New insights on the multidimensionality of fatigue and on its relationship with cognitive impairments in Multiple Sclerosis

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Abstract

Multiple Sclerosis (MS) is an inflammatory disease of the central nervous system (CNS), and it represents the most common cause of irreversible impairment in young adults, affecting about 2.5 million individuals worldwide. In MS, acute attacks of inflammation, leading to demyelination and axonal loss, determine the accumulation of disabilities, varying in number, nature, and severity. Indeed, motor, sensory, cognitive, and behavioral symptoms may manifest at different times during the disease's variable clinical course.

Fatigue is a complex and multifaceted phenomenon and one of the most prevalent and disabling symptoms of MS, affecting 75%–90% of patients. Despite its prevalence, MS-related fatigue is still poorly understood. The absence of a well-validated definition and of clear insights into its pathophysiological causes makes fatigue a hybrid symptom, approached within the context of different disciplines, each with their own methods and tools. As a result, the scientific literature abounds with irreconcilable data, leaving fatigue in a dark shadow zone, at the expense of MS patients still lacking adequate therapies and strategies of management.

The main topic of this thesis relates to the multidimensional nature of fatigue, to its variability, and its effects on attentional processes, most commonly affected in MS patients. Specifically, studies presented in the current thesis address four research issues:

(i) are physical and mental fatigue two distinct constructs?

(ii) how do physical and mental fatigue vary within a short (within a day) and long (within a year) period?

(iii) how do induced physical and mental fatigue impact the attentional functions of alerting, orienting, and conflict resolution in MS?

The main results of the studies are reported:

a) A clear distinction between physical and mental fatigue has been psychometrically documented in MS patients.

b) MS patients reported experiencing more overall fatigue than Controls.

c) A gradual increase in overall fatigue from the morning to the evening was reported by MS participants.

d) Across experiments physical fatigue was significantly more pronounced in MS

patients as compared to Controls.

e) Both MS patients and Controls reported having experienced more overall fatigue in the past (one year ago) than in the present (the last 24 hours).

f) MS patients were slower as compared to Controls in performing attentional tasks; however, inconclusive results have emerged regarding the effects of physical and mental fatigue on attentional processes.

g) Sleep quality and depression were both associated with fatigue across the experiments. The relationship between self-efficacy, general cognitive functioning, functional deterioration, and physical and mental fatigue is fragmented, thus preventing a clear conclusion.

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Thesis structure

Chapter 1 provides an overview of the MS pathology, epidemiology, and clinical course. Specifically, the etiopathogenesis, MS phenotypes, and clinical courses are examined, along with diagnostic criteria and MS symptoms. Finally, this chapter briefly addresses the current pharmacological and non-pharmacological treatments for disease management.

Chapter 2 presents an overview of fatigue, including its historical evolution and the ongoing challenges in defining and understanding it. The chapter delves into the effects and implications of fatigue in modern society owing to its extensive prevalence and noteworthy implications for health, economics, and safety, as well as its effects on individuals afflicted with pathological conditions. It also provides a thorough analysis of the complex and unpredictable nature of fatigue symptoms. The Chapter elucidates the intricate challenges associated with the delineation of fatigue, owing to its multifaceted characteristics, and delves into the inquiry of potential overlaps between fatigue and symptoms such as sleepiness, boredom, and apathy. This Chapter explores fatigue characteristics and discusses environmental factors that may contribute to its onset. Moreover, the chapter provides a summary of the traditional dichotomies associated with fatigue commonly discussed in academic literature, particularly the dichotomy between physical and mental fatigue, as the main goal of this thesis is to examine the current knowledge of physical and mental fatigue. The factors that influence physical and mental fatigue, the interaction between these two components, and the relationship between fatigue and cognitive deficits are examined. Lastly, this chapter provides a summary of the research methods employed in the study of fatigue.

Chapter 3 provides a detailed description of fatigue symptoms in individuals with MS. Fatigue is a symptom of multiple sclerosis that severely impacts various aspects of a patient's life, including physical activity, participation in day-to-day activities, and social interactions. The characteristics of the complex and multifaceted symptom of fatigue in MS and its multiple definitions found in different studies are described. Among the various definitions of fatigue found in the literature, this Thesis focuses on the distinction between physical and mental fatigue, as the primary purpose of this work is to demonstrate the clear separation of these two constructs, whose nature is still unclear. It is on these two components of fatigue that the whole research project is based. There is ongoing debate about whether physical and mental fatigue in MS are distinct or share a common underlying dimension. There is a divergence of views regarding the separate or overlapping nature of these two components of fatigue, as indicated by various studies. Evidence on the relationship between depression, cognitive impairment, and physical and mental fatigue in MS is discussed. Following that, the etiology of primary and secondary fatigue, the more recent theoretical models of the development of the subjective experience of fatigue, and the various environmental factors that contribute to fatigue onset are discussed. Additionally, this chapter describes the current knowledge regarding the characteristics and relationships between fatigue in MS and other symptoms, such as depression, anxiety, and sleep disorders. The last section provides an overview of the evaluation of subjective and objective fatigue, as well as various research methods employed to investigate mental and physical fatigue. Additionally, current therapeutic approaches for managing fatigue are discussed.

Chapter 4 provides an overview of cognitive impairment in MS. An in-depth description of the cognitive functions frequently impaired in MS (such as attention, information processing speed, memory, executive functions, and language) is outlined. The characteristics and neural underpinnings of cognitive impairments in different MS phenotypes are described, and factors (such as depression, fatigue, and sleep disorders) contributing to the cognitive impairment are addressed. Lastly, the risk and protective factors associated with cognitive impairments in MS, the neuropsychological assessment of cognitive functions, and their current treatments are reviewed.

Chapter 5 describes a descriptive review examining the relationship between fatigue and cognitive impairments in MS. By reviewing the current literature, this chapter aims to provide a comprehensive understanding of the relationship between fatigue and cognitive performance in MS patients. The introductory section of the chapter delves into the intricate interplay between fatigue and cognitive impairment. The relationship between cognitive impairment and fatigue is a complex and multifaceted issue that has generated debate within the scientific community. Several studies have attempted to elucidate whether cognitive deficits lead to fatigue or if fatigue, in turn, causes cognitive impairment. The direction of causality is uncertain, and the available evidence portrays a complex scenario characterized by various hypotheses and conflicting findings. Subsequently, the objectives, the search methods, and the results of the undertaken review are presented. Heterogeneous and conflicting results regarding the relationship between fatigue and cognitive decline are described. The differences found in the papers reviewed (such as MS phenotype, age, disability status, disease duration, participants' exclusion and inclusion criteria, methodological procedures, the fatigue construct, type of examined fatigue, mood and fatigue evaluation, and neuropsychological assessment) have made it impossible to conduct a comparative analysis across studies and, above all, to draw definitive conclusions on the relationship between fatigue and cognitive impairment. The heterogeneity of the research conducted so far on the topic explains the limited progress made in the last decade on fatigue in MS and highlights the need for further studies in the field. In the last section of the chapter, the need to develop shared protocols and standardized procedures for fatigue in MS research is discussed. The review's findings have made it clear that the heterogeneity of the studies and the lack of progress in MS-fatigue are linked to several factors, including the tools employed so far, which are poorly suited for the investigation of such a complex and multifaceted symptom as fatigue, as well as the methodology employed across studies. Given this complexity, further longitudinal studies are needed to provide a more comprehensive understanding of the interaction between cognition and fatigue in the context of MS.

Chapter 6 describes the development of a new self-report questionnaire, the Multi-Temporal Assessment of Fatigue (MtAF). The experimental part starts with a comprehensive analysis of the weaknesses of the most widely used self-report questionnaire used so far to investigate fatigue in MS. These questionnaires fail to differentiate between mental and physical fatigue and primarily focus on the impact of fatigue on daily functioning, neglecting the examination of both short and long-term physical and mental fatigue. The MtAF, committed exclusively to the estimation of the presence and severity of fatigue with respect to short and long-time frames, aimed to fill the gap present in the literature and improve understanding of the characteristics of fatigue in MS patients. Moreover, an additional survey has been conducted to investigate the characteristics of physical and mental fatigue specific to MS. Internal and external triggers of fatigue, its effect on different domains, and the most effective strategies for its remission have been explored. The MtAF discriminated, for the first time, between three distinct factors corresponding to mental fatigue, physical fatigue, and a third unexpected factor identified as sleepiness. The third factor was identified as sleepiness, as it was associated with items measuring physical and mental fatigue upon awakening and in the early hours of the day, and it also showed a correlation with overall sleep quality. The inherent characteristics of the third unanticipated factor necessitate further scrutiny and examination; therefore, it was not incorporated in the subsequent studies. The MtAF revealed that both MS patients and controls rated the fatigue experienced in the past as the highest and the fatigue experienced in the last 24 hours as the lowest, showing a positivity bias in accordance with literature studies. The analysis of fatigue within a short-term time frame showed that MS patients reported higher levels of physical fatigue compared to Controls.

Fatigue in both MS patients and Controls increased in the evening, in accordance with literature studies. In accordance with literature studies, both physical and mental fatigue showed correlations with BDI scores, while sleep quality was correlated with mental fatigue. In the MS group, physical and mental fatigue experienced by MS patients did not correlate with age, disease duration, or self-reported mobility level.

Chapter 7 describes an experiment aimed at evaluating whether MS patients and controls differ with respect to the pattern of daily changes in physical and mental fatigue evaluated by means of the ecological momentary assessment (EMA). Due to the COVID-19 pandemic outbreak in 2020, the experiment endeavour has been revised due to an inability to carry out in-person investigations. To ensure participant safety, the research was to move to a remote mode of research, and the experiment was conducted remotely by means of participants' mobile phones. The results of the study showed that individuals with MS reported higher levels of daily fatigue compared to the control group. Further analysis revealed that MS patients rated physical fatigue as higher than mental fatigue, while controls reported higher mental fatigue than physical fatigue. A gradual increase in overall fatigue from the morning to the evening was reported by MS participants. MS patients and Controls were equally exposed to stressors, and exposure to stressors did not vary across assessments. Correlations between daily physical and mental fatigue in patients with MS and sleep quality suggest that better quality and longer duration of sleep at night are associated with lower levels of physical and mental fatigue.

Chapter 8 describes an experiment aimed at examining the effects of induced mental and physical fatigue and attentional processes, as measured by the Attention Network Task, in MS patients. More precisely, state physical and mental fatigue, as measured by the Visual Analogue Scale, were assessed at baseline, after inducing mental or physical fatigue, after a neutral task, halfway through, and at the end of the ANT. Mental and physical fatigue were induced by requiring participants to perform the N-Back Task and a physical workout created by an expert in motor sciences, respectively, while the neutral task consisted of watching a relaxing video clip. Due to the pandemic's spread, the current experiment has been devised on Pavlovia, a multiplatform software that allows participants to plan and create online experiments that can be performed safely from home. The results of the studies showed that MS patients exhibited slower performance in attentional tasks compared to healthy individuals. A significant relationship was found between trait and state physical and mental fatigue, as measured by the subscales of the MtAF, and the VAS. However, definitive conclusions on the impact of physical and mental fatigue on attentional processes in MS patients cannot be drawn.

Chapter 9 In the last chapter of this thesis, the findings from the experiments are combined and discussed, along with the limits of the study.

My enthusiasm for advancing studies in healthcare for chronic disorders like Multiple Sclerosis and my interest in human sciences inspired this study.

This thesis examined fatigue in Multiple Sclerosis, a symptom that affects a person's physical, emotional, and mental health.

At this moment, almost at the conclusion, I feel amazed at a task that I never appeared to be able to finish, and I want to convey my sincere appreciation to a group of people who have assisted me along the way.

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I would like to dedicate my thesis to Giusy Balzano, a beloved cousin and friend with whom I have many happy memories from my childhood and who, at the age of nineteen, was diagnosed with multiple sclerosis just at the point in life when young women raise their gaze to the sky, dreaming about their future.

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Finally, I would also like to thank my husband and my two little children, Martina and Christian, hoping that one day they will forgive me for neglecting them in the children's loveliest stage for the sake of research.

Thank you all from the bottom of my heart.

This has truly been a difficult "tiring" but valuable journey of learning.

Contents

Tables

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Abbreviations

6MWT	The Six-Minute walking test
AASM	American Academy of Sleep Medicine
ACC	Accuracy
ACC	Anterior cingulate cortex
AI	Ambulation Index
AS	Alertness Subtest
ANT	Attention Network Test
ANOVA	Analysis of Variance
BDI	Beck Depression Inventory
BDI-FS	Beck Depression Inventory Fast Screen
BDI-II	Beck Depression Inventory, Second edition
BICAMS	Brief International Cognitive Assessment for Multiple Sclerosis
BFS	Brugmann Fatigue Scale
BMI	Body mass index
BRBNT	Brief Repeatable Battery of Neuropsychological Tests
BVMT-R	Brief Visuospatial Memory Test Revised
C	Controls
CES-D	Center for Epidemiologic Studies–Depression
CFA	Confirmatory Factor Analysis
CFS	Chalder Fatigue Scale
CFS	Chronic Fatigue Syndrome
CIS	Checklist of Individual Strength
CIS	Clinically Isolated Syndrome
CMDI	Chicago Multi Scale Depression Inventory
CNS	Central nervous system
CRF	Corticotropin-releasing hormone

CSF	Cerebrospinal fluid
CSTC	Cortico-striato-thalamo-cortical
CTIP	Computerized Test of Information Processing
CVLT	California Verbal Learning Test
d′	d-prime
DMTs	Disease Modifying Therapies
DMD	Disease-Modifying Drugs
DRS	Depression Rating Scale
EBV	Epstein-Barr virus
ECG	Electrocardiogram
EDSS	Expanded Disability Status Scale
EEG	Electroencephalography
EMA	Ecological Momentary Assessment
EMG	Electromyography
ERP	Event-related potential
FA	False alarm
FAI	Fatigue Assessment Instrument
FAMS	Functional Assessment of Multiple Sclerosis
FAS	Fatigue Assessment Scale
FDA	Food and Drug Administration
FDS	Fatigue Descriptive Scale
FES	Functional Electrical Stimulation
FIS	Fatigue Impact Scale
fMRI	Functional Magnetic Resonance Imaging
FSMC	Fatigue Scale for Motor and Cognitive Functions
FSQ	Functional Status Questionnaire
FSS	Fatigue Severity Scale
GM	Gray Matter

HADS	Hospital Anxiety and Depression scale
HDRS	Hamilton Rating Scale of Depression
HLA-DRB1	Major Histocompatibility Complex, Class II, DR Beta 1
HPA	Axis hypothalamic-pituitary-adrenal axis
HRQoL	Health-related Quality of Life
HTVL	Human T-Lymphotropic Virus
ICF	International Classification of Functioning, Disability and Health
IFN	Interferon gamma
IL-6	Interleukin 6
IPS	Information Processing Speed
IRT	Immune Reconstitution Therapy
ISS	Incapacity State Scale
LTM	Long-term memory
MACFIMS	Minimal Assessment of Cognitive Function in Multiple Sclerosis
MAF	Multidimensional Assessment of fatigue
MDIS	Major Depression Inventory Scale
MEG	Magnetoencephalography
MF	Mental Fatigue
MFi	Mental Fatigue Index
MFI	Multidimensional Fatigue Inventory
MFIS	Modified Fatigue Impact Scale
MMSE	Mini-Mental State Examination
MoCA 5min	Montreal Cognitive Assessment 5-Minute Protocol
MOCA	The Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
MS	Multiple Sclerosis
MSA	Mobility Self-Assessment

MSIF	Multiple Sclerosis International Federation
MS-FS	MS-Specific Fatigue Scale
MtAF	Multidimensional-temporal Assessment of Fatigue
MVC	Maximal voluntary contraction
NART	National Adult Reading Test
NCS	Nerve conduction studies
NIBS	Non-invasive brain stimulation
NMDA	N-metil-d-aspartato
NMSS	National Multiple Sclerosis Society
NMR	Nuclear magnetic resonance
OCB	Oligoclonal band
PASAT	Paced Auditory Serial Addition Test
PCA	Principal Component Analysis
PD	Parkinson disease
PET	Positron emission tomography
PF	Physical fatigue
PFi	Physical Fatigue Index
PFS	Piper Fatigue Scale
PPMS	Primary Progressive Multiple sclerosis
PRMS	Progressive-Relapsing Multiple sclerosis
PROMIS	Patient Reported Outcomes Measurement Information System
PROMIS F-SF	PROMIS Fatigue Scale Short Form
PSE-MCP	Perceived Self-Efficacy in Managing Complex Problems
QoL	Quality of life
RA	Rheumatoid arthritis
RFD	Rochester Fatigue Diary
RDFS	Real-Time digital fatigue scores
RTFS	Real-time fatigue score

RIS	Radiologically Isolated Syndrome
RRMS	Relapsing-Remitting Multiple Sclerosis
RT	Reaction Time
RTFS	Real-time fatigue score
RTV	Reaction time variability
SDMT	Signal Digit Modalities Test
SEP	Sensory evoked potentials
SLE	Systemic Lupus Erythematosus
SPMS	Secondary Progressive Multiple Sclerosis
TAP	Test Battery for Attentional Performance
TAP-M	Test of Attentional Performance - Mobility Version
ToT	Time on Task
tDCS	Transcranial Direct Current Stimulation
TMS	Transcranial Magnetic Stimulation
U-FIS	Unidimensional Fatigue Impact Scale
VAS	Visual Analogue Scale
VAS-F	Visual Analogue Scale for Fatigue
WAIS	Wechsler Adult Intelligence Scale
WBC	Whole-body cryotherapy
WHO	World Health Organization
WHODAS	World Health Organization Disability Assessment Schedule
WM	White matter

1. INSIGHTS INTO MULTIPLE SCLEROSIS

1.1. Introduction

Multiple sclerosis (MS), also known as disseminated encephalomyelitis, is one of the most common chronic, progressive, autoimmune neurodegenerative diseases that affect the central nervous system (CNS), impairing patients' physical and cognitive functions (Al-Araji & Oger, 2006; Reich, 2018). According to the 2020 Atlas of MS, the prevalence of MS in the world is estimated to be 2.8 million, which indicates that one in three people on the planet suffers from the disease(http://www.atlasofms.org).

MS may begin at any age, although the average age of diagnosis is 30-33 years across the six WHO regions (http://www.atlasofms.org). In terms of gender, there are at least twice as many females (69%) as males (31%) affected by MS. The term "multiple sclerosis" derives from the existence of hardened regions or plaques (*skleros* from the Greek word) distributed in different regions (*multus*, many) of the CNS that are caused by the aberrant activation of the immune system that attacks the myelin sheath.

MS has an unpredictable course, is associated with a wide range of symptoms, and is considered the second most common cause of long-term and non-traumatic impairment in people of working age (after traumatic damage), resulting in significant psychological stress, social and economic difficulties (Belgian, Sherri Giger, Director, Pfohl, & M. S. C. N., 2013). An American study in 2020 showed that MS sufferers were less likely to participate in everyday chores, as well as leisure and social activities, because of the disease's symptoms (Goverover, Chen, Costa, Chiaravalloti, & DeLuca, 2020). Moreover, some studies have suggested that maintaining a paid job for people with MS is a critical problem (Simmons, 2010). Several studies have indicated that MS is a significant cause of early retirement and unemployment (Weiland et al., 2015). The unemployment rate among individuals with MS is much larger than that observed in the general population (Julian, Vella, Vollmer, Hadjimichael, & Mohr, 2008). According to different studies, MS patients have a higher risk of mortality and a shorter lifetime expectancy of approximately 10 years when compared to the general population. This is especially true for MS patients who have comorbid conditions such as mental disorders, cerebrovascular and cardiac disease, diabetes, or melanoma (Thormann, Sørensen, Koch-Henriksen, Laursen, & Magyari, 2017). However, current studies employing statewide samples from Denmark and Norway have shown that the life expectancy among people with MS has grown significantly over the previous six decades (Koch-Henriksen, Laursen, Stenager, & Magyari, 2017).

1.2. Etiopathogenesis of Multiple Sclerosis

It is not yet clear what causes MS, but some research suggests that at least three factors, i.e., immunological, environmental, and genetic, may play an important role in the onset of MS (Ramagopalan, Dobson, Meier, & Giovannoni, 2010).

As for the immunological factors, studies indicate that MS is an autoimmune disease in which the cells of the immune system, the auto-reactive lymphocytes, mistakenly attack the body's own cells, the oligodendrocytes, prompting an abnormal inflammatory response. This inflammatory response causes the destruction of the myelin sheath that protects the CNS nerve fibers, resulting in demyelination and axonal degeneration. In a healthy brain, the myelin sheath and the nodes of Ranvier enable jumpy conduction that accelerates the propagation of the action potentials, allowing for rapid transmission of information in the brain. In MS, following the demyelinating process, the action potential is no longer able to propagate from one node to another, and therefore the nerve impulse proceeds more slowly (Bertora, 2015). The loss or impairment of the ability of the nerve fibers to conduct electrical impulses or the slowing of the nerve impulse due to myelin damage interferes with communication between the brain, spinal cord, and other regions of the body, causing a variety of symptoms (DeLuca & Nocentini, 2011; Pakenham & Cox, 2012). However, in the acute and early stages of the disease, a loss of function can be partially recovered with the regression of inflammation, an attempt at remyelination, and the use of alternative conduction pathways. As the inflammation subsides, the oligodendrocytes fight demyelination by restoring myelin integrity, giving rise to the so-called "shadow plates". This pathophysiological condition corresponds to the clinical phase of the disease, characterized by relapses and remissions. If this process is chronic, the damaged neuron cannot regenerate, and axons that are chronically demyelinated are destined to atrophy. The lack of remyelination processes determines the demyelination plaques located in the white matter (WM), both at the level of the brain and the spinal cord, which indicate the appearance of permanent clinical disability (Frischer et al., 2015). The axonal damage corresponds to the lack of regression of the symptoms and the stabilization of the neurological deficit, or the chronic-progressive phase of the disease. The destruction of the myelin sheaths that leads to the formation of plaques represents the hallmark of MS pathology (Ozawa et al., 1994).

There is considerable scientific evidence indicating that both genetic susceptibility and environmental factors contribute to the onset of MS (Olek & Mowry,2018)

As for genetic factors, some evidence suggests that although MS is not passed down through families, some genetic variants might enhance the likelihood of developing the disease. Several studies have tried to identify the genes responsible for the onset of MS. The HLA-DRB1 (Major Histocompatibility Complex, Class II, DR Beta 1) gene on chromosome six seems critical in the development of MS (Thompson et al., 2018).

As for environmental factors, infectious and non-infectious factors seem implicated in the onset of MS (Ghezzi et al., 2013). Several viruses, including mumps, rubella, and measles, viruses belonging to the Human T-Lymphotropic Virus (HTVL) family, Herpes viruses, and Epstein-Barr virus (EBV; Harley et al., 2018), have been linked to the onset of disease; however, the findings are still unclear. Some studies have indicated that a deficiency in naturally produced vitamin D, which appears to support immune function, and a reduced exposure to sunlight are both associated with an increased risk of MS (Ramagopalan et al., 2010; Tarlinton et al., 2019). According to some evidence, smoking, persistent use of inhaled or swallowed street cannabis, obesity, a higher body mass index (BMI), and excessive salt consumption have also been linked to inflammatory processes in MS (Amato et al., 2018; Honarmand, Tierney, O'Connor, &

Feinstein, 2011; Michel, 2018). Recent studies have investigated the role of microbiota (a collection of bacteria that help maintain a good internal environment for gastrointestinal motility) and the presence of heavy metals in the body in the onset of MS and other neurodegenerative diseases (Dehghani-Firouzabadi & Mirmohammadi, 2019). Despite the rising number of studies, further research is required.

1.3. Phenotype and clinical course of Multiple Sclerosis

MS is characterized by attacks caused by the emergence of new inflammation in the CNS, determining the disease's clinical progression due to myelin and axonal degeneration (Lublin & Reingold, 1996). An attack (also known as an acute episode or relapse) is defined as the introduction of a new symptom or the worsening of an already existing symptom that lasts longer than 24 hours and has been separated from the previous episode for at least a month. Symptoms can be acute (lasting a few hours) or subacute (lasting a few days) and may subside spontaneously within a few weeks (Mutani, Lopiano, Durelli, Mauro, & Chio, 2012). It is possible, though, that recovery after an attack might be incomplete, nonexistent, or take up to six months. The amount of recovery from each episode and the frequency of attacks are consequently unpredictable and fluctuate over time. Nonetheless, they are higher in the early stages of the disease. Since there are no biochemical indicators that can pinpoint the clinical course of MS, it is impossible to precisely predict how the disease will develop. Generally, the occurrence of more separated relapses throughout time and excellent remissions relate to a favorable prognosis (Olek & Mowry, 2018). A more unfavorable outcome is linked to male sex, a high frequency of relapses with partial recovery, fast development of motor, cerebellar, and sphincter dysfunction at the beginning, and a short inter-relapse interval (Ghezzi et al., 2013; Bergamaschi et al., 2013).

The National Multiple Sclerosis Society Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis used MS clinical descriptors to categorize the disease: relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), and MS with a progressive course with relapse (PRMS); (Lublin & Reingold, 1996). However, the rise in knowledge of MS revealed that the above-cited classification, although valuable for clinical research and theory, was reliant on patient recall and lacked biochemical and imaging connections. Lublin et al. (2014) issued an updated taxonomy of phenotypes to better reflect the complexity of disease morphologies. The new taxonomy retained many of the basic characteristics of the initially defined disease courses. However, it highlighted the importance of:

- disease activity (as opposed to inactivity), as determined by relapses and radiological activity, is defined as the presence of plaques that take contrast and/or an increase in the number or volume of lesions T2;
- disease progression during a specific time period in patients who are in a progressive stage of the illness as determined by sequential imaging and clinical assessment (appearance or lack of an evident

worsening of impairment as defined by the Expanded Disability Status Scale - EDSS) depending on exacerbation (Lublin & Reingold, 1996).

In 2014, Lublin identified two primary illness courses: relapsing-remitting and progressive. The two groups of individuals with progressive disorders may be divided into two categories based on the presence or absence of activity (new or unequivocally expanding T2 lesions and/or contrast enhancement on Magnetic Resonance Imaging (MRI) images or a clinical relapse, i.e., progressive disease with or without activity). In the following paragraphs, the basic MS phenotypes are described.

1.3.1. Relapsing-Remitting Multiple Sclerosis

The most prevalent form of MS is RRMS, which accounts for around 85% of the diagnosed patients. It is so named because it is marked by relapses, or poussées (acute attacks), in which there must be at least 24 hours of symptoms (Schumacher, Smith, & Williams, 1965), followed by an extended period of symptom remissions (complete or partial recovery) with an improvement in one's well-being (Lublin & Reingold, 1996). Relapses bring on new symptoms or intensify old ones which can be attributed to the formation of a new lesion in the myelinated sheath or the reactivation of a pre-existing injury. Over 80% of these patients are predicted to acquire SPMS. RRMS may also be classified as active or inactive (active MS causes relapses and/or new MRI activity) and worsening or not worsening (an increase in impairment with time; Lublin, 2014).

1.3.2. Primary Progressive Multiple Sclerosis

PPMS affects roughly 10% of patients with MS and refers to a degenerative disease caused by a singular demyelinating lesion of the CNS at a crucial place along the corticospinal tract of the spinal cord, brain stem, or subcortical WM. PPMS is characterized by no severe episodes but a steady and chronic impairment progression that may settle at times or continue for months or years, regardless of whether or not there is any type of recovery following episodes. Neurodegeneration is linked to relapses and remissions, especially during the transition from RRMS to SPMS, but eventually a progression-oriented picture emerges (Lublin, 2014).

PPMS can also be categorized as active (active MS causes relapses and/or new MRI activity) or inactive and as progressive or non-progressive (a progressive illness can have or not have relapses).

1.3.3. Secondary Progressive Multiple Sclerosis

The epidemiology of SPMS has changed dramatically in the past fifteen years. Epidemiological studies in patients studied in the 1980s' reported that up to 75% of RRMS patients convert to SPMS after 30 years (Tremlett, Zhao, Joseph, & Devonshire, 2008). Recent research indicates that the delay in conversion to SPMS has been prolonged since the availability of disease-modifying therapies (DMT), and thus the proportion of converting patients has decreased (Tedeholm et al., 2013; Trojan et al., 2007).

People are classified in the SPMS phenotype when there is absence of a recurrence, a confirmed ‘three strata’ disability progression at 3 months with an increase in disability in the dominant functional system, at a minimum of 4 on the EDSS, and the pyramidal functional system scored at least 2 (Lorscheider et al., 2016). In SPMS, there are isolated acute episodes, but the remission is incomplete, and the impairment develops between attacks. The frequency of acute episodes diminishes while impairment rises. SPMS can also be categorized as active or inactive (people with active MS have relapses and/or new MRI activity) and as progressive or not progressive (a progressive illness can have relapses or not).

1.3.4. Clinically Isolated Syndrome

A novel trait dubbed Clinically Isolated Syndrome (CIS) was introduced in 2013 (Lublin, 2014). The CIS, which must continue for at least 24 hours, is a symptom of MS but does not fulfill the criteria for a MS diagnosis because it does not necessarily evolve into a full-blown disorder (Lublin, 2014). It is the earliest sign of inflammation and demyelination in the CNS. It is considered a mono-focal episode if the patient experiences one symptom or sign caused by one lesion of the CNS, while it is a multifocal episode if the patient complains of more symptoms and signs and the MRI shows more lesions in different parts of the CNS. The CIS may be an isolated event with no consequences, or it may arise as a secondary episode with symptoms or lesions caused by neuronal damage (Tintoré et al., 2000). Different studies have shown that having CIS and abnormalities on an MRI of the brain makes it more likely that a person has MS. It has four clinical manifestations: optic neuritis (inflammation of the optic nerve), CIS of the brain stem, CIS of the spinal cord, and CIS supratentorial.

1.3.5. The Radiologically Isolated Syndrome

The radiologically isolated syndrome (RIS) is not considered a form of MS. Demyelination of the cerebral cortex or spinal cord may be seen on MRI scans of patients, even if they do not exhibit any neurological symptoms or have neurological exams that reveal abnormalities. Most of the time, these patients had undergone an MRI to investigate other symptoms, such as a migraine or trauma to the area, and it was discovered that they had lesions that were clinically comparable to those observed in MS patients. There are few suggestions for how to treat RIS, and more research is needed to find out what factors raise the risk of MS.

1.4. Diagnosis of Multiple Sclerosis

Formulating a diagnosis of MS is challenging as patients' symptoms can be multiple and traced back to various pathological frameworks, as there is no specific examination that can unequivocally define the presence or absence of the pathology. Nowadays, the diagnosis of MS is formulated based on several factors. The initial phase involves the collection of clinical data through a neurological examination using the McDonald criteria (2017). The McDonald criteria, originally published in 2001 and revised over the years, have been used for the diagnosis of MS in both research and clinical practice to accelerate the diagnostic process and reduce the risk of misdiagnosis (Thompson et al., 2018). The International Panel on the Diagnosis of MS reviewed the McDonald criteria in 2005, 2010, and more recently in 2017. Following clinical evaluation, patients undergo diagnostic tests (Olek & Mowry, 2018), such as the MRI, which can detect lesions (active and inactive plaques) disseminated throughout the CNS (Bertora, 2015), the sensory evoked-potential (SEP), which is able to identify damaged brain areas not visible through neuroimaging techniques (Schumacher et al., 1965), and the cerebrospinal fluid (CSF) examination, which is able to detect a distinct oligoclonal band (OCB) indicative of the existence of autoimmune disorders affecting the CNS (Johnson & Sexton, 2016; Poser et al., 1983). Nuclear magnetic resonance (NMR; Chernoff & Stark, 2010) and functional magnetic resonance imaging (fMRI; Rocca et al., 2007) are also used to find lesion burden (Chernoff & Stark, 2010) and the brain's activity (Rocca et al., 2007).

1.5. Symptoms of Multiple Sclerosis

MS is a disorder in which symptoms vary from person to person, both in severity and duration (Belgian et al., 2013), depending on the location and size of the damage in the CNS (Herndon & Horak, 2000). In the early stages of the illness, some of these symptoms may come and go, be vague, happen at any time, and may also be similar to those of other medical conditions. While most MS symptoms are associated with limitations in daily activities, the way symptoms influence such activities is unique and varies depending on the individual and the activity itself (Goverover et al., 2020). Multiple studies have classified the symptoms of MS into primary, secondary, and tertiary. Primary symptoms encompass gastrointestinal and sphincter impairments, visual impairments (i.e., optic neuritis, diplopia, and nystagmus), sensory impairments (i.e., paresthesia, dysesthesias), pyramidal impairments (i.e., hyposthenia, stiffness in one or more limbs, paraparesis or paraplegia), and cerebellar impairments (i.e., balance disturbances, dizziness, tremors, smoothness, and ataxia, dysarthria);(Baker & Tamplin, 2011; Darija et al., 2015; Ghezzi et al., 2013; Inoue & Yokoi, 2020; Olek & Mowry, 2018; Osborne & Balcer, 2018; Patejdl & Zettl, 2017; Vanzetta, 2007).

Hyposthenia in one or more limbs is the first symptom in 40% of MS patients, followed by optic neuritis (22%), a subjective sensitivity condition (such as paresthesia and dysesthesias) (21%), transverse myelitis, diplopia, dizziness, or urination problems.

Secondary symptoms include breathing difficulties (i.e., coughing, heavy breathing, hiccups), sexual disorders, urinary disorders, sleep disturbances, and fatigue (Drulovic, Kisic-Tepavcevic, & Pekmezovic, 2020; Ghezzi et al., 2013).

Among the disorders that afflict MS, sleep disturbances are of particular importance as they are quite frequent in MS and have a detrimental influence on the general health and quality of life (QoL) of MS patients (Lobentanz et al., 2004). Specifically, sleep disturbances may cause fatigue, excessive daytime sleepiness, difficulty concentrating, memory loss, cognitive impairment, mood disorders, behavioral problems, poor motivation or energy, and reduced performance in both the social and work spheres (American Academy of Sleep Medicine [AASM] 2014). According to a recent review, insomnia, sleep motor disorders, breathing sleep disorders, circadian rhythm disorders, narcolepsy-cataplexy syndrome, and rapid eye movement are the most frequent sleep disorders in MS (Allen et al., 2014; Bjorvatn & Pallesen, 2009; Braley, Segal, & Chervin, 2014; Hensen, Krishnan, & Eckert, 2018; Nishino, 2007; Sakkas, Giannaki, Karatzaferi, & Manconi, 2019). Besides sleep disturbances, fatigue is one of the most common symptoms affecting MS (Rommer et al., 2019). Fatigue can be defined as a subjective perception of tiredness, breathlessness, and loss of energy despite having performed exercise (Brenner & Piehl, 2016). The characteristics of fatigue, its causes, assessment, and treatment will be extensively dealt with in the third chapter of the present Thesis.

Tertiary symptoms include anxiety, pain, depression, and cognitive impairment (Boeschoten et al., 2017; Gill, Santo, Blair, & Morrow, 2019; Kalia & OConnor, 2005).

