examine the interplay between cognitive and motor processes by means of its effect on behavior and neural correlates in people with Multiple Sclerosis and healthy individuals. It will be achieved through the study of the cognitive-motor interference during dual-task performance in people with Multiple Sclerosis and healthy individuals, as well as through the study of oscillatory brain activity potentially associated with the cognitive demand during motor control in a healthy sample. The focus is not only theoretical but also applied since the cognitive-motor interference is evaluated for its applicability to the cognitive functional assessment of people with Multiple Sclerosis.

The first study consisted of a mixed methods systematic review about cognitive-motor interference during gait in people with Multiple Sclerosis and healthy individuals. The mixed-methods approach allowed a comprehensive and detailed review of the highly heterogeneous literature in terms of procedures, and the identification of variables that might account for the differences between studies. It showed that people with Multiple Sclerosis had significant cognitive-motor interference, and that the use of the Verbal Fluency task while walking and the measurement of the gait parameter of double support time were sensitive and specific to cognitive-motor interference in people with Multiple Sclerosis; thus, providing a rationale for the use of the cognitive-motor interference paradigm with this procedure for the assessment of people with Multiple Sclerosis. The need to assess cognitive-motor interference over cognitive performance,

give standardized instructions and evaluate between-group (people with Multiple Sclerosis *versus* healthy controls) as well as intragroup changes was emphasized.

The second study examined cognitive-motor interference under different instructions of prioritization and explored its association with other neuropsychological, symptomatic, physiological and clinical variables in people with Relapsing-Remitting Multiple Sclerosis and healthy controls. Results revealed significant cognitive-motor interference over cognitive performance in people with Multiple Sclerosis, but not in healthy controls. The instructions of dual-task prioritization had an effect over motor and cognitive performance. Furthermore, cognitive-motor interference was associated with neuropsychological, symptomatic and psychophysiological variables (P3 component of the event-related potentials) suggesting that it might be a potential marker of cognitive decline in people with Multiple Sclerosis.

The third study involved an electroencephalography recording of healthy young adults for the examination of oscillatory beta activity (~13-35 Hz) in supplementary and primary motor cortical regions with respect to cognitive demand during the performance of a center-out visuomotor task. The task consisted on navigating on a digitizing tablet to reach a target shown on the screen with a pen under a normal unperturbed (automatic) condition and an anti-movement (controlled) condition with inverted axes representation. Results revealed significantly greater power in beta oscillations (or less beta desynchronization) in the supplementary motor area during motor preparation in controlled compared to the automatic condition, which was associated with improved motor performance (i.e. less trajectory error to reach the target). The results demonstrate an association of beta oscillations in the supplementary motor area with cognitive control during motor preparation. The findings shed light on cortical oscillatory mechanisms of inhibition and corroborate a role for medial frontal cortex for cautious control in movement execution.

Overall, the findings of this thesis add to the evidence supporting the link between cognitive and motor processes.

**Keywords:** dual task, cognitive-motor interference, multiple sclerosis, cognitive control, beta oscillations.

# 1

# Introduction

## 1.1. Introduction

This doctoral thesis is devoted to the study of the interplay between cognitive and motor processes by means of its effect on behavior and neural correlates. For this purpose two approaches will be considered: (i) a behavioral approach based on the cognitive-motor interference raised during dual tasking in people with Multiple Sclerosis and healthy individuals and (ii) a neurophysiological approach based on the study of cortical oscillatory activity associated with the cognitive demand during motor control in a healthy sample. The focus is not only theoretical but also applied as the interference created by the simultaneous performance of a motor and a cognitive task (i.e. cognitive-motor dual task) is evaluated for its applicability to the clinical assessment of people with Multiple Sclerosis. Accordingly, the introduction of the present thesis will provide an overview on general features of Multiple Sclerosis, followed by a closer focus on cognitive impairment in people with Multiple Sclerosis and other factors related (i.e. depression, fatigue and quality of life). The topic of cognitive-motor interference while walking will be next covered, first centered on general aspects derived from the literature on healthy adults and people with other neurological disorders and, then, on the literature about this subject specifically in people with Multiple Sclerosis. Lastly, the neural correlates of cognitive control will be outlined, targeting the frontal network for motor control and predominant oscillatory activity in this network.

## 1.2. Multiple Sclerosis

Multiple Sclerosis (MS) is a chronic, neurodegenerative, inflammatory disease of the central nervous system (CNS) that predominantly affects young adults. It is characterized by demyelination, neuronal damage and axonal loss, leading to multifocal sclerotic plaques from which the disease gets its name (Compston & Coles, 2002).

### 1.2.1. Etiology

Although the exact etiology of MS remains unknown, autoimmune mechanisms are definitely involved in the pathogenesis of the disease, triggered by environmental factors in a genetically susceptible individual (Baecher-Allan et al., 2018).

In the past three decades, there has been extensive research concerning the genetic etiology of MS. This research is not only worth for MS risk prediction, but to understand the mechanisms of the disease, which might ultimately aid the discovery of new therapeutics (Ramagopalan et al., 2009). The genetic component of MS is evidenced by the clustering of affected individuals within families and the directly proportional increment in risk with the degree of relatedness. Specifically, it has been found that first-degree relatives have an increased risk of developing MS (2%-5%), there is higher concordance in monozygotic twins (20-30%), and the prevalence rate is different across different ancestral groups (Hollenbach & Oksenberg, 2015).

Despite genetics being a strong vulnerability factor, others such as epigenetic and environmental factors are recognized to contribute to MS pathogenesis. Interestingly, some of the environmental factors involved in the development and course of MS are modifiable, which leads to potential prevention and therapeutic lines, especially in cases of known genetic susceptibility (e.g. having close relatives with MS). Therefore, much research has focused as well on the identification of modifiable risk factors and to which extent they contribute to the etiology of MS. Among the environmental factors vitamin D deficiency, cigarette smoking, obesity in early life, and Epstein-Barr virus infection have been consistently associated with MS susceptibility (Marrie, 2004; Thompson, Baranzini, et al., 2018).

### 1.2.2. Epidemiology

The most recent estimations from the Multiple Sclerosis International Federation point to a prevalence of 50-300 cases per 100000 people, and approximately 2.3 million of people living with MS globally (MSIF, 2013). However, these values are likely to be underestimated due to the lack of data from several populations of Africa, India and China (Thompson, Baranzini, et al., 2018).

Although MS is present in all the regions of the word, its prevalence varies considerably between countries according to a latitudinal gradient, so that it generally increases as the distance from the equator increases, with some exceptions (Kurtzke, 1975; Simpson et al., 2019). For instance, North America and Europe are considered high-risk regions, with an estimated prevalence of 140 and 108 per 100000 people respectively, including Spain (100 per 100000 people); whereas Sub-Saharan Africa and East Asia are considered low risk regions, with a prevalence of MS estimated at

2.1 and 2.2 per 100000 respectively (MSIF, 2013) (see Fig. 1). The latitudinal gradient of MS is likely to be influenced by both genetic variations across the geography and environmental factors. This is illustrated by migration studies, which show that people migrating before adolescence from a low-risk to a high-risk country have an increased risk to develop MS and *vice versa* (Ahlgren et al., 2012; Gale & Martyn, 1995).

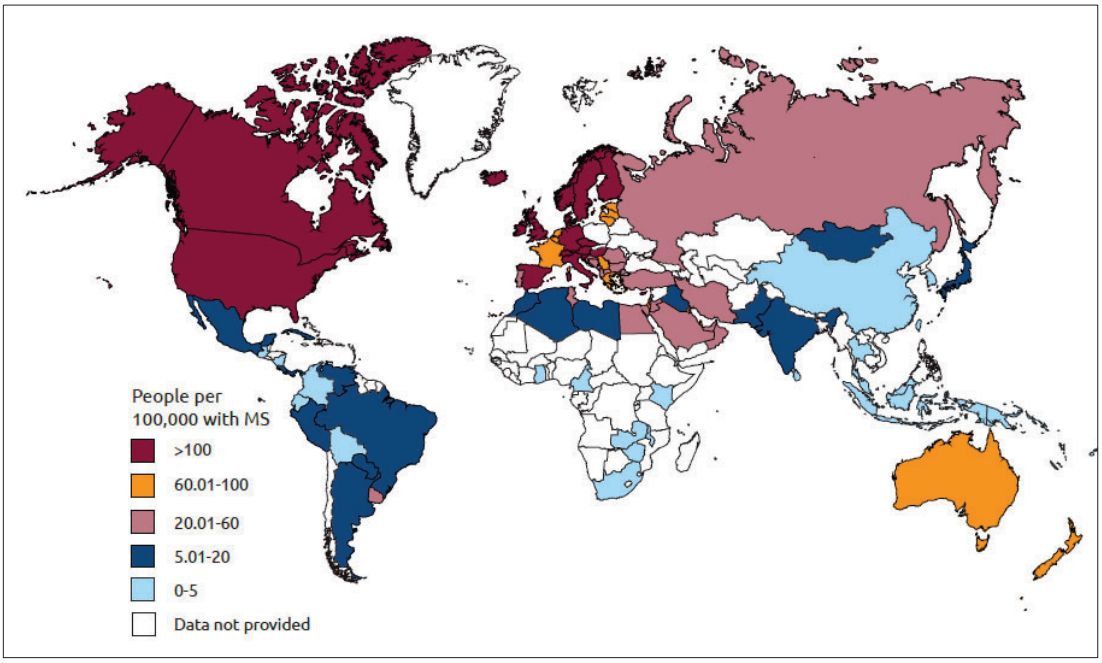


**Fig. 1. Global prevalence of MS by country.** Source: Reproduced with permission from Atlas of MS 2013, MS International Federation (MSIF, 2013).

The onset of MS generally occurs in young adulthood, between 20 and 40 years of age, with a mean age at onset of 28 years. Although MS can begin at any moment in the lifespan, its onset is less frequent during childhood or late adulthood (Goodin, 2016). It is recognized that usually the onset of the disease precedes the first clinical manifestation, since changes in the CNS, highly suggestive of demyelinating disease, might be observed by Magnetic Resonance Imaging (MRI) many years before its clinical manifestation, which is referred to as Radiologically Isolated Syndrome (RIS) (Okuda et al., 2009). The different clinical courses will be explained in more depth below (section <<1.2.5 Clinical courses and diagnosis>>).

MS is more common in women, so that the ratio of women to men is 2:1. However, this ratio varies between countries and studies have reported that it has increased notably in the last years because of increased incidence of MS in women (Elhami et al., 2011; Izquierdo et al., 2015; Orton et al., 2006).

### 1.2.3. Pathogenesis

The pathogenesis of MS consists of a cascade of events that involves the immune system and includes the breakdown of the blood-brain barrier, multifocal inflammation, demyelination, oligodendrocyte loss, reactive gliosis, and axonal or neuronal loss (Trapp & Nave, 2008).

Specifically, the pathogenic process of MS has been described as a breakdown of the blood-brain barrier associated with inflammation, in which myelin is the primary target of the autoimmune response (McDonald, 1994). In the inflammatory response triggered by the immune system in MS, T cells and B cells are known to play a primary role, and together with macrophages, microglia and astrocytes lead to the formation of the MS plaques (Brück et al., 2002). However, the specific mechanism underlying the initiation and maintenance of the autoimmune response in MS is still unclear (Thompson, Baranzini, et al., 2018). The MS plaques may appear throughout the CNS, but are frequently located in the optic nerves, spinal cord, brainstem, cerebellum, and periventricular white matter, leading to the clinical manifestations of the disease (Brück et al., 2002; Trapp et al., 1999). Despite the evidence supporting the role of the autoimmune system in the etiology of MS, it remains to be determined whether the inflammatory response is primary or secondary to the degenerative process of the CNS (Lucchinetti et al., 1996; Trapp & Nave, 2008).

It is known that neuronal loss or neurodegeneration is present from disease onset, and not only as ultimate consequence of the pathogenic cascade, as it was initially thought. Neurodegeneration can occur acutely in new inflammatory regions or gradually over time in chronically demyelinated axons, and it is the major cause of permanent disability in people with MS (pwMS) (Thompson, Baranzini, et al., 2018; Trapp et al., 1999).

On the other hand, processes of remyelination can also take place in the damaged cells, mainly in the early stages of the disease and sparsely in chronic demyelinated cells. Remyelination could promote survival and restoration of the axonal function after acute demyelination and, hence, contribute to symptom alleviation (Franklin & Ffrench-Constant, 2008; Irvine & Blakemore, 2008; Jeffery & Blakemore, 1997; K. J. Smith et al., 1979). Additionally, processes of neural plasticity consisting on functional cortical reorganization would account for the masking or recovery of clinical

symptoms by allowing to compensate for the impaired function (Audoin et al., 2003; Kerschensteiner et al., 2004; Tomassini et al., 2012). The evidence strongly supports the relevant role of neural plasticity in pwMS since it is preserved regardless of age, stage and phase of the disease (Tomassini et al., 2012). This emphasizes the need and relevance of specialized clinical interventions -e.g. neuropsychological- that effectively drive neuroplasticity. Moreover, it remarks the need of profound and expert assessment for the detection of subtle symptoms in pwMS in order to start the intervention as early as possible, which is one purposes that this work aims to contribute to.

### 1.2.4. Clinical features

MS is a heterogeneous disease in terms of both symptomatic presentation and clinical course. Depending on the location of the lesions along the CNS and the neurodegenerative process, pwMS experience a wide variety of clinical features that may include sensory, motor, cognitive and/or psychiatric symptoms, which can fluctuate in time (Brassington & Marsh, 1998; Chiaravalloti & DeLuca, 2008).

MS frequently presents with sensory impairment (45%), mainly consisting on paresthesia and numbness of limbs or trunk; motor impairment (40%), characterized by weakness in one or more limbs; and less frequently with brainstem symptoms (25%) such as dysarthria, diplopia, dysphagia, and vertigo; vision loss (20%) due to inflammation of the optic nerve (optic neuritis) or lesion in the optic chiasm are characteristic of MS but less frequent as initial symptom, which often presents in the form of reduced visual acuity or blurred vision; cerebellar dysfunction (10-20%), which manifests as ataxia, imbalance, incoordination, and cerebellar dysarthria (Fernández-Fernández, 2002).

Cognitive impairment is also a common symptom that affects 43-70% pwMS during both late and early stages of the disease (Chiaravalloti & DeLuca, 2008), even before definite diagnosis of MS (Achiron & Barak, 2003; Pelosi et al., 1997). However, at the beginning of the disease, cognitive impairment is often subtle, thus it may remain unnoticed.

During the disease course, most of the neurological functional systems will be affected. Dysfunction of the motor (90%), sensory (77%) and cerebellar (70%) systems are the most frequent (Fernández-Fernández, 2002). These deficits would account for gait

disturbances and altered spatiotemporal parameters (speed, cadence, step length, base of support, double support), which can present even early in the disease process and in pwMS with low disability (Comber et al., 2017; C. L. Martin et al., 2006; Motl, 2013). In particular, gait disturbances affect up to 45% of pwMS within the first month of diagnosis and nearly all (93%) within 10 years of the disease (van Asch, 2011). Taking into account that the onset of MS is during young adulthood, the impact of motor and cognitive symptoms in the quality of life of these patients is paramount (Campbell et al., 2017; van Asch, 2011). Since both cognitive and motor functions constitute the core of the present research work, these will be described in more detail in other sections of this thesis.

Other symptoms and signs experienced by pwMS include: fatigue, pain, bladder and bowel dysfunction, sexual dysfunction, psychopathological disorders such as depression, Lhermitte's sign and Uhthoff's phenomenon (Gelfand, 2014). Lhermitte's and Uhthoff's phenomena are particularly characteristic of MS. Lhermitte's sign consists on brief electric shock sensations running down the spinal cord after neck flexion (Kanchandani & Howe, 1982), and Uhthoff's phenomenon (or heat sensitivity) refers to the temporary worsening of symptoms with heat or exercise due to slowed conduction in demyelinated nerves at higher temperatures (Davis & Jacobson, 1971).

The Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) is the most widely accepted measure of disability in pwMS. The EDSS examines 8 functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral -or mental-, and other domains) and provides a score ranging from 0 (normal neurological exam) to 10 (death due to MS). The functional systems' scores the determine EDSS below 4.9, and scores between 6.5 and 9.5 are determined by gait and self-care abilities (Saccà et al., 2017). The EDSS is mainly a measure of physical dysfunction, in which mental (cognitive and affective) symptoms make a slight contribution to the final score.

### 1.2.5. Clinical courses and diagnosis

Despite the variability concerning the presentation and evolution of MS, several clinical courses of the disease have been specified (Lublin et al., 2014) (see Fig. 2):

The majority of pwMS (85%) present with an acute period of neurologic dysfunction or "relapse", which is normally short (lasting hours or days) and suggestive of an

inflammatory demyelination process of the CNS that could be MS (Miller et al., 2005). This first clinical presentation is known as Clinically Isolated Syndrome (CIS). When people with CIS experience a second relapse (dissemination in time), diagnosis criteria for "clinically definite MS" are fulfilled. It is estimated that 30-70% of the people with CIS will convert to MS (Miller et al., 2005). The clinical course characterized by relapses and episodes of stability during which the symptomatology -at least partially- remits is called Relapsing-Remitting MS (RRMS) and it the most common clinical course (85% of the cases) (Compston & Coles, 2008). Over time, the remission of the symptomatology after relapses is more incomplete and persistent symptoms accumulate. Eventually, people with RRMS (65%) may transition to a Secondary Progressive (SPMS) phase of the disease, during which they experience an insidious worsening of function and accumulation of disability (Compston & Coles, 2008; Gelfand, 2014). Approximately 10-20% of the patients show a progressive course from the onset (without relapses), termed Primary Progressive MS (PPMS) (Gelfand, 2014).

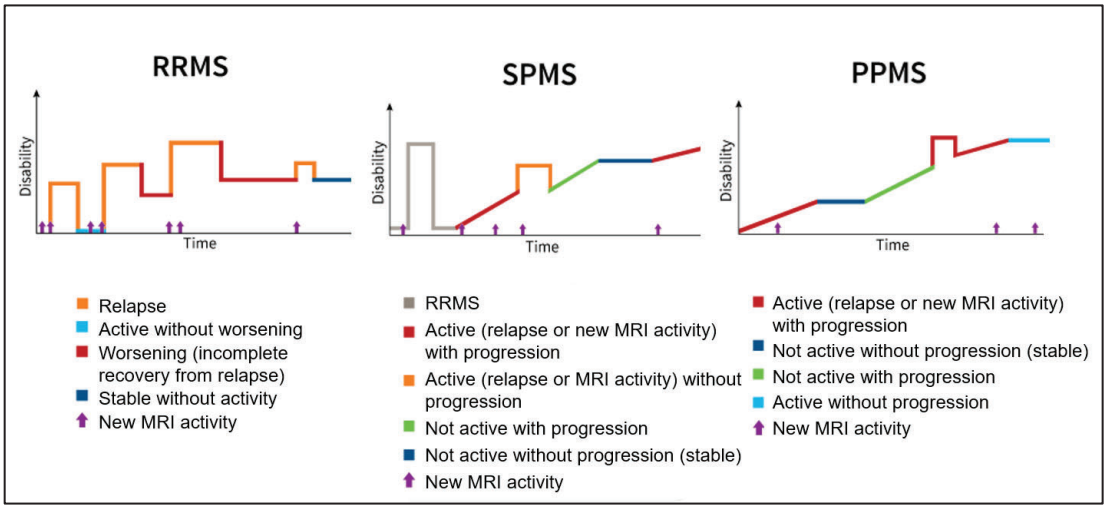


**Fig. 2. Clinical courses of Multiple Sclerosis (MS).** Source: Lublin et al. (2014). Adapted from www.nationalmssociety.org

Diagnosis of MS requires clinical imaging and/or laboratory findings to demonstrate that CNS damage is disseminated in space (2 lesions) and time (2 relapses), and the exclusion of other neurological conditions (differential diagnosis). Nowadays, the most widely used diagnosis criteria are the McDonald Criteria (Polman et al., 2011; Thompson et al., 2018), which have proved increased sensitivity without losing specificity relative to previous criteria (Deangelis & Miller, 2014). Since in the **Study**

**2** of this thesis, pwMS were included based on diagnosis with the 2010 McDonald Criteria (Polman et al., 2011), these are shown in Table 1.