Among the tertiary symptoms that afflict MS, depression is of particular importance as it ranges from 30% to 40% (Boeschoten et al., 2017; Marrie, 2017). The prevalence of depression in MS seems to be lower in the progressive than in the relapsing-remitting course of MS (Zabad, Patten, & Metz, 2005). Psychological aspects and pathophysiological processes have been individuated as factors that may interplay and explain the frequency of depression in MS (Dalton & Heinrichs, 2005; Siegert & Abernethy, 2005). Psychological factors such as social support, coping strategies, stress, self-knowledge, and perception of the disease would influence the modulation of the onset of depression (Arnett, Barwick, & Beeney, 2008). The pathophysiological processes of depression in MS patients are still being debated. Studies have shown that depression may be due to cortical lesions and structural damage in brain networks that are involved in emotional processing (Nunnari et al., 2015; Rocca et al., 2018).

Besides depression, cognitive impairment is another frequent symptom of MS. Cognitive impairment can occur even at an early stage of the disease and is considered one of the main sources of neurological disability in MS patients due to its severe impact on people's quality of life (Pitteri et al., 2019). The cognitive deficit in MS, its causes, assessment, and treatment will be extensively dealt with in the fourth chapter of the present Thesis.

1.6. Treatment of Multiple Sclerosis

Currently, there is no pharmacological treatment that may entirely eliminate the illness; hence, in MS it is advisable to employ a blend of pharmacological and non-pharmacological interventions. Current therapies aim:

- to reduce the duration and severity of relapses by administering "attack therapy" during an acute phase.
- to prevent relapses and slow the course of the illness.
- to control comorbidities (e.g., psychiatric disorders, vascular diseases).
- to control patients' symptoms (e.g., rigidity, urinary dysfunction, fatigue, mood problems).
- to provide psychological support.
- to enhance patients' QoL and employment opportunities through rehabilitation techniques and lifestyle changes.

1.6.1. Pharmacological treatment

Until recently, MS sufferers had limited options for easing their symptoms. In recent years, there has been a significant increase in the number of drugs that may reduce the frequency and severity of relapses in MS patients. DMT is a treatment for MS that aims to reduce the frequency and severity of relapses, mitigate short-term disability (McGinley, Goldschmidt, & Rae-Grant, 2021), and reduce the progression of disabilities (Filippi et al., 2021). The existing DMTs, which work by reducing inflammation, exhibit a variety of mechanisms of action, routes of administration, and levels of effectiveness. Among the DMTs approved to treat RRMS or active SPMS, there are:

Injectable medications. Among injectable medications, there are Interferons (Interferon Beta 1a and Beta 1b) and Glatiramer acetate, which are immunomodulatory drugs and anti-inflammatory agents that reduce the rate and severity of relapse, and impede the progression of neurological disability.

Oral medications. Oral medications encompass S1PR modulators (fingolimod, siponimod, ozanimod, and ponesimod), fumarates, teriflunomide, and cladribine. These medications function by reducing the number of circulating lymphocytes and limiting the migration of inflammatory cells into the CNS. S1PR modulators display variability in their efficacy in reducing relapse rates among MS patients (McGinley et al., 2021).

Ponesimod, a second-generation medication, is employed for the treatment of adults with relapsing forms of MS. Clinical studies have demonstrated that ponesimod effectively prevents relapse in individuals diagnosed with RRMS and exhibits greater efficacy when compared to teriflunomide. Nevertheless, data from extensive studies on the long-term effectiveness and safety of the treatment and more direct comparative analyses with alternative DMTs are required (Alnaif, Oiler, & D’Souza, 2022).

Fumarates (dimethyl fumarate and diroximel fumarate) are anti-inflammatory and neuroprotective therapies that reduce relapse rates and impede the advancement of disability in RRMS (Cross & Riley, 2022). Teriflunomide is an immunomodulatory drug with anti-inflammatory properties. It works by inhibiting enzymes, thereby preventing lymphocyte proliferation, immunological response, and nerve damage associated with relapses. Teriflunomide reduces the frequency of relapses and delays the progression of disabilities. It is often used for newly diagnosed patients who cannot be treated with either interferon or glatiramer acetate (Tilly et al., 2021).

<u>Cladribine</u> is an immunosuppressant with selective action indicated for the treatment of adult patients with MS who exhibit a high degree of disease activity defined by clinical features or diagnostic imaging. It represents a significant advancement in the treatment of patients with relapsing forms of MS, as it is the first oral therapy to be approved with a short-course, limited-cycle dosing schedule. Clinical studies have shown that cladribine exhibits efficacy in treating different manifestations of RRMS (Rammohan et al., 2020).

Monoclonal antibody infusions. Monoclonal antibody infusions have higher efficacy than intravenous and oral DMTs (Hauser et al., 2017). Within the realm of monoclonal antibody infusions, there are several notable options. Natalizumab, for instance, operates by mitigating relapses and the progression of disability in RRMS patients. Alemtuzumab, on the other hand, stands as an efficacious and well-tolerated pharmaceutical agent employed specifically for the treatment of highly aggressive RRMS cases (Rammohan et al., 2020; Syed, 021).

Ofatumumab demonstrates its efficacy by significantly reducing the annualized recurrence rate, MRI-detected lesion activity, and disability progression associated with MS (Kang & Blair, 2022). Lastly, Ocrelizumab is the only DMT to have garnered approval for the treatment of progressive forms of MS (Rammohan et al., 2020). Lately, the Food and Drug Administration (FDA) has approved new medicines known as "immune reconstitution therapy (IRT)", that have the potential to achieve long-term remission with improved compliance and reduced adverse effects (Karussis & Petrou, 2018). Therapeutic interventions that facilitate the process of remyelination possess the capacity to decelerate or even reverse the progression of disability. Numerous potential targets for therapeutic intervention in early aggressive MS are presently being examined, one of which is autologous hematopoietic stem cell transplantation (Simpson, Mowry, & Newsome, 2021).

In MS, several symptomatic treatments are also available. Pharmacological therapy may alleviate several MS symptoms, including spasticity, pain, cognitive impairment, bladder and bowel issues, gait dysfunction, mood dysregulation, and sleep disturbance (Doshi & Chataway, 2017). Fampridine is one of the symptomatic treatments utilized for the management of symptoms associated with MS. At therapeutic dosages, this intervention has been found to be safe while also demonstrating significant impacts on ambulatory function for short distances (Ghorbanpour, Rahimibarghani, Rohani, Rastkar, & Ghajarzadeh, 2023; Valet et al., 2019).

1.6.2. Non-pharmacological treatment

As for non-pharmacological treatment, rehabilitation is the cornerstone of MS treatment. Its advantageous outcomes have been demonstrated in various research studies in the following domains: motor, swallowing, speech, cognitive, and fatigue (DeLuca, Chiaravalloti, & Sandroff, 2020; Donzé & Massot, 2021). Among the rehabilitation treatments, kinesiotherapy is often recommended to MS patients suffering from spasticity, though data supporting its effectiveness is lacking (Blanchard-Dauphin & Allart, 2017). Secondary symptoms such as fatigue can be improved with exercise, psychoeducation, and psychological interventions (Blanchard-Dauphin & Allart, 2017). Mindfulness interventions show beneficial effects on QoL, mental health, fatigue, balance, and pain and are promising interventions for MS patients (Simpson et al., 2014). In recent times, there has been a proliferation of emerging technologies that offer the potential to enhance the management of disabling symptoms (Centonze, Leocani, & Feys, 2020). Among these are whole-body cryotherapy (WBC), functional electrical stimulation (FES), and non-invasive brain stimulation (NIBS). Specifically, NIBS is an innovative neuromodulator technique that has demonstrated favorable therapeutic outcomes for various neurological disorders and, in the context of MS, has exhibited both safety and efficacy in alleviating MS-related fatigue. Further investigation is warranted in the realm of alternative treatment modalities, given their apparent efficacy and minimal occurrence of adverse effects.

2. EXPLORING FATIGUE

2.1. Historical perspective

Fatigue has been an integral part of human life since ancient times. In pre-modern times, fatigue was an everyday occurrence, like drowsiness or hunger, and was not considered an unpleasant source of complaint (Hockey, 2013).

The initial medical depiction of fatigue as a symptom emerged towards the conclusion of the 1800s, coinciding with the emergence of the term "neurasthenia" (Léotard, 2021), a broad term encompassing various conditions and causes, such as depression, psychosis, or fatigue (Torres-Harding & Jason, 2005). In the late nineteenth century, several disorders (such as DaCosta's condition, neurocirculatory neurasthenia) included unexplained fatigue as a key symptom (Torres-Harding & Jason, 2005), with fatigue being ascribed to a combination of organic (e.g., disease or overwork) and physical factors (e.g., psychogenic or personality factors) (Muncie, 1941). The topic of fatigue received significant attention during the Industrial Revolution. At that time, there was a rise in the rate of labor, increased control over work, and attention to time-oriented processes (2013); in a high-demand workplace, employees started to work less as they felt tired (Torres-Harding & Jason, 2005). Fatigue received considerable attention due to its association with reduced performance and productivity among factory workers (Torres-Harding & Jason, 2005). Therefore, with the advent of the Industrial Revolution, the societal view of fatigue started to take on a negative cultural connotation and to be perceived as a sickness characteristic of contemporary times (Hockey, 2013). From this point forward, studies into the phenomenon of fatigue begin to emerge (Hockey, 2013).

Over the years, several theoretical frameworks have been developed, and much empirical research on fatigue has been carried out. The first research focused on sleep deprivation as a major contributor to fatigue, and various studies began looking into fatigue as a clinical result of neurological illnesses (Hockey, 2013). Several academic disciplines, including psychology, cognitive neuroscience, human factors and engineering, exercise physiology, biology, the medical sciences, and ergonomics, have investigated fatigue in recent years. For instance, in the field of exercise physiology, fatigue has been described as a temporary decline in exercise performance that results in the incapacity to generate maximal force output, which may be attributed to the accumulation of metabolites or depletion of substrate (Gibson & Noakes, 2004). Instead, biologists have mostly looked at fatigue in the context of sleep-wake regulation, with a focus on fundamental processes like subjective perception, well-being, cognitive function, and neurophysiology. Ergonomics has interpreted fatigue as evidence that the human body is unable to adequately meet the requirements of today's workplaces. Despite fatigue having been extensively studied for a long time in various disciplines, there is no consensus on the core term. Indeed, the definition of fatigue varies depending on the study field, and, across studies, no well-developed theory has been described. The several terms used to describe fatigue have led to misunderstandings and poor communication, which have hampered knowledge acquisition and cooperation across research fields.

2.2. Why is fatigue a social problem?

According to recent research, fatigue is one of the most common complaints in outpatient visits, and it is often a key driving factor for individuals who actively seek medical attention from their primary care physician (Maisel, Baum, & Donner-Banzhoff, 2021). It has been estimated that about one in ten people experiences chronic fatigue that lasts longer than six months (Byung-Chul, 2014). Numerous studies have indicated that fatigue has a significant impact on several aspects of people's lives, including their general physical and mental well-being, physical and mental health, safety, and also on the broader economic context (Fan & Smith, 2017; Kapur & Webb, 2016). Fatigue can compromise immune function, increase vulnerability to mental and chronic illnesses, and lead to adverse effects on both personal and professional relationships. Individuals experiencing fatigue may require medical evaluation, the potential administration of pharmacological agents, and the implementation of specific therapeutic approaches. The implementation of these interventions can impact individual and familial financial funding as well as the overall economic resources allocated for investments and consumption. Consequently, this may result in an escalation of healthcare expenditures.

In the contemporary workplace, employees are required to continuously enhance their competencies, manage their time effectively, possess soft skills, and consistently display strong motivation. People trying to meet such high standards can feel fatigued due to the associated pressure. The state of fatigue within the present-day occupational setting can exert a detrimental influence on the well-being and performance of employees. Fatigue impedes an individual's capacity to engage in creative, innovative, and flexible thinking and increases people's susceptibility to errors, leading to a notable reduction in worker productivity and a decline in the quality of output (Sadeghniiat-Haghighi & Yazdi, 2015). Moreover, fatigue may lead to employee turnover, increased absence due to illness, and time off requests (Bidasca & Townsend, 2014). These phenomena can have negative consequences for businesses, limiting profits and overall economic efficiency (McCrone, Darbishire, Ridsdale, & Seed, 2003; Reynolds, Vernon, Bouchery, & Reeves, 2004).

In the workplace, fatigue can also endanger people's safety, as fatigued individuals may be more prone to making mistakes that jeopardize their own well-being as well as that of others. In this context, fatigue contributes significantly to fatalities and injuries, particularly in high-stress circumstances (Spurgeon et al., 1997). According to Spurgeon et al. (1997), in a working setting, there are primarily two reasons why fatigue jeopardizes safety. First off, being tired makes it harder for someone to perceive and respond to new information (Lorist et al., 2000; Reiner & Krupinski, 2011); second, fatigue impairs a person's capacity to assess danger; therefore, fatigued people unconsciously take a larger risk than under normal circumstances (Tixier et al., 2014). Several studies have shown that specific occupations requiring prolonged working hours, disruption of circadian rhythms, and inadequate sleep have the potential to lead to or exacerbate fatigue (Sadeghniiat-Haghighi & Yazdi, 2015). Studies have demonstrated that fatigued shift workers are often involved in catastrophic accidents (Sadeghniiat & Haghighi et al., 2013). Accidents can result in a disruption of productive activities, additional costs for healthcare and compensation, as well as a decrease in worker confidence and the image of the involved companies.

The phenomenon of fatigue can potentially exert an influence on the realm of public safety as well. According to some studies, fatigue is a major cause of transport accidents (Williamson et al., 2011). In the United States, fatigue has been found to be a significant factor in over 1500 fatalities, 100,000 motor vehicle accidents, and 76,000 injuries on a yearly basis (Caldwell et al., 2008). Several studies have shown that transport operators such as seafarers, truck drivers, and bus drivers facing increased workloads and fatigue are at a higher risk of being involved in accidents (Smith, Allen, & Wadsworth, 2008).

Fatigue not only affects healthy individuals, but it also has adverse consequences for individuals who suffer from various pathologies. Fatigue in patients may elicit a sense of despair as it impacts domestic, social, and professional domains. In individuals affected by pathological conditions, fatigue can exacerbate and worsen an already marked symptomatology, thus resulting in a notable escalation of consequential limitations in patients' functional activity. These impairments can interfere with patients' recreational pursuits, social responsibilities, and occupational standing (Jason & Choi, 2008), often leading to an increased burden on healthcare systems and significant social and economic costs for societies. Reynolds et al. (2004) estimated that US household and labor productivity losses due to fatiguing illnesses, like chronic fatigue syndrome (CFS), cost $9.1 billion annually.

The above considerations make it clear that fatigue is a societal issue and call for measures able to prevent or reduce the pervasive effects that it has on different aspects of individuals' everyday lives and communities. Public education initiatives, employment guidelines that prioritize balancing work and personal life, regulations pertaining to road safety, and the provision of healthcare and social support systems may be useful in this regard. Through the acknowledgement and implementation of measures aimed at mitigating the effects of fatigue, it is plausible to enhance the welfare of individuals, promote social interactions, and cultivate a more robust and efficient society.

2.3. Defining fatigue

2.3.1. Multiple definitions of fatigue

The term fatigue is commonly used to describe a prevailing sensation of extreme tiredness, diminished vitality, a state of complete depletion (Shen, Barbera, & Shapiro, 2006), or drowsiness that arises from inadequate sleep, prolonged periods of mental or physical exertion, stress, and anxiety. Fatigue is characterized by a reduced capacity to effectively manage perceived pressures (e.g., Aaronson et al., 1999; Dantzer, Heijnen, Kavelaars, Laye, & Capuron, 2014; Micklewright, St Clair Gibson, Gladwell, & Al Sal-man, 2017), resulting from a state of lassitude or depletion of mental and/or physical energy (Gander et al., 2011; Hallowell et al., 2010) that has disabling effects on both physical and cognitive functions. In the scientific literature, the expression fatigue is employed to depict a variety of distinct, occasionally interconnected occurrences, including localized and whole-body physical fatigue (Chaffin, 1973), lack of sleep (Shen et al., 2006), and mental fatigue (Van der Linden, Frese, & Meijman, 2003). The multidimensional nature of fatigue leads to a lack of a universal definition (Ericsson et al., 2013) and the emergence of numerous definitions (Pattyn, Van Cutsem, Dessy, & Mairesse, 2018). "Lack of energy," "reduced consciousness," "lack of motivation," "tiredness," "sleepiness," “diminished vitality,” "asthenia," "lassitude," "general weariness," “sense of depletion”, and "exhaustion" are just a few terms found in literature to indicate fatigue.

Accordingly, these various definitions of fatigue cause semantic ambiguities, misunderstandings, poor communication, and poor cooperation across researchers, hampering knowledge acquisition (Pattyn et al., 2018; Skau et al., 2021).

The lack of a well-defined conceptualization of the phenomenological encounter with fatigue poses challenges in accurately assessing it, consequently impeding a comprehensive comprehension of the phenomenology associated with fatigue (Dittner et al., 2004). As a result, the existing knowledge regarding fatigue has remained scattered, fragmented, and lacking in organization, and a comprehensive understanding of fatigue has not been universally embraced by the entire research community. Therefore, there is a critical need to develop a common terminology for fatigue, to characterize the phenomenon, to devise a structured methodological approach to conduct an accurate evaluation of fatigue, and to devise efficacious interventions (Enoka & Duchateau, 2016; Kluger et al., 2013).

2.3.2. Sleepiness, boredom, apathy, and fatigue: overlapping symptoms or distinct constructs?

In the absence of a universally accepted definition of fatigue, it is nonetheless possible to engage in a debate regarding what fatigue is. In our daily lives, people frequently encounter states such as drowsiness, boredom, and fatigue. Even though fatigue, sleepiness, and boredom are distinct constructs, they have frequently been employed interchangeably as they may exhibit some degree of interconnectivity.

Sleepiness is a biological reaction, a sensation of lethargy that signifies an intense requirement for rest. It develops in response to an increase in sleep demand and is controlled by the body's natural 24-hour cycle. The state of being sleepy can be impacted by various factors, including insufficient sleep, sleep-related ailments, pharmacological agents, or specific pathological states. The phenomenon is frequently linked to a reduction in vigilance, challenges in maintaining wakefulness, and a strong inclination to enter a state of somnolence. According to Duntley (2005), although sleepiness and fatigue exhibit overlapping symptoms, they must be considered distinct phenomena as they arise from independent neurophysiological mechanisms.

Contrary to sleepiness, fatigue is a comprehensive concept that encompasses a sensation of utmost weariness, absence of vitality, and depletion due to physical or mental strain. It is linked to periods of activity, insufficient rest or sleep, psychological pressure, or pre-existing medical ailments. In contrast to sleepiness, fatigue is alleviated by rest rather than sleep itself (Mairesse et al., 2019), it is not characterized by sleepiness signs such as heavy eyelids, yawning, and drifting off and may arise from diverse factors beyond the mere necessity for sleep.

Boredom is a psychological state characterized by a feeling of disinterest, apathy, restlessness, or discontentment due to a lack of stimulation or engagement, which subsequently results in a reduction in the level of self-directed or voluntary attention (Hockey, 2013). The phenomenon of boredom is associated with motivation and the dilemma of whether to persist with or avoid a particular task. As per existing literature, the experience of boredom frequently emerges in situations where the environmental stimuli are limited, resulting in a condition of reduced cognitive load (Hockey, 2013; Pattyn, Neyt, Henderickx, & Soetens, 2008). Fatigue and boredom are comparable mental conditions; however, it is imperative to regard them as discrete occurrences. Fatigue, unlike boredom, can arise due to physical or mental strain, prolonged stress, inadequate rest or sleep, or underlying medical conditions. According to some researchers, distinguishing between boredom and fatigue can potentially be comprehended by considering the disparity in the level of arousal elicited by the perceived requirements of the task. According to Pattyn et al. (2008), boredom may arise from low work demands, also known as 'underload', while fatigue may be elicited by high work demands.

Apathy is defined as a lack of motivation to initiate action and interest, including behavioral/social, cognitive, and emotional components (Ang et al., 2017; Kuppuswamy et al., 2017). Fatigue is linked to deficiencies in activation-related systems, where individuals experience a desire to initiate action but perceive an inability to do so. Apathy and fatigue are both associated with impairments in self-initiated, goal-directed behavior, although Kuppuswamy (2017) suggested that the distinction between apathy and fatigue may be intricately linked to their respective effects on motivational components. A noteworthy finding from a study conducted by Ang et al. (2017) indicates that apathy and fatigue may exhibit variations depending on the level of emotional involvement. Fatigue is linked to emotional experiences, suggesting that it is a construct heavily influenced by affective factors, whereas apathy appears to be associated with a tendency to withhold emotional investment.

2.4. Understanding the complex phenomenon of fatigue

2.4.1. Characteristics of fatigue

In relation to fatigue characteristics, sufferers commonly report various qualitative facets of weariness, including emotional manifestations (lack of interest and desire), mental (lessened cognitive function and performance), behavioral (lessened efficiency), and physical (e.g., muscular stiffness) aspects (Maisel et al., 2021). For instance, Aaronson et al. (2003) undertook a comprehensive inquiry on fatigue in healthy individuals. The authors suggest that fatigue may cause physical, emotional, mental, and behavioral symptoms, signaling the need for rest, sleep, or reprioritization. In their study, participants indicated that a healthy lifestyle with enough sleep, a healthy diet, physical exercise, a positive outlook, and social support could prevent fatigue over time. As for the triggers of fatigue, studies are conflicting. While some evidence indicates that fatigue may manifest without any discernible underlying cause (Torres-Harding & Jason, 2005), others indicate that several factors can contribute to fatigue. Within this set are an individual's duration of wakefulness, workload demands, stress, personal health status, lifestyle choices, medication or substance abuse, situational circumstances, insufficient sleep, and physical activity.

As for the relationship between age, gender, ethnicity, and fatigue in healthy subjects, studies have shown mixed results. According to some research on the relationship between age and fatigue, there is no significant difference in fatigue levels between older and younger individuals (Yoon, Schlinder-Delap, & Hunter, 2013); however, other studies have found conflicting results (Al-Mulla, Sepulveda, & Colley, 2011).

As for the impact of gender on fatigue, some studies have indicated that females are more prone to experiencing fatigue (Loge et al., 1998; Nisenbaum et al., 1998) and to reporting more intense fatigue compared to males (Loge et al., 1998; Nisenbaum et al., 1998). However, other studies did not confirm the above-mentioned results (Buchwald, Pearlman, Kith, & Schmaling, 1994).

Several studies on ethnicity and fatigue have posited that individuals belonging to minority groups are more likely to experience fatigue and stress due to discriminatory and prejudiced attitudes toward them (Shulz et al., 2000; Torres-Harding et al., 2002). Dinos et al. (2009) conducted a narrative synthesis and meta-analysis of population studies in the United States, revealing a greater prevalence of chronic fatigue in certain ethnic minority groups when compared to individuals of white ethnicity.

2.4.2. Environmental factors as potential contributors to fatigue onset

Numerous environmental factors have been identified as potential contributors to fatigue. Within this set, there are noise, light, temperature, elevated workload, social environment at the workplace, workplace design, diet, lifestyle factors, emotional predisposition, distress, and sleep deprivation.

Noise. Noise pollution is a phenomenon that involves the exposure to unwanted or harmful sound that can interfere with regular activities (Syaiful, 2022). Prolonged or excessive exposure to high decibel levels or uninterrupted sound has been linked to a variety of adverse health outcomes, including low sleep quality, daytime sleepiness, cognitive and physiological depletion, diminished efficiency, and fatigue (Landström & Lundström, 1985; 1987). Prolonged exposure to elevated levels of auditory stimuli may impede an individual's ability to concentrate and focus, resulting in mental fatigue and diminished cognitive aptitude. For instance, Kjellberg et al. (1998) demonstrated that prolonged exposure to low-frequency noise results in mental fatigue among airplane mechanics and boat patrol crews. Research suggests that nocturnal noise can disrupt the intrinsic circadian rhythm of the human body, leading to reduced sleep quality and increased daytime fatigue (Fontana, Tserga, Sarlus, Canlon, & Cederroth, 2019). Some studies indicate that exposure to prolonged noise is linked to elevated levels of cortisol, a stress hormone that may lead to fatigue and other adverse health consequences (Zare et al., 2019).

Light. Various field studies have demonstrated that lighting is an environmental factor that can affect the mental health and productivity of office employees (Mills, Tomkins, & Schlangen, 2007; Smolders, De Kort, Tenner, & Kaiser, 2012). Several studies have found a positive correlation between inadequate illumination and subjects' fatigue (Park & Gotoh,1993). For instance, Maas, Jayson, and Kleiber (1974) investigated the impact of various spectrums of environmental illumination on subjects' fatigue levels. They did not identify significant disparities in the self-reported states among participants; nevertheless, objective assessments revealed a decrease in perceptual fatigue and an enhancement in visual acuity upon exposure to lighting that closely resembled the spectral quality of natural sunlight as opposed to conventional cool-white lighting.

Temperature. The occurrence of fatigue in certain individuals can be attributed to extreme temperatures, whether they are excessively high or low (Andriani, 2016). Some studies indicate that the incidence of physical fatigue is heightened by extreme temperatures, specifically those falling below 35 F and above 95 F (Gonzalez-Alonso, 1999; Zivin & Shrader, 2016). Studies on the exposure of individuals to low temperatures indicate that cold temperatures can cause vasoconstriction, reducing the delivery of oxygen and blood to muscles and other tissues. This phenomenon may result in physical fatigue, particularly in peripheral body parts such as the distal upper and lower limbs (Castellani & Young, 2016). Gonzalez-Hidalgo et al. (2011), in their study, found that healthy individuals experienced increased fatigue levels in environments characterized by high air temperatures and humidity. Fuji and colleagues (2015) investigated the impact of increasing air temperature on fatigue and sleep quality among a sample of healthy individuals in Japan during three time points in the summer season. This study demonstrated that elevated temperatures affected the quality of sleep, thereby producing fatigue, among a group of healthy participants. No significant correlation was found between fatigue score and temperature in individuals reporting good sleep quality. However, in individuals reporting poor sleep quality, fatigue levels were observed to increase at higher temperatures (Fujii, Fukuda, Narumi, Ihara, & Watanabe, 2015).

Workload. Several studies have been conducted on the relationship between fatigue and workload, a prevalent issue in industrialized settings (Kodz et al., 2003). Studies indicate that elevated work demands, extended work hours, and psychological strain may lead to the development of both mental and physical fatigue, which can have adverse effects on an individual's physical and mental health (Åkerstedt et al., 2002). In situations where the amount of work is significant, individuals may experience a sense of urgency to perform tasks with speed and efficacy, thereby resulting in psychological strain and mental fatigue (Ribet & Derriennic, 1999). According to Ribet and Derriennic (1999), excessive workloads have an adverse effect on individuals sleep patterns, thereby impeding the recuperation process and leading to the accumulation of fatigue debt. Furthermore, individuals that need to face a substantial number of mandatory tasks and are not provided with the choice of less demanding alternatives can develop psychological fatigue due to a disparity between the effort exerted and the rewards received (Boksem et al., 2008). Moreover, individuals who are burdened with an overwhelming amount of work may encounter challenges in achieving a satisfactory equilibrium between their professional obligations and other domains of their existence, such as familial, social, or recreational pursuits (Baulk et al., 2009; Folkard & Tucker, 2003). This phenomenon may result in heightened levels of stress and fatigue, particularly in cases where individuals perceive a lack of agency regarding their work schedules or workload. Several studies on the relationship between fatigue and overtime have demonstrated that when employees are compelled to work beyond the regular working hours in a setting that is beyond their jurisdiction, have to undertake tasks that are exceedingly arduous, or perceive the additional remuneration as inadequate recompense, they feel the most profound mental fatigue, job dissatisfaction, occupational burnout, unfavorable work-life balance, and delayed recuperation (Beckers et al., 2008; Van Der Hulst & Geurts, 2001).

Social environment at the workplace. Numerous investigations have been undertaken to explore the intricate interplay between fatigue and the social environment at work (Tepper, 2000; Zapf & Gross, 2001). Most workers spend one-third to one-half of their waking hours at work. Some studies indicate that relationships with co-workers, supervisors, and subordinates can influence mental fatigue (Bültmann et al., 2001). Hardy et al. (1997) observed that workplace confrontations and adverse situations can lead to mental fatigue. Workplace abuse, such as regular harassment or abusive monitoring, may produce significant mental fatigue (Tepper, 2000; Zapf & Gross, 2001). Job uncertainty, limited autonomy, and high emotional demands have also been found to contribute to subjects' mental fatigue (Taris et al., 2007).

Workplace design. Empirical studies have demonstrated that the physical surroundings have the potential to impact the degree of mental fatigue experienced by individuals. Numerous studies have indicated that contextual and ambient factors, such as office arrangement, indoor vegetation, or external vistas, can rejuvenate office employees and facilitate their recovery from stress or mental fatigue (e.g., Dijkstra, Pieterse, & Pruyn, 2006; Veitch, 2011). This suggests that the design of the workplace is a crucial factor that can affect employees' performances and their level of mental fatigue. Inadequate ergonomics, such as the provision of uncomfortable chairs, incorrect desk height, or the adoption of awkward postures, can have a considerable impact on the level of fatigue experienced by workers (Yazuli, Karuppiah, Kumar, Tamrin, & Sambasivam, 2019).

Diet. Several studies indicate that diet can play an important role in the onset of fatigue, as it can affect energy levels and overall health. Studies indicate that fatigue may result from malnutrition, dehydration, excessive use of caffeine or alcohol (Ho et al., 2013; WHO, 2003), a diet missing iron, vitamins B12 and D, magnesium, omega-3 fatty acids, or based on excessive sugar consumption (Pharr, 2010). For instance, the state of dehydration has the potential to induce fatigue and hinder both bodily and cognitive capabilities (WHO, 2003). As for the consumption of caffeine, studies are mixed. While some studies have demonstrated the potential of caffeine to enhance mood, alertness, and concentration and to mitigate the adverse effects of mental fatigue on both physical and cognitive capabilities (Azevedo et al., 2016; Van Cutsem et al., 2018), others have found that excessive intake or consumption of caffeine during the late hours may disrupt sleep and intensify fatigue in certain individuals (Ho et al., 2013).

Moreover, several studies have indicated that sensitivity or dietary allergies, such as to mercury and nickel, may also induce fatigue (Sterzl et al., 1999).

Lifestyle factors. Lifestyle factors refer to the various behaviours and habits that individuals engage in their daily lives. As per certain research, several lifestyle factors are noteworthy risk factors for the emergence of fatigue and psychological distress among people. In a longitudinal study conducted by Bültmann et al. (2002), a robust association was discovered between the minimum level of physical activity during leisure time and fatigue in men. Moreover, the study revealed that fatigue onset is positively correlated with being overweight and abstaining from alcohol consumption, while no significant association was observed between smoking and fatigue onset in men.

Emotional predisposition and distress. Some studies indicate that the manifestation of fatigue is subject to individual variability based on one's emotional disposition. For instance, a field study conducted by Bültmann et al. (2001) examined a sample of 11,020 workers from distinct companies. The study revealed that individuals who exhibit a higher propensity for negative emotions are more susceptible to experiencing mental fatigue as compared to those who are less emotionally susceptible. Studies indicate that fatigue is frequently intensified during periods of heightened stress. For instance, Ala-Mursula and colleagues (2005), in a study involving 16,139 public sector employees, found that stressful conditions could hasten the onset of fatigue, particularly among individuals who were emotionally susceptible (Ala-Mursula, Vahtera, Linna, Pentti, & Kivimäki, 2005).

Sleep deprivation. Sleep deprivation is a growing concern in contemporary society. Sleep deprivation is a consequence of irregular schedules and competing priorities that undermine the quality and quantity of sleep and is a significant factor contributing to both physical and mental fatigue (Åkerstedt, 1990; Bliwise et al., 1992). According to Dawson and McCulloch (2005), sleep deprivation is considered a significant antecedent to fatigue. According to the authors, the extent of sleep obtained by a worker in the 24-48 hours preceding a shift can serve as a reliable predictor of fatigue. The authors contend that pre-work sleep patterns are a more reliable predictor of occupational fatigue than on-the-job observations. Apart from fatigue, sleep disturbance results in compromised physical performance, reduced job contentment, heightened stress, and disrupted subsequent sleep cycles (Harrison & Horne, 2000; Philibert, 2005). A comprehensive examination carried out on a cohort of healthy young adults has revealed a significant correlation between non-restorative sleep and various manifestations of daytime dysfunction. These include both objective indicators and subjective perceptions, such as diminished performance on behavioral assessments of executive functioning and heightened levels of fatigue reported on a daily basis (Tinajero et al., 2018).

2.5. Taxonomy of fatigue

An enduring inquiry persists regarding the conceptualization of fatigue and its subjective experience. To fully comprehend fatigue, it is imperative to acknowledge its multidimensional nature. The following is a concise overview of traditional dichotomies pertaining to fatigue that are commonly discussed in literature.

Physiologic vs. Pathological

Physiologic fatigue is an acute, transient, non-pathological symptom that can be attributed to a specific cause and can be alleviated through the treatment of the underlying condition. Typically, physiologic fatigue endures less than three months and can be attributed to a discernible cause, such as exercise, an acute febrile or flu-like illness, work, mental stress, overstimulation or under stimulation, jet lag, active recreation, boredom, sleep deprivation, or an endocrinopathy. This form of fatigue is typically self-limiting, and it does not impede the routine tasks and duties of an individual (Kluger, 2013).

Pathological fatigue is a more intense form of fatigue compared to the physiological fatigue commonly experienced by individuals who are in good health, and it is hard to eradicate. It is characterized by heightened intensity and is usually long-lasting. Pathological fatigue is a common experience among individuals with chronic illnesses, and it is often considered part of the condition. Patients with Parkinson disease (PD; Herlofson & Kluger, 2017), brain injury (Mollayeva et al., 2014), post-polio syndrome (Trojan & Cashman, 2005), stroke (De Doncker et al., 2018) MS (Lerdal, Gulowsen Celius, Krupp, & Dahl, 2007; Schwid, Covington, Segal, & Goodman, 2002), systemic lupus erythematosus (SLE; e.g., Jacobson, Gange, Rose, & Graham, 1997), rheumatoid arthritis (RA; e.g., Nikolaus et al., 2013), and patients undergoing cancer treatment (Bower, 2014) may report fatigue.

Central vs. Peripheral

Central fatigue can be characterized as a reduction in maximal voluntary contraction (MVC) during isometric, isokinetic, or dynamic exercise in the absence of task failure (Finsterer & Mahjoub, 2014). Peripheral fatigue refers to the inability to maintain force or power output due to a breakdown in neuromuscular transmission, sarcolemma excitation, or excitation-contraction coupling.

Acute vs. Chronic

Fatigue can be classified into two distinct categories, namely acute and chronic (Canadian Centre for Occupational Health and Safety, 2017). Acute fatigue is a transient and brief condition of weariness that commonly arises due to physical or mental strain, insufficient sleep, or stress and can be ameliorated within a brief period by identifying and addressing the root causes and engaging in activities that promote rest, sleep, and relaxation. Chronic fatigue is a condition that is distinguished by enduring and prolonged sensations of physical and mental fatigue that persist for a prolonged duration, usually lasting for not less than six months. The condition is not alleviated by periods of rest or sleep and can have a substantial effect on an individual's daily activities.

State vs. Trait

State fatigue refers to a temporary and subjective feeling of fatigue or task-related fatigue (Behrens, Broscheid, & Schega, 2021; Enoka & Duchateau, 2016; Gruet, 2018), which causes an abrupt and brief decrease in physical or mental performance that changes over time and can be affected by both internal and external factors. Trait fatigue, which lasts weeks or months, is usually stable and is caused by primary disease-related mechanisms (e.g., neurodegeneration, inflammation) and secondary mechanisms (e.g., depression, sleep problems, medication, e.g., Enoka & Duchateau, 2016; Marrelli, Cheng, Brophy & Power, 2018). It refers to the steady state of an individual, which reflects a general condition that is unrelated to external obstacles and does not change substantially over time. The existing studies have mostly focused on trait fatigue.

Subjective vs. Objective

Subjective fatigue, or perceived fatigability, encompasses any alteration in perception that contributes to the regulation of the individual's performance (Enoka & Duchateau, 2016). It is common for the subjective aspect of fatigue to be erroneously combined with or used interchangeably with constructs such as the perception of effort (Marcora, 2019). Although there is a connection between them, it is important to note that the perception of effort and fatigue are separate constructs (Halperin & Emanuel, 2020), as proved by empirical evidence. For instance, the sensation of fatigue may be encountered following a period of physical effort, even during periods of rest. However, the perception of effort cannot be experienced in the absence of purposeful action (Micklewright et al., 2017).

Objective fatigue, or performance fatigability, offers a more impartial evaluation of the effects of fatigue on mental and physical performance. It describes the quantification of an individual's physical or cognitive ability to perform work (Enoka, Almuklass, Alenazy, Alvarez, & Duchateau, 2021) and refers to a decline in performance that is dependent on both the person and the specific task at hand. Objective fatigue and subjective fatigue may not always correspond, owing to various factors.

Physical vs. Mental

The differentiation between physical and mental fatigue is discussed in both the scientific literature pertaining to individuals in good health and those afflicted by chronic conditions. The differentiation between physical and mental fatigue constitutes a primary area of focus within this thesis and, as such, will be thoroughly examined in the subsequent paragraphs.

2.6. Physical and mental fatigue: a remarkable dichotomy

The term physical fatigue, or motor fatigue, pertains to the state of bodily exhaustion and arises from rigorous physical exertion (Alonso, Esteban, Useche, & López de Cózar, 2016). It is a transient reduction in physical capabilities as subjectively or objectively observed (Dotan, Woods, & Contessa, 2021). Physical fatigue is characterized by a decline in muscular strength, decreased endurance, compromised coordination, and discomfort throughout the body (Pasupathy & Barker, 2012; Shen et al., 2006).

A decrease in strength during prolonged muscular contractions affecting endurance performance and motor skills, for example, might indicate the onset of physical fatigue (Bigland-Ritchie, Cafarelli, & Vollestad, 1986). There is evidence indicating that physical-demand tasks, including lifting, pushing, and carrying, are factors that most frequently lead to physical fatigue (Steege, Drake, Olivas, & Mazza, 2015).

According to several studies, the changes in physical performance have been ascribed to both central and peripheral alterations of neuromuscular function that govern the transmission of muscle action potentials (Allen, Lamb, & Westerblad, 2008; Cheng, Place, & Westerblad, 2018; Taylor, Duchateau, Meeusen, & Rice, 2016).

Physical fatigue may be categorized as either subjective or objective. Subjective physical fatigue, also known as perceived motor fatigue, pertains to the rise in subjective perception of physical fatigue that arises during the execution of a motor task, which can have an impact on the performance of the task (Micklewright et al., 2017; Venhorst, Micklewright, & Noakes, 2018), whereas objective physical fatigue, also known as motor performance fatigue, refers to a reduction in an individual's motor performance (Gandevia, 2001).

Mental fatigue, or cognitive fatigue, pertains to the depletion of mental energy (Dotan et al., 2021) that manifests during extended periods of engagement in cognitively demanding activities (de Lange, Faber, Maurits, & Lorist, 2012; Van der Linden et al., 2003) and poses challenges for individuals in sustaining their task performance at a satisfactory level (Boksem, Meijman, & Lorist, 2006).

Numerous definitions of mental fatigue have been proposed across studies (Hockey, 2013). For instance, Boksem and Tops (2008) proposed a conceptualization of mental fatigue as a "psychophysiological state characterized by alterations in mood, information processing, and behavior." Slimani and colleagues (2018) present a more comprehensive definition of mental fatigue, characterizing it as a psychobiological state that arises from prolonged engagement in demanding cognitive tasks and is associated with subjective, behavioral, and physiological manifestations (Slimani, Znazen, Bragazzi, Zguira, & Tod, 2018). According to Agyemang et al. (2021), mental fatigue may be defined as the incapacity to sustain an optimal level of performance during a prolonged cognitive task. Van As and colleagues (2021) have defined mental fatigue as a multifaceted psychobiological condition that arises from the exertion of cognitive effort. Mental fatigue can arise from a multitude of factors, such as emotional stress, prolonged or intense concentration, or cognitively demanding tasks (Lundberg et al., 2010; Alonso et al., 2016). The presence of acute mental fatigue has been shown to have negative effects on performance and safety across various contexts (Caruso et al., 2006; Lal & Craig, 2001).

A multitude of studies have provided evidence suggesting that mental fatigue can be attributed to the compensatory brain activation observed during the performance of cognitive tasks (Emery, Heaven, Paxton, & Braver, 2008; Terentjeviene et al., 2018).

Mental fatigue may manifest subjectively and/or objectively. Subjective mental fatigue, also known as perceived cognitive fatigue, pertains to the rise in the individual's subjective experience of fatigue that arises during the performance of prolonged and/or demanding cognitive activities (Boksem & Tops, 2008; Genova et al., 2013). In some studies, subjective mental fatigue is described as a sensation of fatigue and debilitation accompanied by a reluctance to persist with the current undertaking (Boksem &Tops, 2008; Muller & Apps, 2019).

Objective mental fatigue, also known as cognitive performance fatigue, is characterized by a decline in measurable cognitive performance indicators during and following prolonged and/or demanding cognitive activities.

2.6.1. Factors influencing subjective and objective physical and mental fatigue

There is evidence indicating that subjective and objective physical and mental fatigue are influenced by primary subject-specific factors (such as age, gender, comorbidities, and the level of physical fitness; e.g., Smith, Chai, Nguyen, Marcora,& Coutts, 2019; Terentjeviene et al., 2018), by the features of the task (such as duration, extent, contraction mode, and speed), by chronic stressors (such as exposure to extreme temperatures), by therapies (Enoka & Duchateau, 2016; Gruet, 2018; Hunter, 2018; Husmann, Bruhn, Mittlmeier, Zschorlich, & Behrens 2019; Kluger et al., 2013; O'Leary, Collett, Howells, Morris, 2017), and by the setting (e.g., competition, incentives).

The main factors impacting subjective and objective physical and mental fatigue are discussed in the subsequent section.

<u>Factors influencing the degree of subjective and objective physical fatigue.</u>

As for the relationship between gender and age in relation to subjective physical fatigue, the current corpus of research is inconclusive, as the feeling of fatigue seems to be heavily influenced by the characteristics of the motor task being studied (Behrens et al., 2021).

Regarding objective physical fatigue, existing research suggests that it is subject to the influence of individuals' age. The process of aging is intricately linked to various alterations within the neuromuscular system, encompassing modifications in muscle mass, muscle quality, functional capacity, and neural activation. These age-related changes contribute to the degree of physical fatigue experienced by individuals (Mau-Moeller, Behrens, Lindner, Bader, & Bruhn et al., 2013; Nilwik et al., 2023). As for the relationship between objective fatigue and gender, there are discernible variations in the extent of objective physical fatigue when considering different genders (Ansdell et al., 2020).

Studies indicate that both subjective and objective physical fatigue are more noticeable in clinical populations compared to healthy individuals (Kluger et al., 2013; Severijns, Lemmens, Thoelen, & Feys, 2016; Zijdewind, Hyngstrom, & Hunter, 2020).

The characteristics of the task itself (such as the type of exercise; Hollander et al., 2003), the extent of muscles involved (Zhang, Iannetta, Alzeeby, MacInnis, & Aboodarda, 2021), and homeostatic mechanisms linked to exercise intensity (Venhorst et al., 2018) can also affect both subjective and objective physical fatigue (Hunter, 2018; Taylor, 2016; Ducrocq, Hureau, Bgseth, Meste, & Blain, 2021).

Additionally, subjective physical fatigue can be influenced by external and internal stimuli, such as motivation, incentives, and feedback (McCormick, Meijen, & Marcora, 2015; Terry et al., 2020).

<u>Factors influencing the degree of subjective and objective mental fatigue</u>.

As for the effect of age on subjective and objective mental fatigue, several studies indicated that as individuals age, they exhibit alterations in the structure and function of the brain, along with impaired neural network functionality (Murman, 2015). These changes lead to increased compensatory brain activation, resulting in objective and subjective mental fatigue. Terentjeviene et al. (2018) observed that young participants experienced more fatigue, increased cognitive effort, temporal demand, stress, and decreased vitality during a 120-minute inhibition task than senior ones. Younger people find prolonged cognitive activities more difficult, demanding, and tiring than older ones. However, the existing literature on the impact of age on mental fatigue appears inconsistent.

With respect to gender differences, studies on subjective mental fatigue in healthy subjects yielded mixed findings, as the feeling of subjective mental fatigue is heavily influenced by the characteristics of the cognitive task employed. As for objective mental fatigue, empirical investigations suggest that objective mental fatigue remains unaffected by variations in gender. According to recent research conducted by Jaydari and colleagues (2019), no significant variation in cognitive task performance, specifically in terms of error rate and reaction times, has been found between individuals of different genders (Jaydari, Fard, & Lavender, 2019). Furthermore, emerging research indicates that the degree of objective mental fatigue may be impacted by the overall well-being of the central nervous system and by the degree of disease severity. However, the effects of age, gender, and illnesses on objective mental fatigue can vary depending on the task being performed

(Borragán et al., 2017; O’Keefe, Hodder, & Lloyd, 2020; Shashidhara, Mitchell, Erez, & Duncan, 2019; Smith et al., 2019).

According to some investigations, the type of task (working memory, reaction inhibition) and its features (duration, cognitive load) might influence an individual's subjective and objective experience of mental fatigue (Boksem & Tops, 2008; Borragán, Slama, Bartolomei, & Peigneux, 2017; Hopstaken, van der Linden, Bakker, & Kompier, 2015; O’Keefe et al., 2020; Smith et al., 2019). For instance, prior research has frequently demonstrated that subjective mental fatigue tends to escalate as the duration of the task increases (Hopstaken et al., 2015) and cognitive activities are more difficult (Borragan et al., 2017). However, studies on this issue are quite inconclusive (Brown & Bray, 2017; Evans, Boggero, & Segerstrom, 2016; Hagger et al., 2010; Hockey, 2011; Inzlicht & Berkman, 2015; Kurzban, 2016; Milyavskaya, Berkman, & de Ridder, 2019; Van Cutsem et al., 2017).

Moreover, several studies indicate that negative mood and emotional factors such as stress, anxiety, frustration, hopelessness, tension, boredom, and people's personality traits are significant contributors to subjective mental fatigue (Hockey, 2013; Jaydari et al., 2019; Milyavskaya, Inzlicht, Johnson, & Larson, 2019; Saunders, Milyavskaya, & Inzlicht, 2015). According to Ackerman and Kanfer (2009), there is a positive relationship between neuroticism, anxiety, and self-reported mental fatigue; conversely, individuals who are driven by achievement and learning tend to experience lower levels of mental fatigue. Moreover, homeostatic disruptions such as sleep deprivation, heat, and stress (Hocking, Silberstein, Lau, Stough, & Roberts, 2001) can also influence levels of subjective mental fatigue during a given task (Massar et al., 2019).

On the other hand, objective mental fatigue has been linked to motivation in previous investigations (Boksem et al., 2006; 2008). Some studies indicate that individuals with high levels of motivation may be able to sustain their performance even in challenging situations (van der Linden, 2011).

As for the investigation of the interactions between objective and subjective mental fatigue, numerous studies have documented both alterations in objective and subjective mental fatigue during and following prolonged cognitive tasks. Various studies, however, have observed a significant increase in subjective mental fatigue without any consistent indication of a decline in cognitive task performance (Borragán et al., 2017; Hockey, 2011; O'Keefe et al., 2020; Shigihara et al., 2013; Smith et al., 2019). It is worth mentioning that engaging in extended cognitive activities does not inevitably lead to noticeable declines in cognitive functioning, a phenomenon that has frequently been ascribed to a learning effect that would overcome fatigue-induced performance loss or an augmented compensatory cognitive endeavour (Hockey et al., 2011; 2013; Pergher, Vanbilsen, & van Hulle, 2021).

2.6.2. Interaction between physical and mental fatigue

In recent times, there has been a surge in research exploring the relationship between physical and mental fatigue across diverse domains. Several studies have indicated interactions (including causation) between these two types of fatigue.

The impact of physical fatigue on mental fatigue. A strand of studies have demonstrated that physical fatigue induces mental fatigue, affecting consequently cognitive performances (e.g., Mashiko, Umeda, Nakaji, & Sugawara, 2004; Xing et al., 2020; Xu et al., 2018). According to some studies, as physical fatigue levels increase, individuals are required to exert greater effort to successfully accomplish the task. Therefore, the regulation of motion constitutes a form of cognitive function that may elicit mental fatigue (Xing et al., 2020; Xu et al., 2018). Recently, Dambroz and colleagues (2022), in their systematic review pertaining to the cognitive performance of soccer players under conditions of physical fatigue, found that physical fatigue negatively affected soccer players cognitive performances (Dambroz, Clemente, & Teoldo, 2022). According to the review, a considerable proportion of the examined studies revealed methodological discrepancies, such as the use of various protocols for inducing physical fatigue and the use of various performance evaluation tasks (tactical, cognitive, technical, and physical). These methodological discrepancies would explain inconsistencies across studies.

The impact of mental fatigue on physical fatigue.

In recent years, an increasing amount of scholarly research in the fields of sport, exercise psychology (Bray et al., 2008), and exercise physiology (Marcora et al., 2009) has delved into the potential impact of mental fatigue on physical fatigue and subsequent performances (MacDonell & Keir, 2005; Van Cutsem et al., 2017).

Some studies have suggested that mental fatigue can alter the way sensory information is processed in the central nervous system, leading to an increased perception of effort among participants. The elevated perception of exertion caused by mental fatigue leads to a reduction in exercise endurance (Marcora et al., 2008; 2009).

A recent meta-analysis and review of the literature has indicated that antecedent cognitive effort has noteworthy negative carryover effects of small-to-medium magnitude on various aspects of physical task performance that necessitate sustained effort regulation, such as endurance (both aerobic and anaerobic), resistance, and motor performance (Brown et al., 2020).

Considerable research attention has been devoted to investigating physical and mental fatigue in isolation. Few studies on the combined impact of physical and mental fatigue on physical performance suggested that mental fatigue can impede muscular performance when individuals engage in a concurrent task that involves both a mentally fatiguing and physical component (MacDonell & Keir, 2005).

2.6.3. Relationship between cognitive function and physical and mental fatigue

As far as the relationship between physical fatigue and cognitive functions is concerned, the field of human factor research has consistently investigated the potential negative impacts of fatigue resulting from exercise on people performance (Lambourne &

Tomporowski, 2010). The existing body of evidence, including narrative (Brisswalter, Collardeau, & Arcelin, 2002; McMorris & Graydon, 2000; Tomporowski, 2003) and meta-analytic review (Lambourne & Tomporowski, 2010), has brought attention to the contradictory findings found in the literature and does not provide definitive conclusions on the effect of physical fatigue on cognitive performance (Dambroz et al., 2022). Some studies have found improvements in cognitive functions such as short-term memory after exercising (Hancock & McNaughton, 1986; Davey, 1973). For instance, a meta-analysis examining the impact of various exercise-induced fatigues on cognitive functions revealed enhancements in memory, executive functions, reasoning, attention, and processing speed (Ludyga, Gerbe, Pühse, Looser, & Kamijo, 2020). Other studies, however, did not discover any improvement in cognitive functions or even observe a decline in cognitive function (Casanova et al., 2013; Etiner et al., 1997; McMorris et al., 1996; McMorris, Collard, Corbett, Dicks, & Swain, 2008).

Studies, attempting to comprehend the impact of physical fatigue on cognitive performance by evaluating exercise duration and intensity, found that the impact of physical fatigue on cognitive performance is contingent upon both the intensity and duration of the exercise (Kamijo et al., 2007; Tomporowski, 2003).

Studies on the length of physical exercise on cognitive performances found mixed results. For instance, some studies indicated that brief intervals of physical exercise resulted in enhanced cognitive performance among adult individuals (Hancock & McNaughton, 1986), others observed that engaging in extended periods of sub-maximal physical exercise led to a decline in cognitive functioning (Clarkson-Smith & Hartley, 1989; Hogervorst, Riedel, Jeukendrup, & Jolles, 1996). In the same vein, while some studies found that intermittent physical exercise had a detrimental effect on perception, information processing, and anticipation abilities (Casanova et al., 2013), other studies found no differences in reaction time, accuracy, incorrect responses, or omitted responses between the control group (not exercising) and the experimental group (intermittently exercising); (Lemmink & Visscher, 2005).

Theories on the correlation between fatigue resulting from exercise and cognitive functioning suggest that high-intensity exercise reduces cerebral blood volume per heartbeat by a factor of four compared to rest. Therefore, the brain operates with limited resources, so it may prioritize maintaining neural activation in motor neurons over other structures responsible for cognition (Dietrich, 2006). This limited capacity and inability to acquire more resources may lead to a redistribution of activation, decreasing activation in some structures while increasing it in others (Dietrich, 2006).

As far as the relationship between mental fatigue and cognitive functions is concerned, decline of cognitive functions have been frequently found to be associated with mental fatigue. Specifically, the executive functions (Holtzer et al., 2010; van der Linden et al., 2003), the sustained attention (Dorrian et al., 2007; Langner et al., 2010; Lim et al., 2010), the goal-directed attention (Boksem, Meijman, & Lorist, 2005), the alternating attention (van der Linden et al., 2003), the divided attention (van der Linden and Eling, 2006), the response inhibition (Kato, Endo, & Kizuka, 2009), the planning (Lorist et al., 2000, 2008), and the novelty processing (Massar et al., 2010) are the cognitive functions more associated with mental fatigue. Specifically, the relationship between mental fatigue, executive functioning, and processing speed has been extensively shown in healthy individuals (e.g., Boksem et al., 2005, 2006; Kato et al., 2009; Tanaka, Shigihara, Funakura, Kanai, & Watanabe, 2012; van der Linden et al., 2003; Wang, Trongnetrpunya, Samuel, Ding, & Kluger, 2016).

Some studies indicate that mental fatigue arises from a decline in executive control that led to a decrease in cognitive flexibility, reduced efficiency in planning, and a diminished ability to regulate perceptual and motor functions to adapt to changing task demands (Van der Linden et al., 2003). Among the various components of executive function, selective attention, particularly conflict-controlling selective attention (response inhibition), is highly vulnerable to mental fatigue (Tanaka et al., 2012).

Overall, a substantial body of research indicates that mental fatigue leads to a decline in cognitive efficiency; however, despite its widespread recognition, the impact of mental fatigue on cognitive performance is poorly understood (Boksem et al., 2006; de Lange et al., 2012). Numerous contemporary theories have endeavoured to elucidate the correlation between mental fatigue and cognitive functioning. Studies indicate that cognitive tasks that have been thoroughly learned or become automatic can be executed for extended durations without inducing fatigue in the subjects, whereas activities that necessitate intentional regulation can lead to fatigue (van der Linden et al., 2003). Ongoing research is being conducted on this topic, and as of now, no definitive conclusions have been reached due to the discrepancies observed among various studies.

2.7. Tools to evaluate fatigue

The existing body of literature encompasses a variety of questionnaires and scales that have been specifically developed to evaluate subjective mental and physical fatigue across different contexts (Christodoulou, 2005).

As for the assessment of objective mental fatigue, traditionally, two distinct methodologies have been employed: the probe task approach as described by Hockey (2013) and the Time on Task (ToT) approach utilizing a continuous work method. Both the ToT and probe techniques offer benefits and drawbacks. The probe methodology examines the impact of induced fatigue on subsequent performances. The probe strategy, in practice, entails evaluating the effects of fatigue using a "probe" task that is performed before, after, or during a "loading task" that is taxing. It is possible to evaluate the objective fatigue effects of the loading task by comparing performance on repeated probing tasks (for example, before and after fatigue induction). Some studies assess cognitive performance both prior to and after a loading task; however, this approach exhibits several limitations, including practice affecting repeated task outcomes. In other studies, two groups are recruited, with one group assigned to engage in a task that induces fatigue while the other group is assigned to perform a control task, typically involving activities such as watching movies or reading magazines, for an equivalent duration.

The ToT technique evaluates the effects of a prolonged and uninterrupted task on performance decline or variability. The underlying concept is that task performance is bound to decline with an increase in the duration of task engagement, and this phenomenon can be expressed mathematically (Hockey, 2013).

As for the assessment of objective physical fatigue, most studies employ maximum (e.g., maximal voluntary contractions, leaps) and submaximal motor performance measurements (e.g., force fluctuations during submaximal isometric contractions, coefficient of variation of kinematic gait parameters; Behrens et al., 2018; Contessa, Adam, & de Luca, 2009; Millet, Martin, Martin, & Vergès, 2011; Komi, 2000; Shema-Shiratzky et al., 2019).

In addition to the aforementioned measurements, a wide array of tools and methodologies can be employed in the comprehensive examination of fatigue.

Physiological indicators of fatigue offer significant insights into the fundamental mechanisms of fatigue. Skin conductance (a parameter that exhibits a high degree of sensitivity to sympathetic nervous system activity) and heart rate are some physiological measures used to assess fatigue. Studies have indicated that the phenomenon of electrodermal activity has been found to have associations with mental fatigue, effort, and arousal (Heaton et al., 2020; Pakarinen, Pietila, & Nieminen, 2019).

Eye metrics have garnered heightened attention in the realm of fatigue research in recent years. Studies have indicated that eye metrics such as blinks, eye movements, eyelid closure, and pupil variations are indicators of mental fatigue (Bafna & Hansen, 2021; Cori et al., 2019; Rodriguez et al., 2018 for comprehensive reviews). For instance, Bafna and Hansen (2021) reported a correlation between heightened fatigue and a reduction in the variables of pupil dilation (mean, peak, and range) and saccade velocity (mean and range), as well as an increase in blink count and frequency. Moreover, to quantify modifications during fatiguing performances and to determine fatigue causes, several technologies are used in fatigue research. These include blood chemical investigations, nerve conduction studies (NCS), and measures of brain activity such as electroencephalography (EEG), trans mastoid spinal cord stimulation, fMRI positron emission tomography (PET), magnetoencephalography (MEG), electromyography (EMG), and high-frequency paired pulse-evoked response (Al-Mulla et al., 2011; Craig, Tran, Wijesuriya, & Nguyen, 2012; Janssens et al., 2013; Kluger et al., 2013; Lim et al., 2010; Shigihara et al., 2013; Yoshitake, Ue, Miyazaki, & Moritani, 2001).

3. EXPLORING FATIGUE IN MULTIPLE SCLEROSIS

3.1. Fatigue in Multiple Sclerosis

Fatigue is a prevalent and impairing symptom experienced by individuals with MS, with a reported prevalence ranging from 36.5% to 78.0% (Oliva Ramirez et al., 2021). Fatigue impacts MS patients' QoL, job performance, mental well-being, physical health, social and private lives (Ayache & Chalah, 2017; Gullo, Fleming, Bennett, & Shum, 2019; Penner & Paul, 2017; van Zanten, Douglas, & Ntoumanis, 2021). It is unsurprising to note that approximately one-third of patients perceive fatigue as their most severe and distressing symptom (Krupp, Alvarez, LaRocca, & Scheinberg, 1988; Penner et al., 2020).

Fatigue in MS is a widespread phenomenon and a multifaceted symptom that has been fundamentally difficult to characterize, define, depict, and evaluate because it is not yet fully understood. It has physiological and psychological components in equal measure and may be described in a variety of ways (Kos et al., 2004).

Physical or mental exertion may cause fatigue in healthy individuals (Finsterer & Mahjoub, 2014), but the effects are short-lived, and fatigue can be alleviated by addressing the underlying causes, through the rest and sleep (Christodoulou et al., 2005). Conversely, pathological fatigue in MS patients is an intense feeling of fatigue that may occur even in the absence of effort. It is often long-lasting, can be very distressing, and the healing process is lengthy. MS patients describe fatigue as excessive weakness even in the absence of exertion, or an excessive, continuous, and persistent feeling of fatigue and a complete lack of physical or mental energy (Krupp, 2003). Fatigue in MS differs from normal fatigue in its severity, frequency, length, the type of recovery that it requires, and its impact on the performance of daily functional tasks (Christodoulou et al., 2005). In MS patients, fatigue may be triggered by limited exertion, and it is exacerbated by physical or mental work, critical infection (Bol et al., 2012; Leavitt, Wylie, Genova, Chiaravalloti, & DeLuca, 2012), the consumption of food (heavy meals), discomfort, laziness, tension, psychological stress, heat, and humidity. Cooler temperatures usually reduce the severity of fatigue (Krupp et al., 1995; Mills & Young, 2008). Fatigue in MS is gender neutral (Bakshi, 2003; Flachenecker et al., 2002), and it may strike at any time of the day or night (Christodoulou et al., 2005; Newland, Starkweather, & Sorenson, 2016). It peaks in the late afternoon, tends to persist over time (Tellez et al., 2006), usually lasts for years (Mills, Young, Pallant, & Tennant, 2010), and might occur sporadically or continuously over the course of the illness (Fisk, Pontefract, Ritvo, Archibald, & Murray, 1994; Pittion-Vouyovitch et al., 2006). The experience of fatigue is associated with powerlessness (Hanken, Eling, Kastrup, Klein, & Hildebrandt, 2015; Schreiber, Lang, Kiltz, & Lang, 2015), negative affectivity (Bol, Duits, Hupperts, Vlaeyen, & Verhey, 2009; Kaminska, Kimoff, Schwartzman, & Trojan, 2011), stress (Morris & Maes, 2013), and cognitive failure (El-Tamawy, Darwish, Ahmed, Abdelalim, & Moustafa, 2016).

3.2. Fatigue a social issue in Multiple Sclerosis

Fatigue exerts a significant influence on the quality of life, occupational functioning, psychological state, physiological well-being, and interpersonal and personal domains of individuals diagnosed with MS. The impact of fatigue on the ability of MS patients to engage in work and daily social activities has been extensively studied (Raggi et al., 2016). Several research studies have consistently reported a decline in employment status among fatigued MS patients when compared to control groups (Jaworski et al., 2021; Vijayasingham & Mairami, 2018). For instance, Jaworski et al. (2021) discovered that approximately 25% of MS patients experienced a decline in their employment status. This decline was marked by a reduction in working hours or the manifestation of unfavorable work-related incidents, spanning a duration of three years. This decline would occur due to several factors, one of which was fatigue. Therefore, the state of fatigue in MS patients can result in a decline in productivity, increased rates of absenteeism, and early retirement, thereby potentially causing economic consequences for both patients and society.

It is crucial to emphasize that fatigue and various symptoms associated with MS arise during early adulthood, typically between the ages of 20 and 40 (Battaglia & Bandiera, 2019), a critical period of life often marked by increased levels of activity and productivity (Global Burden of Disease Neurological Disorders Collaborator Group, 2017; Staff, Lucchinetti, & Keegan, 2009; Sutliff, 2010). Several studies have demonstrated that fatigue in individuals with RRMS leads to a decline in occupational responsibilities during the early stages of the disease, as evidenced by disease-related absenteeism and reduced productivity (Sainz de la Maza et al., 2022). Therefore, the diminished level of productivity during the early stages of life due to fatigue can impose an important burden on patients not only in terms of economic implications but also in relation to self-perception, social interactions, and overall well-being (Aroson et al., 1997; Janardhan & Bakshi, 2002). The financial burden of fatigue in MS is one of the highest among brain disorders and is substantial due to a combination of medical expenses and indirect costs associated with decreased work productivity and premature retirement. The psychological distress that arises from fatigue, including increased levels of depression and anxiety, melancholy among MS patients (Young et al., 2021; Ruet et al., 2013), and other emotional problems, contributes to elevated healthcare costs related to interventions for mental health that have substantial social and economic implications for society (Adelman et al., 2013; Gupta et al., 2014). Fatigue not only exerts influence on MS patients in a direct manner but also possesses a wider-reaching effect on their familial (caregivers), social, and communal networks. Caregivers who have the responsibility of providing continuous assistance to people affected by MS may have an increased level of physical demands and emotional pressures, which can contribute to their own experience of fatigue, stress, and diminished QoL. Consequently, this can give rise to supplementary societal difficulties associated with the burden placed on caregivers. Therefore, due to its significant impact on MS patients and society, fatigue is considered a societal concern.

There is a paucity of data on whether fatigue is a societal issue more so in MS than in other neurological conditions. Research on fatigue has indicated that individuals with MS experience more intense, widespread, unpredictable, and disabling fatigue. They also exhibit higher levels of fatigue, reduced activity, and decreased motivation compared to the general population (Mills & Young, 2008) and individuals with other medical conditions (Krupp et al., 2010). These differences are due to the extent of injury to the central nervous system, the involvement of various sections of the brain and spinal cord, and the prevalence of additional symptoms such as pain, melancholy, and sleep disturbances. It is, however, reasonable to deduce that its influence on patients' physical, psychological, social, and economic well-being in society may be higher than that of other diseases that, unlike MS, generally occur later in life (Battaglia et al., 2022).

3.3. Taxonomy of fatigue in Multiple Sclerosis

The examination of several studies has highlighted the variability of the fatigue construct and the absence of a consistent definition (Rudroff, Kindred, & Ketelhut, 2016). About the variety of definitions that may be found in the literature, Dittner et al. (2004) wrote: "*Before a concept can be measured, it must be defined, and before a definition can be agreed upon, there must exist an instrument for assessing phenomenology. There is unfortunately no ‘gold standard’ for fatigue, nor is there ever likely to be*." The lack of a widely accepted definition and description of fatigue, highlighted by several authors, makes it difficult to compare studies and explains the slow progress in the research field on fatigue in MS (DeLuca, 2005; Krupp, 2003). The development of a unified taxonomy of fatigue and its accurate application in research are critical for future progress. Across the literature, numerous definitions, and descriptions of fatigue in MS have been formulated. Fatigue may be described differently depending on its source (central or peripheral; primary or secondary), manifestation (subjective versus objective), and modality (mental or physical).

Central vs. peripheral fatigue. Several studies rely on the distinction between central and peripheral fatigue (Chaudhuri & Behan, 2000). This categorization distinguishes between various sources of fatigue, which are said to stem either from the muscles (peripheral) or from the CNS (central). The term "central fatigue" refers to a sense of exertion and limited stamina during long-term physical and mental activities that require self-awareness and internal cues experienced in the absence of evidence of cognitive or mental failure or motor vulnerability. The feeling of fatigue could be caused by damage to the limbic and reticular systems as well as the basal ganglia (Tedeschi et al., 2007). Conversely, peripheral fatigue refers to the inability to maintain contraction or work rate during exercise and is caused by muscle and tissue fatigue. The neuronal mechanisms that underlie peripheral fatigue encompass axonal loss, demyelination, or conduction block. The muscular mechanisms that contribute to muscle dysfunction can be attributed to various factors, such as the loss of electrical conduction along the muscle membrane to the T-tubule system, impaired release of calcium from the sarcoplasmic reticulum (also known as excitation-contraction uncoupling), impaired interaction between actin and myosin during crossbridge cycling, impaired reuptake of calcium, or bioenergetic failure due to impaired oxidative phosphorylation or glycolysis (Davis & Walsh, 2010).

Primary vs. secondary fatigue. The distinction between primary and secondary fatigue depends on whether fatigue is induced directly by a CNS injury or arises because of MS symptoms (Dalgas et al., 2018). To qualify as primary, fatigue must have a direct relationship with the MS disease process (such as brain injury, inflammation, demyelination, or axonal loss) and be unrelated to any other MS symptoms (Genova et al., 2013; Penner, 2016). Primary fatigue can be experienced even before the onset of the disease (Bergamaschi, Romani, Versino, Poli, & Cosi, 1997) and is associated with changes in functional brain connectivity (Cruz Gómez, Ventura Campos, Belenguer, Ávila & Forn, 2013), a dopamine imbalance (Dobryakova, Genova, DeLuca, & Wylie, 2015), neuroendocrine changes in the immunological markers (e.g., proinflammatory cytokines; Braley & Chervin, 2010; Gottschalk et al., 2005; Heesen et al., 2006; Tellez et al., 2006; Zellini, Niepel, Tench, & Constantinescu, 2009), and compensatory brain patterns (Kos, Kerckhofs, Nagels, D'hooghe, & Ilsbroukx, 2008; Leocani, Colombo, & Comi, 2008).

Secondary fatigue is caused by factors other than the illness, such as dietary or lifestyle changes, medication for the symptoms of MS (Coote et al., 2017; Kos et al., 2008; MacAllister et al., 2005), depression (Patrick, Christodoulou, Krupp, & Consortium, 2009; Pittion-Vouyovitch et al., 2006Strober & Arnett, 2005), sleep disturbances (Fleming & Pollak, 2005; Lobentanz et al., 2004; Merlino et al., 2009; Mills et al., 2010; Veauthier &

Paul, 2014), poor self-esteem (Tellez et al., 2008), and temperature (Bakshi, 2003; Bol et al., 2012; Crayton et al., 2004). MS patients may experience both primary and secondary fatigue (Kos et al., 2008), which makes it difficult to distinguish one from the other (Finlayson, Preissner, & Cho, 2012).

Subjective vs. objective fatigue. The feeling of fatigue may be experienced either subjectively or objectively. Kluger et al. (2013) developed a unified classification according to which the symptom of fatigue is determined both by perceptions of fatigue and by objective fatigue.

Subjective fatigue, or perceived fatigue, has been defined as a general feeling of fatigue, a lack of motivation, or a subjective sense of reduced energy that makes daily physical and cognitive tasks challenging (Aldughmi, Bruce, & Siengsukon, 2017; Kluger et al., 2013; Schwid et al., 2002).

Objective fatigue, or performance fatigability, is defined as a measure of the change in the performance of a physical or mental task over time (Kluger et al., 2013; Severijns et al., 2017). Kluger et al. (2013) defined objective fatigue (performance fatigability) as "*the magnitude or rate of change in a performance criterion relative to a reference value over a given time of task performance or measure of mechanical output*." Objective fatigue is measured with reference to declines in mental or motor performance after or during a strenuous activity.

Physical vs. mental fatigue. A prevalent differentiation observed in research pertaining to the pathophysiological aspects of fatigue in individuals diagnosed with MS is the dichotomy between mental and physical fatigue (Greim et al., 2007).