**Table 1. The 2010 McDonald Criteria for Diagnosis of MS.** Adapted from Polman et al. (2011).

| Clinical presentation | Additional data needed for MS diagnosis |
|---|---|
| 2 or more attacks;<br>Objective clinical evidence of ≥ 2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack | None |
| ≥ 2 attacks;<br>Objective clinical evidence of 1 lesion | Dissemination in space, demonstrated by:<br>≥ 1T2 lesion in at least two MS typical CNS regions (periventricular, juxtacortical, infratentorial, spinal cord); OR<br>Await further clinical attack implicating a different CNS site |
| 1 attack;<br>Objective clinical evidence of ≥ 2 lesions | Dissemination in time, demonstrated by:<br>Simultaneous asymptomatic contrast-enhancing and non-enhancing lesions at any time; OR<br>A new T2 and/or contrast-enhancing lesions(s) on follow-up MRI, irrespective of its timing; OR<br>Await a second clinical attack |
| 1 attack;<br>Objective clinical evidence of 1 lesion (clinically isolated syndrome) | Dissemination in space, demonstrated by:<br>≥ 1T2 lesion in at least two MS typical CNS regions (periventricular, juxtacortical, infratentorial, spinal cord); OR<br>Await further clinical attack implicating a different CNS site<br>AND<br>Dissemination in time, demonstrated by:<br>Simultaneous asymptomatic contrast-enhancing and non-enhancing lesions at any time; OR<br>A new T2 and/or contrast-enhancing lesions(s) on follow-up MRI, irrespective of its timing which reference to a baseline scan; OR<br>Await a second clinical attack |
| Insidious neurological progression suggestive of MS (PPMS) | One year of disease progression (retrospectively or prospectively determined) AND at least 2 out of 3 of the following criteria:<br>Dissemination in space in the brain based on ≥1 T2 lesion in periventricular, juxtacortical or infratentorial regions;<br>Dissemination in space in the spinal cord based on ≥2 T2 lesions; OR<br>Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index). |

If the Criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is ‘‘MS’’; if suspicious, but the Criteria are not completely met, the diagnosis is ‘‘possible MS’’; if another diagnosis arises during the evaluation that better explains the clinical presentation, then the diagnosis is ‘‘not MS”.
MS = multiple sclerosis; CNS = central nervous system; MRI = magnetic resonance imaging; PPMS = primary progressive multiple sclerosis; CSF = cerebrospinal fluid; IgG = immunoglobulin G.

Nonetheless, there has been a more recent revision of the McDonald Criteria (2017), in which the following changes were made: presence of oligoclonal bands in the cerebrospinal fluid and dissemination in space (clinical or MRI-based) allows for the diagnosis of MS, cortical lesions can be used to prove dissemination in space, and both symptomatic and asymptomatic lesions can demonstrate dissemination in time and space (Thompson, Banwell, et al., 2018).

## 1.3. Cognitive impairment in people with Multiple Sclerosis

The first description of cognitive impairment in pwMS was probably done by Charcot, by the end the 19th century. He described that in many pwMS could be observed "marked enfeeblement of the memory; conceptions are formed slowly; the intellectual and emotional faculties are blunted in their totality" (Charcot, 1877). However, cognitive impairment in MS was disregarded until the end of the 20th century, when the seminal work by Rao et al. reinstated the interest towards it (Rao, 1986; Rao et al., 1989, 1991). Since then, research on cognitive impairment has grown exponentially and it is recognized as a core symptom of MS. As noted previously, the prevalence of cognitive dysfunction in MS is 43-70% (Benedict et al., 2006; Chiaravalloti & DeLuca, 2008; Peyser et al., 1990). It can begin at any moment in the disease course, even in the earliest preclinical stages, namely CIS and RIS (Amato et al., 2012; Khalil et al., 2011). Indeed, cognitive dysfunction at CIS predicts conversion to clinically definite MS (Zipoli et al., 2010) and disability progression (Deloire et al., 2010; Langdon, 2011). Moreover, cognitive impairment might progress independently from physical disability and it has a great impact *per se* on the quality of life, employment and social life of pwMS (Benedict et al., 2005; Benito-León et al., 2002; Campbell et al., 2017; Saccà et al., 2017).

Therefore, an early detection of cognitive dysfunction is essential in order to prevent its detrimental effect on the life of pwMS. Indeed, the inclusion of the neuropsychological assessment in the clinical evaluation leads to more accurate EDSS calculation and improved recognition of cognitive impairment (Saccà et al., 2017).

### 1.3.1. Profile of cognitive impairment and neuropsychological assessment

There is considerable variability on the type and severity of cognitive impairment among pwMS, according to the diffuse lesions and complex pathogenesis that characterizes the disease. However, some cognitive domains are commonly affected by MS such as information processing speed, episodic memory, complex attention, executive functions (including verbal fluency), and visuospatial analysis, with relative preservation of language (Chiaravalloti & DeLuca, 2008; Rao et al., 1991).

Deficit in information processing speed is the most prevalent cognitive alteration and one of the first symptoms that can be detected in pwMS (DeLuca et al., 2004; Van Schependom et al., 2015). Information processing speed refers to the amount of time needed by an individual to execute a cognitive task. It is a complex construct because rather than a cognitive function per se, it has been defined as a "measure of efficiency of cognitive function" (Sweet et al., 2010). Processing speed is a multidimensional feature, as it closely related to other cognitive functions (i.e. working memory). Depending on the cognitive demand of the task, processing speed is considered to be simple (minimal cognitive demand) or complex (increased working memory requirement). Various theoretical models have been proposed to explain the role of cognitive processing speed in MS. The most supported theory (Costa et al., 2017) is the Relative Consequence Model proposed by DeLuca et al. (2004), which suggests that cognitive impairment in pwMS might result from a primary processing speed deficit (DeLuca et al., 2004). The neuropsychological test most commonly used for the assessment of processing speed in pwMS is the Symbol Digit Modalities Test (SDMT) (A. Smith, 1982) (Costa et al., 2017). It has proven to be a valid measure of processing speed and has been recognized as the most reliable and sensitive neuropsychological test to detect cognitive impairment in pwMS (Benedict et al., 2017). In consequence, the SDMT has further been proposed as screening test for cognitive impairment, which is cost and time-effective since it takes five minutes for administration and scoring (Benedict et al., 2017; Parmenter et al., 2007).

Attentional function is often confounded with processing speed and executive processes. The simple or more automatic types of attention (e.g. attentional span) are generally preserved in pwMS (Amato et al., 2008; Rao et al., 1991). However, specific

deficits have been described in complex types of attention such as selective, sustained, divided and alternating attention (Adler & Lembach, 2015; McCarthy et al., 2005; Migliore et al., 2018; Oreja-Guevara et al., 2019; Vázquez Marrufo et al., 2014), which rely to some extent on executive control processes.

Executive function (also called executive control or cognitive control) refers to the cognitive processes that enable goal-directed behavior and adaptation to the changing demands of the environment. Executive function consists of effortful, top-down cognitive processes. Core executive functions are working memory, cognitive flexibility and inhibition (including inhibitory control and interference control), which would form the basis for higher-order executive functions such as reasoning, problem solving and planning (Diamond, 2013). Executive dysfunction in pwMS has been understudied, which might be due to its relatively low prevalence (15-25%) found in initial studies in contrast to other cognitive functions (Bagert et al., 2002; Rao et al., 1991; Rocca et al., 2015) or maybe because of its time-consuming assessment. However, a recent study reported that 40.8% out of 1040 pwMS had executive function impairment assessed with the Stroop and Verbal Fluency tests (Ruano et al., 2017). Another study that employed a comprehensive evaluation of executive function (Drew et al., 2008), showed that ~66% of pwMS scored lower than 1SD below the normative group in at least one measure of the Delis–Kaplan Executive Function System (DKEFS) (Delis et al., 2001). The DKEFS is a battery for the assessment of executive function composed of nine frequently used neuropsychological tests (Trail Making, Verbal Fluency, Design Fluency, Color-Word Interference, Card Sorting test, 20 Questions, Word Context, Tower Test and Proverbs) that provide a total of 20 primary measures. It should be noted that in the same study, only 17% of the pwMS had widespread executive dysfunction as characterized by lower than average scores on more than 5 measures of the DKEFS, and no typical pattern of executive dysfunction could be identified (Drew et al., 2008). Another study based on two subtests of the same battery (DKEFS subtests: Trial Making and Color-Word Interference), revealed that 17-22% of a sample of pwMS had executive dysfunction; whereas the with the Weekly Calendar Planning Activity test (Toglia, 2015) -a performance-based test- the rate of executive impairment in the same sample of increased to 27-46% (Goverover et al., 2019). In agreement with these results, performance-based tests have been recommended for an ecological assessment of executive function, as those may rather

detect the most subtle executive deficits by better capturing real-life requirements (Weiner et al., 2012). While performance-based tests are more reliable, they are time consuming and can be impractical in many clinical settings (Amato et al., 2013). It remarks the need for the development and validation of ecological screening tests in pwMS.

The already mentioned Stroop Test or Color-Word Interference subtest of the D-KEFS are widely used for the assessment of executive function. However, a color-free, multilingual non-reading alternative to this test has been developed, namely, the Five Digit Test (Sedó, 2004). It consists of four trials with increasing demand of executive control processes: reading numbers, counting, choosing to count under incongruent numeric stimuli and, shifting between reading and counting. Performance is measured by the time to complete each of the four trials and two additional indexes -inhibition and flexibility- may be calculated. It allows to measure information processing speed and executive function (Sedó, 2004), like the Stroop or Color-Word Interference subtest of the D-KEFS.

Relative to executive functioning, deficits in verbal fluency have also been evidenced in pwMS, generally with lower performance in phonemic over semantic fluency (Arnett & Strober, 2011). Verbal Fluency tasks require reciting words according to some restrictions, i.e. starting with a certain phoneme or belonging to a certain semantic category, thereby relying on cognitive flexibility processes (Diamond, 2013). Because it is a timed task, information processing speed might also account for deficits in this test, and even dysarthria or oral-motor deficits (Arnett & Strober, 2011). Sepulcre et al. (2011) examined lexical access strategies during semantic and phonemic verbal fluency tests in a prospective study. It proved that verbal fluency impairment is a frequent and early phenomena in pwMS, that is based on lexical retrieval problems (related to cognitive flexibility) rather than lexical pool impairment (Sepulcre et al., 2011). Furthermore, Verbal Fluency has been proposed as one of the most sensitive markers of cognitive impairment in pwMS based on a meta-analysis (Henry & Beatty, 2006).

Memory impairment is considered the most frequent cognitive dysfunction in pwMS, with a prevalence of 40-65% (Calabrese, 2006). The memory dysfunction in pwMS often seems to stem from a difficulty in the acquisition of new information; whereas

delayed recall and recognition would be preserved (Chiaravalloti & DeLuca, 2008; DeLuca et al., 1994, 1998; Gaudino et al., 2001). The difficulty in learning new information might as well be associated to deficits in other cognitive domains such as processing speed, attention, executive function (Chiaravalloti & DeLuca, 2008). A widely used test for the assessment of auditory/verbal memory is the California Verbal Learning Test (CVLT) (Delis et al., 1987), which has been validated in pwMS (Stegen et al., 2010). The Spanish adaptation of the CVLT is named Test de Aprendizaje Verbal España-Complutense (TAVEC) (Benedet & Alejandre, 1998). The TAVEC comprises a 16-item shopping list, in which the items belong to four different categories (four items per category) and are randomly ordered.

Several neuropsychological batteries have been validated for the assessment of cognitive dysfunction pwMS. The Minimal Assessment of Cognitive Function in MS (MACFIMS) (Benedict et al., 2002, 2006) covers the essential features of MS-related cognitive impairment, is unique in measuring executive dysfunction with DKEFS, and it takes around 90 minutes for completion. The MACFIMS was developed by experts based on a shorter battery (45 minutes) named the Brief Repeatable Neuropsychological Battery (BRNB) (45 minutes approx..) (Rao et al., 1991). These two batteries assess similar cognitive domains and are comparable in their sensitivity the cognitive status of the individual (Amato et al., 2013; Strober et al., 2009). For a shorter assessment (15 minutes), the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) (Langdon et al., 2012) might be used. The BICAMS is the short version of the MACFIMS and shows 94% of sensitivity and 84% of specificity (Benedict et al., 2012).

In sum, cognitive impairment is highly variable -as most symptoms- among pwMS. Slowed information processing speed is the hallmark cognitive deficit in MS, which can impact other higher-order cognitive functions. Nevertheless, there is evidence of direct cognitive impairment of other cognitive functions as well (e.g. executive function, verbal fluency, attention, memory/learning). There is no consensus concerning the instruments that should be used for the cognitive assessment of pwMS. The National Multiple Sclerosis Society recommends as minimum a baseline screening and an annual reassessment with the same test or battery, for which the SDMT -or other validated screening tool- can be used (Kalb et al., 2018). Thus, ecologically valid screening tests in pwMS are needed.

### 1.3.2. Neural correlates of cognitive impairment

An increasing amount of work over the last years have focused on the relationship between cognitive impairment and neuropathology of MS. The specific neuropathological mechanisms that underlie cognitive dysfunction are still poorly understood, albeit important advances in this area have taken place. It is now recognized that global and regional white and grey matter damage, characterized by focal lesions and diffuse abnormalities together with atrophy, play an important role in the presence and severity of cognitive dysfunction in pwMS (Preziosa et al., 2016).

MRI-based evidence of disseminated white matter lesions in the CNS is essential for the diagnosis and clinical management of pwMS (Filippi et al., 2016; Thompson, Banwell, et al., 2018). White matter lesion volumes have been associated with impaired processing speed, verbal memory (Deloire et al., 2011; Fulton et al., 1999), sustained attention and executive functions (Deloire et al., 2011). It has further been suggested that lesion location might be associated with cognitive dysfunction rather than the overall lesion load (de Medeiros Rimkus et al., 2016; Penner, 2016). The location of lesions is heterogeneous in pwMS, although it is not entirely random, and greater lesion loads are frequently observed in frontal and parietal lobes (Lazeron et al., 2005; Sperling et al., 2001). For instance, correlations have been identified between specific regional lesion load and cognition such as: information processing, sustained attention and executive function (including verbal fluency) with lesions in frontal, parietal and temporal lobes; verbal memory with lesions in temporal lobes; and visuospatial memory with parietal and temporal lesions (de Medeiros Rimkus et al., 2016; Lazeron et al., 2005). In addition, lesions in the corpus callosum have been more frequently identified (almost twice as often) in cognitively impaired than cognitively preserved pwMS (Rossi et al., 2012). MRI studies using diffusion tensor imaging (DTI) have shown that microstructural abnormalities in normal-appearing white matter in regions of the corpus callosum and other sites are associated with cognitive dysfunction in pwMS (de Medeiros Rimkus et al., 2011; Dineen et al., 2009; Mesaros et al., 2009; Preziosa et al., 2016). It has further been evidenced that normal-appearing white matter damage has a predictive value of overall cognitive function (Pinter et al., 2015) and of cognitive status within 7 years (Deloire et al., 2011). Together this evidence seems to support the hypothesis postulating that cognitive dysfunction in pwMS is, at least partly, a consequence of a “multiple disconnection syndrome”

(Calabrese & Penner, 2007) between grey matter structures, secondary to damage located in specific white matter areas.

Traditionally, MS was thought to be exclusively a white matter disease. However, it is now known that it also involves grey matter lesions, which can present at any moment during the disease course and contribute to cognitive impairment (Audoin et al., 2010; Cruz-Gómez et al., 2018; de Medeiros Rimkus et al., 2016; Geurts & Barkhof, 2008). Grey matter pathology in MS can present in the form of focal lesions, diffuse microscopic changes and/or irreversible tissue loss or atrophy. It affects cortical as well as deep grey matter structures, such as thalamus, basal ganglia and hippocampus (de Medeiros Rimkus et al., 2016). Thalamic atrophy can be detected in the earliest stages of the disease, i.e. RIS (Azevedo et al., 2015; Minagar et al., 2013) and has proved to be a predictor of overall cognitive status (Minagar et al., 2013; Papathanasiou et al., 2015; Schoonheim et al., 2012). Thalamic atrophy has also been related to specific cognitive deficits in information processing speed, executive functions and attention (Schoonheim et al., 2012). In addition to the thalami, basal ganglia nuclei (especially the putamen) have also been associated with slowed or inefficient processing of information (Batista et al., 2012). Hippocampal damage has been mainly associated with memory impairment (Sicotte et al., 2008). Moreover, whole brain and diffuse grey matter atrophy is associated with cognitive dysfunction can be found in all stages of the disease, even in RIS and CIS (Amato et al., 2012; Geurts et al., 2012; Paul, 2016). Nonetheless, cortical pathology appears to be more prone to increase and accumulate during chronic progressive clinical courses of MS (SPMS and PPMS) (Kutzelnigg et al., 2005; Roosendaal et al., 2009). In a longitudinal study over 3 years it was found that the number of cortical lesions was higher at baseline and follow-up in SPMS than in RRMS patients (with similar disease duration and white matter lesion counts), and it was associated with reduced neuropsychological performance in the two cognitive domains assessed, i.e. processing speed and visuospatial memory (Roosendaal et al., 2009). Riccitelli et al. (2011) showed a greater degree of grey matter atrophy in cognitively impaired vs. cognitively preserved pwMS across all clinical phenotypes (RR, SP, PP), which supports the role of grey matter in cognitive impairment in pwMS. In addition, a different pattern of regional cortical and subcortical grey matter atrophy was identified among cognitively impaired pwMS according to their clinical phenotype (Riccitelli et

al., 2011). Specifically, cognitively impaired SPMS patients showed grey matter atrophy in more areas than cognitively impaired PPMS patients (including the fronto-temporal lobes, the left hypothalamus and thalami). Although to a lesser extent, this pattern was replicated when comparing regional distribution of grey matter loss between RRMS and PPMS patients. In contrast, areas showing grey matter atrophy did not differ between RRMS and SPMS (Riccitelli et al., 2011). These data suggest that patients with RRMS and SPMS represent a more homogeneous group in terms of brain pathology than patients with PPMS. Additionally, in RRMS and SPMS there was a parallelism between the location of white matter lesions and grey matter atrophy -spatially closed or functionally linked- in several areas, that was not found in PPMS (Riccitelli et al., 2011).

These findings may support the idea that in RRMS and SPMS show a similar pattern of brain pathology, in which probably white matter lesions would lead to axonal damage and ultimately grey matter atrophy. Other studies have shown more atrophy in SPMS than RRMS, supporting that disease progression is related to accumulation of neurodegeneration (Trapp & Nave, 2008). A different pattern of grey matter atrophy was also observed by Riccitelli et al. (2011) between cognitively impaired RRMS and SPMS patients, that is in support of the notion that deep gray matter atrophy is more pronounced in the initial stages of the disease (i.e. RRMS), whereas cortical grey matter atrophy predominates in later stages of the disease (i.e. SPMS) (de Medeiros Rimkus et al., 2016).

In line with an integrated view of the mechanisms of cognitive impairment in pwMS (Di Filippo et al., 2018), it can be concluded that: in the early stages of MS, in which focal demyelination is thought to be predominant, white matter changes (lesions and microstructural abnormalities) would be related to different cognitive deficits, mainly through an information processing speed deficit. Together with it, thalamic damage may contribute to the disruption of cortico-subcortical and cortico-cortical connections and to information processing speed impairment. In later stages, the progressive accumulation of cortical damage, especially present in progressive courses (SP and PP), would account for the deficits in specific cognitive domains beyond information processing speed (e.g. executive function and frontal lobe damage).

On the other hand, it should be noted that the study of the brain activity *in vivo* with fMRI has demonstrated that often cognitively preserved pwMS display increased recruitment of areas normally active in healthy in controls or even a more widespread activation, which has been interpreted as a compensatory mechanism (Hillary et al., 2003; Penner et al., 2003; A. M. Smith et al., 2009). It might as well be related to cortical reorganization after accumulation of structural damage (Paul, 2016), in order to keep with an efficient cognitive performance. However, if a certain threshold of structural brain damage is exceeded, the brain's capacity to compensate through enhanced cortical recruitment would be exhausted, leading to cognitive impairment and other symptoms -i.e. fatigue- (Paul, 2016; Rocca et al., 2015).

### 1.3.3. Event-Related Potentials for the assessment of cognitive function

Electrophysiological techniques such as Event-Related Potentials (ERPs) have also been used for the study of cognitive function in pwMS. One of the advantages of the ERP technique is that it offers a direct measure of the electrical activity from the neurons related to diverse cognitive processes (Vázquez-Marrufo, 2017). Moreover, it informs of the brain activity with a time resolution of miliseconds. For instance, an attentional modulation can be observed in the amplitude of early ERP components such as P1 and N1, which appear between 100-200 ms after specific sensory stimulation (Periáñez-Morales et al., 2008). Attending to a specific stimulus leads to enhanced P1 (80-120 ms) and N1 (160-200 ms) amplitudes after the attended stimulus in contrast with non-attented stimulus presentations (Hillyard et al., 1973; Hillyard & Anllo-Vento, 1998; Woldorff & Hillyard, 1991). These early components modulated by attention -P1 and N1- are related to initial information processing in sensory cortices according to the sensory modality of the stimuli (Herrmann & Knight, 2001). Such early modulation has been considered proof that attention has an amplifying effect over the neural response of sensory regions related to modality-specific information processing (Periáñez-Morales et al., 2008) that affects stimulus encoding. It should be noted that N1 generators have also been identified in other associative cortices, i.e. frontal and parietal cortices (Hillyard & Anllo-Vento, 1998). Furthermore, a dissociation of the attentional modulation of P1 and N1 components have been identified in different tasks (e.g. spatial orientation), which suggests that each component reflect complementary neural mechanisms required for selective

attention (Periáñez-Morales et al., 2008). Nevertheless, early components (N1 and P1) are informative of the first and more sensory-related stages of information processing in contrast with late ERP components, which would provide a more sensitive method for assessing higher-order information processing (Gonzalez-Rosa et al., 2011).