The notion of dualistic physical and mental fatigue (Power, Arafa, Wenz, & Foley, 2021) has been underlined in several fatigue definitions. For instance, the MSCP Guidelines (MSCP,1998) defined fatigue as "*a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities*". Schwid et al. (2002) distinguished between physical fatigue, mental fatigue, and lassitude.

Physical fatigue was defined as a reduction in strength coupled with sustained muscular contractions, whereas mental fatigue was defined as a decline in cognitive function during tasks that require constant attention. Lassitude was defined as the subjective experience of having a reduced level of energy, which could not be measured objectively. Similarly, Rudroff et al. (2016) defined fatigue as the decline in physical and/or mental performance due to changes in the CNS (neurotransmitter concentrations and intrinsic neuronal excitability) in psychological (mood disorder, perception of effort, drive, and alertness) and/or peripheral components (changes in physiological factors).

The investigation of physical and mental fatigue in MS represents a central aspect of interest in this research study. Consequently, it will be comprehensively explored in the forthcoming sections.

3.4. Physical and mental fatigue in Multiple Sclerosis

The term physical fatigue (or motor fatigue) within the realm of MS is often used to describe the inability of a muscle to operate at a certain rate during activity and usually refers to a reduction in muscle strength and weakness that occurs during prolonged exercise (Schwid et al., 2003). Recent research has revealed that the intensified physical fatigue observed in MS patients can be attributed to central and supraspinal fatigue factors rather than peripheral mechanisms (Leodori et al., 2023). The impact of physical fatigue on MS patients is substantial across various domains, including occupational engagements as well as other activities. Sellitto et al. (2021) assert that physical fatigue exerts a notable influence on manual dexterity, walking ability, and language proficiency, thereby yielding substantial ramifications from social and emotional perspectives.

Physical fatigue can be measured both subjectively and objectively (Linnhoff, Fiene, Heinze, & Zaehle, 2019).

Subjective physical fatigue is characterized by a subjective perception of physical fatigue and can be measured through questionnaires, whereas objective physical fatigue (or motor fatigability) is conceptualized as a decrease in maximum force after exercise (Harrison, Silber, McCracken, & Moss-Morris, 2015) and can potentially be evaluated through the assessment of muscle contractions executed during a prolonged physical task. Severijns and colleagues (2017) have shown that individuals diagnosed with MS often have heightened objective physical fatigue compared to healthy subjects. Variations in physical fatigue between healthy individuals and those with MS are contingent upon the nature of the tasks (sustained or intermittent), the level of muscle contraction (maximal or submaximal), and the specific limbs under examination (upper or lower limb).

Mental fatigue (or cognitive fatigue) is a psychobiological condition that arises as a result of engaging in extended periods of cognitively demanding activities. MS patients who complain of mental fatigue may commit more errors because they are less able to maintain the effort that is necessary to meet the demands of a task over time and require additional time to complete tasks (Mills & Young, 2008).

Mental fatigue's description and operationalization differ across studies because of the lack of a universally accepted definition. For instance, in some studies, mental fatigue has been defined as a subjective impression of an inability to focus, while in others it has been described as a challenge in maintaining focus and cognitive clarity (Kluger et al., 2013). Still others have described mental fatigue as a gradual decline in performance. This construct is premised on the notion that fatigue is cumulative and longitudinal, meaning that the longer individuals work on a task, the more they experience mental fatigue. However, it has also been claimed that mental fatigue manifests through an increase in response variability during specific mental assignments. Those who suffer from mental fatigue may experience intermittent gaps in concentration. During those lapses, more effort may be required to mobilize the mental reserves that are needed to complete a job rapidly and effectively.

Some studies have shown that, during sustained attention tasks, individuals with MS are more susceptible to the effects of mental fatigue, which often manifests as a breakdown during performance. Conversely, healthy individuals can exert effort to obtain a reward, such as increased task performance, even during periods of substantial fatigue (Lorist et al., 2009).

Mental fatigue can be measured both subjectively and objectively (Linnhoff et al., 2019). Subjective mental fatigue is characterized by a subjective perception of fatigue, whereas objective mental fatigue (or cognitive fatigue) is described as a "*decrease in processing speed, response time, or accuracy over time after performing demanding mental skills*" (Harrison et al., 2015).

3.4.1. Physical and mental fatigue in Multiple Sclerosis: are they two distinct constructs?

The question of whether physical and mental fatigue are distinct or have a common underlying dimension has excited much controversy (Gullo et al., 2019; Chen et al., 2020). The community-based study of fatigue has been one of the early efforts to distinguish between physical and mental components of fatigue (Chalder, Berelowitz, Pawlikowska, Watts, Wessely, & Wright, 1993).

Distinguishing between the two modalities is of utmost importance, as each domain expresses itself in different ways, depicts different futures, exhibits unique interactions with various symptoms, shows different effects on health, is driven by different factors, and may be contingent upon disparate mechanisms (Penner et al., 2009).

Some studies indicate that physical and mental fatigue in MS are not necessarily concurrent and can be experienced separately (Watson et al., 2021). For instance, Watson et al. (2021) gathered qualitative data from individuals diagnosed with progressive MS to delineate the concept of MS-related fatigue and its effects on health-related quality of life (HRQoL). In their study, although physical fatigue was a common experience among all patients, some individuals did not report experiencing mental fatigue, and a significant proportion of patients, approximately one-third, reported experiencing mental fatigue without any accompanying cognitive disruption.

Other studies suggest that physical and mental fatigue often coexist, are intertwined, and can have overlapping effects on an individual's well-being. For example, some studies indicate that physical fatigue can lead to increased mental fatigue as individuals expend more effort to compensate for physical limitations (Claros Salinas et al., 2012; Gonzales et al., 2017). As for the impact of mental fatigue on physical fatigue, studies on healthy subjects have demonstrated that mental fatigue can exacerbate physical fatigue, as cognitive challenges can drain people's energy resources. However, in the MS literature, evidence is scarce, and the impact of mental fatigue on physical fatigue has not been thoroughly investigated.

Some studies indicate that the severity of physical fatigue is higher than mental fatigue (Krupp et al., 2003; Schreurs et al., 2002) and that physical fatigue outweighs mental fatigue in MS patients (Krupp et al., 2003; Marchesi et al., 2020; Schreurs et al., 2002).

Moreover, studies on the correlation between physical and mental fatigue and their respective impacts on daily life functioning have shown that, while physical fatigue was associated with lower levels of physical QoL and with disease-related factors (Gullo et al., 2019; Ruban, Hilt, & Petersen, 2021; Trojan et al., 2007), mental fatigue was associated with significant mental health aspects of QoL, role fulfillment, social and emotional functioning, mental health (Gullo et al., 2019; Ruban et al., 2021), stress, depression, anxiety (Ford et al., 1998; Mackay, Johnson, Moodie, Rosehart, & Morrow, 2021), self-efficacy (Trojan et al., 2007), and sleep disturbances (Chinnaudari et al., 2018).

There is converging evidence showing that while physical fatigue is primarily associated with older age, gender, longer illness duration, and physical impairment (Bergamaschi et al., 1997; Colosimo et al., 1995; Krupp et al., 2003; Marchesi et al., 2020; Pittion-Vouyovitch et al., 2006; Schreurs et al., 2002), mental fatigue correlates with depression (e.g., Bakirtzis et al., 2020; Ford et al., 1995; Krupp et al., 2003; Lobentanz et al., 2004; Marchesi et al., 2020; Merkelbach, Sittinger, & Koenig, 2002; Schwartz, Coulthard-Morris, & Zeng, 1996; Schreurs et al., 2002; Takeda et al., 2021; Trojan et al., 2007; Yalachkov et al., 2019).

Distinguishing between the physical and mental dimensions of fatigue in individuals with MS could indeed potentially provide insight into the varying effectiveness of treatments on specific dimensions of a patient’s fatigue, as the management and recovery of physical and mental fatigue may necessitate distinct strategies and interventions. The differentiation between physical and mental fatigue can assist individuals in optimizing their productivity and performance across various domains and fostering holistic well-being.

3.4.2. Physical and mental fatigue in Multiple Sclerosis and their respective associations with depression

The manifestation of fatigue symptoms in MS patients is influenced by a multitude of variables, with depression being identified as a prominent determinant.

As shown in the previous paragraph, converging literature seems to indicate that depression correlates mainly with mental fatigue (e.g., Bakirtzis et al., 2020).

Some studies seem to indicate that the association of mental fatigue with depression exhibits temporal variability. For instance, Krupp et al. (2010), in their cross-sectional analysis, revealed a significant association between mental fatigue, reduced motivation, and depression. However, no significant relationship was observed in the longitudinal analysis. The authors suggested that the occurrence of mental fatigue and diminished motivation was more closely associated with depression rather than occurring prior to or after it. They also hypothesized that depression, mental fatigue, and diminished motivation could exert mutual influence over shorter temporal intervals. Similarly, Schreurs and colleagues (2002), in a cross-sectional analysis, observed a significant relationship between mental fatigue and depression. One year later, the presence of depression was not demonstrated to act as a significant predictor for subsequent mental fatigue, nor was depression shown to be predicted by earlier feelings of fatigue. The author proposed that it would be beneficial to do longitudinal studies on fatigue in individuals with MS since the associations between fatigue and mental health may vary over a year. However, conflicting results have been found in the literature (Morrison & Stuifbergen, 2016; Schreus et al., 2002). While some studies found that depressive symptoms were the strongest direct predictor of subjective mental fatigue (Morrison & Stuifbergen, 2016), others did not confirm such results (Schreurs et al., 2002); some studies showed that depressive symptoms were rather predictors of sleep quality (Berard et al., 2019).

As for the relationship between physical fatigue and depression, few studies have found a correlation between depression and both mental and physical fatigue (Penner et al., 2009; Tellez et al., 2008). Variability within the research literature may relate to the measurement tools applied to the assessment of depression found across studies. For instance, Penner et al. (2009), found that the two subscales of the MFIS (namely, mental and physical) exhibited a stronger association with depression as compared to the FSS. This observation suggests that the correlation between fatigue and depression may vary depending on the specific fatigue measurement instrument utilized.

3.4.3. Physical and mental fatigue in Multiple Sclerosis and their respective associations with cognitive deficit

Literature studies generally indicate that fatigue tends to have a negative impact on cognitive domains, particularly memory, attention, information processing, verbal abilities, and executive function (e.g., Diamond, Johnson, Kaufman, & Graves, 2008; Fiene et al., 2018; Heesen et al., 2010; Kos et al., 2004), while language is the domain least affected by fatigue.

Limited research has been conducted to examine and evaluate the distinct impact of physical and mental fatigue on cognitive deficits.

Nevertheless, some studies on the relationship between mental fatigue and cognitive functions seem to suggest that mental fatigue impacts mostly processing speed, sustained attention, alertness, and working memory (Andreasen et al., 2019; Claros-Salinas et al., 2013; Diamond et al., 2008; Greim et al., 2007; Guillmein et al., 2022; Heesen et al., 2010; Neumann et al., 2014; Rotstein et al., 2012; Sander et al., 2017; Weinges-Evers et al., 2010); however, discrepancies arise across studies (Golan et al., 2018; Morrow, Weinstock-Guttman, Munschauer, Hojnacki, & Benedict, 2009; Niino et al., 2014).

A series of investigations within the realm of literary research on the relationship between subjective and objective mental fatigue demonstrates that patients do not necessarily report mental fatigue despite showing changes in cognitive performance (Hanken et al., 2015; Parmenter, Denney, & Lynch, 2003; see Chapter 5 for further details). Likewise, several studies indicate that fatigue complaints seem unrelated to the deterioration of cognitive functions. For instance, some authors found that MS patients reported feeling fatigued after engaging in cognitive tasks, but their objective performances were the same as at the start of the study (Paul et al., 1998).

As for physical fatigue, most studies have focused on the nature and extent of the relationship between self-reported physical fatigue and subjects' physical performances, which have shown conflicting results. While some investigations have found a relationship between self-reported physical fatigue ratings and power generation (Huisinga, Filipi, & Stergiou, 2011), as well as changes in gait characteristics across different kinematic and kinetic parameters (Burschka et al., 2012; Filli et al., 2018; Motl, Sandroff, Suh, & Sosnoff, 2012; Motta et al., 2016; Sacco, Bussman, Oesch, Kesselring, & Beer, 2011; Sandroff et al., 2014; Shema-Shiratzky et al., 2019; Taborri et al., 2019; Van der Linden et al., 2018); others have not (De Pin, Sagawa Jr., Moulin, & Decavel, 2016; Leone et al., 2016; Morris, Cantwell, Vowels, & Dodd, 2002; Nogueira et al., 2013; Severijns, Lamers, Kerkhofs, & Feys ,2015; Van Emmerik, Remelius, Johnson, Chung, & Kent-Braun, 2010).

Less research has been conducted on the relationship between physical fatigue and cognitive functions, and the available research findings are inconsistent. Nevertheless, studies seem to indicate that reduced attention and processing speed are linked to both cognitive and physical fatigue, although the association seems to be somewhat less evident for physical fatigue (Andreasen et al., 2019; Heesen et al., 2010; Pokryszko-Dragan et al., 2016; Takeda et al., 2021). However, studies indicate that when accounting for confounding variables such as depression and disability, the aforementioned correlations exhibit decreased clarity (Andreasen et al., 2019; Jougleux-Vie et al., 2014).

Aldughmi et al. (2017) investigated the effects of physical and mental fatigue on cognitive functions in a cohort of fifty-two MS patients. In their studies, three distinct performance measures were used, namely the percentage alteration in walking distance covered, the percentage alteration in force exerted, and the variability in reaction speed as measured by the Continuous Performance Test. The Neurological Fatigue Index (NFI-MS) was used to assess subjective physical and mental fatigue. The results of the study indicated that both the scores on the physical and cognitive domains of the NFI-MS correlated with attention.

In the study conducted by Guillmein et al. (2022), a cohort of twenty-nine individuals diagnosed with MS and twenty-eight healthy controls were subjected to a thorough and comprehensive neuropsychological evaluation. Within the MS cohort, it was observed that the characteristic of self-reports of physical fatigue exhibited a noteworthy relationship with the working memory score. Mental fatigue emerged as a significant predictor for both executive functioning performance and processing speed.

Literature studies show conflicting results on the relationship between physical and mental fatigue and cognitive functioning, and definite conclusions cannot be drawn.

3.5. The etiology of fatigue in Multiple Sclerosis

Numerous studies have endeavoured to elucidate the underlying mechanisms of fatigue in MS; however, due to its multifaceted character, it is difficult for scientists to describe its causal factors. The pathophysiological causes of fatigue in MS are highly complex and varied. Direct and indirect factors appear to be at play (Ayache & Chalah, 2017). To describe its pathophysiology, several researchers have distinguished between primary and secondary causes of fatigue in MS.

3.5.1. Primary causes of fatigue in Multiple Sclerosis

The onset of fatigue in MS is influenced by several pathophysiological mechanisms, namely inflammatory processes and endocrine influences, structural brain damage, dysfunctional neural networks, and metacognitive mechanisms.

3.5.1.1. Inflammatory processes and endocrine effects

The onset of fatigue in MS is predominantly influenced by cytokine and endocrine levels.

In the inflammatory phase of the disease, the occurrence of damage to the myelin sheath triggers the synthesis of proinflammatory cytokines (Dantzer & Kelley, 2007). The available evidence suggests that the presence of proinflammatory cytokines plays a role in the development of fatigue in MS patients (Heesen et al., 2006; Pokryszko-Dragan et al., 2012). To substantiate these findings, multiple studies have demonstrated elevated levels of cytokines in fatigued individuals with multi-focal MS compared to control subjects (Gold et al., 2011; Khademi et al., 2000). It has been observed through various studies that individuals with MS who experience fatigue exhibit higher concentrations of inflammatory cytokines, such as tumor necrosis factor and interferon gamma (IFN), compared to non-fatigued MS patients (Malekzadeh, de Geer-Peeters, De Groot, Elisabeth Teunissen, & Beckerman, 2015). Moreover, some studies have demonstrated that immunomodulatory drugs, such as interferons or vaccines, which intensify the release of proinflammatory cytokines, cause fatigue in MS patients (Harrison et al., 2015). Nevertheless, research examining inflammatory markers in individuals with MS has failed to establish a reliable correlation between inflammation and levels of fatigue (Penner & Paul, 2017).

Several research studies have endeavoured to elucidate the potential mechanisms through which inflammation may exert an influence on the manifestation of fatigue. There have been scientific hypotheses suggesting that inflammation in the CNS triggers the activation of microglia, leading to the production of cytokines that have the potential to disrupt dopaminergic transmission (Dantzer et al., 2014). The altered neural connectivity between the striatum and prefrontal cortex has been proposed as a potential explanation for the perception of fatigue (Chaudhuri & Behan, 2004; Dobryakova et al., 2015). The effectiveness of this connection relies on the dopaminergic meso-prefrontal afferents and has been associated with reward-based learning and motivation (Haber, 2014). In summary, according to this perspective, fatigue is understood as a form of altered response to reward and a subsequent decline in motivation.

Furthermore, some studies have demonstrated that stress levels that affect the functioning of the hypothalamic-pituitary-adrenal (HPA) axis (responsible for the regulation of stress via the secretion of corticosteroid hormones from the adrenal gland) and the serotonergic pathway (Bol et al., 2009) increase the production of cytokines and thus cerebral inflammation, exacerbating fatigue in MS (Morris & Maes, 2013).

Further evidence of the involvement of the HPA in the onset of fatigue is supplied by the strand of literature that shows that cortisol appears to play a role in the onset of fatigue, although it is not clear whether it is the primary cause (Powell, Moss-Morris, Liossi, & Schlotz, 2015). It is well known that the enhanced activity of the HPA raises the levels of corticotropin-releasing hormone (CRF) and cortisol in clinical trials (Kos et al., 2008). However, conflicting findings have emerged about the involvement of the HPA axis in the onset of fatigue in MS patients (Heesen et al., 2010). Thus far, the identification of a dependable biomarker for fatigue remains elusive (Penner & Paul, 2017).

3.5.1.2. Structural brain damage

As evidenced in Chapter 1, structural brain damage in MS is characterized by the presence of spatially and temporally dispersed lesions within the CNS. The occurrence of widespread damage to both WM and gray matter (GM) in individuals with MS can lead to atrophy in specific brain regions as well as overall brain volume reduction.

Extensive research has been conducted on the association between WM and fatigue. Several studies have established a correlation between global damage to WM and fatigue (Chalah et al., 2015; Sepulcre et al., 2009; Tedeschi et al., 2007); however, contrasting findings have also been reported (Papadopoulou, 2013; Van der Werf et al., 1998). These inconsistencies across studies could potentially be attributed to the techniques used for estimating structural abnormalities in the brain and to the variability observed among individuals (Bisecco et al., 2016; Rocca et al., 2014).

Numerous theoretical frameworks have been put forth to elucidate the connection between WM impairment and fatigue. For instance, it has been suggested that demyelination could potentially diminish the activation of synaptic targets in both the central and peripheral nervous systems, thereby potentially resulting in an increased susceptibility to fatigue (McDonald & Sears, 1970; Snooks & Swash, 1985). The development of fatigue has also been attributed by some authors to the disruption of interactions between brain regions, specifically those involved in motor planning and execution (Filippi et al., 2002).

As evidenced, MS is characterized by the presence of diffuse GM lesions in several brain regions, namely the insular cortex, anterior cingulate cortex (ACC), thalamus, basal ganglia, amygdala, substantia nigra, and hypothalamus (Bø, Vedeler, Nyland, Trapp, & Mørk, 2003; Vercellino et al., 2009). GM lesions have the potential to cause fatigue through various mechanisms. Some authors claim that the disruption of the large-scale networks that govern motor and cognitive activities due to lesions triggers compensatory activity that is responsible for the onset of fatigue (Morgen et al., 2004). Moreover, neuroimaging studies of fatigued patients reveal impairments of the functional connectivity of the basal ganglia (Finke et al., 2015), of the sensorimotor regions (Cruz et al., 2013), and of the default mode network (Bisecco et al., 2018). The presence of profound lesions in the GM of the brain has the potential to directly impact an individual's state of alertness, arousal, and motivation, thereby leading to the experience of fatigue. The hypothalamus is a notable example. Frequent hypothalamic lesions have been observed in individuals with MS (Qiu et al., 2011). According to Bonvalet and colleagues (2017), the presence of lesions in hypothalamic areas containing orexin-producing neurons results in a reduction in orexin levels, thereby contributing to the manifestation of fatigue in individuals with MS (Bonvalet, Ollila, Ambati, & Mignot, 2017). The precise mechanism by which orexin triggers fatigue remains uncertain, primarily due to conflicting findings in the literature (Constantinescu, Farooqi, O'Brien, & Gran, 2011). Moreover, the presence of GM lesions in the hypothalamus or brainstem nuclei has been found to potentially disrupt the regulation of the HPA and the descending neural control of the autonomic nervous system (Melief et al., 2013; Powell et al., 2015; Zellini et al., 2009), which could result in endocrine, autonomic problems and fatigue (Gottschalk, 2005; Heesen, 2001). Finally, GM lesions change large-scale motor and cognitive networks. Metacognition may detect network function changes causing fatigue (Morgen et al., 2004).

3.5.1.3. Dysfunctional neural networks

Beyond the structural alterations in the brains of fatigued MS patients, scientists have also suggested that functional alterations in specific neural networks are associated with fatigue (Bertoli & Tecchio, 2020). For instance, it has been suggested that lesions and/or inflammation may alter the integrity of the parieto-striatal network (Colombo et al., 2000), the fronto-striatal network (Pardini, Bonzano, Mancardi, & Roccatagliata, 2010; Specogna et al., 2012), and the cortico-cortical network, which mainly involves the fronto-frontal and fronto-parietal regions (Bisecco et al., 2016; Pravatà et al., 2016). Widespread damage to WM and GM may lead to the disruption of networks controlling certain cognitive activities, causing abnormal cortical activity to maintain cognitive performance after inflammation-induced network function loss. For instance, functional MRI studies have shown that fatigued MS patients have increased distributed brain activity during performances compared to those without fatigue and healthy controls (Filippi et al., 2002; Genova et al., 2013; Tartaglia, Narayanan, & Arnold, 2008). The disruption of networks leads to compensatory mechanisms (López-Góngora et al., 2015). Several studies suggest that self-monitoring mechanisms may identify the activation of "atypical" and compensatory "typical" areas (for further details, see next section).

3.5.1.4. Metacognitive mechanisms explain the occurrence of fatigue

The studies that have been reviewed so far purport to identify the potential physiological mechanisms underlying the onset of fatigue but do not explain the potential causes of subjective fatigue in MS. Recently, a metacognitive perspective that is based on self-monitoring has been proposed as an explanation of the development of the subjective experience of fatigue. Three metacognitive mechanisms of subjective fatigue have been proposed, namely: (1) interoception (the perception of physiological bodily states), (2) network-level functions, and (3) perceived movement effort.

According to the interoception theory, fatigue is related to core interoceptive deficits (i.e., disruptions in inner-body signal processing, e.g., Dantzer et al., 2014; Hanken, Eling, & Hildebrandt, 2014; Morris et al., 2018; Quadt, Critchley, Garfinkel, Tsakiris, & De Preester, 2018). According to the theory, fatigue is caused by inferences about the ability of the brain to manage physiological conditions. When the brain fails to control bodily states, no action to counteract states of dyshomeostasis is identified. A sensation of fatigue translates into a state of mind in which further activity is futile. A recent study suggests that disruptions of the neurocognitive markers that serve interoception may constitute a signature of fatigue in MS (Gonzales Campo et al., 2020). The ability of the brain to control physiological states is represented by a compact information-theoretic quantity (i.e., interoceptive surprise) that may be accessible by metacognitive regions. Interoceptive surprise may be calculated neuronally by using prediction-error signals that measure the difference between predicted and actual physiological conditions. Pyramidal cells in the supragranular layers of the interoceptive regions (e.g., the insula and the ACC) are hypothesized to communicate these prediction mistakes, which need ionotropic glutamatergic receptors, notably N-metil-d-aspartato (NMDA) (Seth, 2013). The exact mechanisms are unknown at present, but the underlying notion is confirmed by empirical data from several studies that draw on experimentally controlled conditions of dyshomeostasis to show the connection between activity in the insula and the anterior hypothalamus and subjective fatigue (Harrison et al., 2009).

Recent neuroimaging studies in MS patients have shown disruption of the electrophysiological indicators of interoception as well as structural atrophy and aberrant functional connections in the insula and the ACC (Salamone et al., 2018). Therefore, there must be several underlying causes of fatigue, which have important clinical implications. Interoceptive surprise may occur when any part of the closed-loop link between interoception, physiological control, and metacognition is disrupted (Petzschner, Weber, Gard, & Stephan, 2017). Interestingly, apparent dyshomeostasis may cause interoceptive surprise. This may occur if the cortical regions that interpret bodily experiences are disturbed, for example, by the focal lesions of the insula that are common in MS (Haider et al., 2016). The resulting illusion of dyshomeostasis would lead to dyshomeostatic body states that would precipitate and make chronic the first false interoceptive surprise. Similarly, initial changes in interactions, such as those brought about by inflammatory lesions in visceromotor regions such as the ACC (Haider et al., 2016), the hypothalamus (Huitinga, Erkut, van Beurden, & Swaab, 2004), or the brainstem nuclei, would result in long-lasting changes in body states.

Fatigue may also result from various types of prediction mistakes that the brain is unable to correct (McMorris, Barwood, & Corbett, 2018; Stephan et al., 2016). All cognitive domains entail self-monitoring of performance and the employment of domain-independent mechanisms of metacognition (Morales, Lau, & Fleming, 2018) that can "read out" error signals from domain-specific functional networks (Petzschner et al., 2017). As shown previously, in MS, lesions beyond the interoceptive pathways affect performance levels in numerous cognitive and motor activities (Loitfelder et al., 2014).

The sensorimotor system is the focus of the third suggested metacognitive process of fatigue (Kuppuswamy, 2017). This theory proposes that decreased sensory attenuation during movement execution determines proprioceptive prediction errors, leading the brain to believe that motion requires more effort than expected. Fatigue is the direct result of an unexpectedly high perceived effort during movement (proprioceptive surprise).

3.5.2. Secondary causes of fatigue in Multiple Sclerosis

Fatigue of a secondary nature pertains to the manifestation of fatigue that arises as a consequence of various factors intricately linked to the underlying ailment, notably disruptions in sleep patterns (Braley & Chervin, 2010; Mills & Young, 2011; Riccitelli et al., 2021), oxidative stress (Chalah et al., 2015), mood disturbances (Bol et al., 2009), and medication (e.g., muscle relaxants, anticonvulsants, and interferon betas).

Sleep disturbances. Several studies on the relationship between sleep disturbances and fatigue have been conducted in recent years. The role of sleep deprivation in the onset of fatigue has been demonstrated in several investigations (Braley, Segal, & Chervin, 2012; Brass et al., 2014; Kaminska et al., 2012; Kaynak et al., 2006; Manconi et al., 2008; Moreira et al., 2008; Strober, 2015; Veauthier et al., 2011). It has been found that 92% of MS patients who suffer from fatigue are poor sleepers (Bøe Lunde et al., 2012). A study on overall sleep duration indicated that over 85% of individuals with MS reported sleeping between five and 10 hours per night; however, a mere 63.7% of participants indicated experiencing heightened fatigue because of their sleep disturbances. The scientists discovered a V-shaped link between sleep duration and fatigue rather than a linear one. A comparison of sleep patterns revealed that the participants who slept the longest were the least tired (Mills et al., 2010). Associations between obstructive sleep apnea, restless legs syndrome, insomnia severity, and fatigue have been reported (Braley et al., 2016; Brass et al., 2014; Kaminska et al., 2012; Veauthier et al., 2011). According to a recent study conducted by McNicholas et al. (2021), the treatment of obstructive sleep apnea in individuals with MS yielded positive outcomes in terms of reducing fatigue levels and enhancing verbal memory performance. Nevertheless, the causal links between sleep problems and fatigue in MS are not clear, and more randomized and controlled clinical trials in which selection bias is minimized are required.

Oxidative stress. Oxidative stress's influence on the development of fatigue in MS has been the subject of scholarly investigation. Oxidative stress inhibits the sodium-potassium pump, which has negative effects on muscle performance and mitochondrial dysfunction. Some authors hypothesize that fatigue is a consequence of these changes, which are triggered by oxidative stress (Chalah et al., 2015).

In a recent study conducted by Katarina et al. (2020), it was found that fatigue and depression in MS patients can be attributed to both low-grade inflammation and oxidative stress. The authors suggested that these two factors must be considered simultaneously when examining the etiology of these symptoms.

Mood disturbances. The degenerative alterations associated with MS have the potential to induce psychological disorders in individuals affected by MS. These psychological disorders, in turn, can give rise to symptoms of fatigue.

Depression is the most common mood disorder that affects MS patients (Paparrigopoulos, Ferentinos, Kouzoupis, Koutsis, & Papadimitriou, 2010), and its relationship with fatigue has been well documented (Bol et al., 2009; Ford et al., 1998; Induruwa, Constantinescu, & Gran, 2012; Kaminska et al., 2011; Kos et al., 2008; Pittion-Vouyovitch et al., 2006). For instance, Bol et al. (2009) found that depressed and anxious individuals report more feelings of fatigue. However, they only discovered a modest linear relationship between fatigue, depression, and anxiety, possibly because psychological and personal characteristics may also be influential through behaviours such as avoidance, coping, and motivation. According to some authors, the psychological characteristics of MS patients affect the link between fatigue and depression (Fernández-Jimenez & Arnett, 2015). Some authors reported that MS patients with significant depression have high scores on the mental, physical, social-role, and psychological subscales of the Fatigue Impact Scale (FIS; Pittion-Vouyovitch et al., 2006). However, the literature is not unanimous. For instance, some studies found no association between Depression Rating Scale (DRS) scores and fatigue measured by using a visual analogue scale (VAS) in a group of MS patients (Krupp et al., 2010).

The discrepancies between studies may be due to the size of the samples used in the studies. Although the etiology of these interactions is unknown, similar pathophysiological processes may underpin mood disorders, psychological factors, and fatigue. Accordingly, some research indicates that depression and fatigue share neurological correlates (Gobbi et al., 2014).

Some studies have investigated the role of anxiety in the onset of fatigue. According to the results of some research, anxiety seems implicated in the exacerbation of fatigue (Newland et al., 2016); however, other studies have failed to validate these associations (Chwastiak et al., 2002). Moreover, some studies indicate that depression, anxiety, and fatigue in MS may all be traced to malfunctioning dopaminergic, histaminergic, and serotonergic pathways as well as the HPA axis (Bol et al., 2009). However, further research is needed.

Pharmacological treatments. Fatigue is a commonly observed side effect of various drugs employed in the treatment of MS. Therefore, knowledge of MS treatments and the associated side effects is critical in the study of fatigue in MS (Gottberg, Gardulf, & Fredrikson, 2000). Analgesics, muscle relaxants, anxiolytics, antidepressants, hypnotics, pain medication, antihistamines, anti-convulsants, and beta-blockers are all involved in the onset of fatigue in MS (Braley & Chervin, 2010). Disease-modifying drugs, interferon, immunomodulatory and immunosuppressive treatments, and the corticosteroids that are used to treat MS relapses in the short term have been shown to induce or worsen fatigue (Braley & Chervin, 2010; Shah, 2009; Smith & Hale, 2007).

3.6. Environmental factors contributing to fatigue in Multiple Sclerosis

There are various environmental factors that can trigger or exacerbate the likelihood of experiencing fatigue in individuals with MS.

Ambient temperature. The influence of temperature on fatigue exacerbation, particularly for individuals who suffer from neurological conditions such as MS, is well known (Bakshi, 2003; Bol et al., 2012; Crayton et al., 2004). Heat intolerance is a prevalent manifestation noticed in individuals diagnosed with MS (Davis et al., 2010). Elevated temperatures compromise the conduction of electrical signals (caused by lesions in the myelin sheath), reducing the capacity to regulate body temperature, leading to the consequent manifestation of heat intolerance and increased fatigue (Bergamaschi et al., 1997; Christogianni et al., 2018; Kos et al., 2008; Krupp, 2003; Rudroff et al., 2016). Studies show that even slight elevations in body temperature can exacerbate fatigue and other associated symptoms in MS. The transient exacerbation of neurological symptoms resulting from an elevation in body temperature is commonly referred to as Uhthoff's phenomenon (Uhthoff, 1890). Recently, it has been observed that fatigue in MS patients exhibits inherent temporal variability. The level of fatigue experienced by MS patients was found to be greater during the summer season in comparison to the winter season (Grothe, Gross, Süße, Strauss, & Penner, 2022).

Johnson (2008) found that individuals with MS reported that humidity, rather than temperature alone, was a trigger for the manifestation of unfavorable symptoms, such as fatigue. However, it is worth noting that there were other patients who did not observe any noticeable changes in their overall state of health when exposed to heightened levels of heat or humidity. Some studies have indicated that mitigating the core body temperature of individuals with MS seems effective in alleviating fatigue (Flesner & Lindencrona, 2002; NASA/MS Cooling Study Group, 2003). Some authors have revealed that patients who are exposed to lower temperatures exhibit decreases in leukocytes, which may explain the reduction in the feeling of fatigue (Beenakker, Van der Hoeven, Fock, & Maurits, 2001). According to the NASA/MS Cooling Study Group (2003), demyelinated nerves exhibit a decrease in neural conductivity when subjected to high temperatures, while cooling these nerves results in an increase in conductivity. It is postulated that this augmented conductivity may alleviate fatigue. There is evidence that MS patients who use cooling suits see their self-reported fatigue, muscle strain, mental fatigue, and social problems decrease (Schwid et al., 2003). However, the data on the relationship between fatigue and temperature in MS patients remains inconclusive.

Diet. Several studies have reported on the significance of nutrition in the progression of MS and associated complications, including fatigue (Payne, 2001). Diet can play an important role in fatigue, as what individuals consume can impact their energy levels and overall health, as well as contribute to or relieve fatigue (Snetselaar et al., 2023). Several studies have demonstrated that an imbalanced diet (either hypercaloric or deficient in nutrients) may trigger fatigue. According to several studies, a starchy plant-based diet with low fat (Yadav et al., 2016) or a modified Paleo diet (Bisht et al., 2015) may lead to an improvement in self-reported fatigue levels, whereas a low-fat diet may exacerbate fatigue (Weinstock-Guttman et al., 2005). Recently, Moravejolahkami and colleagues (2020) assessed the correlation between acute and chronic fatigue and dietary patterns. The research findings indicate a negative correlation between the severity of fatigue and adherence to a healthy dietary pattern (Moravejolahkami, Paknahad, & Chitsaz, 2020). Several studies have indicated that the inadequacy of essential nutrients such as iron, vitamin B12, magnesium, and folate can result in fatigue (Bitarafan et al., 2014). For instance, some studies have shown that the administration of supplements to MS patients such as vitamin B12, iron (Van Rensburg et al. 2006), and coenzyme Q10 (Sanoobar, Dehghan, Khalili, Azimi, & Seifar 2016) yielded favorable outcomes in reducing fatigue.

Sedentary lifestyle. Individuals affected by MS exhibit lower levels of physical activity in comparison to their healthy counterparts (Motl, McAuley, & Snook, 2005; Ng & Kent-Braun, 1997). Research conducted on the impact of a sedentary lifestyle on the development of fatigue has yielded inconsistent findings. Some studies indicate that individuals with MS may experience an exacerbation of fatigue because of extended periods of physical inactivity or a sedentary way of life. Petajan et al. (1996) have suggested that a 10-week program of aerobic exercise leads to a reduction in the self-reported fatigue score, as assessed by the Profile of Mood States. Comparable results in studies in which MS patients followed exercise training (Oken et al., 2004). Conversely, certain investigations have indicated that self-reported fatigue did not exhibit any correlation with the diminished activity level among persons afflicted with MS (Vercoulen et al., 1997) and that there was no amelioration in the severity of fatigue scores following a brief exercise regimen lasting between 3 and 4 weeks (Mostert & Kesselring, 2002; van den Berg et al., 2006).

3.7. Factors linked to fatigue in Multiple Sclerosis

Several studies have examined the link between fatigue, disability, the duration of illnesses, the MS subtype, sociodemographic factors, and psychosocial factors.

A positive correlation between disability and the degree of fatigue that MS patients experience has been suggested in several studies (Aygünoğlu, Celebi, Vardar, & Gürsoy, 2015; Biberacher et al., 2018;

Bisecco et al., 2016; Gobbi et al., 2014; Hesse et al., 2014). For instance, some authors found that fatigued MS patients have considerably higher degrees of impairment over a period of two years (Lerdal et al., 2007). In their study, Motl and McAuley (2009) discovered a significant correlation between self-reported fatigue and both physical and psychological functional impairment in MS patients. In a study conducted by Mills et al. (2010), it was observed that there was a correlation between impaired ambulation (EDSS 5.5) in patients with MS and an increase in fatigue experienced by these patients. Pittion-Vouyovitch et al. (2006) posited a hypothesis suggesting a positive correlation between elevated EDSS scores and heightened levels of physical and social fatigue components in MS patients. Nevertheless, a lack of correlation between the characteristics of mental fatigue and the degree of impairment has been observed. This observation suggests that EDSS may have greater applicability for assessing physical impairments and social disturbances than mental indicators of fatigue.

As far as disease duration is concerned, there are controversial results on its relationship with fatigue in MS (Codella et al., 2002). While some studies have found that fatigue in MS increases with the duration of the illness (Biberacher et al., 2018; Cavallari et al., 2016; Kister et al., 2013; Mills et al., 2010), others have failed to replicate those results (Bisecco et al., 2016; Ghajarzadeh et al., 2013; Yaldizli et al., 2011). These disparities may be due to differences in methodology or instrumentation used across studies.

As for the relationship between MS phenotype and fatigue, several studies have found that fatigue in MS is recorded for all phenotypes but differs across illness patterns and subtypes (Braley & Chervin, 2010; Kroencke, Lynch, & Denney, 2000). The evidence indicates that RRMS patients are often less fatigued than PPMS ones (Zhang, Pan, Sun, & Tang, 2018), while SPMS patients are more fatigued than those with PPMS (Aygünoğlu, Celebi, Vardar, & Gürsoy, 2015; Mainero et al., 1999). However, more data and further investigations are needed because the link between MS phenotypes and fatigue currently varies across analytical techniques and control selections.

The effect of fatigue on MS patients has also been studied in relation to sociodemographic factors such as age, gender, education, and employment. According to several papers, fatigue in MS is observed throughout the illness, regardless of age (Ghajarzadeh et al., 2013; Morrison & Stuifbergen, 2016), and there is no significant correlation between fatigue, gender, MS phenotype, and disease duration (Bakshi, 2003; Derache et al., 2013; Gobbi et al., 2014). However, other studies have demonstrated that subjective fatigue in MS patients increases with age and disease duration (Ghajarzadeh et al., 2013).

The existing body of literature pertaining to the association between gender and fatigue exhibits a range of perspectives (Aygünoğlu et al., 2015; Fazili & Shayesteh-Azar, 2012). Several studies have shown that fatigue is experienced by individuals of various ages and genders (Mills et al., 2010; Tola et al., 1998). Conversely, there is evidence suggesting that female patients with MS report higher levels of fatigue compared to their male counterparts (Fjeldstad, Brittain, Fjeldstad, & Pardo, 2010). Nevertheless, it is worth noting that several other studies have not been able to validate or support the aforementioned findings (Lerdal et al., 2003).

Concerning education, there is evidence indicating that educational attainment among individuals with MS may have an impact on the perception of fatigue in MS patients (Kroencke et al., 2000; Lerdal et al., 2003; Razazian, Shokrian, Bostani, Moradian, & Tahmasebi, 2014). Some studies have shown a link between high fatigue and lower educational attainment (Aygünoğlu et al., 2015; Lerdal et al., 2003; Tedeschi et al., 2007; Weiland et al., 2015). Supporting these results, Lerdal et al. (2003) found a significant inverse association between fatigue and education. The researchers discovered that individuals with higher levels of education may possess a greater familiarity with coping strategies and a higher capacity for mental adaptation. This enhanced ability may contribute to their improved management of feelings of fatigue. In line with these results, Weiland et al. (2015) have shown that more educated individuals are more inclined to take responsibility for their own health and well-being. However, these results are not conclusive, and other perspectives exist on the relationship between education and fatigue (Mills et al., 2010; Razazian et al., 2014).

Some researchers have shown that fatigued patients have a lower QoL (Pittion-Vouyovitch et al., 2006) and that higher self-perceived fatigue is linked to worse physical QoL in MS patients. In a study by Yamout et al. (2013), the impact of several demographic, clinical, physical, social, economic, and psychological variables on the QoL of such patients was examined. The results indicate that low fatigue scores on the FSS are predictors of higher QoL.

Some authors have focused on the relationship between fatigue in MS and self-efficacy (Trojan et al., 2007). Self-efficacy, the confidence to handle difficult situations (Bandura, 1977), is particularly crucial in unpredictable chronic illnesses such as MS. According to Bradley et al. (1984), patients who believed that they had little control over their illness exhibited lower levels of self-esteem and showed lower expectations for their ability to self-manage, all of which might contribute to the development of fatigue. The QoL of MS patients might potentially be improved via increased self-efficacy, according to research (Aalto, Uutela, & Aro, 1997).

As for the relationship between fatigue and cognitive impairment, studies are conflicting, and the causative links between these two distressing symptoms still need to be properly understood. The exposition will return to the topic in Chapter 5.

3.8. Assessment of fatigue in Multiple Sclerosis

Various approaches to measuring subjective and objective fatigue in MS have been highlighted in different reviews (Flachenecker et al., 2002; Khan, Amatya, & Galea, 2014; Krupp, LaRocca, Muir-Nash, & Steinberg, 1989; MSCP, 1998; Penner et al., 2009; Téllez et al., 2005). The paragraphs that follow provide an overview of the main methods for evaluating subjective and objective fatigue that emerge from the literature.

3.8.1. Assessment of subjective fatigue in Multiple Sclerosis

Self-report questionnaires are the most used measures of subjective fatigue in clinical practice and research (Schwartz, Jandorf, & Krupp, 1993) because they generate insights into the individual's perspective and their experience of the symptom (MacAllister et al., 2005). A variety of tools have been developed in recent years that purport to evaluate subjective mental and physical fatigue in MS (Penner et al., 2015). Indeed, some scales are unidimensional (collect feedback on a single dimension of the experience of fatigue), while others are multidimensional (focus on many dimensions of fatigue, such as intensity or nature of fatigue; Dittner et al., 2004). Unidimensional scales (or target scales focused on a singular aspect) are simple to use, trustworthy, and provide a more profound evaluation of fatigue, covering matters such as severity, affective and motivational feelings, and the impact of fatigue on mental and physical performance (Dittner et al., 2004; Mills et al., 2010); however, information about some underlying aspects is omitted from them (Christensen & Piper-Terry, 2004).

As shown previously, subjective fatigue may be conceptualized both as trait fatigue and as state fatigue. As for trait fatigue, it can be examined through interviews, diaries, and scales. Most of the devised scales focus on the severity and impact of fatigue on physical and cognitive functions (which are investigated through items that measure the disruption of basic quotidian activities) and on the core feelings of fatigue elicited through items that concern motivation and affective emotions (Zifko, 2004; Mathiowetz, 2003).

Among the most common scales are the Fatigue Severity Scale (FSS; Krupp et al., 1989), which evaluates the intensity, frequency, and daily impact of fatigue, and the Modified Fatigue Impact Scale (MFIS; Fisk et al., 1994), and the Fatigue Impact Scale (FIS; Fisk et al., 1994) which assess the impact of fatigue on the daily lives of MS patients. The core feeling of fatigue is evaluated by the Piper Fatigue Scale (PFS; Piper et al., 1998) and the Multidimensional Fatigue Inventory (MFI; Stein et al., 1992). The MFI and the Checklist of Individual Strength (CIS; Stein et al., 1998) are focused on motivation. Subjective fatigue is also commonly evaluated through the Fatigue Scale for Motor and Cognitive Functions (FSMC; Penner et al., 2009), which assesses the intensity of mental and physical fatigue, patient motivation, learning, and attention, and by the Fatigue Assessment Scale (FAS; Michielsen et al., 2003), which covers both the physical and mental components of fatigue (Michielsen et al., 2003; 2004). The Fatigue Assessment Instrument (FAI; Schwartz et al., 1993) yields comprehensive analyses of the quantitative and qualitative aspects of fatigue.

The tools available for addressing state fatigue are, however, considerably restricted. Likert scales and VAS (Lee, Hicks, & Nino-Murcia, 1991) have commonly been employed to evaluate state fatigue due to their efficiency in assessment and ease of interpretation (Christodoulou, 2005; Terry, Lane, & Fogarty, 2003).

The VAS includes a horizontal straight line on which patients are asked to rate their current state of fatigue on a scale from 0 to 10, with 0 representing "no fatigue" and 10 representing "extreme fatigue". VAS scales are often used to evaluate changes in fatigue over time or to compare fatigue after a taxing activity to fatigue after a control task. As for the evaluation of subjective physical fatigue, various scales and questionnaires focused on effort perception, exercise-induced pain, and discomfort perception are used (Micklewright et al., 2017). A recent review indicated that there are three questionnaires that have significantly gained popularity in the last few years: the Brugmann Fatigue Scale (BFS; Mairesse et al., 2019), the Multidimensional Assessment of Fatigue (MAF; Belza, Miyawaki, Liu, Zhang, & Fessel, 2015), and the MFIS (Billones, Liwang, Butler, Graves, & Saligan, 2021).

Despite the proliferation of measures for assessing fatigue, there is still no consensus on the most appropriate questionnaire for the clinical context. The tools have several limitations, and their outputs may be difficult to interpret in research settings. Consequently, objective indicators of fatigue are often preferred in research protocols.

3.8.2. Assessment of objective fatigue in Multiple Sclerosis

Although subjective self-reports have been widely used to evaluate fatigue, these instruments do not yield objective indicators. As for the evaluation of objective fatigue, mental and physical performance measurements have been used across studies (Linnhoff et al., 2019; Tommasin et al., 2020; Smith et al., 2019).

Protocols for the evaluation of objective physical fatigue in MS patients include the assessment of body function level (changes in performance during a functional activity) and the activity levels of the subjects (walking; International Classification of Functioning, Disability, and Health: ICF; Geneva, Switzerland: WHO; 2001).

The body function level is evaluated through isometric maximal contractions in the lower and upper extremities to assess the rate of strength decline in patients with MS. Subjects' activity levels are evaluated through measures of ambulatory fatigue (Burschka et al., 2012; Schwid et al., 1999) that examine indices of walking speed, distance, and/or specific gait kinematics (Engelhard, Dandu, Patek, Lach, & Goldman, 2016). For example, the 6-minute walking test (6MWT; Solway, Brooks, Lacasse, and Thomas, 2001) enables the calculation of resistances and paths as well as the determination of walking velocity and changes in gait kinetics and kinematics (Goldman et al., 2008). Currently, there is no agreement on the optimal method for assessing objective fatigue in patients with MS, and there is insufficient information about psychometric methods.

A wide range of methods have been used to quantify objective mental fatigue. Objective mental fatigue may be measured as the decrease in performance that occurs during periods of acute and sustained mental effort on various cognitive tasks, known as cognitive work (Schwid et al., 2003; Bryant et al., 2004). In general, the decrease in cognitive abilities with reference to baseline performance on demanding tasks (DeLuca, 2005; Linnhoff et al., 2019) is used to quantify objective mental fatigue. Three approaches have been used to assess objective mental fatigue, defined as a performance decline over time (Linnhoff et al., 2019). The first method measures objective mental fatigue over a long period of time, in which the individuals repeat the test procedure on numerous occasions. The results are compared to a baseline. The second method entails measuring the loss of performance on a mental or cognitive task before and after a loading task; however, this approach has various disadvantages, including test-retest reliability. The third method involves measuring objective mental fatigue during periods of acute and sustained mental effort and comparing performance at the start of the period to performance at the end of the period.

Most researchers quantify objective mental fatigue behaviorally by measuring changes in response time, accuracy, and processing speed in vigilance tasks (Linnhoff et al., 2019). In relation to response times, several studies have demonstrated that individuals diagnosed with MS exhibit prolonged reaction times compared to control groups during cognitive tasks. One potential implication that can be inferred is that extended reaction times could potentially serve as an indicator of mental fatigue (Bruce, Hancock, Arnett, & Lynch, 2010; Cehelyk et al., 2019; Claros-Salinas et al., 2013; Fiene et al., 2018; Huolman et al., 2011; Kujala, Portin, Revonsuo, & Ruutiainen, 1995; Neumann et al., 2014; Weinges-Evers et al., 2010).

In a study conducted by Bruce et al. (2010), the researchers employed reaction time variability (RTV) as an alternative measure for assessing mental fatigue in individuals with MS during extended periods of cognitive engagement. The authors hypothesized that mental fatigue may not result in a linear drop in mental ability but in periodic attention lapses. During these gaps, more effort may be needed to assemble the mental reserves that are necessary to complete a task effectively and consistently (Bruce et al., 2010).

Several markers of objective mental fatigue have been identified. These include the Test Battery for Attentional Performance (TAP; Zimmermann & Fimm, 2002), the Alertness Subtest (AS) of the computerized test battery for attentional performance (TAP-M/version mobility; Zimmermann, Gondan, & Fimm, 2005), the Symbol Digit Modalities Test (SDMT; Smith, 1982), and the Paced Auditory Serial Addition Test (PASAT; Gronwall, 1977). The PASAT, which is a measure of information processing speed and deficiencies in working memory, is used in research on mental fatigue when sustained attention is required because of its established sensitivity and validity. The sensitivity of the PASAT varies with the scoring system (Walker et al., 2012). Several scoring methods have been used to evaluate fatigue during the experimental task. In one way, the performance on the PASAT's first 20 items and final 20 items are evaluated. The other method employed the slope of linear regression of valid PASAT answers for consecutive 10-item groups (Schwid et al., 2003). Other methods rely on the dyad score method (Snyder & Cappel Jeri, 2001) to determine the effectiveness of the examination and the extent to which correct responses reflect task-related performance (total number of correct responses, total dyad score, and percent dyad score). According to Berard et al. (2018), the percent dyad technique is more sensitive to mental fatigue than performance levels when taken in isolation (Berard, Smith, & Walker, 2018), which is consistent with earlier research (Bryant et al., 2004). The outcomes, however, differ depending on the approach chosen. Some authors have also used information processing speed measures, such as the Computerized Test of Information Processing (CTIP; Tombaugh, Lindsay, Berrigan, Walker, & Freedman, 2010; e.g., Walker et al., 2012), to evaluate mental fatigue.

In conjunction with behavioral signs of mental fatigue, several techniques may be used to evaluate neurological functioning as well as structural alterations in the brains of fatigued MS patients. EEG, MEG, and fMRI are all used in conjunction with mental or physical activity to visualize the abnormalities in brain functioning that are linked to MS fatigue. Several studies draw on EEG or event-related potential (ERP; Sutton, Braren, Zubin, & John, 1965) measurements to objectively assess the neural alterations that are related to mental fatigue. P300 and ERP have been extensively employed as markers of cognitive functioning in a variety of mental and neurological illnesses (Sur & Sinha, 2009). Transcranial magnetic stimulation (TMS) is another approach to test corticospinal tract excitability and cortical connectivity.

3.9. Treatment of fatigue in Multiple Sclerosis

Given the complexity of fatigue in MS, a multidisciplinary and tailored approach seems warranted. Currently, MS fatigue is treated with various pharmacological and non-pharmacological therapies. However, the effects of these interventions vary widely, and their benefits have yet to be demonstrated. Contemporary pharmacological therapies for fatigue in MS, such as dopaminergic medications and psychostimulants, are not particularly effective despite their wide availability and constant development. Amantadine (Shaygannejad, Janghorbani, Ashtari, & Dehghan, 2012), Modafinil, and Fampridine are the most commonly used antifatigue medicines in clinical practice (Lange, Volkmer, Heesen, & Liepert, 2009; Mitsikostas et al., 2021). In contrast to the most prevalent drugs, which have modest benefits, non-pharmacological therapies seem to enhance patient QoL by reducing the effect and severity of long-term fatigue (Induruwa et al., 2012). The available non-pharmacological interventions include aerobic exercise, resistance training, yoga, tai chi, cooling therapies, and psychological and cognitive approaches (e.g., cognitive behavioral therapy, education programs, and mindfulness interventions; Brenner & Piehl, 2016). Within the realm of non-pharmacological interventions, there are also energy conservation measures that are critical for managing fatigue in MS patients (Olek & Mowry, 2018). One of the most effective programs is the Fatigue Management Program, which is administered by ergo therapists (MacAllister et al., 2005; Tur, 2016) who use energy conservation measures to minimize fatigue and promote self-efficacy (Mathiowetz, Finlayson, Matuska, Chen, & Luo, 2005). Finally, non-invasive brain stimulation methods have generated considerable interest in the study of numerous neuropsychiatric illnesses in recent years, and they seem to help with fatigue in MS patients.

Some studies have shown that repeated TMS and transcranial direct current stimulation (tDCS) modulate fatigue in those with MS (Chalah et al., 2015; Liu, Fan, Xu, & Cui, 2019).

4. COGNITIVE IMPAIRMENT IN MULTIPLE SCLEROSIS

4.1. Introduction

Although cognitive impairment in MS has been ignored for far too long, it is now clear that it is a clinically relevant manifestation of the disease. The prevalence rates of cognitive impairment in adults with MS range from 40% to 70% in Europe and North America (DiGiuseppe, Blair, & Morrow, 2018). Cognitive impairment seems to affect between 20% and 25% of individuals with CIS and RIS, between 30% and 45% of individuals with RRMS, and between 50% and 75% of individuals with SPMS (Benedict, Amato, DeLuca, & Geurts, 2020). Cognitive decline in MS affects several functions, such as attention, processing speed, episodic memory, problem solving, executive skills, and visual perception; it affects all MS subtypes (Johnen et al., 2017; Ruano et al., 2017), and its pattern varies between patients (i.e., cognitive phenotypes; Drew, Tippett, Starkey, & Isler, 2008; Leavitt, Tosto, & Riley, 2018). Cognitive impairment negatively affects daily functioning, including disruptions in social interactions and employment (Bobholz & Rao, 2003). Furthermore, cognitive impairment affects coping methods, treatment compliance, and the patient's ability to benefit from rehabilitative measures (Amato, Portaccio, & Zipoli, 2006; Goretti et al., 2009).

4.2. Clinical variables of cognitive deficit in Multiple Sclerosis

Cognitive impairment in MS progresses slowly (Amato, Ponziani, Siracusa, & Sorbi, 2001; Ruano et al., 2017); it can occur during any of the phases of the disease, even the early ones, and it may unfold before the MS diagnosis can be confirmed (Benedict et al., 2017; Glanz et al., 2007). In patients with RIS, the cognitive deficits can predate the appearance of other neurological symptoms and signs (Amato & Portaccio, 2012; Benedict et al., 2006; Deloire et al., 2006; Deloire, Ruet, Hamel, Bonnet, & Brochet, 2010; Van Schependom et al., 2014). Manifesting cognitive deficits before the diagnosis of MS is a negative prognostic sign (Glanz et al., 2006; Zipoli et al., 2010), as it may precede the identification of severe structural abnormalities.

MS duration and the severity of cognitive impairment have been examined often in longitudinal (Amato et al., 2001; Jennekens-Schinkel, Laboyrie, Lanser, & van der Velde, 1990) and cross-sectional studies (Achiron et al., 2013; Rogers & Panegyres, 2007), but the relationship between them remains unclear. Some researchers have found that cognitive impairment worsens with illness duration (Achiron et al., 2013; Dackovic et al., 2016) and increases with disability severity (Yigit, Acikgoz, Mehdiyev, Dayi, & Ozakbas, 2021); however, other studies have failed to confirm these results (Brandes, Callender, Lathi, & O'Leary, 2009; Chiaravalloti & DeLuca, 2008; Lynch, Parmenter, & Denney, 2005; Rogers & Panegyres, 2007). Several studies have focused on the relationship between the age of MS patients and cognitive impairment, finding inconsistent results (Leclercq et al., 2014; Ruano et al., 2017). For instance, according to several authors, 77.4% of older MS patients exhibit cognitive decline (Branco et al., 2019), but it seldom leads to dementia (Staff et al., 2009). According to some studies, the cognitive profiles of elderly MS patients are defined by slower processing speeds and decreased language ability (Jakimovski et al., 2019). However, recent research has demonstrated that older and younger MS patients have comparable cognitive impairment profiles, suggesting that cognitive impairment is a consequence of MS (Branco et al., 2019). One strand of the literature concerns the relationship between the complaints of patients and objective cognitive impairment. While most studies have found a relationship between self-reported cognitive complaints and objective tests (Benedict et al., 2004; Chiaravalloti, Christodoulou, Demaree, & DeLuca, 2003; Hoogervorst et al., 2001; Maor, Olmer, & Mozes et al., 2001; Randolph, Arnett, & Higginson, 2001), others failed to report this association (Benedict, Fishman, McClellan, Bakshi, & Weinstock-Guttman, 2003; Gold et al., 2001; 2003).

4.3. Cognitive deficit in Multiple Sclerosis

Information processing speed, complex attention, working memory, long-term memory, spatial reasoning, and executive functioning are the cognitive functions that are impaired most often in MS (Benedict et al., 2006; Brissart, Morele, Baumann, & Debouverie, 2012; Chiaravalloti & DeLuca, 2008; Deloire et al., 2011); language and visual processing deficits have also been noted, but their incidence is lower (Benedict et al., 2006; Rao, Leo, Bernardin, & Unverzagt, 1991).

4.3.1. Attention

It is estimated that 5% to 25% of MS patients exhibit specific attentional impairments (Islas & Ciampi, 2019). Attention is a multidimensional phenomenon. In Posner's seminal model, activation, selection, and control are involved in the construct of attention (Posner, 1980). Posner's model assumes that attention is an autonomous system that is separated into subsystems that underlie distinct brain regions that are interrelated and comprise a complex structure (Posner, 1989). According to Posner's model, the attention system has three main networks: an alerting system, which achieves and maintains an adaptive alert state; a spatial orienting system, which identifies information from relevant visual areas; and an executive control system, which identifies, monitors, and solves conflicts in the information processing flow (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005; Fan, McCandliss, Sommer, Raz, & Posner, 2002; Posner & Dehaene, Attentional Networks, 1994).

Attention deficits are present early in MS, and they may be considered an important indicator of cognitive decline as they are likely to represent the early neuropsychological manifestations of the disease. Attentional problems in MS are not always widespread and may be process-specific (Penner, Rausch, Kappos, Opwis, & Radü, 2003). For instance, MS patients exhibit abnormalities in divided and sustained attention on tests (McCarthy, Beaumont, Thompson, & Peacock, 2005); notably, their reaction times are slower.

4.3.2. Information processing speed

Information processing speed is present in 40% to 70% of patients (Migliore et al., 2017). Evidence shows that information processing speed is the domain that MS affects most severely (Bergendal, Fredrikson, & Almkvist, 2007; Chiaravalloti & DeLuca, 2008). Information processing speed is the speed at which basic cognitive processes can be completed (Costa, Genova, DeLuca, & Chiaravalloti, 2017), regardless of whether the information is visual, auditory, or kinetic.

Several studies indicate that information processing speed is lower in MS patients than in controls (Demaree, DeLuca, Gaudino, & Diamond, 1999; Kail, 1998) and that patients with SPMS often exhibit more dramatic deteriorations in information processing speed than patients with RRMS and PPMS (Bergendal et al., 2007). Several studies indicate that information processing speed can be impaired at an early stage of the disease (Migliore et al., 2017) and that it tends to worsen as the disease progresses. It has been suggested that information processing speed may be related to the impairment of other domains of cognition (Chiaravalloti & DeLuca, 2008), such as long-term memory, working memory (Grzegorski & Losy, 2017), and executive function (Leavitt, Lengenfelder, Moore, Chiaravalloti, & DeLuca, 2011; Macniven et al., 2008).

4.3.3. Memory

Memory impairment is a common cognitive deficit in MS. It affects between 33% and 65% of patients (Guimarães & Sá, 2012). Both long-term memory, the capability to acquire new knowledge and to remember previously acquired information, and working memory, the ability to retain a small amount of information and employ it for cognitive activities, are usually affected by MS (Chiaravalloti &

DeLuca, 2008; Guimarães & Sá, 2012). As far as long-term memory is concerned, MS patients exhibit difficulties in learning (Chiaravalloti & DeLuca, 2008), information encoding (Thornton, Raz, & Tucker, 2002), storage processes (DeLuca, Gaudino, Diamond, Christodoulou, & Engel, 1998), and long-term recall (DeLuca et al., 1998; Amato et al., 2010). Some authors have speculated that memory deficits in MS derive mainly from inadequate retrieval processes from long-term storage (Caine, Bamford, Schiffer, Shoulson, & Levy, 1986; Rao, Leo, & Aubin-Faubert, 1989), while others have hypothesized that memory issues are related to difficulties in the initial learning phase (Thornton et al., 2002;Trenova et al., 2016); however, it remains unclear which memory component provides the best explanation for memory deficits in MS (Thornton et al., 2002).

Working memory deficits can be found (for a review, see Brissart et al., 2012) at every stage of the illness (Audoin et al., 2005) and across different illness trajectories (Grigsby, Ayarbe, Kravcisin, & Busenbark, 1994), especially in the progressive and relapsing-remitting forms of MS (Mousavi, Zare, Etemadifar, & Taher Neshatdoost, 2018). According to some authors, deficits in working memory may be secondary to impairments in processing speed (Silveira, Guedes, Maia, Curral, & Coelho, 2019). Future thinking and autobiographical memory are compromised early in MS (Ernst, 2020), while implicit memory (non-declarative memory), which facilitates the completion of tasks by enabling knowledge to be recalled without effort (González Torre et al., 2017), is typically spared (Borragán et al., 2022; Tomassini et al., 2011).

4.3.4. Executive functions

Deficits in executive functions affect from 20% to 30% of MS patients (Grech et al., 2017) and are less common than deficits in memory and information processing efficiency (Arnett & Strober, 2011; Denney, Sworowski, & Lynch, 2005). Executive function is a complex domain that subsumes mental control and self-regulation as well as verbal reasoning, problem solving, planning, sequencing, sustaining attention, resistance to interference, responding to feedback, multitasking, organization, shifting, self-monitoring, information processing speed, working memory, inhibition, and cognitive flexibility (Burgess, Veitch, de Lacy Costello, & Shallice, 2000). Deficits in executive functions in MS patients can affect several domains, including abstract and conceptual reasoning, response inhibition, problem solving, decision-making (Grech et al., 2017), and verbal fluency in both its phonemic and semantic aspects (Henry & Beatty, 2006). However, no typical pattern of deficits has been identified (Drew et al., 2008).

4.3.5. Language

According to recent research, language impairment affects between 20% and 58% of individuals with RRMS or SPMS (Ntoskou et al., 2018). While episodic memory and information processing speed have been extensively examined, language deficits in MS are understudied. The language domain encompasses a wide range of activities, including receptive language, object naming, word searching, fluency, grammar, and syntax (Sachdev et al., 2014). Low performance in verbal fluency tests, particularly on phonemic fluency tasks and in verbal comprehension tasks, is very common in MS patients (Arnett & Strober, 2011). According to some studies, working memory, information processing speed, and executive dysfunction may be responsible for several language deficits. Aphasia disorder is relatively rare in MS patients.

4.4. Cognitive impairment in different Multiple Sclerosis phenotypes

In the literature, studies that examine cognitive patterns in patients with different MS subtypes have yielded conflicting findings. Some of the extant literature suggests a global pattern of cognitive abnormality in MS that occurs irrespective of the course of the illness, with a progressive amplification of expression that depends on the progression of the disease (Potagas et al., 2008). Other studies indicate that the cognitive profile of MS patients varies across subtypes (Potagas et al., 2008; Ruano et al., 2017).

There is evidence for the proposition that both RRMS and CIS patients exhibit deficiencies in information processing speed, verbal and visuospatial memory, and executive functions (Potagas et al., 2008). However, some studies have demonstrated that RRMS patients exhibit superior verbal memory and verbal fluency (Ruano et al., 2017) than CIS patients (Potagas et al., 2008). The studies that compare the cognitive profiles of RRMS and PPMS patients indicate that the latter exhibit more severe cognitive deficits than the former. PPMS patients tend to experience impairments in memory and executive function (Branco et al., 2019; Ruano et al., 2017). They suffer from a variety of cognitive deficits, while those with RRMS only experience lapses in information processing speed, working memory, and attention (Ruet et al., 2013). A large Dutch study indicates that cognitive impairment is more severe in PPMS and SPMS patients than in RRMS patients, but SPMS and PPMS patients were found to be equally impaired (Huijbregts et al., 2004).

According to some authors, deficits in processing speed and working memory are more common in SPMS than in other MS phenotypes (DeLuca, Chelune, Tulsky, Lengenfelder, & Chiaravalloti, 2004). A study of 101 patients with different MS subtypes indicates that the frequency with which patients with SPMS experience impairments in information processing speed, executive function, verbal fluency, verbal episodic memory, working memory, and visuospatial construction is twice as high as that observed among those with RRMS (Planche, Gibelin, Cregut, Pereira, & Clavelou, 2016). Some studies have shown that patients with PPMS or SPMS encounter more difficulties in cognitive tests than those with other forms of MS, such as CIS and RRMS (Dackovic et al., 2016). No firm conclusions can be drawn about the cognitive profile of RIS patients due to the scarce evidence (Brochet & Ruet, 2019).

4.5. Neural basis of cognitive impairment in Multiple Sclerosis

In MS, cognitive impairment has been linked to the magnitude of WM abnormalities and lesion loads (Tekok-Kilic et al., 2007; Zivadinov et al., 2001), to linear measure changes (Butzkueven et al., 2008), to whole-brain atrophy (Summers et al., 2008), to focal cortical injuries (Calabrese et al., 2009), to diffuse cortical atrophy (Calabrese et al., 2009; Steenwijk et al., 2016), and to deep GM structures such as the corpus callosum (Cocozza et al., 2017; Di Filippo, Portaccio, Mancini, & Calabresi, 2018; Planche et al., 2018). For instance, there is evidence for the proposition that memory and learning impairments in MS are connected to injury to the mesial temporal lobe, while lower performance on a word-list learning test may be connected to hippocampal atrophy (Sicotte et al., 2008). Several studies have shown a link between hippocampus damage and memory (González Torre et al., 2017). Cerebellar atrophy has traditionally gone unnoticed (Ciampi et al., 2018; Moroso et al., 2017); however, its posterior atrophy has been shown to be linked to information processing speed dysfunction in MS patients (D'Ambrosio et al., 2017; Moroso et al., 2017).

Structural injuries do not explain cognitive problems because lesion load, the burden of atrophy, and cognitive performance are often dissociated (Benedict et al., 2020).

The advent of diffusion tensor imaging and voxel-based statistics resulted in the finding that neural circuit dysfunction may occur in MS even if WM and GM function normally. For instance, WM lesion volume is associated with memory and information processing speed losses, likely owing to cortico-cortical and cortico-subcortical disconnections (Artemiadis, Anagnostouli, Zalonis, Chairopoulos, & Triantafyllou, 2018; Matías- Guiu et al., 2018).

Several studies have focused on the role of the thalamus in the onset of cognitive impairment in MS patients because it is a crucial hub responsible for information exchange (Van Schependom et al., 2015) and a relay station for both cortico-subcortical and cortico-cortical networks (Kern et al., 2014). Studies indicate that the thalamus is affected early in MS and that its shrinkage causes impairment, fatigue, and cognitive problems. The thalamus has several nuclei with different structural connections, and recent studies have related this thalamic functional connectivity to cognitive decline and fatigue (Lin et al., 2018). Deficits in working memory and processing speed have been attributed to the thalamus and to cerebellum damage (Moroso et al., 2017; Bisecco et al., 2018).

Studies indicate that the brain is resilient to lesion load and can endure structural damage with neural efficiency mechanisms, which are partially mediated by cognitive reserve (Fuchs et al., 2019).

4.6. Factors that contribute to cognitive impairment in Multiple Sclerosis

Psychiatric comorbidities such as depression and anxiety, MS symptoms such as fatigue and sleep disturbances, the side effects of medication, metabolic dysfunctions, and substance abuse have been identified as being among the main factors contributing to cognitive impairments in MS patients (Benedict et al., 2020; Miller, Morel, Redlicka, Miller, & Saluk, 2018).

Studies on the relationship between depression and cognitive impairment in MS have yielded conflicting results. Several studies indicate that depression seems to worsen subjects' performance in several cognitive domains, such as attention and working memory (Heesen et al., 2010; Sundgren, Maurex, Wahlin, Piehl, & Brismar, 2013), learning (Demaree, Gaudino, & DeLuca, 2003), information processing speed and visual-spatial abilities (Sundgren et al., 2013), abstract reasoning, capacity-demanding (Arnett, Higginson, & Randolph, 2001), and executive functioning (Demaree et al., 2003; Sundgren et al., 2013). Other studies, however, have failed to confirm those findings (Golan et al., 2016; Feinstein, 2006).

There is a sizeable body of literature on the link between fatigue, depression, and cognitive impairment (Genova et al., 2020; Hu, Muhlert, Robertson, & Winter, 2019; Yigit et al., 2020). According to studies on symptom clusters, fatigue, cognitive deficits, and depression may have similar causes (Ayache, Riachi, Ahdab, & Chalah, 2020; Podda et al., 2021). Recent research suggests that depression, cognitive deficits, and mental fatigue influence everyday functioning differently and that significant levels of fatigue may occur without cognitive decline or depression (Gullo et al., 2019). There are few studies on the relationship between anxiety and cognitive impairment (Tsivgoulis et al., 2007). The few studies that have been published appear to demonstrate that anxiety causes nonverbal memory to deteriorate (Leavitt et al., 2020; Whitehouse et al., 2019). Several studies have investigated the relationship between fatigue and cognitive deficits. The exposition returns to this topic in Chapter 5.