Among the late ERP components, P3 is probably the most widely investigated in the field of cognition in pwMS. The P3 (or P300) is a positive deflection that peaks around 300 ms after the target stimulus onset, whose latency can extend from 250-500 ms (Vázquez-Marrufo, 2017) and with topographical distribution over the centroparietal region (Periáñez-Morales et al., 2008). In contrast with early ERP components (P1 or N1) linked to the sensory modality of the stimuli, the P3 has multiple generators in associative regions, independent of the sensory modality, which include the thalamus, temporal lobe, hippocampus and the insula (Herrmann & Knight, 2001) among others. It is typically evoked by relevant and infrequent target stimuli and not by standard frequent stimuli presented in a randomized order, as in the so-called oddball tasks (Herrmann & Knight, 2001). The P3 represents late phases of the perceptual process and involves diverse higher-order cognitive processes, with a strong consensus on the fact that it reflects the timing of cognitive processing and working memory (Donchin & Coles, 1988; Vázquez-Marrufo, 2017). Applied to the assessment of pwMS, alterations in the P3 component have been observed regarding its latency (increased) and amplitude (decreased) indicating higher-order information processing impairment in pwMS, potentially related to demyelination and axonal degeneration (Comi et al., 1999; Gonzalez-Rosa et al., 2011; Váquez-Marrufo et al., 2014; Vázquez-Marrufo et al., 2009). The evidence suggests that in early phases of MS, ERP alterations are generally limited to later components, whereas earlier components tend to be preserved (especially N1) and eventually become altered with longer disease durations (Gil et al., 1993; Gonzalez-Rosa et al., 2011; Vázquez-Marrufo et al., 2009).

## 1.4. Depression, fatigue and quality of life in people with Multiple Sclerosis

In the neuropsychological assessment of pwMS several confounders should be accounted for, as those might adversely affect cognitive performance. Frequent

confounders include depression and fatigue, which also have a great impact on their quality of life.

Depression is the most frequent neuropsychiatric disorder in pwMS, with a lifetime prevalence of approximately 50% (Feinstein, 2004), which makes it more common than in the general population (10-15%) (Alonso et al., 2004). It might be assumed that depression in pwMS is reactive in nature, as a consequence to the diagnosis and to the symptomatology or disability associated. Nevertheless, it is more prevalent in MS than in other chronic conditions, including other neurological disorders with similar deficits (Holden & Isaac, 2011; Patten et al., 2003; Thielscher et al., 2013). Therefore, other mechanisms related to the MS pathology might play role. This idea has been supported by a review of brain imaging studies that remarked the association between depression in pwMS with lesion volume, cerebral atrophy and, especially, with subtle changes in normal-appearing white and grey matter in frontal and temporal regions (Feinstein et al., 2014).

It is well-stablished that depression adversely affects cognitive performance, with an important impact on working memory, executive function, and information processing speed (Arnett et al., 1999, 2001; Demaree et al., 2003; Lubrini et al., 2016). Hence, it is an important aspect to consider when performing a neuropsychological assessment on pwMS.

One of the most widely used scales to screen for depression is the revised Beck Depression Inventory (BDI-II) (Beck et al., 1996, 2011), which was employed in **Study 2** of this thesis. BDI-II is a self-report multiple choice inventory, consisting on 21 items to be graded using a Likert scale with 4 points distributed on scores from 0 to 3. The total score indicates the severity based on the following cutoff values: 0–13, no or minimally depressed; 14–19, slightly depressed; 20–28, moderately depressed; and 29–63, severely depressed. The evidence-based guidelines developed by the American Academy of Neurology, recommended the BDI-II as the scale of choice for the assessment of pwMS (Minden et al., 2014).

Together with depression, fatigue is a common disabling symptom of MS, with an estimated prevalence of 53-90% in pwMS (Arnett & Strober, 2011; Bakshi et al., 2000). Fatigue is defined as an overwhelming sense of tiredness, lack of energy, or exhaustion, that is often present even at rest (Comi et al., 2001). The fatigue

experienced by pwMS seems to be qualitatively different to that experienced by healthy individuals or those with other neurological conditions (Krupp, 2003). Performance-based measures of cognitive and motor tasks show a decline in performance over time in pwMS, interpreted as a manifestation of fatigue (Krupp, 2003; Krupp & Elkins, 2000; Kujala et al., 1995; Schwid et al., 2003). However, the association between self-reported fatigue and cognitive (or motor) performance is mixed (Andreasen et al., 2010; Bailey et al., 2007; Langdon, 2011). The mismatch between subjective fatigue and cognitive or motor performance in pwMS has been postulated to be due to higher cognitive load required in order to maintain an efficient cognitive or motor performance, or to an overestimation of it (Leocani et al., 2008), which would explain self-perceived fatigue while showing a proper performance the task. Despite the complex etiology of fatigue in pwMS, an important role appears to be played by the CNS, with a selective involvement of frontal cortex and basal ganglia (Leocani et al., 2008), potentially through dysfunction of the fronto–striato–subthalamic–pallidal network.

In **Study 2** of this thesis, self-reported fatigue was assessed with the Spanish adaptation of The Fatigue Impact Scale for Daily Use (D-FIS) (Fisk & Doble, 2002; Martinez-Martin et al., 2006). The D-FIS (Spanish version) instrument is composed of eight items assessing both cognitive and physical fatigue, that has proved to be a feasible and valid instrument for the detection of MS-related fatigue (Benito-León et al., 2007).

Considering that the onset of MS is normally during young adulthood (20-40 years), the diagnosis and the uncertainty in the prognosis might make them adjust their life expectations in a moment when many decisions are being taken regarding employment, family and social life. Thus, beyond the symptomatology, other psychological and social factors will affect the quality of life of pwMS (Arnett & Strober, 2011). Health-related quality of life is a multidimensional construct that considers physical, mental and social health (Vickrey et al., 1995) and is concerned with whether disease or impairment limits the individual's ability to derive satisfaction from meaningful behavior (Meyers et al., 2000). The use of health-related quality of life instruments allow the identification of disease impact areas that may otherwise remain unnoticed by the clinician. Indeed, several studies have reported a discrepancy between clinicians and pwMS, so that clinicians are more concerned about physical

deficits, whereas pwMS are more concerned about vitality, mental and emotional health (Rothwell et al., 1997).

In **Study 2** of this thesis, the Spanish adaptation of the Multiple Sclerosis Quality of Life-54 (MSQOL-54) (Aymerich et al., 2006; Vickrey et al., 1995), was included for the measurement of health-related quality of life. The MSQOL-54 comprises of 54 items in total, 52 distributed in 12 subscales along with two composite scores (physical health composite and mental health composite), and two individual elements (satisfaction with sexual function and change in health). The subscales are: physical function, role limitations-physical, role limitations-emotional, pain, emotional well-being, energy, health perceptions, social function, cognitive function, health distress, overall quality of life, and sexual function. The scores range from 0 to 100, where higher values indicate a better perception of quality of life. The MSQOL-54 has demonstrated good test-retest reliability, internal consistency and construct validity (Vickrey et al., 1995; Yamout et al., 2013), and it is one of the most commonly applied instruments for the assessment of health-related quality of life in pwMS (Mitchell et al., 2005).

## 1.5. Cognitive-motor interference while walking

### 1.5.1. The cognitive-motor dual task paradigm

The main purpose of the neuropsychological assessment has evolved over time, from assisting in the diagnosis of brain pathology before the development of neuroimaging techniques, towards predicting the individuals' performance in their everyday lives (Chaytor & Schmitter-Edgecombe, 2003). The classical assessment of motor and cognitive function has been performed independently of each other; however, an important part of our daily-life activities consists on the concurrent performance of a motor a and cognitive task. For example, it is common to walk while thinking on a shopping list, crossing a busy street or talking to someone. In these cases, a so-called cognitive-motor dual task (DT) is performed. Thus, cognitive-motor DT stands as an assessment that might closely reflect real-life performance, i.e. an ecologically-valid assessment (Leone et al., 2015; McFadyen et al., 2017). Besides its potential clinical implications, the cognitive-motor DT assessment has been used to investigate the

relative contribution of cognition to gait (Woollacott & Shumway-Cook, 2002; Yogev-Seligmann et al., 2008).

DT 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). The performance of a cognitive-motor DT often leads to a decrement on one or both tasks compared to the performance of each task in isolation or single task (ST) condition. Such decrement is referred to as cognitive-motor interference (CMI) (Fig. 3).

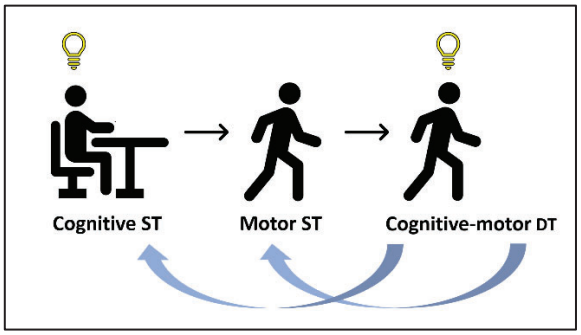


**Fig. 3. Cognitive-motor interference.**

CMI is often operationalized as absolute or *direct* dual-task scores, or as relative or *dual-task costs* (DTC) scores. The DTC is calculated by the following formula (Baddeley et al., 1997):

$$DTC = \frac{single\ task - dual\ task}{single\ task} x\ 100$$

Plummer et al. (2013) proposed nine possible outcomes of DT (see Table 2) based on the performance of each task compared to ST, which consist either on facilitation or interference of the cognitive or the motor task, as well as the combination of these outcomes, and no changes in any task (Plummer et al., 2013).

**Table 2. Possible outcomes of cognitive-motor dual task performance.** Adapted from Plummer et al. (2013).

| Motor performance | | Cognitive performance | | |
|---|---|---|---|---|
| | | **No change** | **Improved** | **Worsened** |
| | **No change** | No dual-task interference | Cognitive facilitation | Cognitive interference |
| | **Improved** | Motor facilitation | Mutual facilitation | Motor priority trade-off |
| | **Worsened** | Motor interference | Cognitive priority trade-off | Mutual interference |

Probably the interest on the study of CMI while walking began with the seminal work by Lundin-Olsson et al. (1997) and their observation of the "stops walking when talking" sign in frail elderly people, which was predictive of future falls (Lundin-Olsson et al., 1997). Since then, research on this topic has increasingly grown over the years and demonstrated the interplay between cognitive and motor processes (i.e. gait) in healthy and neurological populations such as Dementia, Stroke, Parkinson's Disease, and Multiple Sclerosis (Al-Yahya et al., 2011; Kelly et al., 2012; Leone et al., 2015; Montero-Odasso et al., 2017; Plummer et al., 2013; Woollacott & Shumway-Cook, 2002).

For the purpose of this thesis, the focus will be on CMI while walking, which has been the most investigated motor task in the cognitive-motor DT paradigm. Nevertheless, it should be noted that other motor tasks have been used for the cognitive-motor DT assessment, such as standing balance and upper-limb tasks (Bank et al., 2018; Raats et al., 2018; Wajda & Sosnoff, 2015).

### 1.5.2. Theoretical models of cognitive-motor interference

The exact mechanisms underlying CMI are still under debate. Generally, they have been described in terms of competence for cognitive or structural neural resources that are shared between both tasks in the DT. Several theoretical models have been proposed to explain CMI, though there is no consensus on which model better fits it. The most widely referred "attentional" models in the context of CMI are the bottleneck, capacity-sharing, and cross-talk models.

The bottleneck model postulates that when two tasks require the same neural processor or networks, a bottleneck is created in the serial processing, thus leading to a delay or deterioration in the performance of one or both tasks. In other words, bottleneck processors act serially on one task at a time, so the processing of the second task might be impaired or delayed until the processor has completed the processing of the first task (Pashler, 1994; Ruthruff et al., 2001; Tombu & Jolicoæur, 2003). According to this model, as far as the neural networks between gait and the cognitive task in DT overlap, a bottleneck will be created in the processing of each task, leading to slowed walking or delayed performance of the cognitive task (Yogev-Seligmann et al., 2008). The main support of the bottleneck model derives from experiments manipulating the

psychological refractory period. These experiments consist on the presentation of two stimuli separated by a variable interval of time. Generally, it is found that decreasing the temporal gap between the two stimuli, leads to an increasing delay in the response to the second stimulus as the first is still occupying the bottleneck processor (Pashler, 1994).

The capacity-sharing model posits that task performance depends on a limited pool of cognitive resources (Kahneman, 1973; Tombu & Jolicoæur, 2003). In contrast to the serial processing of the bottleneck model, the capacity-sharing model assumes parallel processing and distribution of the limited cognitive resources. To the extent that one or both tasks are less automatic, they would require more cognitive control; thus, creating higher competence for the shared and limited resources. Consequently, two possible scenarios would arise during cognitive-motor DT: 1) no reduction in performance (i.e. no CMI) in gait nor the cognitive task, when both require few resources and the limited capacity of the system is not exceeded; 2) CMI or decrement in the performance either on gait, the cognitive task or both, when the limited capacity has been exceeded. This theory also assumes that it is possible to voluntarily allocate the resources to a specific task (Tombu & Jolicoæur, 2003). Regarding the general capacity-sharing model, two tasks would compete for common resources from a central or undifferentiated pool; however, other authors have extended this theory and proposed that they would compete for resources from multiple pools (Friedman et al., 1982; Wickens, 2002, 2008). Wickens (2002, 2008) described multiple resources pools dedicated to different processing stages (e.g. perceptual/cognitive processing, responding), perceptual modalities (e.g. visual, auditory), visual channels (focal or ambient), and processing codes (spatial/analogue, linguistic/verbal) across all stages (perception/cognition, response). According to the multiple resources model, CMI will occur if the two tasks require common limited resources. Thus, CMI will occur by means of task complexity (as the central capacity-sharing model) and by similarity between the two tasks. For example, walking while performing a cognitive task might not lead to CMI, whereas walking while performing another motor task might (e.g. carrying a tray with a glass) (Yogev-Seligmann et al., 2008).

In contrast with the multiple resources model, the cross-talk model proposes that if both tasks are from a similar domain and use the same neural resources, they will not interfere with each other (Navon & Miller, 1987). Indeed, it predicts that the use of the

same neural populations might increase processing efficiency and lead to facilitation between tasks. In line with this model, walking while carrying a tray with a glass might facilitate gait, whereas performing a cognitive task might worsen gait (i.e. cause CMI) (Bayot et al., 2018).

These theoretical models of DT are derived from studies mainly examining cognitive-cognitive DT performance. Despite being commonly referred as possible models to explain CMI, there is limited work directly examining this link. Nevertheless, there is growing evidence that supports shared cognitive and neural resources between walking and cognitive tasks. This evidence will be outlined in the next section.

### 1.5.3. Cognitive and neural correlates of cognitive-motor interference

For a long time, walking was considered a merely automatic task. Nowadays it is recognized that purposeful and safe walking requires cognitive control, specifically attention and executive function (Woollacott & Shumway-Cook, 2002; Yogev-Seligmann et al., 2008). For instance, walking in the real world requires paying attention to the environment, while integrating information from sensory systems (i.e. visual, vestibular and proprioception) with motor information to enable gait adaptation and avoid hazards (Hausdorff et al., 2001; Montero-Odasso, Verghese, et al., 2012). Deficits in attention and executive function have been associated with gait disturbances (Yogev-Seligmann et al., 2008). In addition, slowed gait has been proposed as marker of cognitive impairment (Buracchio et al., 2010; Camicioli et al., 1998), progression to dementia (Beauchet et al., 2016), and a threshold of gait velocity at 0.8 m/sec has been recommended for the prediction of adverse outcomes (Abellan Van Kan et al., 2009).

The degree of cognitive control needed during walking increases under more complex or challenging conditions such as performing a DT, but also when dealing with obstacles or turning (Mirelman et al., 2018). Particularly, there is consistent evidence showing that healthy individuals -even young adults- reduced their gait speed during cognitive-motor DT compared to ST (Al-Yahya et al., 2011; Duncan et al., 2016). The reduction in gait speed during DT represents the CMI and brings to light the competence for shared limited cognitive resources between gait and the other cognitive task. Moreover, the degree of CMI varies according to the DT complexity, and so due to its demand for cognitive resources. For example, walking while serially subtracting

7s from a given number leads to higher CMI than less cognitively-demanding tasks such as walking while serially subtracting 3s (Srygley et al., 2009) or than counting forward (Mirelman et al., 2014).

The competence for shared cognitive and/or neural resources between gait and other cognitive tasks can also be observed when considering healthy (i.e. aging) and pathological (i.e. neurological disorders) states that affect motor and/or cognitive functions. In these cases, higher demand for cognitive resources would be expected together with less cognitive reserve, which will more easily exceed their capacity and lead to more prominent CMI. During healthy aging, structural changes affect the prefrontal cortex and white matter, which have been associated with declines in executive function (Gunning-Dixon & Raz, 2003; Harada et al., 2013) and, specifically, with gait control (Seidler et al., 2010). Importantly, it occurs in a moment when age-related peripheral dysfunctions in neuromuscular and sensory systems affect their motor function and increased cognitive control of gait is needed, therefore limiting their ability to compensate. That is, during healthy aging, motor control generally relies on more widespread prefrontal and basal ganglia networks and demands higher executive control, which at the same time are the brain systems most affected by the aging process (Seidler et al., 2010). Therefore, it is not surprising that healthy older adults tend to perform worse during cognitive-motor DT than in ST conditions and have higher CMI than healthy young adults (Al-Yahya et al., 2011; Ruffieux et al., 2015; Woollacott & Shumway-Cook, 2002). Likewise, there is robust evidence showing that people with neurological disorders (e.g. MS, Parkinson's disease, post-stroke, Alzheimer's disease) exhibit CMI and that it is larger than in age-matched healthy controls (Al-Yahya et al., 2011; Kelly et al., 2012; Leone et al., 2015; Montero-Odasso et al., 2017; Plummer et al., 2013; Woollacott & Shumway-Cook, 2002). Common symptoms of these disorders are loss of gait automaticity and cognitive impairment, including deficits in executive function (Yogev-Seligmann et al., 2008). The rationale is similar to that of healthy aging: structural and cognitive dysfunction -especially in executive functioning- together with loss of gait automaticity or increased motor control demands are likely to further compound their deficits during DT and lead to CMI in people with certain neurological disorders. In this context, it has been proposed that the cognitive-motor DT assessment would stand as a "brain stress test" that might unveil subclinical cognitive decline (Montero-Odasso

et al., 2017) and CMI as a potential functional marker cognitive decline. Gait disturbances during cognitive-motor DT predicted risk of progression to dementia in cognitively-healthy adults (Ceïde et al., 2018) and adults with mild cognitive impairment (Montero-Odasso et al., 2017), who respectively increased gait variability and slowed gait during DT. In both studies ST gait was not associated with progression to dementia (Ceïde et al., 2018; Montero-Odasso et al., 2017), supporting that DT gait may uncover deficits earlier than ST gait. Moreover, numerous studies have documented an inverse correlation between CMI and executive functioning (McFadyen et al., 2017; Montero-Odasso et al., 2009; Springer et al., 2006; Stuart et al., 2019).

Concerning the neural correlates of walking, neuroimaging studies have shown that gait control requires cortical areas of the brain that are also involved in higher-order cognitive functions. Two neural pathways for locomotor control have been described: the direct pathway, which operates via primary motor cortex, cerebellum and spinal cord; and the indirect pathway, which modulates gait via the prefrontal cortex, premotor area, supplementary motor area and basal ganglia (la Fougère et al., 2010). Goal-directed walking and, specifically, cognitive-motor DT has been related to the indirect pathway and, particularly, to the prefrontal cortex (Bayot et al., 2018; Holtzer et al., 2011). The prefrontal cortex is a key structure for executive functions and top down-down regulation of other cortical and subcortical structures, through which it plays a crucial role in the monitorization and control of cognitive and motor processes (Funahashi & Andreau, 2013). Prefrontal cortical activity is heightened during the performance of cognitive, motor tasks and cognitive-motor DT (Clark, 2015). Several studies have been conducted to explore the neural correlates of CMI by making use of advanced techniques that enable the assessment of brain activation while walking, namely functional near-infrared spectroscopy (fNIRS) and mobile brain/body imaging (MoBI).

FNIRS is an optical imaging technique that measures changes in cortical oxygenated and deoxygenated hemoglobin concentrations (Irani et al., 2007). Studies using fNIRS during DT walking have generally reported an increase in oxygenated hemoglobin (i.e. increased activation) in the prefrontal cortex relative to ST walking in healthy young and older adults (Holtzer et al., 2011; Lu et al., 2015; Meester et al., 2014, 2019; Mirelman et al., 2014, 2017), and adults with neurological disease (for a detailed

review see (Herold et al., 2017)). Interestingly, Mirelman et al. (2014) showed that the degree of prefrontal activation varied in relation to the cognitive demand during walking. Indeed, oxygenation levels in the prefrontal cortex were higher during the counting while walking DT than walking in ST; and even higher during serially subtracting 7s while walking DT, which is a more complex, cognitively demanding DT (Mirelman et al., 2014). Moreover, the performance of serial 7s subtractions while standing was associated with a decrease in oxygenation levels, suggesting that the prefrontal activation was not a solely response to the verbalization of words or to all types of DT, but rather reflected the increase in cognitive demand during DT walking (Mirelman et al., 2014). Relative to aging, Holtzer et al. (2011) found that younger adults presented a more pronounced increase in prefrontal cortex activation than older adults during DT walking vs ST walking, which would suggest that older adults would under-utilize the prefrontal cortex in the more cognitively demanding DT conditions. In contrast, others have found that older adults present a more prominent increase in prefrontal cortex activation than younger adults during DT (Mirelman et al., 2017; Ohsugi et al., 2013), in agreement with aging theories which posit that increasing task demands is associated with increase in brain activity in older adults (Steffener & Stern, 2012). However, these studies only include examination of the prefrontal activations, therefore limiting the ability to capture changes on other potentially involved cortical regions (e.g. parietal cortex).