4.7. Risk and protective factors that are associated with cognitive impairment in Multiple Sclerosis

Although the accumulated knowledge on the risk and protective factors that are related to the development of cognitive impairment in MS is still limited, various facets of the problem, such as comorbidities, lifestyle factors (cannabis use and smoking), individual differences (age and disease phase), and genetic factors, have been explored (Benedict & Zivadinov, 2011). For instance, the prolonged use of cannabis through inhalation or ingestion has been linked to impaired cortical compensatory mechanisms (Pavisian et al., 2014) and cognitive impairment in MS patients (Honarmand et al., 2011). Smoking has also been identified as a risk factor (Ozcan et al., 2014). Furthermore, impaired neuropsychological performance appears to be linked to aging (Ruano et al., 2017). MS patients who are in the degenerative phase of the disease are more likely to exhibit cognitive impairments, and age and disability seem to be the primary drivers of both the profiles and the severity of the deficiencies in question (Ruano et al., 2017).

Turning to protective factors, some authors have investigated the relationship between cognitive reserve, physical exercise, and cognitive function. Cognitive reserve is the ability to adapt to cognitive activity despite brain injury (Stern et al., 2002) and serves as a mediator in the relationship between disease-related impairment and functional results. It is influenced by genetic and environmental factors, such as intellectual enrichment (Fuchs et al., 2019),MACFIMS and can attenuate the influence of structural impairment (Chillemi et al., 2015). Although there is no standard approach, intelligence, literacy, schooling, and vocational accomplishment are the most common indicators of cognitive reserve (Stern, 2009). MS patients with higher premorbid intellectual quotients have been shown to exhibit superior cognitive performance (Sumowski & Leavitt, 2013; Amato et al., 2013). Benedict and colleagues (2010) revealed that cognitive reserve, assessed through level of education and performance on the National Adult Reading Test (NART; Nelson & Willison, 1991), moderates the decline of information processing speed among MS patients over a five-year period (Benedict, Morrow, Guttman, Cookfair, & Schretlen, 2010). These findings suggest that, despite the compromised structural integrity of the GM and WM, the brain may withstand injury through neuronal efficiency processes that are regulated in part by cognitive reserve.

Some studies indicate that exercise may enhance memory and thinking skills, possibly by improving the operation of the hippocampus (Pereira et al., 2007). Exercise, when coupled with cognitive stimulation, can prevent cognitive deficits in MS patients (Motl, Sandroff, & DeLuca, 2016).

Some studies also indicate that certain personality traits may affect the development of cognitive decline in MS (Sandroff, Schwartz, & DeLuca, 2016). Maladaptive profiles that are characterized by higher neuroticism and lower extraversion and conscientiousness have been found in cognitively impaired patients (Roy et al., 2016).

4.8. Neuropsychological assessment

Much effort has been put into the design of accurate assessments of the cognitive performance of MS patients. Long and broad test batteries have lately been abandoned in favor of more focused, sensitive, and comprehensive neuropsychological examinations because cognitive functions are often interconnected, which makes it difficult to unravel the contribution of each function to the cognitive impairment of a patient (Sumowski et al., 2018).

Most cognitive assessment batteries focus on recent memory, sustained attention, verbal fluency, visual-spatial learning, and information processing speed. The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS; Langdon et al., 2012), the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS; Benedict et al., 2006), and the Brief Repeatable Battery of Neuropsychological Tests (BRB-N; Rao et al., 1990) identify cognitive impairment and the domains that are affected. These tests are specific and sensitive and enable the identification of cognitive areas that are most often afflicted (for the BICAMS, the MACFIMS, and the BRB-N, see Table 1).

The BICAMS is a global scale that encompasses the SDMT, the California Verbal Learning Test II (CVLT II; Delis et al., 2000), and the Brief Visuospatial Memory Test-Revised (BVMT-R; Benedict et al., 1997). It is considered a default means of rapidly screening cognitive states in many countries (the mean application time is between 15 and 20 minutes). The BICAMS has external clinical validity and can be administered and interpreted even by individuals without neuropsychological training (Langdon et al., 2012).

The MACFIMS is an extension of the classic BRB-N battery. It assesses various domains, including processing speed, working memory, learning, language, visuospatial perception, and executive function. The MACFIMS and the BRB-N batteries exhibit high sensitivity, discriminant validity, and accuracy (Strober et al., 2009) in assessments of cognitive impairment in MS. The BRB-N, also known as "Rao’s battery", is the most widely used battery in clinical and research settings (Rao et al., 1990). It tests verbal and visual episodic memory, attention, processing speed, and executive function. The Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) is a diagnostic tool that measures short-term memory, executive function, visuospatial ability, language, attention, concentration, and working memory, as well as temporal and spatial orientation (Nasreddine et al., 2005). The MoCA is a sensitive tool not only for examinations of the spectrum between mild cognitive impairment and Alzheimer's disease (Roalf et al., 2013) but also for impairments that are associated with other clinical conditions (Pendlebury, Cuthbertson, Welch, Mehta, & Rothwell, 2010). It is well validated, widely recognized globally, and highly recommended as a short cognitive screening tool (Gauthier et al., 2011). The consistency of the findings on global cognitive function has led to the widespread use of the MoCA in clinical and research settings. Kaur, Kumar, and Singh (2013) assessed the MoCA and its 5-minute protocol in the context of MS. They found that both versions of the MoCA are helpful in identifying cognitive deficits in the population under observation.

Table 1 Comparison of BICAMS, BRB-N, and MACFIMS

Battery	Tests included	Domains	Time required (min)
BICAMS	SDMT	Visual processing speed	15
	CVLT-II	Auditory and verbal memory (learning and recalling)	
	BVMTR	Visual and spatial memory (learning and recalling)	
BRBN	SRT	Auditory and episodic verbal memory (learning and recalling)	20–45
	10/36 spatial recall test	Visual and spatial episodic memory (learning and recalling)	
	COWAT	Expressive language, verbal fluency, spatial processing and executive functioning	
	PASAT	Auditory processing speed and working memory	
	SDMT	Visual processing speed	
MACFIMS	PASAT	Auditory processing speed and working memory	Over 90
	SDMT	Visual processing speed	
	CVLT-II	Auditory and verbal memory (learning and recalling)	
	BVMTR	Visual and spatial memory (learning and recalling)	
	DKEFS test	Executive functioning	
	JLO	Spatial processing	
	COWAT	Expressive language, verbal fluency, spatial processing, executive functioning	

BICAMS, the Brief International Cognitive Assessment for MS; SDMT, Symbol Digit Modality Test; CVLT-II, California Verbal Learning Test-II; BVMTR, Brief Visuospatial Memory Test-Revised; BRBN, Brief Repeatable Battery of Neuropsychological Tests; MACFIMS, Minimal Assessment of Cognitive Function in MS; SRT, Selective Reminding Test; COWAT, Controlled Oral Word Association Test; PASAT, Paced Auditory Serial Addition Test; DKEFS, Delis-Kaplan Executive Function System; JLO, Judgment of Line Orientation Test.

Source: Grzegorski, T., & Losy, J. (2017). Cognitive impairment in multiple sclerosis–a review of current knowledge and recent research. Reviews in the Neurosciences, 28(8), 845-860.

Several authors have recently investigated cognitive deficits by using targeted tests. The SDMT is an excellent example. It is a default tool for assessing information processing speed in MS patients (Benedict et al., 2017). Due to its sensitivity, specificity, and reliability, it is extensively used as a monitoring tool across the world as well as in clinical studies (Benedict et al., 2017). The PASAT is a sensitive measure of cognitive impairment in MS. It assesses working memory and sustained attention, as well as calculation ability. It also gauges the speed and flexibility of the processing of auditory information (Gronwall, 1977). Although it has been extensively used in clinical studies, it has several drawbacks, such as limited consistency, poor tolerability, and test-related anxiety. Its best use is as a cognitive processing task that may be employed to compare findings from different studies (Sumowski et al., 2018). The CVLT is a verbal memory test that is used to diagnose cognitive impairment in MS patients. It is recommended for use in clinical settings, and it is highly sensitive. The strong normative data account for age and gender. The BVMT-R evaluates visual memory. It is recommended for clinical settings and research because it saves time, is highly sensitive, and is easy to administer. However, it appears to be unsuitable for individuals with severe motor impairments (Sumowski et al., 2018).

4.9. Treatment of cognitive impairment in Multiple Sclerosis

There are currently no recognized therapies for cognitive impairment in MS. According to the findings of a comprehensive study, there is insufficient evidence of the effectiveness of medications that aim to alleviate cognitive impairment in individuals who are diagnosed with MS (Chen et al., 2020). Two types of therapy are suggested: pharmacological and non-pharmacological treatment (psychological and physical rehabilitation) (Miller & Soundy, 2017). As far as pharmacological interventions are concerned, psychostimulant or wake-promoting medications are often prescribed by clinicians to treat both fatigue and cognitive impairment (Wilken et al., 2008). Research on the efficacy of those treatments is inconsistent and complicated due to the use of different assessment methodologies, analytical techniques, and trial populations. The most commonly used medications are interferon beta 1a, which improves several cognitive domains (Fischer et al., 2000); interferon beta 1b, which enhances delayed visual reproduction performance (Pliskin et al., 1996); and natalizumab, which reduces the risk of progressive working memory deficits (Weinstock-Guttman et al., 2012). Turning to non-pharmacological treatments, neuropsychological interventions have been shown to exert a positive influence on cognitive performance and related skills in some studies. Clinical trials are still lacking due to methodological issues (Rosti-Otajärvi & Hämäläinen, 2014).

The goal of neuropsychological interventions is to help patients compensate for cognitive deficiencies and to enhance awareness of cognitive impairment among patients and their families. Recent studies have shown that a combination of neuropsychological rehabilitation, cognitive behavioral therapy, and computer-assisted training results in consistent improvements in outcomes (Miller et al., 2018). Physical exercise is one of the non-pharmacological interventions that have been shown to prevent deterioration and improve the cognitive performance of MS patients. However, findings on the role of physical exercise in cognitive impairment have yielded inconclusive and mixed outcomes (Carter et al., 2014). Some of those studies indicate that physical exercise has no substantial effect on cognitive impairment (Sandroff et al., 2016; Cramer et al., 2014). At present, the literature that supports the use of cognitive training in patients with MS is more persuasive.

5. ON THE RELATIONSHIP BETWEEN FATIGUE AND COGNITIVE IMPAIRMENTS IN MULTIPLE SCLEROSIS

5.1. Introduction

Fatigue has long been acknowledged to be a multifaceted experience and one of the most upsetting symptoms for patients with MS (Fisk et al., 1994), whose quality of life is negatively impacted by it (Simmons, 2010). Furthermore, over the last few years, cognitive impairment in patients with MS has started to attract the attention of academics due to its recognized impact on the patients' quality of life (Rahn, Slusher, & Kaplin, 2012). Studies on fatigue and cognitive functioning in MS have agreed that these two disabling symptoms hinder patients' daily activities and can exacerbate other symptoms (Murphy & Niemiec, 2014). Moreover, several studies have indicated that patients with MS commonly report that fatigue negatively impacts their performance (Krupp et al., 1988).

Studies investigating the relationship between fatigue and cognitive impairment have reported mixed results. Despite the large amount of work that exists on the topic, open questions remain, and definitive findings need to be found (DeLuca, 2005). Understanding the relationship between fatigue and cognitive impairment is crucial for addressing the potential impact of fatigue on cognitive functions in clinical and research settings. It is also crucial to accurately define the cognitive profile of patients with MS and develop more effective strategies for addressing these distressing symptoms.

5.2. Do cognitive deficits lead to fatigue or vice versa?

The relationship and causal connection between fatigue and cognitive impairments in individuals diagnosed with MS remain a topic of ongoing discussion and investigation (Rocca et al., 2015).

Several studies have examined whether fatigue causes cognitive deficits or if the opposite is true. It has been suggested that cognitive deficits can lead to fatigue due to the heightened cognitive demands and increased effort required to complete tasks (DeLuca, Genova, Hillary, & Wylie, 2008; Engel et al., 2007; Krupp & Elkins, 2000). Moreover, when an individual's cognitive resources are already impaired, engaging in tasks that require attention and mental exertion can result in heightened levels of fatigue (Engel et al., 2007; DeLuca et al., 2008).

Krupp et al. (2000) suggest that cognitive decline in individuals with MS may lead to heightened fatigue. Accordingly, Borragán et al. (2018) proposed that adjusting cognitive load to patients' cognitive deficits may prevent an increased susceptibility to fatigue compared to healthy individuals; however, studies on this topic are conflicting. For instance, in a study conducted by Hildebrandt and Eling (2014), it was observed that cognitive scores obtained through a neuropsychological battery were not indicative of the trajectory of fatigue in individuals with MS over the course of one year.

The reverse causal effect of fatigue on cognitive impairment received larger empirical support (Bakshi, 2003; El-Tamawy et al., 2016; Sandroni, Walker, & Starr, 1992; Sandry, Genova, Dobryakova, DeLuca, & Wylie, 2014). According to certain researchers, it has been postulated that as a pathological condition develops, the fatigue associated with it progressively affects cognition. Specifically, some authors propose that the proper functioning of cerebral and cerebellar neural networks is necessary for cognitive functions. Factors such as depression, stress, and fatigue may disrupt the operation of these networks permanently or momentarily, resulting in transient cognitive impairment (Hämäläinen & Rosti-Otajärvi, 2016). Indeed, previous studies have demonstrated a link between fatigue-related brain activity and decreased performance in individuals with MS (DeLuca et al., 2008). In providing evidence to support this relationship, empirical investigations have demonstrated that levels of circulating markers of inflammation (proinflammatory cytokines; TNF-α, IFN-γ) correlate with the degree of cognitive impairment seen in individuals with MS (Talebi et al., 2021). In a recent study conducted by McNicholas et al. (2021), it was found that treating individuals with MS for sleep disturbances resulted in a reduction in fatigue and an improvement in verbal memory performance. These findings indicate that addressing fatigue can have positive effects on cognitive performance. Nevertheless, the results are conflicting. Some research indicates that fatigue does not determine a decline in cognitive functions (Beatty, Schneider, Blanco, & Hames, 1998; Fraser & Stark, 2003; Krupp & Elkins, 2000; Parmenter et al., 2003; Paul, Morrow et al., 2009). Specifically, studies on mental fatigue experienced over a prolonged period of effort have, for the most part, not provided substantial evidence to support the assertion that fatigue resulting from prolonged effort determines a decline in neuropsychological performance (DeLuca, 2005).

Studies on the association between cognitive deficits and fatigue have suggested that the observed associations between cognitive deficits and fatigue in cross-sectional studies may be attributed to shared underlying mechanisms. For instance, several studies have indicated that patients with cognitive impairment exhibit changes in the overall white matter and in specific tracts of the posterior thalamic radiation and corpus callosum (Pokryszko-Dragan et al., 2018); these alterations have been found to be associated with fatigue by other researchers (Bonnier et al., 2014; ARM et al., 2019).

In MS, discrepancies across studies have been found on the correlation between fatigue and cognitive performance. While some studies reported a lack of correlation between fatigue and cognitive performance (Bailey et al., 2007; Elkins et al., 1998; Golan et al., 2018; Jougleux-Vie et al., 2014; Johnson, Lange,DeLuca, Korn, & Natelson, 1997; Kisinger et al., 2010; Krupp et al., 1989; Morrow et al., 2009), others provided evidence of a correlation between fatigue and cognitive functioning (e.g., Bellew et al., 2022). Specifically, some research has found a significant correlation between fatigue and verbal memory (e.g., Pokryszko-Dragan et al., 2016), information processing speed (e.g., Andreasen et al., 2010; Diamond et al., 2008; DiGiuseppe et al., 2018), performance on the word list generation test (Niino et al., 2014), and attention (e.g., Heesen et al., 2010; Pokryszko-Dragan et al., 2016).

The divergent outcomes observed in studies investigating MS-related fatigue may be attributed to the intricate characteristics of this phenomenon, to the sample-related factors, and to a wide range of interventions and methodologies and neuropsychological assessment and fatigue scales employed in research (Morrow et al., 2009; Walker et al., 2012).

In summary, all of these hypotheses have demonstrated varying degrees of support; however, the current understanding of the relationship between fatigue and cognitive performance in individuals with MS remains inconclusive, and further studies are needed.

The current study aimed to undertake a descriptive review of studies that have examined the relationship between fatigue and cognitive impairment in MS. The goal was to understand how these two disabling symptoms are related and whether fatigue worsens the cognitive performance of patients with MS. The results of this descriptive review may contribute to detangling the complex picture of the relationship between fatigue and cognitive impairment as well as helping to identify cognitive domains that are more impacted by fatigue.

5.3. Methods

The focus of this review is to examine the relationship between fatigue and cognitive impairment in people with MS. In the following subsections, methods and results are outlined.

5.3.1. Search methods

The literature was screened through electronic databases (i.e., PubMed, Google Scholar, and PsycINFO), and relevant articles published between 1997 and 2018 were selected. A literature search was conducted using the following terms: “MS fatigue,” “fatigue in

MS," "subjective fatigue in MS," "objective fatigue in MS," "relationship between fatigue and cognitive impairment," "cognitive impairment and fatigue in MS," "cognitive impairment in MS," "MS" or "MS fatigue causes," "mental fatigue," and "fatigue scale in MS." The aim was to find scientific articles addressing the relationship between MS fatigue and cognitive impairment.

5.3.2. Selection of studies

The search retrieved 85 articles. Only 40 studies were identified based on their relevance to the purpose of the investigation. This review was supplemented by an inspection of the reference sections of the articles, which yielded 10 additional articles for the review. The final sample consisted of 41 articles. The following articles were included: studies written in English, studies that investigated the relationship between fatigue and cognitive impairment, studies that investigated fatigue or cognitive deficits in MS (in which the relationship between fatigue and cognition was a secondary objective). The following articles were excluded: clinical studies evaluating MS psychotherapy treatment or psychotropic medication efficacy and studies with case reports.

The examined papers assessing the relationship between fatigue and cognitive impairment were grouped into the following two main strands: (I) studies that examined objective and subjective fatigue through inductive cognitive or motor tasks or through the assessment of the effects of a prolonged, continuous task regarding performance decrement or variations (see Appendix 1), and (II) studies examining mainly subjective fatigue and its association with cognitive neuropsychological tests (see Appendix 2).

5.3.3. Method

The following data were analyzed and included in the review analysis (see Appendices 1-2 for the studies' characteristics):

- Author's name and year;
- MS sample characteristics (sample size, age, education, MS phenotype, disability status, disease duration, MS treatment, and inclusion and exclusion criteria);
- Control sample features (e.g., number of participants, age, and education);
- Mood (e.g., depression scales and relationship with fatigue);
- Neuropsychological measures at baseline;
- Methods;
- Type of fatigue investigated (e.g., subjective or objective);
- Fatigue construct;
- Subjective fatigue (e.g., fatigue scales);
- Objective fatigue;
- Induction fatigue tasks;
- Neuropsychological testing to evaluate the impact of fatigue on cognitive functions;
- Relationship between subjective and objective fatigue;

- Cognitive functions impacted by fatigue.

5.4. Results

The literature review highlighted a complex picture. Furthermore, highly heterogeneous approaches were found in the examined studies regarding the relationship between fatigue and cognitive impairment. In the following subsection, review results are outlined.

5.4.1. Relationship between fatigue and cognitive functions based on the review findings

Both groups of studies reported mixed results on the relationship between fatigue and cognitive impairment.

(I) Studies that have examined the relationship between objective and subjective fatigue using different approaches have found conflicting results. Some studies have indicated a correlation between fatigue and performance decline, while others have not found such a relationship. For instance, some authors assessed the effects of mental fatigue induction (N-Back task) on subjective state and performance in patients with advanced MS and controls. The participants performed an N-Back test (0- and 1-back) prior to executing cognitive tests that evaluated executive functioning. The authors discovered that fatigue induction may affect future task performance and that higher subjective fatigue did not correspond with a decrease in performance for either group (Bailey et al., 2007). Neumann and colleagues (2014) measured alertness before and after a cognitively demanding activity to assess objective fatigue. The response times of patients with MS increased following cognitive strain, whereas those of controls did not (Neumann et al., 2014).

Among the examined studies, the relationship between fatigue and cognitive impairment was consistently reported in studies that assessed objective performance during sustained mental exertion and compared performance levels at the onset and conclusion of a cognitively demanding task. For instance, Gossmann et al. (2014) found that the performance of patients with MS in a vigilance test was considerably reduced compared with controls. Subjective fatigue assessed through the VAS was correlated with objective fatigue (Gossmann, Eling, Kastrup, & Hildebrandt, 2014). Bryant et al. (2004) also tested patients with MS (cognitively impaired vs. not cognitively impaired) and controls on cognitively demanding activities for two hours, namely the PASAT. Cognitively impaired patients with MS gave fewer accurate answers than either non-impaired patients with MS or controls; however, both MS groups exhibited mental fatigue sooner than the healthy group (Bryant et al., 2004).

(II) Studies that have assessed associations between subjective fatigue and cognitive impairment have found conflicting results. First, some studies investigating the link between subjective fatigue and cognitive performance have been unsuccessful. For instance, in their study, Golan et al. (2018) conducted an assessment to examine the relationship between cognitive scores obtained from a computerized neuropsychological battery and scales measuring depression and mental fatigue. The two scales exhibited significant correlations with processing speed, executive function, attention, and memory. Nevertheless, when assessing the simultaneous impact of both symptoms on cognition within a single model, only depression exhibited an independent correlation with cognitive scores. In a cross-sectional longitudinal study, Morrow et al. (2009) conducted a retrospective study to examine the association between scores obtained from the MACFIMS and fatigue severity as measured by the FSS. The study employed both cross-sectional and longitudinal approaches, with a follow-up period exceeding 1.5 years. Morrow et al. (2009) reported that there was no observed correlation between the severity of fatigue and cognitive functioning in both approaches. Jougleux-Vie et al. (2014) examined the impact of subjective fatigue on verbal memory. The results indicated a correlation between subjective fatigue and memory complaints. However, it was found that subjective fatigue does not serve as a predictor of objective memory scores when accounting for factors such as depression, pharmacological treatment, and EDSS.

Conversely, other studies have suggested a correlation between fatigue and cognition. For instance, Heesen et al. (2010) evaluated the relationship between fatigue and the PASAT, verbal fluency, verbal memory, and attention. Their results indicated that, except for the PASAT and delayed recall on the memory test, fatigue was linked to every measure examined. Similarly, Pokryszko-Dragan and colleagues (2016) investigated the correlation between fatigue and subjects' cognitive performances as evaluated through the SDMT and the PASAT. Fatigue correlated with SDMT and PASAT scores, and this correlation persisted after the researchers controlled for disease duration, disability, and disease severity (Pokryszko-Dragan et al., 2016). This review revealed that the main cognitive domains investigated across the studies have been those most frequently affected in MS, such as memory, information processing, attention, verbal abilities, and executive function. Moreover, the general analysis revealed that fatigue most often negatively affects processing speed (e.g., Diamond et al., 2008), attention (e.g., Heesen et al., 2010), alertness (e.g., Fiene et al., 2018), executive function (e.g., Mattioli, Bellomi, Stampatori, Parrinello, & Apra, 2011), and working memory (e.g., Kos et al., 2004). Overall, the cognitive domains most associated with fatigue are processing speed, attention, alertness, and memory, while language is the domain least affected by fatigue.

5.4.2. Relationship between subjective and objective fatigue

The relationship between subjective and objective mental and physical fatigue in MS has been extensively explored in the literature (e.g., Bailey et al., 2007; Sandry et al., 2014). Some studies have indicated a link between fatigue evaluated through self-reporting instruments (e.g., FSS, MFIS) and objective mental fatigue (e.g., Aldughmi et al., 2017; Claros-Salinas et al., 2013; Jougleux-Vie et al., 2014; Nunnari et al., 2015; Pokryszko-Dragan et al., 2016); however, other studies have not demonstrated such a relationship

(Bryant et al., 2004; Kos et al., 2004; Morrow et al., 2009). In the literature, the link between self-reported fatigue and objective fatigue has not been proven in several studies (Chinnadurai, Venkatesan, Shankar, Samivel, & Ranganathan, 2016; DeLuca, 2005).

Several authors in the literature have questioned the low correlation between subjective and objective fatigue and raised questions about the correspondence between the two constructs (Johnson et al., 1997). The examination of the correlation between objective and subjective fatigue has been overlooked by numerous researchers investigating the phenomenon of fatigue in MS, holding the belief that subjective ratings do not reflect subjects' real performance. According to Leone and colleagues (2015), these discrepancies may be related both to the different measures used, which cannot quantify various types of fatigue, and the different scoring and administration techniques that are employed to calculate objective fatigue (Leone, Patti, & Feys, 2015). According to DeLuca (2005), clinicians should abandon the notion that fatigue always leads to lower performance (objective fatigue) because patients might feel tired even if their performance does not deteriorate. They suggested that the assumption of behavioral decrement as a criterion of fatigue may explain why subjective and objectively observed fatigue in varied groups fail to correlate. Moreover, the expectation that subjective fatigue and objective performance must correspond may also give rise to misconceptions about the validity of measurements of objective fatigue (DeLuca, 2005). As per certain scholarly sources, the observed disparities could potentially be attributed to the inherent challenges faced by participants in accurately gauging their level of fatigue. Multiple research investigations have unequivocally demonstrated that individuals exhibit a notable deficiency in accurately evaluating their own level of fatigue. The assessment of the subjective level of fatigue may potentially be impacted by factors such as anxiety and conscientiousness (Akbar, Honarmand, & Feinstein, 2011) and by a tendency to exaggerate or understate the experience of fatigue (Claros-Salinas et al., 2013). Regarding the disparities between objective and subjective fatigue, some authors have postulated that subjective fatigue may arise from illness induced by inflammation and the subsequent modification of neural processing in the interoceptive and homeostatic regions of the brain (Hanken et al., 2014). Subjective fatigue may lead to signs of objective fatigue, such as declines in performance, through interoceptive interference. According to their theory, changes in objective performance might occur irrespective of subjective fatigue due to cortical atrophies in the attention network, which may explain the mismatch between subjective and objective fatigue.

5.4.3. Limitations found across studies

The current scientific literature is characterized by various studies that have not shared the same methods, procedures, criteria, and constructs regarding MS fatigue; therefore, their heterogeneous findings cannot be compared. For instance, differences across studies have arisen regarding the MS sample characteristics (e.g., MS phenotype, age, disability status, disease duration, participant exclusion and inclusion criteria, and methodological procedures), fatigue construct (the type of fatigue examined), mood and fatigue evaluation, and neuropsychological tests used to induce fatigue and evaluate its impact on cognitive functions. It would be challenging to mention all the differences found across studies; therefore, in the following subsections, some of the main limitations that might explain the heterogeneous results and inconsistencies between studies' findings are described. These observed differences have made conducting comparative analyses across studies impossible; moreover, and above all, they underline how challenging it is to draw definitive conclusions on the relationship between fatigue and cognitive impairment, as well as the need for further studies on the topic. The findings from the current review are presented in the following subsections, each of which contains a discussion of the findings.

MS phenotypes. The literature review revealed that studies differ with respect to the phenotype of patients under consideration. Most studies have enrolled patients with MS who fall under the same phenotype, such as RRMS (e.g., DiGiuseppe et al., 2018). Other studies have listed patients who belong to different subtypes, such as RRMS and SPMS (e.g., Aldughmi et al., 2017) or RRMS and CIS (e.g., Simioni, Ruffieux, Bruggimann, Annoni, & Schluep, 2007). Others still have listed patients with MS belonging to various phenotypes, such as relapsing-remitting, primary-progressive, secondary-progressive, and primary-relapsing (e.g., Diamond et al., 2008). Occasionally, the phenotype of the recruited patients has not been specified (e.g., Claros-Salinas et al., 2010). As demonstrated in previous chapters, patients who belong to different MS subtypes exhibit different disease patterns (e.g., the degree of disability and pathological processes as the illness progresses), which impact MS fatigue and cognitive function in different ways. Several authors have indicated that while fatigue is a symptom that affects patients with MS indistinctly, its effects on various functions as well as its severity vary based on the MS patient's phenotype (Lerdal et al., 2013; Aygünoğlu et al., 2015). For instance, the literature indicates that patients with SPMS are more fatigued than those with PPMS (Aygünoğlu et al., 2015) and that those with RRMS are more fatigued than those with progressive MS (Razazian et al., 2014; Aygünoğlu et al., 2015). Research findings also suggest that the cognitive profile seems to be dependent on the particular phenotype of the patient. For instance, some studies have suggested that patients with MS suffering from CIS or RRMS exhibit deficits mainly in information-processing speed, verbal and visuo-spatial memory impairment, and executive functions (Khalil et al., 2011); by contrast, in progressive forms of the disease, impaired memory and executive function are more common (Ruano et al., 2017). Moreover, some authors indicate that patients with PPMS exhibit more severe cognitive deficits than patients with RRMS, while patients with SPMS exhibit more pronounced impairments than those with RRMS (Ruet et al., 2013). Therefore, a comparative analysis of studies that have focused on patients who fall under different MS subtypes may be deceptive, as patients with MS might not share the same level of fatigue or cognitive profile (Denney et al., 2004).

MS participants' age. The literature review found that the average age of listed patients with MS ranges between 33 and 49 years. In some studies, patients with MS have been older than 55 years (e.g., Bailey et al., 2007); in others, the participants' age was not specified (e.g., Jougleux-Vie et al., 2014). Evidence suggests that fatigue and cognitive impairment differ according to the patient's age (Lerdal et al., 2003). Several studies have indicated that cognitive performance often deteriorates with age (Amato et al., 2001; Ruano et al., 2017). For instance, studies have demonstrated that processing speed improves from youth until the age of 20 and then declines with age, and that it is a cognitive ability that deteriorates more quickly than others. Furthermore, the findings of several studies have indicated that the cognitive profile of elderly patients with MS is characterized by processing speed impairment and poorer verbal fluency.

MS disability status. Review studies have revealed that the disability of patients with MS has mostly been evaluated through the EDSS (Kurtzke, 1983); however, some studies have used different disability scales, such as the Incapacity State Scale (ISS; LaRocca & Foley, 1984; e.g., Holtzer & Foley, 2009), the Functional Status Questionnaire (FSQ; Jette & Cleary, 1987; e.g., Aldughmi et al., 2017), and the Ambulation Index (AI; Hauser et al., 1983; e.g., Sandry et al., 2014). Occasionally, the disabled patient’s status has not been assessed (e.g., Claros-Salinas et al., 2010). The review indicated that most MS patients exhibit a disability degree between 2 and 5 on the EDSS (e.g., Chinnadurai et al., 2016; Schwid et al., 2003), but this score varies across studies. As demonstrated in previous Chapters the evaluation of disability status is crucial, as several studies have reported an association between high disability status and a higher level of fatigue experienced by patients with MS (Gobbi et al., 2014; Hesse et al., 2014; Kroencke et al., 2000; Rocca et al., 2009; Yigit et al., 2021). Studies have also demonstrated an association between high disability status and higher cognitive impairment in patients with MS (Matias-Guiu et al., 2017; Skorve et al., 2019; Yigit et al., 2021). Therefore, studies that have included patients with varying degrees of disability should be carefully examined, as disability severity may impact patients’ fatigue and cognitive functions differently.

MS disease duration. The disease duration across studies has ranged from 5 to 10 years (e.g., Fiene et al., 2018). In some studies, the disease duration was >10 years (e.g., Gossmann et al., 2014; Spiteri et al., 2017), while in others it was < 5 years (e.g., Andreasen et al., 2010); occasionally, the disease duration of patients with MS was not addressed (e.g., Holtzer & Foley, 2009). Studies in the literature have demonstrated that high disease duration is associated with more cognitive deficits (e.g., Dackovic et al., 2016; Achiron et al., 2013) and more fatigue (Biberacher et al., 2018; Yigit et al., 2021), especially when patients are required to perform challenging tasks (Biberacher et al., 2018; Cavallari et al., 2016; Chalah et al., 2019; Ghajarzadeh et al., 2013; Stuke et al., 2009). For instance, a longitudinal study demonstrated that information processing speed impairments in patients with MS increase with disease duration (Forn, Belenguer, Parcet-Ibars, & Avila, 2008). Like disability degree, MS phenotype, and subject age, disease duration is another key factor that must be carefully addressed as it impacts fatigue and cognitive functions in patients with MS differently.

Inclusion and exclusion criteria. The literature review revealed heterogeneity regarding inclusion and exclusion criteria across studies. This subsection outlines some of the main differences found across studies. In some studies, patients have been excluded or included based on fatigue scale scores, and the thresholds used to determine patient inclusion or exclusion have been based on the authors' choices (e.g., Fiene et al., 2018; Kos et al., 2004). For instance, Andreasen et al. (2010) rejected patients whose FSS score was between 4 and 5, while Neumann et al. (2014) recruited patients with MS whose FSMC score was equal to or higher than 22. Similarly, Fiene et al. (2018) enrolled patients with MS whose fatigue score was equal to or higher than 9. Despite the progression of MS (exacerbation phase) being widely recognized to be able to affect patients' general functioning (Lublin et al., 2014), fatigue, and cognitive performance (Morrow, Jurgensen, Forrestal, Munchauer, & Benedict, 2011), few studies have sought to determine whether patients were in the exacerbation phase. This review revealed that some studies have excluded patients in their exacerbation phase (e.g., Huolman et al., 2011); however, these studies differ in terms of the timeframes used (e.g., Gossman et al., 2012; Lehmann et al., 2013). The review also revealed that few studies have screened patients' vision abilities before testing (Chinnadurai et al., 2016), even though this assessment is critical in experimental research assessing cognitive abilities (Benedict et al., 2002). Moreover, in several studies, patients with major depression (e.g., Holtzer & Foley, 2009; Krupp & Elkins, 2000) have been excluded; in some studies, however, patients have been enrolled based on cut-off points on scales as well as the authors' choices. As demonstrated in Chapter 3, patients exhibiting different degrees of depression can exhibit different levels of fatigue and cognitive performance (Pittion-Vouyovitch et al., 2006). Sleeping disorders have been scarcely addressed, despite the literature suggesting that sleep problems worsen subjects' cognitive performance and overlap with fatigue symptoms. Only a few studies have addressed the sleep disorders encountered by patients with MS (e.g., Andreasen et al., 2010; Neumann et al., 2014); furthermore, a few studies excluded MS patients who suffered from sleep disorders (e.g., Wilting et al., 2016). Notably, the MS pharmacological treatment has been an exclusion criterion in several studies (e.g., Holtzer & Foley, 2009; Krupp & Elkins, 2000); however, in other studies, the MS treatment has not been investigated, and patients have been enrolled regardless of the type of MS treatment (e.g., Fiene et al., 2018). For instance, Krupp and Elkins (2000) recruited patients who were taking psychotropic medications, as long as the dose had been the same for at least one month prior to the assessment (Krupp & Elkins, 2000). Andreasen et al. (2010) did not include patients who altered their treatment during the previous three weeks since the beginning of the experimental research. Studies have indicated that some medications, such as anti-spasticity drugs, immunosuppressants, corticosteroids, or interferon, worsen or induce fatigue (Saah, 2009; Smith & Hale, 2007), increase depressive mood (Arnett & Randolph, 2006; Goeb et al., 2006), cause drowsiness or sedation, and affect cognitive functions. The assessment of MS treatment in clinical research should never be neglected, as findings indicate that some pharmacological treatments may affect fatigue and cognitive function, leading to deceptive data.