More recent fNIRS studies have extended the assessment to more areas of the frontal lobe beyond prefrontal cortex (Lu et al., 2015; Stuart et al., 2019). Lu et al. (2015) confirmed the increased activation of prefrontal cortex from the previous studies, but also reported increased activation of other frontal regions such as the premotor cortex and the supplementary motor area during DT walking, which correlated with declines in walking performance. In contrast with the previous reports, Stuart et al. (2019) did not find a significant increase in prefrontal cortical activation during DT in healthy young and older adults, neither did it differ between these groups. However, they identified increased activation over the premotor cortex, supplementary motor area and primary motor cortex, which was associated with higher executive function across young and older adults (Stuart et al., 2019). Possible reasons for the difference in prefrontal cortex activation observed by Stuart et al. (2019) in contrast with other studies might be related to the nature of the motor task (treadmill walking) and the

cognitive task (vigilance-based attentional task), which might be both less demanding on executive control resources.

Some studies have used the MoBI technique, which integrates high-density electroencephalography (EEG) recordings with simultaneously acquired body tracking data (i.e. recordings of gait parameters). Studies making use of the MoBI technique have provided evidence of more widespread neural activity during cognitive-motor DT than those using fNIRS. The performance of a DT consisting on a Go/No-Go task while walking on a treadmill, led to increased stride time in young adults during DT and no change in cognitive performance, accompanied by modulations of ERP components N2 and P3 associated with inhibitory control (De Sanctis et al., 2014). More specifically, ERP modulations occurred at earlier (decreased N2 amplitude) and later stages (earlier P3 latency and more frontally distributed P3 topography) of the processing stream during DT in contrast with the -sitting- cognitive ST (De Sanctis et al., 2014). De Sanctis et al. (2014) proposed that these neural changes would reflect a shift towards a controlled mode of action, optimizing performance through flexible allocation of neural resources during DT. Using the same experimental paradigm (De Sanctis et al., 2014), it was found older adults decreased cognitive performance and increased stride length during DT (Malcolm et al., 2015). These CMI parameters in older adults were accompanied by attenuated and delayed neural reconfiguration during DT as ERPs modulations were limited to later processing stages (increased P3 amplitude) (Malcolm et al., 2015). These results were interpreted to be indicative of a postural prioritization strategy for safe walking and an age-associated loss in the flexible allocation of resources during DT (Malcolm et al., 2015).

Recently, the MoBI technology have been used during DT walking in the “real world”, outside the laboratory (Pizzamiglio et al., 2017, 2018). Both studies included two DT conditions consisting on walking while conversing with someone and walking while texting on a smartphone in an urban environment. Pizzamiglio et al. (2017) showed frequency-specific modulations over frontal and parietal regions related to each DT, which were thought to be recruited as top-down mechanism for adaptive, optimized DT performance. Subsequently, it was shown that power spectral density in specific frequency bands in the left posterior parietal cortex was predictive of gait stability during ST (theta band) and DT (alpha band for walking while talking and beta band for walking while texting) (Pizzamiglio et al., 2018). However, no association was

found between prefrontal cortex activity and gait parameters in DT (Pizzamiglio et al., 2018). Considering their results, the authors suggested a possible role of the left posterior parietal cortex in sensorimotor integration and gait control during DT in real-life conditions through frequency-specific oscillatory activity (Pizzamiglio et al., 2018).

In agreement with the capacity-sharing and bottleneck models, the presence and degree of CMI is modulated by the complexity of DT and its subsequent competence for limited cognitive resources, as well as by means of the individual's cognitive/neural capacity as in the case of healthy older adults and more so in those with neurological disorders (and cognitive impairment), whose limited resources would be reduced -and more "easily" exceeded. Nevertheless, the bottleneck model posits that CMI occurs when gait and the cognitive task in the DT share the same neural networks, which based on behavioral observational studies is only hypothesized according to the neural bases described during gait or the performance of cognitive tasks in isolation. The study of the neural activity during DT walking has used fNIRS and MoBI techniques. However, most of these studies do not include an assessment of the neural activity during the cognitive ST, thus making it difficult to test the bottleneck model as it is not proved that the neural resources were indeed shared between each single task. Therefore, more often the explanation revolves around the capacity-sharing model for its simplicity thereby attributing CMI to a capacity overflow, with no need to infer the neural mechanisms. Overall the evidence shows that DT walking involves the prefrontal cortex, but also other areas such as the premotor cortex, supplementary motor area and parietal cortex during DT. These brain regions are part of the indirect locomotor pathway and the frontoparietal network, which together with the evidence that CMI is modulated by the complexity of the DT and the individual's resources support that gait requires cognitive control, a demand that is increased under DT. The assessment of cognitive-motor DT performance with portable (fNIRS and MoBI) as well as traditional neuroimaging techniques (e.g. fMRI, positron emission tomography, etc.) during other -not walking- DT have given support to both, capacity-sharing and bottleneck models as concluded on a recent systematic review (Leone et al., 2017).

### 1.5.4. Factors influencing cognitive-motor interference

Currently, there is no agreement on the cognitive-motor DT procedures, so a wide variety of tasks, measures, and instructions have been used for the assessment of CMI. These variations have an effect over CMI and might account for the inconsistencies found among studies.

It has already been mentioned that CMI has been assessed with diverse motor tasks, and not only during walking (e.g. standing balance). When considering the studies that focus on the walking DT assessment, it appears that walking has been evaluated under different physical constraints, such as on a treadmill, over narrow-base path, or dealing with obstacles, which lead to differences in CMI when compared to overground unobstructed DT walking (Kelly et al., 2008; Simoni et al., 2013; Veldkamp et al., 2019; Wrightson & Smeeton, 2017). Such differences in CMI would be due to differences in the complexity of the sensory processing and motor control required for walking under the different constraints.

Regarding the cognitive domain, a variety of tasks have been as well used concurrently to "normal" walking. Some of the cognitive tasks used in DT are standardized and, in many cases, derived from the neuropsychological tradition such as phonologic and semantic verbal fluency, serial subtractions of 3s or 7s, digit span (direct or inverse), N-back and Stroop tests among others (Benton & Hamsher, 1989; Folstein et al., 1975; Friend et al., 1999; Stroop, 1935; Wechsler, 1987). Often the combination of such standardized tasks while walking are not direct simulations of real-life activities, although they produce appropriate DT challenges that tap into real-life cognitive function (McFadyen et al., 2017). Furthermore, standardized tasks have the advantage of enabling reproducibility, replicability of results and comparisons between studies in contrast with non-standardized tasks. However, non-standardized tasks are often more ecologically valid (Al-Yahya et al., 2011) as they better reproduce real-life activities, such as walking while conversing with someone, talking on the phone or texting. Definitively, the different cognitive tasks (standardized or not) would tap on different cognitive functions often including verbal fluency, mental tracking or working memory, attention, decision-making, reaction-time, inhibitory control and cognitive flexibility, which are known to also have a differential effect on CMI in healthy and neurological populations (Al-Yahya et al., 2011; Patel et al., 2014).

Therefore, not only the complexity (as explained in the previous section) but also the type of cognitive task influences CMI. Al-Yahya et al. (2011) performed a systematic review and meta-analysis in which the DT studies were classified according to the cognitive task domains of verbal fluency, mental tracking, working memory, decision making and reaction time. Findings from this meta-analysis suggested that cognitive tasks in DT involving internal interfering factors such as verbal fluency or mental tracking tasks (e.g. serial subtracting 7s) would produce greater CMI than those involving external interfering factors (e.g. reaction time tasks) (Al-Yahya et al., 2011). It may suggest that the competence for higher-order shared networks would lead to greater CMI than the competence for lower-order shared networks (Bayot et al., 2018).

Concerning the measures of CMI, gait speed is the most reported outcome of DT performance, probably reflecting the practical simplicity to obtain this measure (Al-Yahya et al., 2011). CMI effects in terms of reduced gait speed have been robustly reported across different types of DT and populations, such as in people with neurological disorders, in healthy older adults, and even in healthy younger adults in which CMI is typically confined to this gait parameter (other aspects of gait remain unaffected) (Mirelman et al., 2018). Changes in other spatiotemporal gait parameters have been as well reported including: decreased cadence (steps/min), decreased stride length, increased stride time and increased stride time variability (Al-Yahya et al., 2011). Unlike distance or gait speed, the assessment of these and some other gait parameters require specialized equipment like accelerometry, force-sensitive insoles, force platforms, or motion capture systems, which can be costly and require professional operating staff (e.g. for gait data analysis). Nevertheless, these parameters offer additional information regarding the quality of gait and some (e.g. gait variability) may be more sensitive to subtle cognitive or gait alterations resulting from normal aging or neurological pathology (Beauchet et al., 2017; Ceïde et al., 2018; Herman et al., 2010; Kalron et al., 2018). Note that the measures of cognitive performance vary according to the type of cognitive tasks used in DT.

The instructions given to the individual on how to perform the DT are also of importance. One of the main aspects of the DT instructions concern which task to prioritize (motor, cognitive or both), if any, as they will likely affect CMI. Indeed, it has been observed in studies that have compared the effect of different instructions of prioritization on DT performance (Verghese et al., 2007; Yogev-Seligmann et al.,

2010). In contrast, other studies have given no instructions of prioritization, or have not reported them (Kirkland et al., 2015; Mirelman et al., 2015; Plummer et al., 2013; Springer et al., 2006; Wajda et al., 2016). Studies including explicit instructions of prioritization might be informative of the ability to adapt to the demands of the situation, whereas those not giving explicit instructions of prioritization might reveal the natural or spontaneous strategies of the participants.

In summary, CMI is likely dependent on multiple factors including the type and complexity of the cognitive task performed while walking, the gait parameters assessed, and the DT instructions; themselves mediated by the personal characteristics of the individual performing the DT (e.g. cognitive or physical status). These factors must be acknowledged when comparing CMI from studies. It should also be considered in order to select the most appropriate DT configuration for the assessment of a specific individual or population depending on personal characteristics and the assessment goals.

### 1.5.5. Cognitive-motor interference while walking in people with Multiple Sclerosis

Extensive work regarding the effect of CMI while walking in different populations (e.g. older adults, people with dementia, Parkinson's disease and stroke) infer the importance of similar work in pwMS. The study of CMI in pwMS is of particular interest since, as previously mentioned, they often experience cognitive, sensory and motor deficits at varying degrees (Compston & Coles, 2008), that might present early in the disease process (Achiron & Barak, 2003; C. L. Martin et al., 2006; Pelosi et al., 1997; Wajda et al., 2014). As result of these deficits, walking may become less automatic and require more cognitive control, while at the same time, pwMS may present cognitive deficits in information processing speed, attention and executive function. Moreover, there is an overlap in the neural regions related to walking and cognition, including frontal and subcortical regions, and these are frequently affected by MS (Benedict et al., 2011; Motl, 2013). All of that, might likely lead to CMI in pwMS. The study of CMI in populations with different characteristics enable the identification of additional factors that might influence CMI, in this case MS-related factors, while it also examines its potential application to the clinical assessment, in this case, of pwMS.

In line with overall CMI studies, those performed in pwMS are also highly heterogeneous in terms of DT procedures. Multiple methods of assessment with different cognitive tasks, measures and instructions have been used for the assessment of CMI in pwMS (Leone et al., 2015). Even though the assessment of CMI in pwMS is a growing body of research, not many studies have been conducted to date, which together with the high heterogeneity in the procedures hampers the comparability of results between studies.

Reviews on this topic have consistently shown that indeed there is CMI over motor parameters in pwMS, which frequently manifests as reduced gait speed during DT across different cognitive tasks used in DT (Leone et al., 2015; Wajda & Sosnoff, 2015). There is limited comparison of CMI in pwMS with healthy controls and the results seem to be contradictory (Learmonth et al., 2017; Leone et al., 2015; Wajda & Sosnoff, 2015). A recent meta-analysis reported that the differences in motor DTC between pwMS and healthy controls were minimal; in other words, that the magnitude of CMI did not differ between groups (Learmonth et al., 2017). It should be noted, though, that the results from this meta-analysis (Learmonth et al., 2017) have mixed studies of walking and standing balance DT, which might have underscored the DTC caused by DT while walking. Walking DT might be a more sensitive to CMI than balance-based DT, since the former is a more complex that would demand greater cognitive control (Jacobs & Kasser, 2012). Furthermore, there is a lack of evidence of CMI over the cognitive domain in pwMS (Learmonth et al., 2017; Leone et al., 2015; Wajda & Sosnoff, 2015), so it was not considered in Learmonth's et al. (2017) meta-analysis, thus limiting the full comprehension of the DT performance. Indeed, more recent studies have identified CMI over cognitive performance in pwMS (Downer et al., 2016; Etemadi, 2017; Saleh et al., 2018; Wajda et al., 2016) and depending on the complexity of the cognitive task (Hamilton et al., 2009). It is still unclear to what extent CMI in pwMS differs from healthy controls respecting both motor and cognitive performance.

More research is needed in order to fill these gaps in the literature of CMI while walking in pwMS. There is also the need to integrate the heterogeneous evidence to comprehend CMI and standardize the DT procedures in pwMS, to which this thesis aims to contribute.

# 2

# Methods and Results

## 2.1. Study 1

Postigo-Alonso, B., Galvao-Carmona, A., Benítez, I., Conde-Gavilán, C., Jover, A., Molina, S., … Agüera, E. (2018). Cognitive-motor interference during gait in patients with Multiple Sclerosis: a mixed methods Systematic Review. *Neuroscience & Biobehavioral Reviews, 94,* 126–148. https://doi.org/10.1016/j.neubiorev.2018.08.016

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## 2.2. Study 2

Postigo-Alonso, B., Galvao-Carmona, A., Conde-Gavilán, C., Jover, A., Molina, S., Peña-Toledo, M.A.,… Agüera, E. (2019). The effect of prioritization over cognitive-motor interference in people with relapsing-remitting multiple sclerosis and healthy controls. *PLoS ONE 14(12):* e0226775. https://doi.org/10.1371/journal.pone.0226775

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RESEARCH ARTICLE

# The effect of prioritization over cognitive-motor interference in people with relapsing-remitting multiple sclerosis and healthy controls

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## Abstract

The cognitive-motor interference (CMI) produced by simultaneous performance of a cognitive and a motor task has been proposed as a marker of real-life impairment of people with Multiple Sclerosis (pwMS), yet there is no consensus on the dual task (DT) procedure. This study aimed to compare DT performance of pwMS and healthy controls (HC) under different instructions and to examine its association with neuropsychological and clinical variables. PwMS (N = 23; relapsing-remitting course) and HC (N = 24) completed the cognitive (Verbal Fluency) and motor (walking) tasks under three conditions: independently or as *single task (ST)*, both tasks simultaneously at best capacity or *double prioritization (DT-DP)*, and only the cognitive task at best capacity while walking at preferred speed or *cognitive prioritization (DT-CP)*. Compared to HC, pwMS walked significantly slower and produced less correct words under all conditions. The distance walked by pwMS and HC significantly differed between conditions (DT-CP< DT-DP< ST). PwMS produced more words during ST respective to DT-DP and DT-CP, with no difference between both DT conditions. HC showed no differences in cognitive performance between conditions. Motor and cognitive dual-task costs (DTC) were similar between groups. Only in pwMS, the cognitive DTC of DT-DP was different from zero. CMI measures correlated with neuropsychological, symptomatic, physiological (cognitive event-related potentials) and clinical variables. These results suggest that cognitive performance while walking is impaired in pwMS, but not in HC. CMI over cognitive performance might be a potential early marker of cognitive decline in pwMS, which may be enhanced by the instruction to prioritize both tasks in DT.

## Introduction

Multiple sclerosis (MS) is a neurodegenerative disease that affects the central nervous system, leading to cognitive and motor deficits among others. Between 40–70% of the people with MS

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(pwMS) exhibit cognitive impairment detectable with neuropsychological evaluation [1,2] and 50–80% have balance and gait dysfunction [3], which might begin early in the disease course [2,3].

Traditionally, cognitive and motor symptoms have been assessed independently. However, in daily life both processes often coexist (e.g. walk while talking to somebody), so it is time to also include in the standard evaluation a dual task (DT) assessment in which a motor and a cognitive task are performed simultaneously, as it might better reproduce the real-life challenges for pwMS [4].

During the DT assessment, it is common that the performance of either one or both tasks decrements compared to the single task (ST) condition, which represents the so called cognitive-motor interference (CMI). To the extent that the tasks in the DT share the same cognitive -and neural- resources, there would be more competence for these limited resources and, hence, more CMI [5]. Consequently, it is important to select the appropriate type and complexity of the tasks for the DT assessment, especially when evaluating a clinical population such as the pwMS, whose cognitive deficits in the first stages of the disease might be mild and even remain unnoticed in clinical evaluations [6,7]. In line with this, by choosing the proper combination of cognitive and motor tasks, the DT might stand as a "brain stress test" [8] and CMI as an early marker of subclinical cognitive decline in pwMS.

Overall, the evidence to date shows that there is CMI over motor parameters in pwMS, but so there is in healthy controls (HC), and the magnitude of CMI does not differ between these groups [9]. However, it is worth noting that the same reduction in performance or CMI when pwMS already perform significantly worse at ST, could represent a greater impact in their everyday-lives. It has further been suggested that there might be a differential pattern of intragroup changes from ST to DT that should be considered for the assessment of CMI [10].

While a variety of tasks have been used for the DT assessment in pwMS, it has been proposed that the Verbal Fluency task while walking might be sensitive and specific to CMI in pwMS. However, more research is needed in this respect, concerning the instructions for the DT assessment, the effect over the cognitive task and including a matched sample of HC [4,9,10].

Considering this evidence, the present study comprised a DT consisting on the combination of walking and Verbal Fluency task, under two DT conditions respective to the instruction of prioritization: both tasks at best capacity or double priority condition (DT-DP) and performing only cognitive task at best capacity while walking at preferred speed or cognitive priority condition (DT-CP).

The present study aimed to: 1) determine the extent to which DT performance affects motor and cognitive parameters in pwMS compared to HC, 2) explore the effect of different instructions of prioritization in the DT in order to guide clinical decision-making regarding the selection of the DT procedure and 3) examine whether CMI over cognitive and motor parameters is associated with neuropsychological, symptomatic, physiological (cognitive event-related potentials) and clinical variables, as one of the interests is to know whether CMI could be used as marker of functional impairment in pwMS.

It was hypothesized that pwMS would have more CMI than HC and that the instructions given for the DT would lead to a gradient in CMI, being the performance better in ST than in any DT, and in DT-CP better than in DT-DP -i.e. highest CMI-, according to the increased demand and level of competence between both tasks for limited cognitive resources.

## Method

The study was conducted in accordance with the ethical standards laid down in the Declaration of Helsinki (1964) and its later amendments. The experimental protocol was approved by

the ethics committee of the Reina Sofía University Hospital (Cordoba, Spain). The procedures of the study were explained to the participants, who provided written informed consent prior to data recollection.

## Participants

This observational case-control study included a convenience sample of 23 pwMS and 24 HC. PwMS were recruited from the neurology service. HC were recruited by word-of-mouth. Both participants with MS and HC were fluent in Spanish. For the pwMS, the most recent Expanded Disease Severity Scale (EDSS) [11] score, disease duration, number of relapses and time from last relapse parameters were extracted from the health record.

The inclusion criteria for pwMS were: (i) neurologist-confirmed diagnosis of relapsing-remitting MS according to the 2010 revised McDonald diagnostic criteria [12,13]; (ii) relapse-free for at least one month; (iii) EDSS score $\leq 6.5$ representing the need of bilateral constant help to walk.

Participants from both groups (pwMS and HC) were excluded from the study if: (i) scored equal or above 29 in the Beck Depression Inventory II (BDI-II), which is the cutoff for severe depression [14,15]; (ii) had neurologic disease (other than MS for the pwMS group), psychiatric disease, visual acuity or field deficits, or any musculoskeletal condition that could interfere with the test procedure.

## Experimental procedure

All participants completed demographic questionnaires, DT assessments, neuropsychological tests and symptomatic scales. Additionally, pwMS underwent an electroencephalography (EEG) recording, which was always performed in the last place. The participants could rest between tasks in the DT, between different tests, and between trials in the EEG recording.

Walking assessments (ST and DT) were performed in a quiet hallway. The rest of the assessment (cognitive ST, neuropsychological, symptomatic, and EEG recording) was performed in a small and quiet room. Complete testing took approximately 2.5 hours.

## Dual-task assessment

The DT assessment consisted on the performance of both cognitive (i.e. Verbal Fluency Test) and motor (i.e. walking) tasks under three conditions: independently at best capacity or *single task (ST)* ("say as many words as possible" or "walk as fast as possible"), both tasks simultaneously at best capacity or *DT with double prioritization (DT-DP)* ("walk as fast possible while reciting as many words as possible"), and performing only the cognitive task at best capacity while walking at preferred speed or *DT with cognitive prioritization (DT-CP)* ("say as many words as possible while walking at your preferred speed. The most important is to say as many words as possible"). The tasks were performed for 60 s under every condition and always in the same order (ST cognitive, ST motor, DT-DP, DT-CP). The selection of these two priority conditions and the order for performance was based on a previous study in older adults without dementia [16].