Mood investigation. Depression is one of the most serious conditions for people with MS. The literature review revealed that some studies have provided an in-depth investigation into subjects' moods (e.g., Hanken et al., 2016), whereas others have neglected such an investigation (e.g., Berard et al., 2018). In various studies, the MS group has been more depressed than the control group (e.g., Bryant et al., 2004; Holtzer & Foley, 2009; Lehman, Burns, Gagen, & Mohr, 2012). A correlation between fatigue and depression has also been demonstrated (e.g., Holtzer & Foley, 2009; Spiteri et al., 2017). While in some studies on the relationship between fatigue and cognitive domains, no significant covariate effects of depression were identified (Archibald et al., 2010), in others, depression showed a significant covariate effect (Denney et al., 2004). Moreover, studies evaluating patients' depression differ on the measures used for mood screening. The BDI is the most frequently used instrument. Various BDI test releases, such as the BDI-II (Beck, Steer, & Brown, 1996; e.g., Neumann et al., 2014) and BDI Fast Screen (BDI-FS; Beck, Steer, & Brown, 2000; e.g., Walker et al., 2012), have also been used across studies. Further instruments found across studies include the Hamilton Depression Rating Scale (HDRS; Hamilton, 1960; e.g., Kinsinger, Lattie, & Mohr, 2010), the Major Depression Inventory Scale (MDIS; Bech, Rasmussen, Olsen, Noerholm, & Abildgaard, 2001; e.g., Andreasen et al., 2010), the Chicago Multi Scale Depression Inventory (CMDI; Nyenhuis & Luchetta, 1998; e.g., Schwid et al., 2003), and the Center for Epidemiologic Studies–Depression (CES-D; Radloff, 1977; e.g., Krupp & Elkins, 2000).The assessment of anxiety has been neglected in several studies, while only a few studies have included anxiety evaluation in trials (e.g., Bailey et al., 2007; DiGiuseppe et al., 2018). The overlap between symptoms of fatigue and depression, their strong correlation, the impact of depression on subjects' cognitive performance, and a pattern of joint occurrence of fatigue with depression and anxiety have been demonstrated in the general literature (Rottoli, La Gioia, Frigeni, & Barcella, 2017). Thus, the assessment of mood disorders with appropriate scales is paramount in MS fatigue research.

Fatigue type across studies. Disparities exist across studies regarding the type of fatigue examined. Some studies have investigated both mental and physical fatigue (e.g., Greim et al., 2007; Neumann et al., 2014; Paul et al., 1998), but most studies have focused exclusively on mental fatigue (e.g., Golan et al., 2016). Furthermore, some studies have examined fatigue without specifying its construct (e.g., DiGiuseppe et al., 2018; Schwartz et al., 1996). Regarding subjective fatigue, some studies have focused merely on trait fatigue (e.g., Nunnari et al., 2015) or state fatigue (e.g., Archibald et al., 2010; Claros-Salinas et al., 2010), while others have focused on both (e.g., Sandry et al., 2014; Spiteri et al., 2017). In the last few years, most studies have included the assessment of objective fatigue along with subjective fatigue (e.g., Lehman et al., 2012; Spiteri et al., 2017). Generally, a theoretical definition of fatigue was not found across studies. In most studies, fatigue was described in a generic manner without its construct being defined, frequently disregarding physical and mental fatigue. In some studies, subjective fatigue has not been investigated, as it has been inferred from variations in cerebral activation (e.g., DeLuca et al., 2008), brain activity, or changes in neural correlates (e.g., Kujala et al., 1995). Studies differ regarding the definition of mental fatigue. In some studies, mental fatigue is defined as the inability to sustain performance throughout the duration of a continuous, complex information-processing task (e.g., Bryant et al., 2004). This description implies that fatigue is progressive and longitudinal;

therefore, the longer a task is performed, the more mental fatigue the performer will feel. Others have contended that mental fatigue may instead impact cognition by raising subjects' response variability when performing specific mental activities. Thus, patients who feel mental fatigue may occasionally encounter attentional failures; during these lapses, much effort may be required to gather the required mental resources for effectively and reliably conducting a given assignment. Finding a consistent fatigue taxonomy and using it correctly in research is vital for any future developments in MS-related fatigue.

Fatigue assessment. Different measures for estimating objective and subjective fatigue have been used across studies. In some studies, subjective fatigue has been estimated by means of a single self-report (Holtzer & Foley, 2009), while in others, several questionnaires have been used (e.g., Greim et al., 2007; Sandry et al., 2014; Spiteri et al., 2017). Across studies, the most frequently used instruments for evaluating trait fatigue include the FSS (Krupp et al., 1989), the MFIS (NMSS, 1998; e.g., Heesen et al., 2010), the FSMC (Penner et al., 2009; e.g., Spiteri et al., 2017), and the Würzburg Fatigue Inventory for Multiple Sclerosis (Weimus; Flachenecker et al., 2006; e.g., Fiene et al., 2018). The instruments most frequently used for evaluating the state of fatigue include Likert (e.g., Greim et al., 2007; Johnson et al., 1997) and VAS (e.g., Gossmann et al., 2014; Lehman et al., 2012; Sandry et al., 2014; Spiteri et al., 2017). Subjective reports used across studies have fundamentally assessed various components of the patients' fatigue experience, such as motivation, concentration, and emotional aspects (e.g., impact and severity), or a combination of these, and even independent concepts. For instance, the MFIS evaluates the impact of fatigue in the areas of physical, cognitive, and psychosocial functioning, while the FSS evaluates the severity of fatigue and its influence on a person's daily performance during the previous week.

In the last few years, most studies have coupled subjective ratings of fatigue with a variety of evidence for objective fatigue. Objective mental fatigue has been estimated in several ways across studies. Changes in accuracy (decrease) or reaction time (increase) in cognitive performance tasks have been the most used parameters across studies for measuring objective fatigue. However, the scoring methods used for evaluating objective mental fatigue during tests vary across studies. In some studies, objective mental fatigue has been assessed by evaluating the drop in performance between the first and second halves of an experimental cognitive task (e.g., Bryant et al., 2004; Kos et al., 2004; Schwid et al., 2003; Walker et al., 2012). In other studies, it has been assessed by calculating the slope of a linear regression that compares the number of correct responses to each of the 10 items on the PASAT with the number of deciles (e.g., DeLuca et al., 2008). Various scoring methods have also exhibited differences regarding the impact of fatigue on cognitive functions. The most frequently used tests for evaluating objective mental fatigue across studies are the SDMT and the

PASAT. In some studies, objective mental fatigue has also been estimated through EEG (e.g., Chinnadurai et al., 2016) or ERP (e.g., Pokryszko-Dragan et al., 2016) to track brain activation during prolonged mental load for objectively evaluating neural processes. Specifically, the P300 has been used as a marker of cognitive performance (e.g., Chinnadurai et al., 2016; Fiene et al., 2018; Pokryszko-Dragan et al., 2016).

Regarding objective physical fatigue, the majority of investigations have primarily directed their attention towards the assessment of alterations in the motor performance of participants. Subjects' gait patterns, muscle strength (e.g., Aldughmi et al., 2017; Greim et al., 2007; Paul et al., 1998), and the rate or persistence of motor responses over time (Aldughmi et al., 2017) have been considered indicators of objective physical fatigue. These functions have been evaluated through instruments such as grip strength (Bohannon, 2001), hand-dynamometer tests (e.g., Aldughmi et al., 2017; Paul et al., 1998), the 6MVT (e.g., Aldughmi et al., 2017), and an ERGO FIT 3000 treadmill (e.g., Claros-Salinas et al., 2013).

Methods. Review studies have revealed differences in the experimental design and methodologies used across studies. This subsection describes the main methods used to investigate objective fatigue (see Appendix 1).

In some studies, objective fatigue has been investigated by measuring the impact of a protracted, continuous task on performance decline or changes at various time periods. In such studies, objective fatigue has been operationalized and assessed as performance changes relative to baseline performance (e.g., Bailey et al., 2007; DeLuca et al., 2008). Using this approach, some studies have reported evidence for a fatigue-related performance decline (e.g., Claros-Salinas et al., 2010; Fiene et al., 2018), while others have not (e.g., Sandry et al., 2014). For instance, Johnson et al. (1997) evaluated participant fatigue four times over the course of a 3-hour exam battery. Patients with MS reported rising levels of fatigue throughout the test battery; however, the three clinical groups and the controls demonstrated comparable degrees of improvement in performance over many PASAT administrations.

Other studies have evaluated objective fatigue by comparing subjects' performance at the onset of sustained mental exertion (a demanding task) and at its conclusion (e.g., Aldughmi et al., 2017; Bryant et al., 2004). Using this method, objective fatigue has been consistently demonstrated (e.g., Bryant et al., 2004). For instance, Gossmann et al. (2014) examined the effects of cooling on mental fatigue and autonomic functioning during a 30-minute vigilance task in patients with MS and controls by using the aforementioned method. They discovered a drop in performance on the vigilance test, which was linked to fatigue evaluated using the VAS.

In addition, some experimental investigations have quantified and assessed objective fatigue as a pre-to-post performance drop in a task while inducing fatigue through a mental- or physical-fatiguing activity in between (e.g., Claros-Salinas et al., 2013). Using this methodology, inconsistent findings have been obtained regarding the relationship between fatigue and cognitive impairment (e.g., Claros-Salinas et al., 2013; Krupp & Elkins, 2000; Paul et al., 1988; Spiteri et al., 2017). For instance, Krupp and Elkins (2000) subjected participants to a 4-hour session of cognitive testing that included a baseline neuropsychological battery. The participants exhibited a decline in performance in visual memory, verbal memory, and verbal fluency, whereas the control group exhibited slight improvements. During the testing session, both MS and control participants reported becoming increasingly mentally and physically fatigued. However, assessing subjects' performance at the beginning of and after a demanding task may lead to misleading results because of the confounding effect of practice.

Experimental tasks. Several experimental tasks have been used across studies to evaluate performance after inducing mental or physical fatigue or to evaluate performance over time during sustained mental effort as well as over an extended period.

Various cognitively demanding tasks were found to have been used in several studies. For example, some studies have used long cognitive batteries to explore a variety of cognitive domains (e.g., Andreasen et al., 2010; Neumann et al., 2014; Paul et al., 1998). Other studies have used focused tests extracted from test batteries, mainly to investigate working memory, processing speed, attention, and vigilance domains, such as the PASAT (e.g., Berard et al., 2018; Bryant et al., 2004; Krupp & Elkins, 2000); the TAP (e.g., Claros-

Salinas, et al., 2010; Gossmann et al., 2014); the N-Back (e.g., Bailey et al., 2007; Spiteri, et al., 2017); and the SDMT (e.g., DeLuca et al., 2008; Sandry et al., 2014). The experimental tasks used across studies were found to differ in length and complexity (high or low). According to the cognitive load hypothesis, task cognitive load plays a role in the genesis of mental fatigue (Bailey et al., 2007). Choosing a demanding task rather than an easy one has an impact on the onset of fatigue. According to this hypothesis, fatigue is higher in situations of high cognitive load (Ackerman, 1988). By contrast, according to the temporal hypothesis, mental fatigue increases as the length of the task increases and does not rely on task difficulty (Jensen et al., 2013; Krupp & Elkins, 2000). Studies that have adopted long or short, demanding tasks in their experimental procedures have reported differences in cognitive performance. Several authors have contended that contradictory outcomes are linked to the choice of mental or physical tasks adopted in experimental studies and the task's capability to induce fatigue (Sandry et al., 2014). According to Sandry et al. (2014), MS fatigue depends more on task duration than on the demandingness of the cognitive task. According to some authors, fatigue in MS is associated with activities based on sustained attention and executive control; hence, if the cognitive activity does not require the involvement of these cognitive abilities, fatigue may not arise (Bol et al., 2009).

Cognitive domain construct. The reviewed studies have indicated differences in the way cognitive domain functions are labeled across studies as well as a lack of a shared cognitive domain construct. For instance, several studies have referred to a broad concept of attentional cognitive function without mentioning the network investigated; only a few studies have specifically mentioned the executive, orienting/selective, and alerting/vigilance attentional networks (e.g., Hanken et al., 2014). As for processing speed, multiple definitions were found across studies. Processing speed has been described as the length of time a person requires to accomplish a cognitive task or, physiologically, as the rate at which the brain can handle information. Some studies have referred to the theory of Salthouse et al. (1996), which holds that information-processing speed deficits are connected to significant delays in early information processing (e.g., Chiaravalloti et al., 2013), while others have referred to a neural noise theory (Kail, 1998), which states that information-processing speed depends on the brain’s signal-to-noise ratio (e.g., Denney et al., 2004). Most studies have adopted a theoretical model that holds that information-processing speed is one of the main cognitive deficits in MS, underpinning other forms of cognitive dysfunction (DeLuca et al., 2004; Parmenter et al., 2007).

Moreover, these studies have indicated that evaluating functions "autonomously" is extremely challenging because some cognitive domains are inextricably linked to others (DeLuca et al., 2004). For instance, tasks based on processing speed also require visuospatial processing (Miyake, Friedman, Rettinger, Shah, & Hegarty, 2001), goal management, and background information filtering functions (Lustig, Hasher, & Tonev, 2006). Likewise, the literature demonstrates that worsening performance in working memory tasks is due to a loss of speed rather than a decrease in short-term memory (DeLuca et al., 2004; Forn et al., 2008; Genova, Lengenfelder, Chiaravalloti, Moore, & DeLuca).

Therefore, studies demonstrating a relationship between fatigue and a given cognitive function should be interpreted carefully, as the deterioration of a function may potentially be related to the deterioration of other cognitive functions.

Neuropsychological evaluation. The review findings revealed that the investigated cognitive domains and batteries used to measure participants' performance at baseline vary across studies. Some studies have investigated multiple cognitive domains through complete neuropsychological batteries, such as the Wechsler Adult Intelligence Scale (WAIS-III; Weschler, 1997) or the BRB-n (e.g., Bryant et al., 2004; Krupp & Elkins, 2000). Others have assessed only a few domains (e.g., Kos et al., 2004) through focused scales, such as the PASAT (e.g., Bryant et al., 2004), the TAP (e.g., Neumann et al., 2014), or the SDMT (e.g., DeLuca et al., 2008); in some studies, patients' cognitive profiles at baseline have not been assessed (e.g., Claros-Salinas et al., 2010; Schwid et al., 2003). Some authors have claimed that investigating a few cognitive areas fails to provide a complete description of a potential cognitive impairment, and therefore, the correlations between fatigue and cognitive dysfunction might be misleading. Furthermore, even though targeted measures are intended to assess the same cognitive function, there is no assurance that they will evaluate the same function due to measurement heterogeneity. For instance, although the reaction time test and the PASAT are both considered indicators of information processing speed (Costa et al., 2017), they do not examine the same components. Therefore, it is challenging to compare studies and arrive at conclusions as studies differ from one another in terms of the cognitive domains investigated and the selected measures.

5.5. Where are we heading?

The aim of the current review was to determine whether and how fatigue impacts cognitive functions. This review has highlighted a complex picture characterized by conflicting findings regarding the relationship between fatigue and cognitive decline in patients with MS, leaving this fundamental topic poorly understood and debated. The inconsistent pattern of findings is undoubtedly the consequence of the significant variety of approaches to the topic found across studies, which differ with respect to the methodology, fatigue protocols, and cognitive domain criteria. Differences among studies have arisen regarding the characteristics of samples (disease duration, age, disability status, disease courses, and inclusion and exclusion criteria), methods (mood investigation, scoring methods, type of investigated fatigue, fatigue and cognitive function assessment, experimental tasks), and fatigue construct. Furthermore, the heterogeneity of the research has made comparison analyses unfeasible, which explains the limited progress made in the last decade on MS fatigue. Despite decades of investigations on the topic, evidence in the literature has indicated a lack of coherence and cohesion among researchers who, rather than moving in the same direction, appear to be pursuing their own paths, choosing methods and protocols based on their own insights and criteria. The picture makes it essential to establish common protocols, which might help provide theoretical underpinnings for explaining fatigue symptoms and their relationship with cognitive impairments. Collaborative studies and multidisciplinary research might provide a comprehensive understanding of this ambiguous symptom and its relationship with cognitive impairment, as well as potentially aid patients in managing this distressing symptom, which still lacks effective treatment (Pucci et al., 2007; Solari, Uitdehaag, Giuliani, Pucci, & Taus et al., 2003). Therefore, an urgent need exists to conduct high-quality studies, which might help minimize contradictory findings and develop a common protocol that is differentiated according to the MS subtype. This might provide guidance on the methodological approaches that could drive MS-related fatigue research. A thorough and standardized procedure in MS fatigue research is crucial, as fatigue, as a multifaceted symptom, is impacted by several clinical factors. Faults in MS fatigue investigations would unquestionably

lead to deceptive data and the halting of advancements in the field. A common protocol should provide directions regarding recruitment criteria (e.g., sample size, age, MS phenotype, degree of disability, and disease duration), reliable measures for assessing fatigue and cognitive impairment, and guidelines regarding treatments that patients are entitled to receive when participating in research and experimental procedures. Specifically, a new protocol should include the following elements.

- **A common fatigue construct.** As demonstrated by the articles examined in this review, there are several definitions of fatigue that differ in semantics and conceptualization; furthermore, their constructs and connections to theoretical models have frequently not been articulated or addressed. According to the review's findings, numerous authors have emphasized that fatigue is not a distinct construct (Kos et al., 2008; Strober & Arnett, 2005), reported the lack of a theoretical framework for MS fatigue (Hu et al., 2019), and indicated the need for a widely accepted definition of fatigue (Hockey, 2013; Kluger et al., 2013; Pattyn et al., 2018). The variety of concepts used for the same phenomenon hinders communication and collaboration and generates confusion and miscommunication, thereby affecting knowledge production. The transmission of new ideas is slowed as a result of the fragmentation of knowledge, which thus leads to lower research quality. Some form of agreement is necessary regarding the meaning of the terms used to describe the phenomena, as opposed to having different meanings for the same terms. Therefore, it is crucial to actively discuss the fatigue construct within the MS community as well as to develop theoretical frameworks and new, reliable, and innovative approaches to examine subjective and objective fatigue in MS, which also includes physical and cognitive components.
- **Reliable and sensitive measures of fatigue**. Different conceptual approaches used to assess fatigue across studies have indicated the

complexity of this distressing symptom and the difficulties of a comprehensive evaluation of fatigue in MS (Rietberg, Van Wegen, & Kwakkel, 2010). As demonstrated, methods used to evaluate subjective and objective fatigue differ across studies. According to the literature, several subjective measures used across studies are unreliable, vulnerable to mood, and do not provide accurate fatigue evaluations (Kroencke et al., 2000). Furthermore, the evaluation of subjective fatigue over the course of time exhibits some flaws; for instance, in the reviewed studies, changes in fatigue over time have been measured through Likert scales that have revealed a restricted range of variability, making it difficult to identify connections with objective fatigue. Moreover, most measures used across studies are not designed to distinguish between various aspects of fatigue (Kos et al., 2004). The existing methods of evaluation are not even close to being able to offer a subjective and objective assessment of the symptoms of fatigue; actually, no consensus exists on the most effective method for quantifying and classifying fatigue in MS (Beckerman, Eijssen, van Meeteren, Verhulsdonck, & de Groot, 2020), nor does a consensus exist on the core collection of fatigue questions that should be asked to patients to investigate MS-related fatigue (Téllez et al., 2005; Paul et al., 2014). Therefore, the recommended standard approach should encourage trustworthy and accurate evaluations of subjective and objective fatigue aimed at overcoming the limitations of previous fatigue investigations. It is critical to provide a new questionnaire capable of differentiating between various types of fatigue, such as physical and mental fatigue, and also of detecting changes in fatigue over time.

- **Short and Long-time frame**. In the literature, the evaluation of fatigue within a short (one day) and long (one year) time frame has not always been considered, and the available questionnaires focus mainly on the impact of fatigue on daily functions. Therefore, a new assessment tool capable of measuring the severity of fatigue with respect to its daily and annual changes, the internal and external triggers of fatigue, its effect on different domains, and strategies for fatigue remission would be highly informative for highlighting the characteristics of fatigue in MS. Moreover, a fatigue questionnaire must include a section that investigates potential confounding factors, such as depression, sleep disturbances, and personality traits. The new instrument must have clear statements that exhaustively characterize fatigue to make it easy for participants to estimate their perceptions of fatigue, even retrospectively. All questionnaires must also be thorough and rely on several questions to provide respondents with enough information to accurately assess changes in fatigue experience. As for objective physical and mental fatigue, it is essential to identify a unique and shared methodology as well as sensitive and suitable tools capable of estimating fatigue in patients with MS. Several studies have indicated that the conflicting results across studies may be due to the instruments employed, which are not sensitive enough to capture even mild impacts of fatigue. It is of the utmost importance to establish defined criteria and an accurate indicator of mental or physical fatigue in patients diagnosed with MS to objectively assess mental and physical fatigue.

- **Multiple assessments of fatigue.** A combination of self-assessment of fatigue at baseline (trait fatigue) and during performance (state fatigue), an investigation of fluctuations of fatigue in the short and long-term, and multiple evaluations of objective fatigue (mental and physical) should be included in each protocol used to study fatigue in MS. Sensible methods for objectively evaluating objective fatigue, such as EEG and ERP, as well as further methods, should be included in studies that investigate fatigue to improve the understanding of MS fatigue-cognition.
- **Screening for mood disorders, anxiety, and sleep disorders.** Furthermore, depression screening should not be neglected, given the overlap between fatigue and depression symptoms. Moreover, even though anxiety has not received the attention it deserves, some data suggest that, along with depression, anxiety is strongly correlated with both mental and physical fatigue (Skerrett & Moss-Morris, 2006). Due to the link between anxiety and fatigue (see Chapter 3), the assessment of anxiety should always be included in an MS fatigue study. Furthermore, screening patients with MS for sleep difficulties is also crucial. Although sleep disorders are widespread in patients with MS (Brassington & Marsh, 1998) and often linked to the presence of fatigue and depression, the majority of research has neglected to address sleep issues in patients with MS. Due to conflicting results, the association between fatigue and sleep disruptions is still unclear. However, the assessment of sleep disorders and sleep quality appears necessary since sleep disturbances seem to affect both participants'

cognitive function and fatigue and may lead to misleading findings.

- **Questionnaires investigate self-efficacy, coping strategies, and the role of stress in patients with MS.** As demonstrated, fatigue in MS is a complex phenomenon affected by various physiological and psychological variables. The way in which patients perceive and manage fatigue may have an impact on how severely they feel fatigued (Bol et al., 2009), and it may also play a part in the condition's persistence. Some research has demonstrated that feeling in control (self-efficacy) reduces fatigue (Trojan et al., 2007), whereas concentrating on body sensations increases it. Those who believe that they can establish acceptable psychological and physical settings report less fatigue and stress.

  Moreover, several studies have demonstrated that stress is linked to MS pathophysiology (Ackerman et al., 2002; Mohr et al., 2000) and affects various cognitive abilities. For instance, Miller et al. (2015) found that free cortisol, or the stress hormone, a marker of the health of the hypothalamic-pituitary-adrenal axis, affected subjects' performance in iconic memory. Psychological factors may contribute to fatigue in MS by causing psychological distress and a persistent neuroendocrine and neurovegetative stress response. When examining the connection between fatigue and cognitive impairment, it is crucial to examine people's subjective coping mechanisms, as they play a role in determining both fatigue and cognitive impairment.

- **Questionnaires investigating affectivity.** Several studies have demonstrated that increased levels of negative affectivity in healthy people may predispose them to the onset or maintenance of fatigue symptoms (Powell, Liossi, Schlotz, & Moss-Morris, 2017). Powell et al. (2017) found that personality traits such as mood, motivation, and satisfaction in one's own life play a part in the aggravation and fluctuation of fatigue during the day. Therefore, a protocol for investigating MS fatigue should include questionnaires that assess patients' negative affectivity. The information gathered through these questionnaires would contribute to clarifying the role of personality traits in the onset and maintenance of fatigue.
- **A systematic methodological approach.** The different methodological approaches used in experimental studies do not provide for a systematic approach. In several studies, cognitively demanding tasks that should serve merely as fatigue-inducing tasks have coincided with measures for evaluating the subjects' cognitive decline or for measuring fatigue. Therefore, to obtain more accurate findings in the investigation of fatigue, it is essential to pinpoint specific processes in the design of the experiment to avoid method overlap. The aim would be to devise a shared protocol that might guide researchers in investigating fatigue in MS, with the goal of ensuring improvements in MS fatigue research.

6. THE NEED FOR A MULTIDIMENSIONAL ASSESSMENT OF FATIGUE

6.1. Introduction

Self-report questionnaires are the most commonly used measures to assess trait fatigue (feelings of fatigue relatively stable over time) in clinical practice and research (Schwartz et al., 1993), as they offer insight into the individual's perspective and experience of the symptom. They do indeed represent, at present, the best tool to evaluate the presence and severity of this symptom, given that a clear definition of fatigue on which to base its objective evaluation is still missing. At the same time, however, the self-report questionnaires available to evaluate trait fatigue are very different from each other and have different limitations that make it difficult to choose which one to use.

Chapter 3 of this Thesis provides an exhaustive description of the different self-reported measures available for measuring subjective trait fatigue in MS (for reviews on this issue, see Amtmann et al., 2012; Flachenecker et al., 2002; Khan et al., 2014; Krupp et al., 1989; Learmonth et al., 2013; Penner et al., 2009; Téllez et al., 2005). Within the realm of self-reported measures to evaluate trait fatigue are the FSS (Krupp et al., 1989), the FIS (Krupp & Elkins, 2000), the MFIS (Fisk et al., 1994), the MAF (Belza et al., 2015), the FSMC (Penner et al., 2009), the FAS (Michielsen et al., 2003), the FAI (Schwartz et al., 1993), the MFI (Smets, Garssen, Bonke, & De Haes, 1995), the Unidimensional Fatigue Impact Scale (U-FIS; Doward et al., 2010), the VAS-F (Leet al., 1991), and the MS-Specific Fatigue Scale (MS-FS; Schwartz et al., 1993), the Chalder

Fatigue Scale (CFS; Chalder et al., 1993) and the Functional assessment of Multiple Sclerosis (FAMS; Cella et al., 1996).

In the following paragraph, the constraints associated with currently accessible instruments are elucidated, and the study designed to address the deficiencies inherent in these tools is presented. The primary objective of this investigation is to enhance comprehension regarding the attributes of fatigue in individuals afflicted with MS.

6.2. Limits of current self-report questionnaires

Despite being valuable, most questionnaires developed to assess trait fatigue in MS present several limitations that might hinder study outcomes in a research setting. Sander and colleagues (2017) highlighted several limitations related to fatigue questionnaires, ranging from lower accuracy to lower stability and reliability. For instance, most fatigue scales require patients to score reported fatigue symptoms retrospectively over quite lengthy periods of time (Kluger et al., 2013). Fatigue scores relying on the subjects' mnemonic skills, often impaired in MS patients, are often faulty and may hinder research outcomes. Moreover, several questionnaires require patients to estimate fatigue without fully defining it, as they often include only a narrow sample of probable origins of fatigue, making the instruments vulnerable to recollection bias, which may impair diagnostic accuracy (Kluger et al., 2013). Several studies also showed that fatigue can alter or change a person's thinking and cognition about what they are experiencing (Kroencke et al., 2000). Hence, an individual's perception of their exhausted experiences may not always be accurate and might potentially diminish quantifiable assessments. Furthermore, several studies have shown a significant correlation between some fatigue scales and scores on measures of depression. As a result, these instruments, which are susceptible to mood influences, may exhibit restricted reliability (Flachenecker et al., 2002).

Most self-reports assess different components of fatigue and, in many instances, independent constructs due to structural differences (Kos et al., 2004). For instance, the FSS and MFIS have modest correlations, indicating that the two scales are connected to some degree but assess distinct elements of fatigue (Elbers et al., 2012; Heine et al., 2015; Rietberg et al., 2010).

As discussed in Chapter 3, fatigue scales can assess the severity, modality, frequency, and daily impact of fatigue differently. The bulk of measures to assess trait fatigue include items or subscales focusing on the degree to which fatigue interferes with respondents' occupational, social, and everyday mental and physical activities. As a result, these scales provide limited information concerning the core feeling of fatigue, fatigue triggers, and the degree of fatigue within a short and long-time frame. Fatigue scales, such as the MFIS and FSI, are examples of questionnaires that include mostly items investigating the impact of fatigue on subjects' daily activities. Despite evidence in the literature suggesting that fatigue is not a stable phenomenon but rather changes in severity from morning to night (Claros-Salinas et al., 2010; Kim et al., 2010), the evaluation of physical and mental fatigue within a short (one day) and long (one year) time frame is not included in the majority of the available scales assessing trait fatigue in MS, therefore limiting the opportunity to adequately characterize it as a symptom. Clinically, studying physical and mental fatigue within a short and long-time frame can help define peaks of fatigue and provide patient-focused guidance in planning mental and physical activities.

6.3. The Multi-Temporal Assessment of Fatigue Questionnaire

The main objective of this study was to develop a new self-report questionnaire committed exclusively to the estimation of the presence and severity of physical and mental fatigue within a short and long- time frame. Contextually, the internal and external triggers of fatigue, its effect on different domains, and the strategies effective for its remission were assessed to highlight the characteristics of fatigue specific to MS. All through the questionnaire, a clear distinction was maintained between the physical and mental components of fatigue, as a further and superordinate purpose of this work was to demonstrate the clear separation of these two constructs, whose nature is still unclear. The questionnaire aimed at estimating the presence and severity of physical and mental fatigue will be referred to from now on as the Multi-Temporal Assessment of Fatigue (MtAF).

6.4. Methods

6.4.1. The survey

The MtAF was included in a survey that included items intended to gather information to better characterize physical and mental fatigue, i.e., items investigating the internal and external triggers of mental and physical fatigue, the effects of physical and mental fatigue on different domains, and the strategies effective in reducing physical and mental fatigue. The MtAF and the other components of the survey are exhaustively described in the following paragraphs.

6.4.2. Construction of the Multi-Temporal Assessment of Fatigue

The MtAF consists of items gained from existing scales and new items aimed at identifying short and long-term variations of physical and mental fatigue. The items initially included in the MtAF are presented in Table 2. The questions "*I have been feeling very fatigued physically/ mentally"* require participants to rate, on a 5-point Likert scale (1 = not at all to 5 = very), whether they experienced physical/mental fatigue "in the last 24 hours", "in the last week", "in the last month", or "in the last year". Previous scales such as the MAF investigated the degree of fatigue during the past week (e.g., "To what degree has your fatigue changed during the past week?"; "Over the past week, how often have you been fatigued?"). The trend of fatigue over the previous month and year has been investigated by adding new items to provide a more complete view of the overall fatigue temporal pattern. The questions "*During the day, I feel more physical/ mental fatigue*" require participants to rate, on a 5-point Likert scale (1 = never; 5 = always), whether they generally experience physical/ mental fatigue "immediately after waking up", "in the morning", "in the afternoon", "in the evening". The items "in the morning" and "in the afternoon" have been extracted from the FAI scale (e.g., "my fatigue is worse in the afternoon"; "my fatigue is worse in the morning”), while the others are new items introduced to examine the physical and mental fatigue diurnal pattern with the aim of identifying peaks in fatigue and short-term shifts in the fatigue experienced by MS patients.

Table 2 Items included in the MtAF

Items	New/Old
I have been feeling very fatigued physically/mentally	
in the last 24 hours	New
in the last week	MAF
in the last month	New
in the last year	New
During the day, I feel more physical/ mental fatigue	
immediately after waking up	New
in the morning	FAI
in the afternoon	FAI
in the evening	New

Face and content validity of these items were tested by a pilot investigation involving 27 lay volunteers (18 females, M age = 41.81, SD = 9.19; M years of education = 16.52, SD = 3.72) and two neurologist experts in MS (2 males, age = 58 and 57; M years of education = 22 and 22).

Face validity is the degree to which the items of an assessment tool appear to be appropriate to the targeted construct and assessment objectives in terms of accessibility and structural clarity. Lay volunteers were asked to rate the suitability of each item on a 0–4 Likert scale (i.e., 0 = “not suitable at all”, 1 = “poorly suitable”, 2 =

“suitable enough”, 3 = “very suitable", and 4 = “highly suitable”). Only items scored between 50 and 100 (i.e., all judges scored 2, 3, or 4 the item) should be retained (Hardesty & Bearden, 2004).

Content validity is the degree to which the items of an assessment tool constitute a representative sample of the universe of possible attributes/theoretical contents related to the construct. Experts were asked to assess the representativeness of each item in relation to the conceptual frameworks (i.e., degree of physical and mental fatigue at different representative times along a short -within a day- and long -within a year- period) using a 0–4 Likert scale (i.e., 0 = “not representative at all”, 1 = “poorly representative”, 2 = “representative enough”, 3 = “very representative", and 4 = “highly representative”). An item is considered valid and consistent with the conceptual framework if at least n–1 rater judge the item as representative, namely, by giving a score of 2, 3, or 4 (Parsian & Dunning, 2009). The two neurologists volunteering for the content validity assessment informally judged all items as equally relevant for the purpose of assessing physical and mental fatigue within a short (one day) and long (one year) time frame.

As concerns content validity, both experts judged all items as highly representative (scoring all items 4) of the construct. The face validity testing showed elevated agreement among raters, with all items getting a score of 96.3 or 100, suggesting highly suitable surface-level characteristics. No rectification or supplementation was requested. Overall, these findings ensured that the psychometric properties of the tool could be explored in its current form.

6.4.3. Selection of the items for assessing the core characteristics of physical and mental fatigue

The items selected to assess the core characteristics of physical and mental fatigue are presented in Tables 3, 4, and 5**.** These items aim at exploring internal and external triggers of physical and mental fatigue, the effects of physical and mental fatigue on different domains, whether physical and mental fatigue decrease spontaneously, and more efficacious strategies for mitigating physical and mental fatigue.

Internal and external triggers of physical and mental fatigue. The questions " *Physical/mental fatigue usually manifests itself",* require participants to rate, on a 5-point Likert scale (1 = never; 5 = always), whether specific internal or external conditions are involved in the onset of fatigue.

The internal conditions refer to sleep, mental exertion, stress, illness, and pain; the external conditions are related to chaos, physical exertion, and weather conditions.

As far as sleep is concerned, there is evidence indicating that both too short and excessive sleep (defined as sleeping less and more than the body requires, respectively) may contribute to the onset of fatigue. For instance, evidence shows that different sleep lengths influence the autonomic nervous system and human vital signs, impacting negatively on a variety of physiological functions, including mood, cognition, alertness, and memory (Miró et al., 2002; Ogawa et al., 2003). Some authors discovered that patients affected by restless leg syndrome who reported lower sleep quality experienced more fatigue (Moreira et al., 2008). According to Goshvarpour et al. (2016), oversleeping may result in fatigue and drowsiness. Accordingly, to investigate the role of sleep length on the onset of physical and mental fatigue, the items "when I slept too little" and "when I slept too much" have been included in the questionnaire. With respect to mental exertion, known to tire MS patients (Westbrook & Braver, 2015), the item "when I have to concentrate for a long time" was included in the questionnaire. It was drawn from the FSMC scale (e.g., "when I concentrate for a long time, I get exhausted sooner than other people of my age"), the MFIS (e.g., "I have had difficulty paying attention for long periods of time"), the FAI (e.g., “when I am fatigued, I have difficulty concentrating for a long time”), and the MFI (e.g., “my thoughts easily wonder”). The new item "when I have to concentrate for a short time" was also included in the questionnaire to determine whether the length of time-on-task plays a role in the onset of fatigue, as suggested by some authors (e.g., Ackerman et al., 2009; Sandry et al., 2014).