During the phonological Verbal Fluency Test, participants orally generated as many words as possible starting with a certain letter. Based on the "Neuronorma" study in Spanish population, the selected words were respectively for each trial: "P" (ST), "M" (DT-DP), "R" (DT-CP) [17]. One experimenter walked nearby the side of the participant while writing down the words generated. At the same time, a second experimenter walked 1 m after the participant and videotaped the performance from the back. Both instruments were used to obtain the number of correct words uttered by the participant. These experimenters assured safety of the participant while walking.

Participants completed all walking (ST and DT) trials along a 24 m long path including a 0.6 m radius in both ends until told to stop by one of the experimenters, who set the chronometer for each trial at 60 s. In this moment, the experimenter set a mark on the floor for measuring afterwards the total distance walked by the participant in each trial.

Therefore, the dual-task measures included distance walked and the number of correct words generated as direct DT scores. Dual-task cost (DTC) scores were also calculated for the motor and cognitive measures in the DT assessment according to the widely used equation [18]:

$$DTC = \frac{single\ task - dual\ task}{single\ task} x\ 100$$

## Neuropsychological assessment

The neuropsychological assessment included the administration of the Symbol Digit Modalities Test (SDMT) -in its written version- [19], which is recognized as a measure of cognitive processing speed and has been widely used for the cognitive evaluation of pwMS [20]. The Five Digit Test (FDT) was employed for the assessment of executive function [21]. It consists of four trials of increasing controlled attentional processes: reading numbers, counting, choosing to count under incongruent numeric stimuli and, shifting between reading and counting. The FDT yields a measure of time to complete each trial and two indexes of inhibition and flexibility (the lower the index, the better the cognitive process). The Test de Aprendizaje Verbal España-Complutense (TAVEC), which is the Spanish version of the California Verbal Learning Test -CVLT- [22], was included for the evaluation of episodic verbal memory [23] with three primary measures: Total trials 1–5, which will hereinafter be referred to as Immediate recall, Short-delay free recall and Long-delay free recall.

## Symptomatic assessment

The symptomatic assessment included: the BDI-II, which was also used for selection criteria as previously specified [14,15], the Spanish adaptation of Multiple Sclerosis Quality of Life-54 Instrument (MSQOL-54) [24,25] and the Daily Fatigue Impact Scale (D-FIS) [26], which has been proved as a feasible and valid instrument for measuring MS-related fatigue [27].

## EEG recording

EEG recordings were performed for the assessment of brain activity of pwMS in relation to an auditory selective attentional task. During the recording, participants were sitting on chair, inside a quiet room. The recording was performed with Nicolet™ Viking Quest system (Natus Medical Incorporated, San Carlos, CA, USA) by using 4 bipolar channels, referenced to the contralateral mastoid, ground electrode placed on the forehead, band width 0.1–100 Hz and sampling frequency of 256 Hz. Disk-scalp electrodes were placed according to the 10–10 International System [28]: Cz, Pz, P7 and P8.

The Viking software was used for the semiautomatic detection of latency and amplitude parameters of event-related potentials (ERPs): P3, P1 and N1 components.

During the EEG recording participants performed an auditory oddball task, consisting on three blocks with 200 trials each, and a pause of at least 1 minute between blocks. There were two sets of stimuli: a 1000Hz tone as target or oddball stimulus and a 500Hz tone as standard or frequent stimulus. All tones had an intensity from 72–100 Db, a duration of 50-150ms and were separated with a SOA (stimulus onset asynchrony) of 1 second. In total, each block consisted of 50 target and 150 standard stimuli. The recording was performed with eyes opened.

## Statistical analysis

Data were analyzed using Statistica 10 (StatSoft, Tulsa, OK, USA) and IBM SPSS 25 (IBM Corp., Armonk, NY, USA) softwares. Descriptive statistics were generated for two groups: pwMS and HC. Normal data distribution was evaluated with Shapiro-Wilk normality test. To compare demographic characteristics between groups, T-Tests were used for the quantitative variables and Pearson chi-square for the categorical variables. Single sample T-Tests were used to compare the mean motor and cognitive DTC scores against a zero mean (i.e. no cost). The analysis of motor parameters in direct DT scores was performed with a two-factorial repeated measures ANOVA (three conditions x two groups) and Bonferroni's post-hoc test. Wilcoxon Matched Pairs Test were used for the comparison of direct cognitive scores and DTC scores between conditions in each group (intragroup analysis). For between-groups comparisons, either T-Test or Mann-Whitney U Test were used according to the normality of the distribution and significance was adjusted for multiple comparisons with Bonferroni's correction. Effect sizes were calculated for ANOVA's main and interaction effects with partial eta-squared ($\eta^2$) interpreted as small, moderate, and large, based on values of .01, .06, and .14, respectively; and for mean contrasts with Cohen's *d*, which was equally interpreted based on values of 0.2, 0.5 and 0.8, respectively [29]. Correlation analyses between CMI measures with neuropsychological, symptomatic and clinical variables were performed with Spearman's Rho.

# Results

## Description of the sample

23 pwMS and relapsing-remitting course (18 women, 5 men) with a mean ± SD age of 46.03 ± 8.07 years, MS duration of 8.34 ± 6.41 years, time from last relapse of 2.65 ± 2.04 years and EDSS median 2 (interquartile range: 2) (range 0–5.5) were tested. None of them required assistance for walking. (See Tables 1 and 2).

24 healthy volunteers (16 women, 8 men) with a mean ± SD age of 41.39 ± 11.38 years served as HC group. There were no significant differences in age, gender or educational level between pwMS and HC ($p > 0.05$) as shown in Table 1.

In terms of neuropsychological performance, pwMS performed significantly worse than HC in the SDMT [pwMS: 44 ± 14.3; HC: 57.9 ± 13 ($p < 0.01$)]. In contrast, there were no differences between groups in the FDT indexes of inhibition and flexibility, neither on the mean time under each condition of this test after correction for overall speed per participant [30]. No significant differences were found either in performance on the TAVEC ($p > 0.05$) (see Table 1).

Concerning the clinical tests, pwMS scored significantly higher on depression (BDI-II), fatigue (D-FIS) and lower on quality of life under all subscales of the MSQOL-54 (in all cases $p < 0.01$) (see Table 1).

## Comparison between direct DT scores

In contrast to our hypotheses, no interaction effects were found in motor performance relative to Condition (ST, DT-DP, DT-CP) and Group (pwMS and HC) ($F_{2,90} = 1.20$; $p = 0.305$, $\eta^2 = 0.03$). Main effects were found for Condition ($F_{2,90} = 76.07$; $p < 0.001$, $\eta^2 = 0.63$) and Group ($F_{1,45} = 35.39$; $p < 0.001$, $\eta^2 = 0.44$), with Bonferroni's post-hoc test indicating that pwMS walked significantly slower than HC in ST ($p < 0.001$, $d = 1.59$) and both DT conditions (DT-DP: $p < 0.001$, $d = 1.5$; DT-CP: $p < 0.001$, $d = 1.58$). Similarly, both groups walked significantly faster in ST in comparison with DT-DP (pwMS: $p = 0.028$, $d = 0.46$; HC: $p = 0.007$, $d = 0.58$) and DT-CP conditions (pwMS: $p < 0.001$, $d = 1.19$; HC: $p < 0.001$, $d = 1.77$), and in

**Table 1. Comparison of demographic, neuropsychological and symptomatic features of pwMS and HC (mean ± SD).**

| | PwMS (n = 23) | HC (n = 24) | p- value [c] | PwMS adjusted scores | HC adjusted scores |
|---|---|---|---|---|---|
| Age (years) | 46.03 ± 8.07 | 41.39 ± 11.38 | 0.11 | | |
| Gender (f/m) | 18/5 | 16/8 | 0.37 | | |
| Years of education | 12.78 ± 4.13 [5–19] | 14.75 ± 3.26 [6–20] | 0.08 | | |
| SDMT (n correct) | 44 ± 14.33 | 57.96 ± 13.01 | 0.001* | Sc = 8.4 ± 2.9 | Sc = 10.8 ± 3 |
| FDT- *Reading* [a] | 0.67 ± 0.13 | 0.67 ± 0.11 | 0.87 | Pc = 29.7 ± 24.1 | Pc = 50.1 ± 31.3 |
| FDT- *Counting* [a] | 0.72 ± 0.12 | 0.73 ± 0.07 | 0.74 | Pc = 26.1 ± 24.1 | Pc = 48.7 ± 30.2 |
| FDT- *Choosing* [a] | 1.11 ± 0.16 | 1.13 ± 0.11 | 0.57 | Pc = 36.3 ± 28.6 | Pc = 52.5 ± 29.2 |
| FDT- *Shifting* [a] | 1.5 ± 0.26 | 1.47 ± 0.13 | 0.59 | Pc = 39.9 ± 32 | Pc = 52.4 ± 27.6 |
| FDT- *Inhibition* (seconds) | 15.26 ± 9.16 | 13.55 ± 7.26 | 0.36 | Pc = 50 ± 31.5 | Pc = 53.7 ± 28.5 |
| FDT- *Flexibility* (seconds) | 33.22 ± 24.03 | 23.12 ± 8.59 | 0.19 | Pc = 46.3 ± 35.9 | Pc = 56.5 ± 27.3 |
| TAVEC- *Immediate recall (Trials 1–5)* (n correct words) | 54.48 ± 13.08 | 59.21 ± 9.4 | 0.16 | Z = 0.13 ± 1.22 | Z = 0.5 ± 1.06 |
| TAVEC- *Short-delay free recall* (n correct words) | 11.3 ± 4.13 | 12.75 ± 2.33 | 0.45 | Z = 0 ± 1.45 | Z = 0.33 ± 0.92 |
| TAVEC- *Long-delay free recall* (n correct words) | 11.65 ± 3.93 | 13.17 ± 2.27 | 0.27 | Z = -0.35 ± 1.58 | Z = 0.08 ± 1.14 |
| BDI-II (score 0–63) | 15.7 ± 7.86 | 4.5 ± 3.95 | < 0.001* | | |
| D-FIS [b](score 0–36) | 15 ± 9.53 | 4.33 ± 4.1 | < 0.001* | | |
| MSQOL-54—*Physical health composite* (score 0–100) | 52.38 ± 23.37 | 85.31 ± 8.82 | < 0.001* | | |
| MSQOL-54—*Mental health composite* (score 0–100) | 60.5 ± 21.61 | 86.28 ± 8.91 | < 0.001* | | |
| MSQOL-54—*Overall quality of life* (score 0–100) | 64.85 ± 14.93 | 83.96 ± 11.28 | < 0.001* | | |

Abbreviations: pwMS, people with multiple sclerosis; HC, healthy controls; SDMT, Symbol Digit Modalities Test; FDT, Five Digit Test; TAVEC, Test de Aprendizaje Verbal España Complutense; BDI-II, Beck Depression Inventory II; D-FIS, Daily Fatigue Impact Scale; MSQOL-54, Multiple Sclerosis Quality of Life-54; Sc, scalar score; Pc: percentile; Z, Standard score.

[a] Direct scores shown correspond to the raw time scores (seconds) corrected for speed per participant as in Faust & Balota (1997). Adjusted scores correspond to the Pc for the raw scores (uncorrected for speed).

[b] D-FIS score is missing from one participant (pwMS n = 22).

[c] P-values correspond to comparisons with T-Tests or Mann-Whitney U Tests of direct scores between pwMS and HC.

* p-value ≤ 0.001

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DT-DP relative to DT-CP (pwMS: $p = 0.0005$, $d = 0.68$; HC: $p < 0.001$, $d = 1.09$) (see Fig 1 and Table 3).

After Bonferroni's correction for multiple testing (corrected $p < 0.05/3 = 0.0167$), the number of correct words was significantly lower in both DT conditions in pwMS vs HC (DT-DP: $p = 0.0058$, $d = 0.85$; DT-CP: $p = 0.0062$) and, although marginally, also in ST ($p = 0.0164$, $d = 0.73$). The group of pwMS produced significantly (corrected $p < 0.05/3 = 0.0167$) more words in ST than in both DT conditions (DT-DP: $p = 0.0085$; DT-CP: $p = 0.009$), with no significant differences between DT-DP and DT-CP ($p = 0.821$). In contrast, no significant differences were found in the number of correct words produced by HC in ST versus both DT conditions ($p > 0.05$ in all cases) (see Fig 2 and Table 4).

## Comparison between DTC scores

Single sample t-tests with Bonferroni's correction (corrected $p < 0.05/4 = 0.0125$) revealed that the motor DTC was significantly different from zero for pwMS and HC in both conditions DT-DP and DT-CP respective to ST ($p < 0.001$). However, the cognitive DTC was significantly different from a zero constant only for the DT-DP condition in pwMS (DT-DP: $p = 0.0069$; DT-CP: $p = 0.0128$), but not for HC (DT-DP: $p = 0.21$; DT-CP: $p = 0.19$) (see Table 5).

**Table 2. Clinical and physiological (ERPs) features of pwMS.**

| | PwMS (n = 23) |
|---|---|
| EDSS | mdn 2 (IQR 2) [0–5.5] |
| Disease duration (years) | 8.34 ± 6.41 [1.25–27.08] |
| Number of relapses | 5.70 ± 3.88 [1–15] |
| Time from last relapse (years) | 2.65 ± 2.04 [0.6–8.24] |
| CzP3—Amplitude | 3.29 ± 2.11 [a] |
| CzP3—Latency | 423.59 ± 57.11 [a] |
| PzP3—Amplitude | 2.86 ± 1.59 [a] |
| PzP3—Latency | 413.55 ± 105.88 [a] |
| P07N1 –Amplitude | -2.86 ± 1.95 [a] |
| P07N1- Latency | 170.68 ± 38.56 [a] |
| P08N1 –Amplitude | -2.97 ± 2.13 [a] |
| P08N1 –Latency | 176.77 ± 37.62 [a] |
| P07P1 –Amplitude | 2.57 ± 1.46 [a] |
| P07P1- Latency | 96.86 ± 15.17 [a] |
| P08P1 –Amplitude | 3.03 ± 1.77 [a] |
| P08P1 –Latency | 95.5 ± 15.7 [a] |

Data are displayed as mean ± SD [range], median (interquartile range) [range], or as otherwise indicated.
Abbreviations: pwMS, people with multiple sclerosis; HC, healthy controls; EDSS, Expanded Disability Status Scale.
[a] ERPs data is missing from one participant (pwMS n = 22).

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No significant differences were found between pwMS and HC in motor nor cognitive DTC in any of the DT conditions (DT-DP or DT-CP) ($p > 0.05$ in all cases) (see Table 5).

Matched pairs tests (corrected $p < 0.05/2 = 0.025$) showed significant differences in motor DTC of DT-DP vs DT-CP in both groups (pwMS: $p < 0.0001$ and HC: $p = 0.0001$). In contrast,

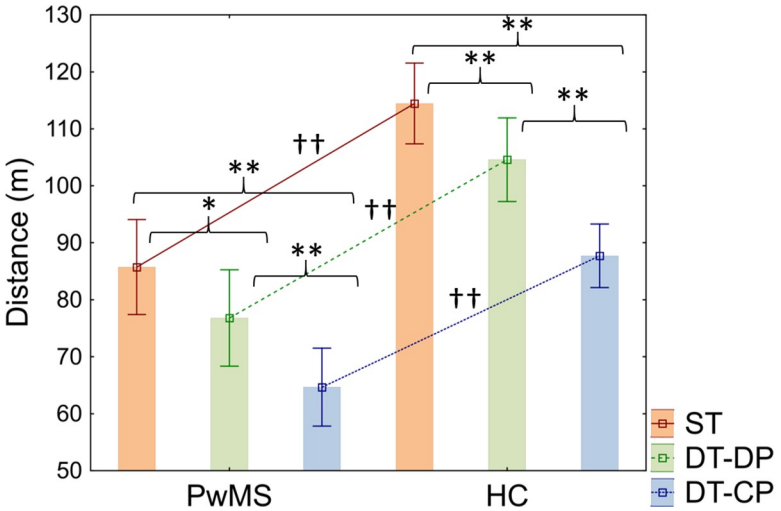


**Fig 1. Cognitive-motor interference over motor performance.** Distance (m) walked (mean ± standard deviation) during single task (ST), dual task with double priority (DT-DP) and dual task with cognitive priority (DT-CP) by people with multiple sclerosis (pwMS) and healthy controls (HC). Significant contrasts are indicated by the black lines over the graph. * $p < 0.05$, ** $p < 0.01$, denoting significant intragroup contrasts -ST vs DT-DP, ST vs DT-CP and DT-DP vs DT-CP- in pwMS and HC, respectively.† $p < 0.05$, †† $p < 0.01$, denoting significant between-group contrasts -pwMS vs HC-.

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**Table 3. Intragroup and between-group comparisons of direct scores of motor performance during DT and ST in pwMS and HC (mean ± SD).**

| | PwMS (n = 23) | HC (n = 24) | Condition | Group | Condition * Group |
|---|---|---|---|---|---|
| ST distance (m) | 85.73 ± 19.3 | 114.45 ± 16.77 | $F = 76.1$ $p<0.0001^{a,b,c}$ $\eta^2 = 0.63$ | $F = 35.4$ $p<0.0001^{d,e,f}$ $\eta^2 = 0.44$ | $F = 1.2$ $p = 0.31$ $\eta^2 = 0.03$ |
| DT-DP distance (m) | 76.79 ± 19.58 | 104.57 ± 17.38 | | | |
| DT-CP distance (m) | 64.66 ± 15.81 | 87.73 ± 13.24 | | | |

Abbreviations: pwMS, people with multiple sclerosis; HC, healthy controls; ST, single task; DT-DP, dual task with double priority; DT-CP, dual task with cognitive priority.

[a] Post-hoc significant differences between ST and DT-DP in both groups -pwMS and HC- ($p<0.05$).

[b] Post-hoc significant differences between ST and DT-CP in both groups -pwMS and HC- ($p<0.05$).

[c] Post-hoc significant differences between DT-DP and DT-CP in both groups -pwMS and HC- ($p<0.05$).

[d] Post-hoc significant differences in ST between pwMS and HC ($p<0.01$).

[e] Post-hoc significant differences in DT-DP between pwMS and HC ($p<0.01$).

[f] Post-hoc significant differences in DT-CP between pwMS and HC ($p<0.01$).

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no differences were found in cognitive DTC of DT-DP vs DT-CP in any of the groups (pwMS: $p< 0.58$ and HC: $p = 0.85$).

## Relationship between CMI measures & neuropsychology

**Direct DT scores.** The Spearman correlation analysis yielded significant positive correlations between SDMT and all direct DT scores in pwMS ($p\leq 0.01$) except for the distance walked in DT-CP ($p> 0.05$). In contrast, in HC, the SDMT correlated with correct words in DT-DP (rho = 0.61; $p = 0.001$) and DT-CP (rho = 0.53; $p = 0.008$) and with the distance walked in DT-CP (rho = 0.51; $p = 0.011$). Only in pwMS, a significant negative correlation was observed between FDT-Flexibility and distance in ST (rho = -0.56; $p = 0.005$) and DT-DP (rho = -0.5; $p = 0.015$), correct words in DT-DP (rho = -0.43; $p = 0.041$) and DT-CP (rho = -0.56; $p = 0.006$). The lower the score in FDT-Flexibility indicates higher cognitive flexibility; hence,

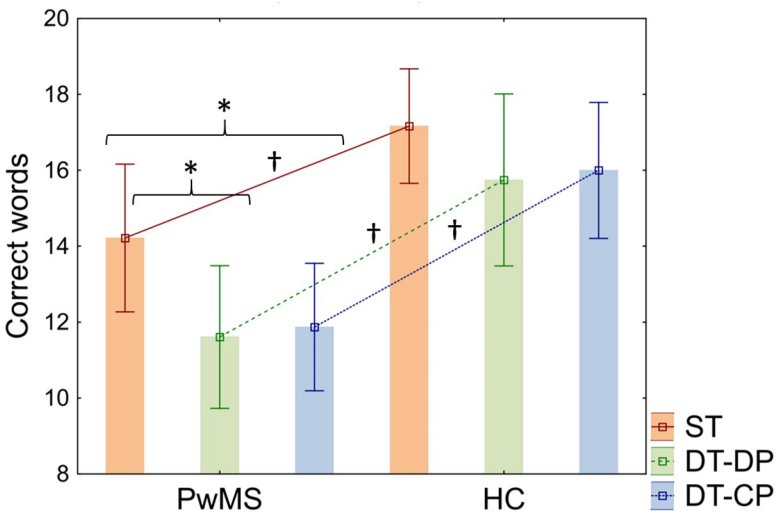


**Fig 2. Cognitive-motor interference over cognitive performance.** Number of correct words uttered (mean ± standard deviation) during single task (ST), dual task with double priority (DT-DP) and dual task with cognitive priority (DT-CP) by people with multiple sclerosis (pwMS) and healthy controls (HC). Significant contrasts are indicated by the black lines over the graph.* Denotes significant intragroup contrasts -ST vs DT-DP, ST vs DT-CP and DT-DP vs DT-CP- in pwMS and HC, respectively. † Denotes significant between-group contrasts -pwMS vs HC-.

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**Table 4. Intragroup and between-group comparisons of direct scores of cognitive performance during DT and ST in pwMS and HC (mean ± SD).**

| | ST | DT-DP | DT-CP | ST vs DT-DP | ST vs DT-CP | DT-DP vs DT-CP |
|---|---|---|---|---|---|---|
| **PwMS (n = 23)** | 14.22 ± 4.5 | 11.61 ± 4.35 | 11.87 ± 3.89 | $Z = 2.63$ $p = 0.0085$* | $Z = 2.61$ $p = 0.0090$* | $Z = 0.23$ $p = 0.8213$ |
| **HC (n = 24)** | 17.17 ± 3.57 | 15.75 ± 5.37 | 16 ± 4.24 | $Z = 1.67$ $p = 0.0944$ | $Z = 1.89$ $p = 0.0582$ | $Z = 0.08$ $p = 0.9353$ |
| **Between-group** | $t = -2.49$ $p = 0.0164$* *Cohen's d = 0.73* | $t = -2.9$ $p = 0.0058$* *Cohen's d = 0.85* | $U = 147$ $p = 0.0062$* | | | |

Abbreviations: pwMS, people with multiple sclerosis; HC, healthy controls; ST, single task; DT-DP, dual task with double priority; DT-CP, dual task with cognitive priority.

* Denotes significant p-values after Bonferroni's correction for multiple testing.

https://doi.org/10.1371/journal.pone.0226775.t004

the more flexibility (lower score), the better motor and cognitive performance in DT (more walked distance and more correct words uttered) in pwMS. No significant correlations were found between FDT-Flexibility and direct DT scores in HC, nor between FDT-inhibition and any DT parameters in any group ($p > 0.05$ in all cases). In addition, there was a significant positive correlation between the TAVEC-Immediate recall and all direct DT scores in pwMS ($p < 0.05$) except for the distance walked in DT-CP ($p > 0.05$), whereas the Long-delay free recall only correlated with the correct words in the three conditions (ST, DT-DP, DT-CP) ($p < 0.05$). In the HC group, only the correct words uttered in ST and DT-CP significantly correlated with TAVEC-Immediate recall, Short-delay free recall and Long-delay free recall ($p < 0.05$).

**DTC scores.** Significant correlations were found only in HC between SDMT and cognitive DTC in DT-DP (rho = -0.44, $p = 0.031$) and between FDT-Inhibition with the cognitive DTC in DT-CP (rho = 0.45; $p = 0.028$). TAVEC- Long-delay free recall showed a significant negative correlation with the cognitive DTC in DT-CP in both groups (pwMS: rho = -0.48, $p = 0.022$; HC: rho = 0.74, $p < 0.001$) (see S1 Table).

## Relationship between CMI measures & symptomatic scales

**Direct DT scores.** Concerning the symptomatic assessment, significant negative correlations were revealed in HC between BDI-II and the distance walked in all conditions (ST: rho = -0.41, $p = 0.047$; DT-DP: rho = -0.52, $p = 0.009$; DT-CP: rho = -0.48, $p = 0.016$), whereas no significant correlations were found between this test and DT parameters in pwMS ($p > 0.05$). On

**Table 5. Comparisons of DTC scores between pwMS and HC (mean ± SD) and contrasts against reference constant (zero value).**

| | PwMS (n = 23) | HC (n = 24) | Between-groups | Single-sample t-test |
|---|---|---|---|---|
| Motor DTC DT-DP | 10.61 ± 9.58 | 8.48 ± 8.77 | $U = 250$; $p = 0.59$ | PwMS: $t = 5.31$; $p < 0.0001$*<br>HC: $t = 4.74$; $p = 0.0001$* |
| Motor DTC DT-CP | 23.37 ± 14.5 | 22.71 ± 10.5 | $U = 537$; $p = 0.76$ | PwMS: $t = 7.73$; $p < 0.0001$*<br>HC: $t = 10.59$; $p < 0.0001$* |
| Cognitive DTC DT-DP | 16.78 ± 26.98 | 7.42 ± 28.47 | $t = 1.16$; $p = 0.25$<br>*Cohen's d* = 0.34 | PwMS: $t = 2.98$; $p = 0.0069$*<br>HC: $t = 1.28$; $p = 0.21$ |
| Cognitive DTC DT-CP | 14.26 ± 25.23 | 5.75 ± 20.82 | $U = 216.5$; $p = 0.21$ | PwMS: $t = 2.71$; $p = 0.0128$<br>HC: $t = 1.35$; $p = 0.1894$ |

Abbreviations: pwMS, people with multiple sclerosis; HC, healthy controls; ST, single task; DTC DT-DP, dual-task cost in the dual task with double priority; DTC DT-CP, dual-task cost in the dual task with cognitive priority.

* Denotes significant p-values after Bonferroni's correction for multiple testing.

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the other hand, significant negative correlations between D-FIS and the distance walked in ST (rho = -0.54; $p = 0.01$) and DT-DP (rho = -0.52; $p = 0.013$) were observed in pwMS, but not in HC ($p > 0.05$). Additionally, significant positive correlations were found between MSQOL-global quality of life and distance walked in all conditions in pwMS (ST: rho = 0.53, $p = 0.009$; DT-DP: rho = 0.5, $p = 0.016$; DT-CP: rho = 0.43, $p = 0.04$), but in HC it only correlated with the distance walked in DT-DP (rho = 0.45; $p = 0.028$).

**DTC scores.** Concerning DTC scores, only a significant positive correlation was found between the motor DTC in DT-DP and D-FIS in HC (rho = 0.45; $p = 0.026$) (see S1 Table).

## Relationship between CMI measures with physiological & clinical variables in pwMS

**Direct DT scores.** Relative to the ERPs (note that data is missing from one participant (n = 22), P3 amplitude in Cz and Pz significantly correlated with distance in ST (CzP3: rho = 0.49, $p = 0.02$; PzP3: rho = 0.5, $p = 0.018$) and with distance in DT-DP (CzP3: rho = 0.45, $p = 0.037$; PzP3: rho = 0.47, $p = 0.028$). Latency of P3 in Cz correlated with correct words in DT-CP (rho = 0.43, $p = 0.046$).

EDSS significantly correlated with distance in ST (rho = -0.66; $p = 0.001$) and DT-DP (rho = -0.71; $p < 0.001$).

**DTC scores.** The P3 amplitude in Cz and Pz significantly correlated with the cognitive DTCs in DT-DP (CzP3: rho = -0.43, $p = 0.049$; PzP3: rho = -0.43, $p = 0.044$) and in DT-CP (CzP3: rho = -0.49, $p = 0.02$; PzP3: rho = -0.47, $p = 0.028$).

No significant correlations were found between the rest of the clinical variables (disease duration, number of relapses, time from last relapse) and any parameters of the DT (direct or DTC) ($p > 0.05$) (see S2 Table).

## Discussion

Our findings confirmed that there is CMI in terms of direct DT scores and DTC over motor performance -i.e. distance walked- in pwMS, and so there is in HC. In contrast, in pwMS there is statistically significant CMI over cognitive performance as well, which is not present in HC. Particularly, pwMS produce less words in DT (DT-DP and DT-CP) than in ST and their cognitive DTC of DT-DP is significantly greater than zero. The instructions of priority had an effect over motor and cognitive performance in this sample.

It should be noted that the sample of present study comprised patients with relapsing-remitting clinical course of MS, in a relatively initial stage of the disease (8.34 ± 6.41 years from diagnosis), free from severe depression, with mild disability [EDSS: median 2 (IQR: 2)] and able to ambulate without assistance.

The presence of CMI over motor parameters in pwMS and HC, together with the fact the motor DTC is comparable between groups is in agreement with current evidence [9,10]. Nonetheless, also in this study, pwMS already had worse motor performance than HC in ST, thus a similar DTC might represent a greater functional impact on the daily life of pwMS.

Despite being overlooked in many cases, the CMI over the cognitive performance in pwMS has been evidenced in other studies as well. As in the present study, pwMS showed significantly reduced performance in DT vs ST conditions -unlike HC- [31,32], and a cognitive DTC significantly greater than zero [33]. However, in our study, no differences were found between cognitive DTC scores of pwMS and HC, in contrast with other studies that identified significant greater cognitive DTC in pwMS than in HC, with no change or even an improvement on a Serial 7s' Subtractions task while walking [32,34]. Of note is that the study by Saleh et al. (2018) comprised a similar pwMS sample, as all patients had relapsing-remitting course of the

disease and similar clinical features. Similarly, in another study, it was found that pwMS performing a digit span task while walking had significant cognitive DTC compared to HC when the number of digits was fixed, but not when it was titrated to each individual's capacity in ST [35]. Thus, it all suggests that CMI over cognitive performance in pwMS is revealed across studies by means of different tasks and measures. The differences in CMI between studies are influenced by the cognitive load coming from the type and complexity of the cognitive tasks concurrent to walking. Moreover, we hypothesize that this is also reason for the differences found between the two DT with different instructions, i.e. DT-DP and DT-CP, as they induce different cognitive loads.

To our knowledge, this is the first study to compare different sets of instructions regarding prioritization of tasks during DT in pwMS. Specifically, in the DT-DP, participants were instructed to perform both tasks at best capacity (walk as fast as possible while reciting as many words as possible), whereas in the DT-CP they were only asked to perform the cognitive task at best capacity while walking at preferred speed. Interestingly, there was a differential pattern of performance between pwMS and HC: while both groups showed significantly reduced motor performance between all conditions according to this gradient (ST > DT-DP > DT-CP), only in pwMS the cognitive performance was significantly reduced from ST to DT-DP and DT-CP respectively, with no significant difference between DT-DP and DT-CP. These results in pwMS are consistent with those obtained in a population of older adults without dementia, who performed the DT consisting on the Alternate Alphabet task while walking under the same conditions of priority -cognitive performance in ST was not assessed- [16]. Additionally, we found that in pwMS and HC, the motor DTC of DT-DP and DT-CP was significant, but only the cognitive DTC of DT-DP was significant in pwMS.

These results suggest that HC successfully prioritized the cognitive task by slowing down in both DT (DT-DP and DT-CP); while pwMS, despite slowing down the same extent as HC, were not able to divert their attention from walking and successfully perform the cognitive task, thus leading to CMI and revealing that their cognitive resources were further exceeded by the DT. In line with this, the CMI over cognitive performance in pwMS was more accentuated in the DT-DP, which is the most cognitively-demanding condition.

Considering this evidence, we would recommend reporting and giving standardized instructions for the DT. Moreover, DT measures are more reliable when participants are given specific instructions of what to prioritize [36]. Specifically, the use of the double-priority instructions would be advised, which might amplify the CMI over motor and cognitive parameters and, therefore, make the DT more sensitive. In support of this, evidence from ST walking have shown that preferred speed is more natural and intuitive [37], but fast walking speed has better metrological properties [38] and has been proposed as more beneficial for the assessment of pwMS because it would rather unveil gait deficits in patients with low EDSS [39].

The neuropsychological, symptomatic scores and clinical features of MS were associated with direct DT and ST measures in a predictable manner, e.g. EDSS and distance in ST and DT-DP. Specifically, it is interesting that cognitive processing speed (SDMT) correlated with all DT scores, except for the distance in DT-CP, in pwMS, suggesting that cognitive processing speed is related to both motor and cognitive processes in ST and DT. However, we replicate the lack of association between SDMT and motor DTC as in previous research [40–42], although it showed a significant association with cognitive DTC in DT-DP in HC. Moreover, greater cognitive flexibility (FDT-Flexibility) was associated exclusively in pwMS with better cognitive performance in both DT-DP and DT-CP -not ST-, and with better motor performance in ST and DT-DP. Therefore, we speculate that the flexibility in allocating cognitive resources to each task might be an important compensatory cognitive process in pwMS for successful performance in DT. Remarkably, no associations were found between clinical

variables of MS such as disease duration like in previous research [43], number of relapses, time from last relapse and any direct or DTC score, suggesting that the symptoms and functional status of the individual are rather related to CMI, independently of these aspects of the disease.

Overall, cognitive DTC scores were associated with various measures of cognition such as processing speed (SDMT) and inhibitory control (FDT- inhibition) in HC, and long-term memory (TAVEC- Long-delay free recall) in pwMS and HC. In addition, cognitive DTC scores in pwMS were associated with physiological measures (ERPs: P3 amplitude in Pz and Cz electrodes). The only significant correlation of motor DTC was with fatigue (D-FIS) in HC during the DT-DP. It should be remarked, because previous studies have not considered the effect over the cognitive task, though it seems to be predominantly associated with the cognitive status of the participants and the motor DTC is not so related to other characteristics of the sample. These results may suggest CMI over cognitive performance as a marker of cognitive status.

In agreement with our results, research found significant associations between CMI and inhibitory measures in HC but not in pwMS, in which it was rather associated with self-perceived difficulty in keeping track of two things at a time [40]. Regarding the physiological results, the P3 amplitude is related with the neural sources required when an attentional task is processed [44], so it can be inferred that the more neural resources are recruited during the attentional task, the better the DT performance.

It is worth noting that different associations have been found with direct DT scores and DTC, which might indicate that they measure different constructs.

The present study is not without limitations. For instance, the sample size is relatively small, and the recruitment was by convenience, which might be a source of bias. Moreover, the mean BDI-II score of pwMS was significantly higher than that of HC, indicative of mild symptomatology of depression at the group level in pwMS. This should be taken into account when considering the results. In addition, the order of the conditions in DT were not counterbalanced. The fact that DT-DP was performed before DT-CP was an informed decision based on previous research [16], but still the ST was always performed prior to DT, so fatigue might have influenced the DT results. Nevertheless, all participants were allowed to rest and sit after each trial or condition. To our knowledge, no previous study has explored the relationship between ERPs and CMI in pwMS. However, the EEG recordings were limited to the pwMS group. Considering that the results were obtained from pwMS with relapsing-remitting course and mild disability, they should not be generalizable to the entire population of pwMS.

Future studies could include other measures of gait performance which might have better captured the effect of CMI, as gait speed or distance have been shown to be sensitive but not specific in pwMS since it also decrements in HC [10].

## Conclusions

The current study examined CMI over cognitive and motor parameters and provided novel data concerning the effect of different instructions of DT prioritization and about its correlates in pwMS and HC. Specifically, it was found that unlike HC, the cognitive performance of pwMS was worse under DT conditions than ST and had a significant cognitive DTC during the DT-DP condition. Furthermore, cognitive DTC scores were associated with neuropsychological and physiological (P3) measures in pwMS. It suggests that CMI over cognitive performance might be a potential early marker of cognitive or functional decline in pwMS, which may be enhanced by the instruction to prioritize both tasks in the DT. Nevertheless, these results should be taken with caution and further research is needed in order to ascertain this question.

## Supporting information

**S1 Dataset.**
(XLSX)

**S1 Table. Correlations between CMI parameters and symptomatic features of pwMS and HC.** Abbreviations: pwMS, people with multiple sclerosis; HC, healthy controls; ST, single task; DT-DP, dual task with double priority; DT-CP, dual task with cognitive priority: DTC, dual-task cost; SDMT, Symbol Digit Modalities Test; FDT, Five Digit Test; TAVEC, Test de Aprendizaje Verbal España Complutense; BDI-II, Beck Depression Inventory II; D-FIS, Daily Fatigue Impact Scale; MSQOL, Multiple Sclerosis Quality of Life-54. Note: Values are Spearman's Rho. D-FIS score is missing from one participant (pwMS n = 22). * p-value $< 0.05$; ** p-value $< 0.001$.
(DOCX)

**S2 Table. Correlations between CMI parameters and clinical and physiological features of pwMS.** Abbreviations: pwMS, people with multiple sclerosis; HC, healthy controls; ST, single task; DT-DP, dual task with double priority; DT-CP, dual task with cognitive priority: DTC, dual-task cost. Note: Values are Spearman's Rho. ERPs data is missing from one participant (pwMS n = 22). * p-value $< 0.05$; ** p-value $< 0.001$.
(DOCX)

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**S1 Table. Correlations between CMI parameters and symptomatic features of pwMS and HC**

| | | SDMT | FDT-Inhibition | FDT-Flexibility | TAVEC-Immediate Recall | TAVEC- Short-term Recall | TAVEC- Long-term Recall | BDI-II | D-FIS | MSQOL- Global quality of life |
|---|---|---|---|---|---|---|---|---|---|---|
| ST distance | PwMS | .587** | -.337 | -.561** | .514* | .458* | .404 | -.250 | -.537* | .535** |
| | HC | .332 | .065 | .027 | .229 | .042 | .059 | -.409* | -.013 | .369 |
| DT-DP distance | PwMS | .511* | -.277 | -.499* | .472* | .448* | .389 | -.168 | -.519 | .495* |
| | HC | .357 | -.068 | -.067 | .218 | -.069 | -.101 | -.522** | -.209 | .449* |
| DT-CP distance | PwMS | .295 | -.212 | -.275 | .181 | .125 | .072 | -.123 | -.232 | .432* |
| | HC | .508* | -.166 | -.355 | -.173 | .032 | .059 | -.486* | -.158 | .217 |
| ST correct words | PwMS | .553** | -.046 | -.308 | .530** | .341 | .439* | -.099 | .190 | .147 |
| | HC | .399 | -.103 | .518 | .455* | .492* | .606** | -.164 | -.131 | -.018 |
| DT-DP correct words | PwMS | .499* | -.211 | -.429* | .483* | .325 | .451* | -.069 | .009 | .179 |
| | HC | .614** | -.220 | -.066 | .374 | .253 | .379 | -.393 | -.282 | .049 |
| DT-CP correct words | PwMS | .538** | -.201 | -.556** | .792** | .707** | .742** | .008 | .162 | .072 |
| | HC | .525** | -.333 | -.036 | .601** | .631** | .778** | -.166 | -.207 | .105 |
| Motor DTC DT-DP | PwMS | .205 | -.256 | -.157 | .164 | .080 | .198 | -.204 | .057 | -.012 |
| | HC | -.094 | .137 | .147 | .031 | .330 | .303 | .275 | .453* | -.077 |
| Motor DTC DT-CP | PwMS | .323 | -.018 | -.212 | .231 | .261 | .327 | -.100 | -.219 | -.075 |
| | HC | -.144 | .133 | .344 | .114 | -.008 | .069 | .134 | .130 | .180 |
| Cognitive DTC DT-DP | PwMS | -.151 | .226 | .289 | -.116 | -.108 | -.180 | -.050 | .176 | -.047 |
| | HC | -.441* | .231 | .161 | -.184 | .090 | -.015 | .400 | .355 | -.196 |
| Cognitive DTC DT-CP | PwMS | -.233 | .181 | .401 | -.426* | -.514* | -.476* | -.101 | .164 | -.025 |
| | HC | -.135 | .449* | .305 | -.368 | -.357 | -.450* | .089 | .296 | -.148 |

Abbreviations: pwMS, people with multiple sclerosis; HC, healthy controls; ST, single task; DT-DP, dual task with double priority; DT-CP, dual task with cognitive priority: DTC, dual-task cost; SDMT, Symbol Digit Modalities Test; FDT, Five Digit Test; TAVEC, Test de Aprendizaje Verbal España Complutense; BDI-II, Beck Depression Inventory II; D-FIS, Daily Fatigue Impact Scale; MSQOL, Multiple Sclerosis Quality of Life-54. Note: Values are Spearman's Rho. D-FIS score is missing from one participant (pwMS n=22).

* p-value < 0.05; ** p-value < 0.001

**S2 Table. Correlations between CMI parameters and clinical and physiological features of pwMS**

| | EDSS | Disease duration (years) | Number of relapses | Time from last relapse (years) | CzP3 amplitude | CzP3 latency | PzP3 amplitude | PzP3 latency |
|---|---|---|---|---|---|---|---|---|
| ST distance | .658** | -.006 | -.293 | .126 | .492* | .002 | .499* | -.016 |
| DT-DP distance | -.711** | -.136 | -.398 | .054 | .447* | -.100 | .467* | -.166 |
| DT-CP distance | -.342 | .254 | -.056 | .021 | .312 | .142 | .285 | .035 |
| ST correct words | -.058 | .014 | .245 | -.094 | .086 | .295 | .032 | .260 |
| DT-DP correct words | -.240 | .145 | .316 | .167 | .370 | .164 | .358 | .084 |
| DT-CP correct words | -.262 | .071 | .145 | -.224 | .198 | .430* | .145 | .200 |
| Motor DTC DT-DP | .151 | .116 | .268 | .124 | .111 | .264 | .034 | .239 |
| Motor DTC DT-CP | -.145 | -.199 | -.059 | .127 | .268 | -.053 | .289 | .049 |
| Cognitive DTC DT-DP | .212 | -.111 | -.200 | -.205 | -.425* | .036 | -.432* | .053 |
| Cognitive DTC DT-CP | .400 | .036 | .045 | .176 | -.491* | -.045 | -.467* | .133 |

Abbreviations: pwMS, people with multiple sclerosis; HC, healthy controls; ST, single task; DT-DP, dual task with double priority; DT-CP, dual task with cognitive priority: DTC, dual-task cost. Note: Values are Spearman's Rho. ERPs data is missing from one participant (pwMS n=22).

* p-value < 0.05; ** p-value < 0.001

## 2.3. Study 3

Postigo-Alonso, B. Galvao-Carmona, A., Hofmann, M., Kühn, A.A., Neumann, W.J. Beta-band activity in the supplementary motor area reflects the cognitive demand in motor control.

**[In preparation]**

# 3

# General Discussion

## 3.1. Summary of findings

The overall aim of this thesis was to contribute to the study of interactions between cognitive and motor processes through its effects on behavior and neural correlates in pwMS and healthy individuals. For this purpose, three studies were performed. **Studies 1 and 2** of this thesis addressed the behavioral approach through the study of CMI that results from the DT performance of a cognitive task while walking in pwMS and healthy individuals. The behavioral DT approach is also of interest from a clinical perspective, since the CMI has been proposed as valid measure of real-life impairment in pwMS (Leone et al., 2015), who often experience motor and cognitive deficits among others (Cameron & Nilsagard, 2018; Chiaravalloti & DeLuca, 2008). Thus, **Studies 1 and 2** also had an applied scope by which the CMI was examined for its utility in the cognitive functional assessment of pwMS.

**Study 1** consisted of a mixed methods systematic review about CMI while walking in pwMS and healthy individuals, which allowed the synthesis of the highly heterogeneous literature and the identification of gait parameters and cognitive tasks that were sensitive and specific for the detection of CMI in pwMS, namely double support time (% of gait cycle) and Verbal Fluency task. Additionally, it discussed other factors that might have accounted for the differences in CMI among studies (e.g. instructions, individual's characteristics). Results from **Study 1** informed the methods of **Study 2**.

**Study 2** was an observational case-control study about CMI in pwMS (relapsing-remitting course) and healthy controls. Based on findings from **Study 1**, the DT assessment used in **Study 2** consisted on the performance of the Verbal Fluency task while walking. Results from **Study 2** corroborated the presence of CMI over gait parameters in both pwMS (relapsing-remitting course) and healthy individuals, which occurred to a greater extent in pwMS. Remarkably, it revealed significant CMI over cognitive performance in pwMS, but not in healthy controls. Additionally, **Study 2** provided novel evidence regarding the effect of instructions of DT prioritization over CMI and about its correlates (neuropsychological, symptomatic, clinical and physiological) in pwMS and healthy individuals.

Complementarily, **Study 3** addressed the neurophysiological approach to the relationship between cognitive and motor processes through an EEG recording during

the performance of a visuomotor task in healthy individuals. **Study 3** showed increased power in beta oscillations (~13-35 Hz) over the SMA during motor preparation in controlled versus automatic conditions. Higher beta power before and during movement was associated with less trajectory error, as well as greater difference in power between conditions. Thus, **Study 3** demonstrated that beta oscillations in the SMA are associated with cognitive control of motor behavior.

## 3.2. Behavioral features displaying the relationship between cognitive and motor processes

### 3.2.1. What should be measured to assess CMI in people with MS?

Several reviews have been conducted to synthesize the evidence of CMI in pwMS, which have performed a narrative synthesis (Leone et al., 2015), or considered only DTC scores in a systematic review (Wajda & Sosnoff, 2015) or meta-analysis (Learmonth et al., 2017) of walking a standing balance DT. Even though these reviews have contributed valuable knowledge about CMI in pwMS, several gaps remained uncovered such as the systematic synthesis of intragroup (DT vs ST) changes -besides DTC scores- and the detailed examination of variables that might account for the differences between studies. **Study 1** aimed to cover these gaps in the attempt to shed light on the most appropriate DT procedures for the assessment of pwMS.

Specifically, **Study 1** showed that both pwMS and healthy individuals present CMI over motor parameters (Learmonth et al., 2017; Leone et al., 2015; Wajda & Sosnoff, 2015). The most frequently reported gait parameter in pwMS was gait speed, as in other populations (Al-Yahya et al., 2011). Other frequently reported gait parameters included cadence (steps/min) and double support time (% gait cycle). Regarding intragroup comparisons of direct scores (DT *versus* ST), it was found that speed and cadence (steps/min) were reduced during DT in both pwMS and healthy subjects in over 75% of the cases in which these parameters were assessed by the studies included the review; whereas an increased double support time (% gait cycle) was frequently identified in pwMS unlike in healthy subjects (89% and 29% of the cases, respectively). These results suggest that speed and cadence are sensitive parameters to CMI in both pwMS and HC, in detriment of its potential clinical relevance.

Remarkably, it also implies that double support time is a sensitive and specific parameter to CMI in pwMS, that discriminates their performance from that of healthy individuals; thus, providing a rationale for its use in future studies. This notion is further encouraged by the fact that increased double support time during DT has been identified even in patients with CIS (Kalron et al., 2010) and in those with definite diagnosis of MS and low disability (Kirkland et al., 2015). More recent studies have also corroborated the increase in double support time during DT in pwMS (Gutiérrez Cruz et al., 2020; Pau et al., 2018).

Gutierrez Cruz et al. (2020) proposed that gait speed in pwMS was slower than in healthy controls, due to shorter step length and increased double support. It could be argued that gait speed, despite being functionally relevant, can be influenced by other spatiotemporal parameters (e.g. reduced cadence, increased double support time or reduced step length), which might indeed provide insight about aspects of gait specifically altered by certain disease (e.g. balance control) (Plummer-D'Amato et al., 2010). For instance, it has been proposed that a "cautious gait" pattern characterized by prolonged double support time is typical in pwMS (Comber et al., 2017) as an attempt to increase postural stability and gait control. In line with this, pwMS present prolonged double support time in ST in contrast with healthy controls (Comber et al., 2017) even in the early stages of the disease and in the absence of pyramidal signs (i.e. without clinical disability) (C. L. Martin et al., 2006), and it might be exacerbated during DT conditions in order to overcome the CMI caused by the cognitive task (Nogueira et al., 2013) and ensure stability. Additionally, increased double support times during DT have been occasionally evidenced in other populations such as stroke, Parkinson's Disease and even older adults (Bowen et al., 2001; Plummer-D'Amato et al., 2010; Verghese et al., 2007). While balance seems to be more compromised in pwMS than in those affected by Parkinson's Disease and stroke (Cattaneo et al., 2016), it remains to be specifically tested during DT walking.

Considering between-group comparisons of relative or DTC scores, **Study 1** showed that the DTC of speed was comparable between pwMS and healthy controls as revealed by most studies and in agreement with the results from a meta-analyses (Learmonth et al., 2017). Nevertheless, it should be acknowledged that the same reduction or DTC in pwMS, who already walk significantly slower than healthy controls in ST, might represent a greater impact in their real-life performance (Postigo-

Alonso et al., 2018). These findings remark the importance of considering intragroup as well as between-group changes, and the use of direct and DTC scores for a more thorough understanding of CMI (Plummer & Eskes, 2015; Postigo-Alonso et al., 2018; Veldkamp et al., 2019).

In agreement with findings from **Study 1**, **Study 2** showed that both pwMS and HC significantly decreased speed during DT vs ST, as expressed by the shorter distance walked during the same time (1 minute). Additionally, the motor DTC did not differ between groups, while the pwMS walked significantly slower than HC in DT, but so did in ST. Considering this, it could be claimed that the DT assessment does not offer anything different to simply walking. Nevertheless, in **Study 2**, the CMI over cognitive performance was also measured, which has been disregarded by most studies as reported in our review (**Study 1**) (Postigo-Alonso et al., 2018) and others (Learmonth et al., 2017; Leone et al., 2015; Wajda & Sosnoff, 2015). Interestingly, it was observed that pwMS produced significantly fewer correct words (indicative of worse cognitive performance) in DT *versus* ST conditions, in contrast with healthy controls, who showed no differences in cognitive performance between conditions. The cognitive DTCs did not differ between groups and pwMS performed worse than healthy controls in both ST and DT. Regarding the patterns of CMI described by Plummer et al. (2013), the findings of **Study 2** would indicate a *mutual interference* between both tasks of the DT in pwMS, while in HC the pattern is of *cognitive-related motor interference* as the cognitive performance remained stable while motor performance deteriorated. Accordingly, the few studies that have assessed CMI over cognitive performance in pwMS have generally shown significant CMI over both cognitive and motor parameters (Etemadi, 2017; Hamilton et al., 2009; Saleh et al., 2018; Wajda et al., 2016) or *motor-related cognitive interference* (Downer et al., 2016). The pattern of CMI while walking in people with stroke is likely to be either *cognitive-related motor interference* or *mutual interference* (Plummer et al., 2013). Similarly, there is evidence supporting a "posture second" strategy in people with Parkinson's Disease (Kelly et al., 2012; Yogev-Seligmann, Hausdorff, et al., 2012), thereby prioritizing cognitive performance by deteriorating gait, which would correspond to the same patterns documented in people with stroke (Plummer et al., 2013). Thus, there seem to be significant CMI over cognitive performance as well, which remains across diverse neurological conditions. Definitively, this evidence highlights the relevance of

assessing CMI over both motor and cognitive performance for a complete understanding of CMI and the trade-off between both tasks.

Another important aspect regarding the selection of CMI measures is the test-retest reliability. For both motor and cognitive parameters, the direct DT scores appear to be more reliable than DTCs across neurological and healthy populations (Muhaidat et al., 2013; Strouwen et al., 2016; Veldkamp et al., 2019; Yang et al., 2016), which further supports the notion of including both scores in the assessment, and not only the widely used DTC scores. In particular, evidence in pwMS suggests that direct DT scores of cognitive and various spatiotemporal gait parameters and motor DTCs could be reliably measured (Rosenblum & Melzer, 2017; Veldkamp et al., 2019), but not cognitive DTCs (Veldkamp et al., 2019). The poor reliability of cognitive DTCs could be explained by the fact that these parameters may be more affected by fatigue and psychological status, or more likely because the type of cognitive tasks used (Serial Subtracting 7s and Digit span backwards) led to learning effects across sessions (Veldkamp et al., 2019).

### 3.2.2. The type and complexity of the cognitive task while walking modulate CMI

**Study 1** also examined the differences in CMI (DT vs ST) over gait parameters according to the cognitive tasks used concurrently to overground walking in pwMS. At that moment, these tasks included: Alternate Alphabet, Serial Subtracting 7s, Serial Subtracting 3s and Verbal Fluency. In this respect, it was found that Alternate Alphabet and Serial Subtracting 7s were sensitive tasks as they led to significant CMI in more than 76% of the cases in both pwMS and healthy individuals, whereas Serial Subtracting 3s was not sensitive in any population (25% and 51%, respectively). However, a differential pattern was shown regarding the use of the Verbal Fluency task, as it showed a tendency towards being sensitive in pwMS but not in healthy individuals (72% and 32%, respectively); thus, being specific for the detection of CMI in pwMS.

Several ideas are worth noting regarding these findings. First, the different tendency whereby walking while Serial Subtracting 7s led to significant CMI, unlike Serial Subtracting 3s, would be in support of the capacity-sharing model (Tombu & Jolicoæur, 2003) by demonstrating that the cognitive load presented by these tasks

would respectively either exceed the individual's limited resources -and lead to CMI- or not. Second, the differential pattern of CMI between pwMS and healthy individuals observed with Verbal Fluency while walking might be explained by the greater cognitive demand imposed by this DT in pwMS, who frequently present verbal fluency impairment (Henry & Beatty, 2006; Rao et al., 1991; Sepulcre et al., 2011). Impaired verbal fluency has been associated with progressive course of MS (Connick et al., 2013), aging in pwMS (Jakimovski et al., 2019), and even with early stages of MS (Achiron et al., 2005; Sepulcre et al., 2011; Viterbo et al., 2013). Therefore, the DT consisting on the Verbal Fluency task while walking would demand the simultaneous performance of two tasks, which are both likely to be affected in pwMS, hence making their limited cognitive resources more easily exceeded and leading to greater CMI according to capacity-sharing models. Additionally, both walking and verbal fluency would compete for attentional and executive functions (Joly et al., 2019; Sepulcre et al., 2011; Tröster et al., 1998; Yogev-Seligmann et al., 2008) as well as for structural resources such as the frontal cortex (Clark, 2015), especially the phonemic rather than the semantic form of Verbal Fluency test (A. Martin et al., 1994). Altogether, it suggests that Verbal Fluency while walking may be the most suitable standardized task for unveiling CMI in pwMS and provides a rationale for its use in subsequent studies. Even though the reliability of cognitive CMI measures using Verbal Fluency while walking in pwMS have not been tested yet, there is evidence showing excellent test-retest reliability of these parameters during standing balance (Prosperini et al., 2016) as well as in its classical sitting application (Ruff et al., 1996; Tombaugh et al., 1999).

It should be remarked that, as **Study 1** shows, the assessment of CMI with the classical Stroop test during standing balance in pwMS has also shown promising results and excellent test-retest reliability (Learmonth et al., 2017; Prosperini et al., 2016). A recent study has for the first time used the Stroop test while walking DT in pwMS and identified greater motor DTC in this group in contrast with healthy controls, while the effect over the cognitive task was not assessed (Coghe et al., 2018). Likewise, the performance of the Stroop test while walking on a treadmill led to significant motor, but also cognitive DTCs in a group healthy older adults (Wollesen et al., 2016). More research exploring the effect of this DT combination is needed. Nevertheless, the Stroop test also imposes a sensory (i.e. visual) interference in addition to the cognitive-motor interference, which should be accounted for in terms of the construct that is

being assessed, as the visual input is central for gait stability (Bauby & Kuo, 2000). Furthermore, it might complicate its applicability in the clinical setting as additional equipment might be needed (e.g. screen to display the words) and in order to ensure safety.

Based on these findings from **Study 1**, the assessment of CMI in **Study 2** consisted on the performance of the phonemic Verbal Fluency test while walking, with the experimental manipulation of the DT instructions of priority. Thus, further results will be considered in the next section.

### 3.2.3. Dual-task instructions modulate CMI

**Study 1** also pointed out the lack of consensus between studies regarding the DT instructions of priority and/or expected performance of each task -if any was given-, and often these were not reported in the studies. The same scenario has been documented in the CMI literature across different populations (Kelly et al., 2012; Plummer et al., 2013; Ruffieux et al., 2015; E. Smith et al., 2016). However, this is a relevant concern of the DT procedures, since the instructions are likely to modulate CMI, as observed in healthy individuals (Verghese et al., 2007; Yogev-Seligmann et al., 2010). On the one hand, not giving explicit instructions of priority or expected performance might reveal natural, spontaneous, self-selected strategies by the individuals (Leone et al., 2015). On the other hand, giving explicit instructions would inform of the ability of the individual to flexibly adapt to the demands of the environment, plus leading to more reliable CMI measures in contrast to those derived from no explicit instructions (Plummer et al., 2015). Moreover, it has been claimed that assessing the same DT paradigm under different instructions of priority would also allow the identification of the behavior that most closely resembles the natural, self-selected strategy (Leone et al., 2015). Similarly, not giving instructions about expected performance -i.e. gait speed- is associated with more natural and intuitive gait (Decavel et al., 2019); but fast walking speed has better metrological properties (Bethoux & Bennett, 2011), has been advised for the assessment of pwMS as it would rather unmask gait deficits in patients with low disability (Comber et al., 2017), and might better represent real-life challenges. Note that the DT instructions of expected performance can imply prioritization (Plummer et al., 2013), e.g. “walk at fastest speed while counting backwards” would imply directing the focus towards gait rather the

cognitive task; but not necessarily the other way around. **Study 1** remarked the importance of giving explicit instructions in order to enable comparisons between studies and minimize confounders (e.g. motivation). To our knowledge, the effect of different sets of explicit instructions of priority had not been tested in pwMS, which motivated the design of **Study 2**.

Considering the findings from **Study 1**, the procedures for the CMI assessment in **Study 2** consisted on the performance of the phonemic Verbal Fluency test while walking, under ST and two DT conditions respective to the instruction of prioritization: both tasks at best capacity or double priority condition (DT-DP) and performing only cognitive task at best capacity while walking at preferred speed or cognitive priority condition (DT-CP).

Thus, beyond the results previously discussed, **Study 2** also provided novel data regarding the effect of explicit instructions of priority over CMI in pwMS. In this respect, it was observed that both pwMS and healthy controls walked significantly less distance across conditions according to this gradient: ST>DT-DP>DT-CP. However, only pwMS produced significantly fewer correct words in both DT conditions (DT-DP and DT-CP) *versus* ST, with no difference between DT-DP *versus* DT-CP. Therefore, regardless of the instructions, pwMS showed the same pattern of *mutual interference* during both DT conditions, whereas healthy controls showed *cognitive-related motor interference* that was increased during the cognitive-priority condition as expected by the instructions. These results suggest that healthy controls successfully prioritized the cognitive task by slowing down in both DT conditions (DT-DP, DT-CP). Conversely, despite slowing down the same extent as healthy controls (similar motor DTCs), pwMS were not able to divert their attention from walking and perform the cognitive task as in ST and not even to flexibility adapt to the demands of the DT-CP conditions; hence, leading to cognitive CMI and manifesting that their cognitive resources were further exceeded by the DT. Additionally, only in pwMS was the cognitive DTC of DT-DP greater than zero, in line with capacity-sharing theories as it is the most cognitively-demanding condition. These findings from **Study 2** confirm that the DT instructions have an effect over CMI in pwMS and healthy controls. It remarks the need to consider the DT instructions and suggests that the detection of CMI in pwMS might be enhanced by the instructions to prioritize both tasks.

Based on these observations from **Study 2**, it can also be inferred that the natural strategies of these populations may be characterized by a posture-second strategy in HC (prioritizing the cognitive task) and a posture-first strategy in pwMS, probably in order to ensure stability and avoid falls. It would be further supported by the fact that during the DT-DP, pwMS presented higher DTCs in the cognitive than in the motor domain, opposite to healthy controls. Moreover, it would be in line with previous observations suggesting that healthy young adults might naturally adopt a posture-second strategy (Agmon et al., 2014; Kelly et al., 2013; Yogev-Seligmann et al., 2010) as they have sufficient postural reserve to successfully prioritize the cognitive task without increasing falling risk (Yogev-Seligmann, Rotem-Galili, et al., 2012). In contrast, pwMS whose postural reserve might be reduced and would thus adopt a posture-first strategy in order to avoid hazards. It should be remarked that the adoption of a posture-second strategy has also been observed in people with other neurological conditions such as Parkinson's disease (Bloem et al., 2006; Yogev-Seligmann, Rotem-Galili, et al., 2012) despite potentially having diminished postural reserve. The adoption of a probably inappropriate posture-second strategy in people with Parkinson's Disease has been explained in terms of impaired executive functioning, specifically, self-awareness or impulsiveness, that might lead to increased risk of falls (Yogev-Seligmann, Hausdorff, et al., 2012). Nevertheless, as shown in **Study 2**, pwMS did not present impaired executive function (inhibition or flexibility), which would support their appropriate capacity of hazard estimation and subsequent adoption of a posture-first strategy.

### 3.2.4. Characteristics of the individuals associated with CMI

The group of pwMS (relapsing-remitting course) from our **Study 2** presented specific impairment on cognitive processing speed (assessed with the SDMT) and verbal fluency, which might as well be influenced by information processing speed (Arnett & Strober, 2011). PwMS presented spared attention, executive function (as shown after time correction of the Five Digit Test) and memory (assessed with the TAVEC). Remarkably, the cognitive status of pwMS assessed with neuropsychology (especially information processing speed, executive function -cognitive flexibility-, memory) and physiological measures (P3 component amplitudes over Cz and Pz electrodes) was associated with numerous cognitive and motor CMI measures. Of note, the association between information processing speed with all motor and cognitive DT and ST scores

is not surprising considering that, as proposed by the tri-factor model, information processing speed deficits in pwMS would rely on three different speed factors: sensorial, motor and cognitive; and the SDMT would demand processing at all three levels (Costa et al., 2017), just as the cognitive-motor DT. Previous studies have as well identified a linkage between CMI and cognition (Kirkland et al., 2015), particularly with information processing speed (Motl et al., 2014; Sosnoff et al., 2014) and executive function (Bloem et al., 2006; Srygley et al., 2009; Yogev-Seligmann et al., 2008). It should be noted though, that the cognitive correlates of CMI in pwMS have been underinvestigated, but research on this is of importance from a theoretical and an applied perspective (Wajda & Sosnoff, 2015). Regarding symptoms in pwMS, depression was not associated with any CMI measure, fatigue only with distance in ST and MSQOL-54 and EDSS exclusively with motor direct ST and DT scores, in partial agreement with other research (D'Esposito et al., 1996; Hamilton et al., 2009; Motl et al., 2014) (see Supplementary Tables 1 and 2 from **Study 2**). No association was found between CMI and other clinical features of MS such as number of relapses, time from last relapse, or disease duration, which is in line with previous research (D'Esposito et al., 1996; Hamilton et al., 2009; Learmonth et al., 2014).

Thus, the link between CMI and cognitive status is emphasized over that with symptomatic and other clinical measures, remarking the importance of exploring the relationship between CMI and specific system impairments rather than medical diagnoses. It would encourage the application of CMI as potential marker of cognitive functional decline in pwMS, although more research is warranted in this respect. CMI has also been associated with fall risk in healthy and other clinical populations (Beauchet et al., 2009; Hausdorff et al., 2003; Montero-Odasso, Muir, et al., 2012), standing as potentially useful for the detection of individuals at increased risk of falls and for rehabilitation purposes. Nevertheless, in pwMS, the relationship between CMI and falls is limited and mixed, with some studies supporting this association (Etemadi, 2017; Wajda et al., 2013), but not others (Gunn et al., 2013).

To sum up, this work adds to a growing body of literature suggesting that cognitive and motor processes are highly interrelated, which is behaviorally evidenced by CMI. According to capacity-sharing and bottleneck models (Ruthruff et al., 2001; Tombu &

Jolicoæur, 2003), the competence between the Verbal Fluency task and walking for the same limited cognitive (i.e. executive function and attention) and structural resources (i.e. prefrontal cortex) would account for CMI. Indeed, it has been proposed that walking can be considered a "natural, physical manifestation of executive function" (McFadyen et al., 2017), whose demand of executive control increases especially under challenging conditions such as cognitive-motor DT. Likewise, the phonemic Verbal Fluency test also requires executive function (Diamond, 2013), thus supporting the notion of competence for cognitive resources between this task and walking. Moreover, pwMS often present motor and cognitive impairment affecting gait and verbal fluency (among other cognitive processes), as evidenced in **Study 2**. Therefore, gait and the Verbal Fluency task would demand increased cognitive control, while potentially relying on a more limited "pool" of cognitive resources in pwMS. Consequently, their limited cognitive resources would be more easily exceeded by the DT and lead to greater CMI in pwMS in contrast with healthy controls. Relative to the structural competence, the prefrontal cortex is involved in verbal fluency (A. Martin et al., 1994), in walking and in cognitive-motor DT (Clark, 2015). In addition, MS often affects those regions that are involved in cognitive, motor and cognitive-motor DT, such as frontal -including prefrontal-, parietal and subcortical structures (Batista et al., 2012; Benedict et al., 2011; Lazeron et al., 2005; Motl, 2013; Sperling et al., 2001), and wider networks also through white matter lesions, i.e. fronto-striatal pathways (Comi et al., 1993, 2001; Johnen et al., 2019). All things considered, the assessment of CMI is clinically relevant in pwMS, since the request to perform both tasks simultaneously would further compound their deficits and might even unmask subtle deficits by functioning as a "brain stress test".

## 3.4. Limitations

Several limitations in the design and analyses must be acknowledged relative to the three studies part of this thesis:

- The studies included in the systematic review (**Study 1**) were heterogeneous in terms of the sample (e.g. disease course of MS, cognitive or motor status) as well as in terms of DT procedures (e.g. CMI measures, motor parameters assessed, cognitive task used while walking, instructions). The mixed methods approach allowed further comparison and interpretability of the results from different

studies. However, these limitations should be accounted for when considering general results and recommendations from this review. The necessity of further research accounting for these confounders and using standardized DT procedures remains.

- In order to overcome the scarce evidence of DT studies comparing the performance of pwMS and healthy controls, we decided to include in **Study 1** also DT studies of only healthy adults. Those studies of individuals with any clinical condition were excluded. Additionally, studies of healthy samples including adults over 65 years old that did not assess cognitive status were excluded, as they might represent a risk population for cognitive decline. Nevertheless, it should be considered as healthy subjects were not necessarily matched to pwMS regarding age or other demographics.
- The sample of pwMS in **Study 2** was limited to those with neurologist-confirmed diagnosis of relapsing-remitting course. Although it was not an inclusion criterion, pwMS did not use walking aids and had mild disability. Therefore, the results should not be generalizable to the entire population of pwMS.
- In **Study 2**, CMI measures of motor performance was limited to distance walked over 1 minute. However, based on **Study 1** and others (Learmonth et al., 2017; Postigo-Alonso et al., 2018), it is not a specific measure of DT performance in pwMS. Other measures such as double support might have better captured differences in DT walking performance between pwMS and healthy controls.
- Main limitations of **Study 3** include that aggregating data across participants might have obscured individual strategies and averaging data across conditions would hide other interesting dynamic oscillatory patterns across trials (e.g. learning effects).

## 3.5. Clinical implications and future directions

The relevance of the present thesis is not limited to knowledge contributions towards the relationship between cognitive and motor processes, but it provides evidence regarding potential practical applications to clinical settings as well.

The cognitive-motor DT assessment would offer an ecological assessment that might better represent real-life impairment of pwMS, who frequently present both motor and cognitive deficits (Leone et al., 2015). **Studies 1 and 2** revealed that pwMS experience

CMI to a greater extent than healthy individuals, thereby remarking the importance of assessing this phenomenon in pwMS. Moreover, the association of CMI mainly with neuropsychological and physiological (P3 component) features in pwMS encourages its inclusion in the cognitive functional assessment of pwMS. **Studies 1 and 2** also provided insights regarding the most useful procedures to detect CMI in pwMS (i.e. motor parameters, cognitive tasks, CMI measures and instructions).

Future research about CMI might benefit from:

- Exploring system impairments associated with CMI rather than medical diagnosis (e.g. people with low versus high cognitive flexibility).
- Longitudinal studies to determine whether CMI has predictive value of cognitive decline in pwMS, in order to check its potential use as an early marker.
- Exploring differences in CMI across different clinical courses of MS.
- Including measures of other spatiotemporal gait parameters, which might be more sensitive to DT differences between pwMS and healthy controls (e.g. double support time). In relation to this it should be noted that Study 2 is a publication part of a wider study, which included the recording of spatiotemporal gait parameters with a tri-axial accelerometer placed on the lower back and whose results are expected to be published in the near future.

Considering that CMI has been associated with adverse outcomes such increased risk of falls, there is increasing interest to target CMI as rehabilitation goal (Wajda et al., 2017). Positive findings (i.e. CMI reductions) have been found after both independent or consecutive cognitive and motor (ST) training as well as after the use of simultaneous DT training in people with neurodegenerative diseases including MS (McIsaac et al., 2018; Wajda et al., 2017). Most of the evidence comes from pilot studies and it is still unclear which type of intervention might be more beneficial (McIsaac et al., 2018). Further investigation is warranted in this recent and growing topic of research.

**Study 3** might also have potential practical implications. For instance, advances in the decoding of neural oscillatory activity associated with motor control might be of use for the development of Brain-Computer Interfaces (Contreras-Vidal et al., 2018; Delval et al., 2020). This work might hypothetically contribute to future adaptive tools for deep-brain stimulation by recreating optimal physiological activity.

Future research regarding the neural underpinnings of motor control might benefit from:

- Exploring modulations in beta oscillations relative to individual differences in performance (e.g. accurate versus non-accurate performers).
- Trial-to-trial analysis would rather unmask oscillatory dynamics along time at a single trial level.

The work of the present thesis also opens a new avenue of research consisting on the assessment neural oscillatory activity over regions of interest during walking DT in pwMS, which might include -but not be limited to- cortical regions of fronto-subcortical and fronto-parietal networks. Such research would be of interest to understand the brain mechanisms of cognitive and motor interactions in pwMS and for the optimization and monitorization of interventions targeting CMI.

# 4

# Conclusions

Overall, the findings of this thesis shed light on the relationship between cognitive and motor processes. It is evidenced in behavioral terms by the CMI that arises from the competence for shared resources between cognitive and motor (i.e. walking) tasks in healthy individuals and -to a greater extent- in people with neurological disorders such as Multiple Sclerosis, supporting the inclusion of cognitive-motor dual tasks in the clinical assessment of pwMS. Additionally, the fact that beta oscillatory activity in the SMA signals the cognitive demand during motor control would suggest that common neural substrates subserve both cognitive and motor processes.

Specific conclusions may as well be extracted from the studies presented on this thesis:

1. PwMS and healthy individuals present significant CMI over gait parameters.
2. The Verbal Fluency task during overground walking and the gait parameter of double support time (% gait cycle) were sensitive and specific to CMI in pwMS. Thus, it provided a rationale for including them in the procedures for the assessment of CMI in pwMS.
3. There was a lack of evidence regarding the effect of CMI over cognitive performance and the effect of DT instructions. Furthermore, there was limited evidence including a matched healthy control group and regarding the correlates of CMI in pwMS. It led to the recommendation of considering these aspects in future studies.
4. PwMS presented CMI over both motor and cognitive performance, whereas healthy controls presented CMI only over motor performance with no significant change in cognitive performance. According to the classification of DT outcomes (Plummer et al., 2013), the performance of pwMS corresponded to mutual interference, whereas that of healthy controls corresponded to cognitive-related interference. These patterns remained regardless of the DT instructions of priority. These findings support the notion that assessing cognitive performance -in addition to motor performance- during DT is essential for a complete understanding of CMI.
5. The DT instructions of priority (double priority and cognitive priority) had an effect over motor performance so that both pwMS and healthy controls walked significantly less distance according to the gradient: ST > DT-DP > DT-CP. Unlike HC, the cognitive performance of pwMS was significantly reduced from ST to DT-DP and DT-CP respectively, with no significant difference

between both DT conditions. Moreover, only pwMS showed a significant cognitive DTC during the DT-DP conditions. These findings indicate that CMI is enhanced by the instruction to prioritize both tasks in DT.

6. PwMS walked significantly less distance and produced fewer correct words than healthy controls under both ST and DT, whereas motor and cognitive DTC scores were comparable between both groups in partial agreement with previous evidence (Learmonth et al., 2017). However, it should be noted that equivalent reductions or DTC would have different impact in the daily life of both groups since pwMS already presented worse performance than healthy controls at ST, and DT would further compound their deficits.
7. CMI measures showed main associations with neuropsychological (i.e. information processing speed and cognitive flexibility) and physiological measures (P3 component) in pwMS. Altogether, it suggests that CMI over cognitive performance might be a signature of cognitive functional decline in pwMS.
8. The importance of considering intragroup and between-group DT changes, as well as the use of direct and DTC scores for a more thorough comprehension of CMI is highlighted (Plummer & Eskes, 2015; Veldkamp et al., 2019).
9. As observed during the performance of a center-out visuomotor reaching task, greater beta power (or less ERD) was identified only in the SMA during controlled versus automatic conditions aligned to the cue onset, unlike any other regions tested (M1r, M1l, pre-SMA). It proves that beta oscillations in the SMA are associated with cognitive control during motor preparation.
10. Greater power in high beta oscillations in the SMA was associated with improved motor performance (i.e. less trajectory error). Moreover, a greater difference in high beta power between controlled and automatic conditions was associated with greater difference in trajectory error. It further supports the role of beta oscillatory activity in the SMA in cautious control of motor behavior at the expense of improved performance.

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# Appendix A: Work dissemination and other curricular merits

## Published articles:

- **Postigo-Alonso, B.,** Galvao-Carmona, A., Conde-Gavilán, C., Jover, A., Molina, S., Peña-Toledo, M.A.,… Agüera, E. (2019). The effect of prioritization over cognitive-motor interference in people with relapsing-remitting multiple sclerosis and healthy controls. *PLoS ONE 14(12):* e0226775. https://doi.org/10.1371/journal.pone.0226775
- **Postigo-Alonso, B.,** Galvao-Carmona, A., Benítez, I., Conde-Gavilán, C., Jover, A., Molina, S., … Agüera, E. (2018). Cognitive-motor interference during gait in patients with Multiple Sclerosis: a mixed methods Systematic Review. Neuroscience & Biobehavioral Reviews, 94, 126–148. https://doi.org/10.1016/j.neubiorev.2018.08.016
- Olabarrieta-Landa, L., Rivera, D., Lara, L., Rute-Pérez, S., Rodriguez-Lorenzana, A., Galarza-del-Angel, J., Peñalver Guia, A.I., Ferrer-Cascales, R., Velázquez-Cardoso, J., Campos Varillas, A.I., Ramos-Usugaj, D., Chino-Vilca, B., Aguilar Uriarte, M.A., Martín-Lobo, P., García de la Cadena, C., **Postigo-Alonso, B.,** Romero-García, I., Rabago Barajas, B.V., Irías Escher M.J., & Arango-Lasprilla J.C. (2017). Verbal fluency tests: Normative data for Spanish-speaking pediatric population. NeuroRehabilitation, 41(3), 673-686. doi: 10.3233/NRE-172240

## Published conference abstracts:

- **Postigo-Alonso, B.,** Galvao-Carmona, A., Conde-Gavilán, C., Jover, A., Molina, S., Peña-Toledo, M.A., Valverde-Moyano, R., & Agüera, E. (2018). Cognitive-motor interference while walking in people with Multiple Sclerosis: A potential marker of functional impairment? *Multiple Sclerosis Journal, 24* (S2), 738–980. doi: 10.1177/1352458518798592
- **Postigo-Alonso, B.,** M. Hofmann, Kühn, A., Neumann, W.J. (2018). P21. Neural correlates of cognitive control in motor processes. *Clinical*

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- **Postigo-Alonso, B.,** Galvao-Carmona, A., Hofmann, M., Kühn, A., Neumann, W.J. *Oscillatory cortical dynamics predict successful motor preparation.* Program No. 312.14. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, 2019. Online.

## Conference presentations:

- Conde Gavilán, C., Barrios Nevado, M.D., Molina Zafra, S., Peña Toledo, M.A., Jover Sánchez, A.M., Carmona Medialdea, C., Galvao Carmona, A., **Postigo Alonso, B.,** & Agüera Morales, E. *Evaluación neuropsicológica de la memoria en deterioro cognitivo leve: una revisión sistemática.* LXXI Reunión Anual Sociedad Española Neurología. (Seville, Spain. November 2019). Poster.
- **Postigo-Alonso, B.,** Galvao-Carmona, A., Hofmann, M., Kühn, A., Neumann, W.J. *Oscillatory cortical dynamics predict successful motor preparation.* 2019 Neuroscience Meeting of the Society for Neuroscience (SfN). (Chicago, United States. October 2019). Poster.
- Morales, L., Galvao, A., Morales, J., Tajadura-Jiménez, A., **Postigo-Alonso, B**. *Boosting cognition with music: ERPs during an auditory, semantic and emotional oddball task*. 21st Conference of the European Society for Cognitive Psychology (ESCOP). (Tenerife, Spain. September 2019). Poster.
- **Postigo-Alonso, B.,** Hofmann, M., Kühn, A., Neumann, W.J. *Beta activity in SMA signals cognitive demand in motor control.* 29th Annual meeting of the Society for the Neural Control of Movement (NCM). (Toyama, Japan. April 2019). Poster.
- **Postigo Alonso, B.**, Galvao Carmona, A., Conde Gavilán, C., Jover Sánchez, A., Molina Zafra, S., Peña Toledo, M.D.L.Á., Valverde Moyano, R., Agüera Morales, E. *Interferencia cognitivo-motora como potencial marcador de deterioro funcional en personas con esclerosis múltiple: un estudio preliminar.* LXX Reunión Anual Sociedad Española Neurología. (Seville, Spain. November 2018). Oral communication.

- **Postigo-Alonso, B.,** Galvao-Carmona, A., Conde-Gavilán, C., Jover, A., Molina, S., Peña-Toledo, M.A., Valverde-Moyano, R., & Agüera, E. *Cognitive-motor interference while walking in people with Multiple Sclerosis: A potential marker of functional impairment?* 34th Congress of the European Committee for treatment and research in Multiple Sclerosis (ECTRIMS). (Berlin, Germany. October 2018). ePoster.
- Galvao-Carmona, A., Morales, L., **Postigo-Alonso, B.,** Llorens, R., and the DOCMA Group. *Disorders of consciousness: An electrophysiological proposal.* First Joint Congress of the SEPEX, SEPNECA and AIP experimental. XII Congress of the Sociedad Española de Psicología Experimental (SEPEX), XI Congress of the Sociedad Española de Psicofisiología y Neurociencia Cognitiva y Afectiva (SEPNECA), XXIV Congress of the Sezione Sperimentale - Associazione Italiana di Psicologia (AIP experimental). (Madrid, Spain. July 2018). Symposium organization.
    - **Postigo-Alonso, B.,** Hofmann, M., Kühn, A., Neumann, W.J. *ERD and ERS analysis in in healthy controls. Towards an evaluation of motor control in DOC patients.* Oral communication.
    - Galvao-Carmona, A., O´Valle, M., **Postigo-Alonso, B.,** Villalba, A., López-Martín, M., Llorens, R., Ferri, J., & Noé, E. *Cognitive evoked potentials associated with a transcranial Direct Current Stimulation intervention in a Minimally Conscious State patient: a 4-month follow-up single case study.* Oral communication.
    - Morales, L., Galvao-Carmona, A., Tajadura, A., **Postigo-Alonso, B.,** & Morales, J. *Boosting cognition with music: Auditory, semantic and emotional oddball in patients with disorders of consciousness.* Oral communication.
- Ibáñez-Alfonso, J.A., Galvao-Carmona, A., **Postigo-Alonso, B.,** Cruz-Ramos, C. *Evaluación de la atención con tareas clínicas y experimentales: ¿miden lo mismo?* II Congreso Iberoamericano de Neuropsicología y XIV Congreso de la Sociedad Andaluza de Neuropsicología. (Almería, Spain. May 2018). Poster.

- **Postigo-Alonso, B.,** Hofmann, M., Kühn, A., Neumann, W.J. *Neural correlates of cognitive control in motor processes.* II Congreso Iberoamericano de Neuropsicología y XIV Congreso de la Sociedad Andaluza de Neuropsicología. (Almería, Spain. May 2018). Oral communication.
- **Postigo-Alonso, B.,** Hofmann, M., Kühn, A., Neumann, W.J. *Neural correlates of cognitive control in motor processes.* 62nd Scientific Annual Meeting of the German Society for Clinical Neurophysiology and Functional Imaging (DGKN). (Berlin, Germany. March 2018). Poster.
- **Postigo Alonso, B**. *Event-related synchronization and desynchronization analysis in Disorders of Consciousness (DoC).* International Symposium on Recent Advances in Disorders of Consciousness. Diagnosis, Treatment and Prognosis. (Valencia, Spain. February 2018). Invited oral communication.
- **Postigo-Alonso, B.,** Hofmann, M., Kühn, A., Neumann, W.J. *Neural correlates of cognitive control in motor processes.* I Berlin Neuroscience Meeting, organized by the Einstein Center for Neurosciences Berlin. (Berlin, Germany. October 2017). Poster.
- Rodríguez-Prieto, P., **Postigo-Alonso, B.,** Ibáñez-Alfonso, J. *Test de lectura para la estimación de la inteligencia: datos preliminares en población escolar.* XI Encuentro Andaluz De Investigación En Lectoescritura. (Seville, Spain. October 2017). Poster.
- **Postigo-Alonso, B.,** Galvao-Carmona, A., Benítez, I., Conde-Gavilán, C., Jover, A., Molina, S., Peña-Toledo, M.A., Bahamonde, C., Agüera, E. *Cognitive-motor interference during gait in patients with multiple sclerosis: a mixed methods review*. 6th Scientific Meeting of The Federation of The European Societies of Neuropsychology. (Maastricht, Netherlands. September 2017). Oral communication.
- Rivera, D., Sánchez-SanSegundo, M., Vergara-Moragues, E., Alcazar Tebar, C., **Postigo-Alonso, B.,** Herranz Merino, M., Olabarrieta-Landa, L., Arango-Lasprilla, J. C. *Stroop Color-Word Interference Test: Normative Data for Spanish Children Population.* 14th European Conference on Psychological Assessment. (Lisbon, Portugal. July 2017). Poster.
- **Postigo-Alonso, B.,** Benítez, I., Conde-Gavilán, C., Jover, A., Molina, S., Peña-Toledo, M.A.; Valverde, R., Bahamonde, C., Agüera, E, Galvao-

Carmona, A. *Interferencia cognitivo-motora durante la marcha en pacientes con esclerosis múltiple: una aproximación mixta.* IX Congreso Nacional de Neuropsicología FANPSE- "Red de Redes". (Barcelona, Spain. March 2017). Poster.

- **Postigo-Alonso, B.,** Galvao-Carmona, A., Benítez, I., Conde-Gavilán, C., Jover-Sánchez, A., Molina-Zafra, S., Peña-Toledo, M.A., Valverde-Moyano, R., Bahamonde-Román, C., Agüera-Morales, E. *Interferencia cognitivo-motora en la marcha en pacientes con esclerosis múltiple: estado del arte e implicaciones en relación al deterioro cognitivo.* LXVIII Reunión Anual de la Sociedad Española de Neurología. (Valencia, Spain. November 2016). Poster.
- **Postigo-Alonso, B.,** Galvao-Carmona, A., Benítez, I., Conde-Gavilán, C., Jover, A., Molina, S., Peña-Toledo, M.A., Bahamonde, C., Agüera, E. *A mixed methods review: Integrating quantitative and qualitative evidence about Cognitive-Motor Interference in gait in Multiple Sclerosis patients.* VII European Congress of Methodology. (Mallorca, Spain. July 2016). Oral communication.

## Conference organization:

- Part of the Scientific Committee for the 16th Conference of the NEUROPSYCHOLOGICAL REHABILITATION SPECIAL INTEREST GROUP OF THE WFNR (NR-SIG-WFNR) and 15th Congress of the Andalusian Society of Neuropsychology (SANP) (Granada, Spain. 27-28 June, 2019).

## Project collaborations:

- Disorders of Consciousness (DoC): enhancing the transfer of knowledge and professional skills on evidence-based interventions and validated technology for a better management of patients. European Commission- H2020. Marie Curie Actions-RISE 2017. Ref: 778234 (January 2018 – December 2021).
- Estudio de datos normativos para pruebas neuropsicológicas en población de 6 a 17 años de edad en España (NORMALATINA). (Seville, January 2016 – May 2017).

## International research stay:

- Predoctoral research stay under the supervision of W. J. Neumann (Dr.med) at Charité Universitätsmedizin Berlin. Department of Neurology, Movement Disorders and Neuromodulation Unit (Berlin, Germany. 22 May – 25 October 2017).

## University teaching:

- Psychophysiology from the Degree of Psychology (6 ECTS per academic year) at Universidad Loyola Andalucía (2016-17, 2017-18, 2018-19).

## Membership in Relevant Associations:

- Member and part of the Executive Committee of the Sociedad Andaluza de Neuropsicología (SANP) (2018-present).
- Adhered member of the Sociedad Española de Neurología (SEN), Neuropsychology Section (2018-present).