As to stress linked to fatigue in MS, either as a cause or as an effect of it (Hart, 1978; Krupp et al., 1988), the item “when I find myself in a stressful situation" was included in the questionnaire. It corresponds to items included in the FSMC scale (e.g., “when faced with stressful situations, I now find that I get physically exhausted quicker”), in the MAF scale (e.g., “to what degree has fatigue caused you distress?”), and in the MS-FS scale (e.g., “stress brings on fatigue”).

Evidence shows that patients facing pain or illness may experience fatigue (Krupp, Christodoulou, & Schombert, 2005). Accordingly, the items "when I feel sick ", and "when I have pain" were included in the survey. These items came from the FAMS instrument.

Moving on to external factors, the items “when there is a lot of confusion" and "when there are many people" have been added to the MtAF to explore the contribution of confusion to the onset of fatigue. Indeed, there is evidence showing that those who live in crowded and highly populated environments may face psychological stress and fatigue due to their exposure to many social interactions. In other words, the capacity for social engagement would be exceeded by these excessive social encounters, which might result in social overload and social retreat (McCarthy and Saegert, 1978). Concerning physical effort, there exists empirical evidence pertaining to its potential impact on fatigue in MS patients (Dalgas et al., 2018). For instance, items referring to the general impact of physical exertion on MS patients are included in the FSS scale (e.g., “exercise brings on my fatigue”), the FAI scale (e.g., "performance of routine daily activities increases my fatigue”; “I experienced prolonged fatigue after exercises"), the FAS scales (e.g., “I get tired very quickly”), and the CFS scales ("do you start things without difficulty but get weak as you go on?"). Accordingly, the following items were included in the MtAF: "after a short physical effort" and "after a prolonged physical effort" to explore whether the length of the physical effort may have a different impact on the onset of fatigue. For instance, McLoughlin et al. (2016) showed that the MS group experienced a rise in fatigue after the 6MWT. Krupp and colleagues (1988) demonstrated that exercise and extended physical activities are associated with fatigue in MS.

With respect to the weather conditions, there is abundant evidence showing that high temperatures contribute to the development of fatigue (Mollaoğlu & Üstün, 2009). The item "when it is too hot," taken from the MS-FS and FAI scales (e.g., "heat brings on fatigue"), was therefore selected. Two new items, "when it is too cold" and "when there is too much humidity," were also included, as evidence shows that being overly damp might induce or worsen fatigue (Braley & Chervin, 2010; Hubsky et al., 1992).

Table 3 Items selected to assess internal and external triggers of physical and mental fatigue

	Items	New/Old (Scale)
Physical/mental fatigue usually manifests itself		
Internal Triggers	when I slept too little	New
	when I slept too much	New
	when I have to concentrate for a long time	FSMC, FAI, MFIS, MFI
	when I have to concentrate for a short time	New
	when I find myself in a stressful situation	FSMC, MAF, MS-FS
	when I feel sick	FAMS
	when I have pain	FAMS
External Triggers	when there is a lot of confusion	New
	when there are many people	New
	after a short physical effort	New
	after a prolonged physical effort	New
	when it is too hot	MS-FS, FAI
	when it is too cold	New
	when there is too much humidity	New

The effects of physical and mental fatigue on different domains. The question "*When I feel physically/mentally very fatigued*" requires participants to rate, on a 5-point Likert scale (1 = not at all; 5 = very), to what extent fatigue affects attention, decision-making, motor and cognitive speed, memory, sleep, mood, and physical strength. There is evidence showing that all these domains are negatively affected by fatigue. For instance, there is abundant evidence indicating a negative impact of fatigue on alertness, vigilance, and attention (e.g., Fiene et al., 2018; Hanken et al., 2015; see Chapters 3, and 5). Similarly, the detrimental effect of fatigue on both motor and cognitive speed in MS patients is well documented (e.g., Kujala et al., 1995; see Chapters 3 and 5). There is also evidence showing that gradual but consistent rises in fatigue have varying consequences on one's ability to make decisions (e.g., Royal et al., 2006). As far as memory is concerned, there are mixed findings (see Chapters 3 and 5), as some studies found that fatigue worsened memory (e.g., Diamond et al., 2008), while others did not (e.g., Jougleux-Vie et al., 2014). Sleep disturbances have been investigated, as evidence has shown an overlap in the symptoms of sleep disturbances and fatigue (Sparasci et al., 2022). Physical weakness is one of the most complained-about symptoms by MS patients and has been associated with fatigue several times (e.g., Krupp et al., 1996; MSCP, 1998).

Two items concerning the effect of fatigue on attention were also selected: "I am easily distracted" and "I am less reactive". The first item is similar to the item present in the FAMS scale (e.g., “I have had trouble concentrating”), in the CFS scale (e.g., “do you have difficulty concentrating?”), in the FSMC scale (e.g., “when I am experiencing episodes of fatigue, I lose concentration considerably quicker than I used to”), and in the MFIS scales (e.g., "I have had trouble concentrating on doing something"). The second item is similar to the item present in the FSMC scale (e.g., "when an episode of exhaustion comes on, I am simply no longer able to react quickly") and to the item in the MFIS scale (e.g., “I have been less alert”).

The item "it is hard for me to take decisions" corresponds to the item included in the FSMC scale (e.g., "when I am experiencing episodes of exhaustion, I am incapable of making decisions") and in the MFIS scale (e.g., “I have difficulties making decisions”).

The items "I easily forget things" and "I have trouble finding the right words" correspond to the items present in the FSMC scale (e.g., "when I am experiencing episodes of exhaustion, certain words simply escape me”; “during episodes of exhaustion, I am noticeably more forgetful"), in the CFS scale (e.g., "do you find it more difficult to find the correct word?"), in the FAMS scale (e.g., "I have trouble remembering things"), and in the MFIS scale (e.g., “I have been forgetful").

The items "I feel mentally lethargic" and "I feel sleepy" were drawn from the CFS (e.g., “Do you feel sleepy or drowsy?”) and the FAI scales (e.g., “I feel drowsy when I am fatigued”).

The item "I am easily irritable" was included as it is similar to the item present in the FAMS scale (e.g., “I feel nervous”). Moreover, there is evidence in the literature showing that fatigue may manifest through moodiness and irritability (Fava et al., 2010; Schreiber et al., 2015).

The item "I feel physically weak" corresponds to that present in the CFS scale (e.g., "do you feel weak?"; "do you have less strength in your muscles?"), in the MFIS scale (e.g., "my muscles have felt weak"), and in the FAMS scale (e.g., "I feel weak all over"). The item "I feel physically slowed down”, corresponds to the item present in the FSMC scale (e.g., "when I am experiencing an episode of exhaustion, my movements become noticeably slower").

Table 4 Items selected to assess the effects of physical and mental fatigue

	Items	New/Old (Scale)
When I feel physically/mentally very fatigued		
Mental Effects	I am easily distracted	FAMS, MFIS, FSMC, CFS
	I am less reactive	FSMC, MFIS
	It is hard for me to make decisions	FSMC, MFIS
	I easily forget things	FSMC, FAMS, MFIS
	I have trouble finding the right words	FSMC, CFS
	I feel mentally lethargic	CFS
	I feel sleepy	CFS, FAI
	I am easily irritable	FAMS
Physical Effects	I feel physically weak	CFS, FAMS, MFIS
	I feel physically slowed down	FSMC

Spontaneous decrease in physical and mental fatigue. The statement *"Usually physical/mental fatigue regresses spontaneously,"* requiring participants to rate the frequency of spontaneous regression of this symptom on a 5-point Likert scale (1 = never; 5 = always), was selected as several symptoms, during periods of disease remission, can disappear spontaneously (Mutani et al., 2012).

Strategies effective in reducing physical and mental fatigue. The statement *"The following strategy is effective in alleviating my physical/mental fatigue"* requires participants to rate, on a 5-point Likert scale (1 = not at all; 5 = very), to what extent specific strategies are effective in reducing physical and mental fatigue.

Several fatigue scales include items assessing the role of rest in alleviating fatigue, as in the MFIS scale (e.g., "I have needed to rest more often or for longer periods"), the FAI scale (e.g., "resting lessens my fatigue"), the CFS scale (e.g., "do you need to rest more?"), and the FAM scale (e.g., "I need to rest during the day"). The FAI scale also includes an item assessing the effect of sleep on fatigue remission (e.g., “sleep lessens fatigue”). However, neither scale investigates whether the length of rest or sleep play a role in reducing fatigue. Accordingly, the new items "short physical rest," "long physical rest," "short daytime sleep," and "long daytime sleep" have been included.

As much evidence indicates, activity pacing aids in controlling fatigue (Murphy, Smith, & Alexander, 2008; Murphy & Kratz, 2014). The items "slowing down the current activity" and "stopping the ongoing activity" were included as they are similar to those present in the MFIS (e.g., “I have had to pace myself in my physical activities”) and in the FSMC scale (e.g., “because of my episodes of exhaustion, I now need more frequent and/or longer rests during physical activity than I used to”).

Table 5 Items selected to assess the degree of spontaneous decrease in physical and mental fatigue and the effectiveness of different strategies in reducing physical and mental fatigue

Items	New/Old (Scale)
Usually physical/mental fatigue regresses spontaneously	New
The following strategy is effective in alleviating my physical/mental fatigue	
short physical rest	New
long physical rest	New
short daytime sleep	New
long daytime sleep	New
slowing down the current activity	MFIS
stopping the ongoing activity	FSMC

6.4.4. Participants

The survey was administered as an online questionnaire using a custom URL that directed to a Google Form webpage on the Google Forms platform. The survey was distributed to participants via email, SMS, and social media platforms (i.e., Facebook, WhatsApp). The study was run between April 2018 and November 2020.

Participants interested in completing the questionnaire provided informed consent through a custom URL that directed them to a Google Form webpage. Moreover, the webpage provided information about the research and its objectives. Participants were informed that their information would be used exclusively for research purposes through the process of informed consent and that they had the option to halt questionnaire completion at any time (see Appendix 3 for further details). Participants did not receive financial compensation for their participation.

A total of two hundred seventy-five Italian adults completed the survey. The recruited participants were university students, friends, colleagues, and acquaintances. The inclusion criteria were being 18 to 70 years old. Exclusion criteria were as follows: having less than 8 years of formal education; neurological or psychiatric diseases or major illnesses that might distort the results of the research, such as diabetes, diabetic therapy, and cardio-vascular dysfunctions; a history of mild or severe traumatic brain injury; the use of drugs affecting fatigue states; substance abuse; visual disturbances that might interfere with the experiment's execution; and, for women, being pregnant. The aforementioned exclusion criteria have been selected to optimize the internal and external validity of the fatigue study. The aim was to provide a controlled environment by eliminating people who possess certain features or circumstances that could interfere with the outcome of the study. For example, participants with fewer than 8 years of formal education have been eliminated, as people with lower levels of education may have challenges comprehending the content of the questionnaire, and possible bias can be introduced in the evaluation of questions (Reynolds, Altmann, & Allen, 2021). Moreover, participants with visual disturbances have been excluded to mitigate the potential influence of visual impairments on participants’ answers. This precaution is necessary as visual impairments might impede participants' accuracy in performing tasks (Skaggs & Hopper, 1996). Also, individuals with pre-existing neurological or psychiatric conditions, major illnesses, or those who are pregnant have been excluded, as they might potentially experience fatigue and/or depression because of their respective conditions (Mozuraityte et al., 2023; Reeve, Sheaves, & Freeman, 2019; Tylee, Gastpar, Lépine, & Mendlewicz, 1999). Participants taking drugs that affect their fatigue state were excluded to avoid confounding factors in the outcome (Zlott & Byrne, 2010).

The examination of the prescribed pharmaceuticals and concurrent pathologies has been undertaken in order to determine if the medications and underlying medical conditions of the subjects may potentially induce symptoms of fatigue and introduce any form of bias into the research study. Regarding participants who engage in substance abuse and drug consumption, it has been shown that substance abuse may modify the degrees of fatigue experienced by individuals (Okkes, Oskam, Lamberts, 2002), hence possibly introducing confounding factors into the outcomes.

These exclusion criteria serve the purpose of minimizing interference from additional factors and confounding variables preventing any potential bias in the findings and guaranteeing a consistent assessment of fatigue across participants. According to the exclusion criteria, data from thirty participants was removed. The final sample included two hundred forty-five healthy individuals (Controls), of whom one hundred seventy-nine were female. Participants had an average age of 44 years (M = 44.00, SD = 10.09) and, on average, 16 years of educational attainment (M = 16.05, SD = 3.74). As for participants' employment status, physical activity patterns, and alcohol and smoking consumption behaviours, the survey revealed that a significant proportion of participants in the study were employed (80.41%), practiced a sport (43.27%), and assumed alcohol (33.06%). A small portion of subjects smoked regularly (20.82%).

The descriptive statistics on demographic variables of the final sample of Controls are presented in Table 6.

A total of two hundred and two MS patients completed the survey. Participants were recruited at the Neurological Clinic of the University of Federico II of Naples, in social virtual groups (i.e., Facebook), and by a snowball sampling strategy. The inclusion criteria were having a clinically definite diagnosis of MS and being between 18 and 70 years old. The exclusion criteria and the rationale for the exclusion were the same as for Controls. Additionally, MS patients with exacerbations within thirty days of the research were excluded. Exacerbations in MS denote periods characterized by heightened disease activity and the manifestation of several symptoms. Furthermore, exacerbations have the potential to manifest as acute and temporary symptoms that may not precisely represent the usual fatigue encountered by people with MS during stable phases (Flachenecker & Meissner, 2008). These exacerbations may have a substantial influence on the capacity of individuals to engage in research endeavours and properly fulfill evaluations. By prioritizing individuals who have not had recent exacerbations and are in a reasonably stable state of illness, the research aims to increase the probability of obtaining useful data from participants to enhance the validity of the results. Furthermore, it is crucial to recognize that the inclusion of participants in an exacerbation phase of the research may impose additional hardships on patients. Prioritizing the well-being of participants and mitigating possible dangers related to study involvement during moments of exacerbation are crucial considerations. According to the exclusion criteria, data from thirty participants was removed. The survey was initially completed by one hundred seventy-two MS patients.

However, due to the predominant representation of patients diagnosed with RRMS within the sample, to maintain sample homogeneity, it was decided to exclude the small number of patients who exhibited different subtypes, namely SPMS and PPMS. The final sample upon which the analyses were performed comprises one hundred sixty RRMS participants, of whom one hundred seven were female. RRMS participants had an average age of 42 years and, on average, 15 years of educational attainment ($M = 15.52$, $SD = 3.90$). As for employment status, physical activity patterns, smoking, and alcohol consumption behaviours, the survey revealed that a significant proportion of RRMS patients were employed (74.38%), a moderate percentage practiced sport (22.50%), a minority of RRMS patients reported alcohol consumption (18.13%), and a significant portion of patients reported regular smoking (31.88%).

Before proceeding with the description of the disease characteristics of the RRMS sample, some clarifications are needed.

In MS, the EDSS tool is employed by neurologists for evaluating patients' disabilities and tracking the progression of the illness (for more details, see Chapter 1). In the present study, the use of neurologist-assessed patient disability was not feasible within the context of online data collection. Due to this rationale, it was decided to prioritize the assessment of the patient's degree of mobility by adapting the comprehensible questions from the original EDSS for the patient's use. The self-report is referred to as the Mobility Self-Assessment (MSA; see Appendix 4). While acknowledging the arbitrary nature of the decision, it was deemed imperative to employ this approach to gauge the patient's degree of impairment and motor dysfunction. The choice to administer a self-report related to the personal degree of mobility was made based on the evidence presented in several studies within the existing body of research showing a correlation between scores acquired from scales derived from the EDSS and the scores reported by patients on the EDSS scale studies (Bowen, Gibbons, Gianas, & Kraft, 2000; Verdier-Taillefer, Roullet, Cesaro, & Alperovitch, 1994). The patient's mobility level has been classified into three distinct categories. The category of full mobility pertains to patients who self-report complete independence in walking. The category of mild mobility impairment encompasses patients who indicate a requirement for mild to moderate assistance, while the category of severe mobility impairment encompasses patients who exhibit progressively severe walking challenges and necessitate assistance as well as aids for moving around. The mean disease duration suggests that the subjects had experienced MS for a significant length of time (M = 12.17, SD = 7.30). As for Mobility Self-Assessment (MSA), a substantial portion of patients reported full mobility (44.38%), a significant number reported mild mobility impairment (35.63%), and a smaller percentage reported severe mobility impairment (3.75%). As for pharmacological MS treatment, a significant proportion of patients in the sample managed their condition without the use of DMT, while others were using various DMT options, with Dimethyl Fumarate being the most common choice (43.13%). Regarding the concomitant medication taken by MS patients, it was found that patients reported taking medications for the treatment of MS symptoms (20.00%) and for the treatment of concomitant diseases (44.38%). The majority of patients (76.88%) did not engage in rehabilitation therapy. The descriptive statistics of RRMS patients' clinical characteristics are presented in Table 6.

The present study has been approved by the Local Ethics Committee of the University of Federico II with number 80/20 and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki, together with the principles that guide the ethical and methodological practice of online research (Das, Ester, & Kaczmirek, 2011), social and behavioral research, and internet-applied methods and strategies (Hunter et al., 2018; see Appendix 3).

6.4.5. Material and procedure

The survey was administered to the participants in a tripartite format. The **first part** contained questions aimed at characterizing the group of Controls and MS patients. Accordingly, socio-demographic information (sex age, education, employment status) was explored. Additional questions were related to self-care practices such as whether at least one sport was practiced (yes or no), whether alcohol and smoking were consumed regularly (yes or no), and clinical aspects such as sleep quality (e.g., no sleep disturbances = 0, experiencing only one sleep disturbance =1, having more than one sleep disturbance = 2), the presence of a disease (e.g., psychiatric disorders, cardiovascular disease, and respiratory disease), and disease treatment (e.g., anticholinesterase agents, steroids). MS patients were required to fill in additional questions related to clinical disease characteristics such as MS phenotype (e.g., RRMS, PPMS, PRMS, SPMS, CIS, RIS), disease duration, current symptoms (e.g., fatigue, vision problems, depression, and anxiety), and mobility impairment (full mobility, mild mobility impairment, severe mobility impairment).

Current treatments such as MS treatment (e.g., Interferon beta-1a; Interferon beta-1b; Fingolimod; Dimethyl fumarate; other, unknown), symptomatic treatment (e.g., mood disorder, medication, fatigue medication, neuropathic pain medication), treatment for concomitant disease (e.g., gastritis medications, thyroid irregularities medications), and rehabilitation activities (yes or no) were also investigated. (For more details, see Appendix 5).

The **second part** of the survey consists of the MtAF and other items aimed at exploring internal and external triggers of mental and physical fatigue, whether mental and physical fatigue decrease spontaneously, which strategies are more effective in reducing mental and physical fatigue, and the effects of mental and physical fatigue on different domains. This part included an introductory section in which the difference between physical and mental fatigue was clarified.

The **third part** consisted of the PSE-MCP, which detects respondents' perception of being able to face problematic life situations, and the BDI, a self-report rating inventory aimed at measuring depressive symptoms. The PSE-MCP requires participants to indicate their agreement on a 5-point Likert scale (0 = by no means*;* 5 = entirely capable) on 24 items assessing the extent to which they feel able to manage certain situations. The scale allows for the obtaining of four distinct scores (range 6–30) relating to emotional maturity, finalization of the action, relational fluidity, and context analysis. Emotional maturity refers to beliefs concerning the ability to handle stressful situations, deal with unforeseen events, and have good self-control over difficult events and situations. Finalization of the action refers to beliefs about the ability to set concrete and achievable goals, prioritize them, adapt them to their skills, and pursue the objectives set. Relational fluidity refers to beliefs about the ability to interact and engage with others, to give and ask for help, to maintain good relations with others, and to manage interpersonal conflicts. Finally, context analysis concerns the belief in the ability to "read" the context in which the links between the different events and the different situations exist, to understand the requests coming from the people in the environment, and to use language appropriate to the different circumstances. The PSE-MCP has been included in the survey as there is evidence in the literature indicating that self-efficacy, helplessness, defensive style, ego strength, stress, and coping strategies are related to fatigue (Bradley et al., 1984; Chatterton et al., 2006; Van der Werf, Evers, Jongen, & Bleijenberg, 2003).

The BDI self-report rating inventory measures depressive symptoms. The concurrent presence of depressive mood in fatigued people has been indicated in several studies (Ford et al., 1998; Induruwa et al., 2012; Kaminska et al., 2011; Kos et al., 2008; Pittion-Vouyovitch et al., 2006). Therefore, screening for mood depression is paramount during fatigue investigations in MS. A clinically significant cutoff point > 15 indicates the likely presence of depressive symptoms. More specifically, depressive symptoms are probably absent if the score is < 10; mild if it is between 10 and 19; average if it is between 20 and 29; and serious if the score is > 30. Completing the questionnaire took approximately 30 minutes. (For more details, see Appendix 5).

Table 6 Descriptive statistics and distributions of Relapsing-Remitting Multiple Sclerosis (RRMS) patients' and Control's (C) characteristics

	RRMS	**C**
N. Total (N. Female)	160 (107)	245 (179)
Age[1]. Mean (SD)	41.99 (10.08)	44.00 (10.09)
Formal education[1]. Mean (SD)	15.52 (3.90)	16.05 (3.74)
Sleep quality. Mean (SD)	0.92 (0.85)	0.51 (0.64)
BDI. Mean (SD)	5.59 (5.23)	4.82 (4.39)
Emotional maturity. Mean (SD)	17.87 (5,00)	17.03 (4.15)
Finalization of the action. Mean (SD)	20.75 (5.53)	19.65 (4.86)
Relational fluidity. Mean (SD)	20.66 (5.21)	19.71 (4.50)
Context analysis. Mean (SD)	22.08 (5.83)	20.95 (4.93)
Employed. N. (%)	119 (74.38)	197 (80.41)
Unemployed. N. (%)	41 (25.63)	48 (19.59)
Practicing sport. N. (%)	36 (22.50)	106 (43.27)
Assuming alcohol. N. (%)	29 (18.13)	81(33.06)
Smoking regularly. N. (%)	51 (31.88)	51(20.82)
Disease duration[1]	12.17 (7.30)	/
MSA. Mean (SD)	1.93 (1.62)	/
Full mobility. N. (%)	71 (44.38)	/
Mild mobility impairment. N. (%)	57 (35.63)	/
Severe mobility impairment. N. (%)	6 (3.75)	/
MS therapy. N (%)		
None	2 (1.25)	/
Interferon beta-1a	27 (16.88)	/
Fingolimod	21 (13.13)	/
Dimethyl fumarate	69 (43.13)	/
Other	13 (8.13)	/
Unknown	28 (17.50)	/

[1] years

6.5. Statistical analyses

Univariate 2 (Group: MS vs. C) analysis of variances (ANOVAs) were used to assess whether there were differences between MS patients and Controls with respect to Age, Education, Sleep quality, BDI scores, and the scores related to the four dimensions of the PSE-MCP.

The first and main purpose of this study was to develop a new questionnaire committed exclusively to the assessment of the presence and severity of fatigue. Accordingly, the psychometric characteristics of the MtAF were assessed. The scale's internal consistency was evaluated by Cronbach's alpha coefficient. Item characteristics, reliability, and scaling assumptions were tested using the corrected Pearson's item-total to adjust for inflation errors. Based on Cohen's conventions (weak, $r < 0.30$; moderate, $r = 0.30–0.50$; strong, $r > 0.50$), an item-total correlation >.30 was deemed acceptable (De Vaus D (2004). Surveys in social research. Routledge, London). As the second main purpose of this study was to assess whether Physical and Mental Fatigue are two distinct constructs, the factorial structure of the MtAF was evaluated by means of a Principal Component Analysis (PCA) with Varimax orthogonal rotation. The Mineigen criterion (eigenvalue > 1; Kaiser, 1960) and the inspection of the scree plot were employed to determine the number of factors to be extracted (Cattell & Vogelmann, 1977). Correlational analyses and simultaneous multiple linear regression analyses were used to assess whether the sociodemographic and clinical variables of MS patients and Controls correlated with the factors extracted by the PCA and could explain their variability. The above analyses were run separately for Controls and

MS patients. Concerning the assessment of Physical and Mental Fatigue within a Short and Long-time frame, as measured by the MtAF, a repeated-measures ANOVA was used, assuming Group as the between-subjects factor and Type of Fatigue and Short and Long-time frame within-subjects factors.

When necessary, follow-up analyses were run, and the relevant pairwise contrasts were reported. A $p \leq 0.05$ was considered statistically significant. As for the internal and external triggers of fatigue, its effect on different domains, and the strategies effective for its remission, only descriptive statistics were reported. A $p \leq 0.005$ (Bonferroni correction) was considered statistically significant. The statistical analyses were conducted through IBM SPSS AMOS (version 22).

6.6. Results

6.6.1. Participants sample descriptive statistics

The descriptive statistics on demographic and clinical variables of the sample of MS patients and Controls are presented in Table 6. The mean age was marginally higher in Controls than in MS patients, $F(1, 405) = 3.87$, $p < 0.05$, $\eta_p^2 = 0.01$, while Education did not significantly differ between the two groups, $F(1, 405) = 1.88$. Sleep quality was significantly better in Controls as compared to MS patients, $F(1, 405) = 29.94$, $p < 0.0001$, $\eta_p^2 = 0.07$. The analyses of the responses to the BDI items indicated equivalent scores in Controls and in MS patients $F(1, 405) < 3.19$. Similarly, scores from the four subscales of the PSE-MCP were equivalent in Controls and MS patients, $Fs(1, 405) < 3.80$.

6.6.2. Psychometric analysis and factorial structure of the Multi-Temporal Assessment of Fatigue in Controls

The MtAF demonstrated more than acceptable psychometric integrity, as shown by the excellent internal consistency according to Cronbach's alpha ($\alpha = 0.90$) and adjusted item-total correlations (De Vaus, 2004; Taber, 2018; see Table 7). Seven out of sixteen items showed strong correlations with the total MtAF score (r range = 0.60–0.69), eight high item-total correlations (r range = 0.50–0.59), and one medium item-total correlation ($r = 0.44$). Considering these findings, all items were maintained and entered in a Confirmatory Factor Analysis (CFA) with Varimax orthogonal rotation, performed to test whether Physical and Mental Fatigue are two independent forms of fatigue, as largely suggested in the literature.

Table 7 Characteristics of items included in the Multi-Temporal Assessment of Fatigue in Controls

Items	M	SD	Corrected item-total correlation	Cronbach's alpha if item removed
PF_in the last 24 hours	2.26	0.90	0.54	0.90
PF_in the last week	2.44	0.87	0.69	0.90
PF_in the last month	2.64	0.88	0.67	0.90
PF_in the last year	2.75	0.95	0.63	0.90
PF_after waking up	2.25	1.02	0.44	0.90
PF_in the morning	2.14	0.94	0.60	0.90
PF_in the afternoon	2.72	1.00	0.58	0.90
PF_in the evening	3.28	0.98	0.51	0.90
MF_in the last 24 hours	2.27	0.97	0.59	0.90
MF_in the last week	2.51	0.94	0.64	0.90
MF_in the last month	2.74	0.94	0.69	0.90
MF_in the last year	2.93	1.03	0.54	0.90
MF_after waking up	2.02	0.97	0.50	0.90
MF_in the morning	2.20	0.95	0.56	0.90
MF_in the afternoon	2.73	1.00	0.60	0.90
MF_in the evening	3.05	1.05	0.57	0.90

Note. Mental Fatigue (MF) and Physical Fatigue (PF); Mean (M), Standard deviation (SD)

A three-factor solution was generated by PCA using the Mineigen criterion (eigenvalues > 1). This three-factor solution presented a clear structure with strong loadings (all > 0.50) and no overlapping items between factors (see Table 8). The first factor was composed of items referring to Mental Fatigue occurring in the last 24 hours, in the last week, in the last month, in the last year, in the afternoon, and in the evening; the items' loadings on this factor ranged from 0.56 to 0.84, with the factor accounting for 23.3 % of their variance. The second factor included items referring to Physical Fatigue occurring in the last 24 hours, in the last week, in the last month, in the last year, in the afternoon, and in the evening; the items' loadings on this factor ranged from 0.60 to 0.74, with the factor accounting for 21.0% of their variance. The third factor included items referring to mental and physical fatigue occurring immediately after waking up and in the morning; the items' loadings on this factor ranged from 0.70 to 0.81, with this factor accounting for 17.3 % of their variance. The first two factors clearly reflect Mental and Physical Fatigue. From now on, they will be referred to as the Mental Fatigue Index (MFi) and Physical Fatigue Index (PFi) of MtAF. The third unexpected factor can be reasonably accounted for as reflecting Sleepiness (Si), as it included items referring to mental and physical fatigue occurring immediately after waking up and in the morning. To support this hypothesis, Pearson's correlations between the three factors and the Sleep quality were computed. The correlations between the Mental and Physical Fatigue factors and Sleep quality were not significant; the correlation between the Sleepiness factor and Sleep quality was low but significant ($r = 0.15$, $p < .05$). Divergent validity was measured by correlating the MFi, the PFi, and the Si scores with the BDI scores and the PSE-MCP mean scores (calculated as the mean scores across the four subscales of the PSE-MCP). Weak but significant correlations with the BDI ($r = 0.18$, $r = 0.14$, $r = 0.15$, $ps < 0.05$) were found. The correlations with the PSE-MCP mean scores were not significant.

Table 8 Rotated component matrix of the Multi-Temporal Assessment of Fatigue in Controls

Items	Factor 1	Factor 2	Factor 3
MF_in the last month	**.84**	.23	.15
MF_in the last year	**.78**	.17	.02
MF_in the last week	**.78**	.21	.18
MF_in the last 24 hours	**.67**	.21	.22
MF_in the evening	**.63**	.37	.02
MF_in the afternoon	**.56**	.22	.34
PF_in the last week	.30	**.74**	.24
PF_in the evening	.25	**.71**	-.05
PF_in the last month	.35	**.71**	.17
PF_in the afternoon	.09	**.67**	.36
PF_in the last 24 hours	.18	**.60**	.29
PF_in the last year	.41	**.60**	.14
MF_immediately after waking up	.23	.05	**.81**
MF_in the morning	.35	.06	**.76**
PF_in the morning	.08	.44	**.71**
PF_immediately after waking up	-.02	.29	**.70**

Note. Mental Fatigue (MF) and Physical Fatigue (PF)

To detect potential effects of the sociodemographic and clinical variables on the MtAF, the correlations of the scores on the three factors with the characteristics of MS patients and Controls were first calculated (see Table 9). Mental Fatigue showed a small negative correlation with Age, while Sleepiness showed small positive correlations with Education and Sleep quality; Mental Fatigue, Physical Fatigue, and Sleepiness were all positively correlated with BDI scores. Age appeared to be negatively correlated with Education, BDI, and PSE-MCP scores. Finally, Sleep quality was negatively correlated with BDI scores.

Table 9 Correlations between the three factors and the characteristics of MS patients and Controls

		1	2	3	4	5	6	7	8	9	10	11
1	**Mental Fatigue**		0.00	0.00	0.06	**-.162***	0.02	0.03	**.178****	0.03		
2	**Physical Fatigue**	0.00		0.00	0.07	-0.01	0.05	0.04	**.136***	0.21		
3	**Sleepiness**	0.00	0.00		-0.02	-0.05	**.196****	**.153***	**.148***	-0.07		
4	**Sex**	**.169***	**.227****	0.00		-0.04	0.03	0.01	0.05	-0.09		
5	**Age**	-0.13	0.11	-0.03	-0.09		**-.323****	-0.02	**-.145***	**-.363****		
6	**Education**	-0.10	**-.157***	**-.182***	0.09	-0.14		-0.03	0.00	0.11		
7	**Sleep quality**	**.278****	0.14	**.388****	-0.02	-0.08	**-.225****		**.135***	0.09		
8	**BDI**	**.309****	**.174***	**.380****	0.06	0.17	**-.213***	**.312****		-0.05		
9	**PSE-MCP**	-0.25	0.13	-0.20	-0.22	**.511****	0.23	-0.16	**-.419****			
10	**Disease duration**	-0.03	0.04	-0.01	-0.03	**.194***	-0.16	0.00	-0.10	0.24		
11	**MSA**	-0.07	0.10	0.05	-0.02	**.194***	-0.13	-0.04	0.16	0.24	**.344****	

Note. Numbers in the bottom left half and numbers in the top right half represent correlations in the groups of MS patients and Controls, respectively. *p<.05; **p<.01.

Separate simultaneous multiple linear regression analyses were performed, assuming the factors indicating Mental Fatigue, Physical Fatigue, and Sleepiness as the dependent variables and variables significantly correlated with them as predictors. The regression models provided a not particularly good fit for the data, and the percentages of explained variance were very low (Mental Fatigue, $R^2 = .22$, $F(2, 243) = 6.389$, $p < .005$; Physical Fatigue, $R^2 = .13$, $F(1, 243) = 4.573$, $p < .05$; Sleepiness, $R^2 = .25$, $F(4, 225) = 5.238$, $p < .005$; see Table 10).

Table 10 Coefficients table of predictors of Physical Fatigue, Mental Fatigue, and Sleepiness in Controls

		Non-Standardized Coefficients		Standardized Coefficients	t	Sig.
		B	SD	Beta		
Mental Fatigue	Age	-.014	.006	-.138	-2.182	.030
	BDI	.037	.015	.157	2.480	.014
Physical Fatigue	BDI	.032	.015	.136	2.139	.033
Sleepiness	Education	.053	.017	.197	3.145	.002
	Sleep quality	-.085	.141	-.038	-.608	.544
	BDI	.035	.015	.150	2.391	.018

6.6.3. Psychometric analysis and factorial structure of the Multi-Temporal Assessment of Fatigue in MS patients

As for Controls, also in MS patients, the MtAF demonstrated more than acceptable psychometric integrity (α = 0.95) and adjusted item-total correlations (De Vaus, 2004; Taber, 2018; see Table 11). Fourteen out of sixteen items showed strong correlations with the total MtAF score (r range = 0.65–0.85) and two high item-total correlations (r = 0.55; 0.54). All items were maintained and entered in a CFA with Varimax orthogonal rotation.

Table 11 Characteristics of items included in the Multi-Temporal Assessment of Fatigue in MS patients

Items	M	SD	Corrected item-total correlation	Cronbach's alpha if item removed
PF_in the last 24 hours	2.53	1.05	0.71	0.94
PF_in the last week	2.69	1.01	0.74	0.94
PF_in the last month	2.79	1.01	0.73	0.94
PF_in the last year	2.93	1.01	0.69	0.94
PF_after waking up	2.58	1.09	0.55	0.95
PF_in the morning	2.56	1.02	0.65	0.94
PF_in the afternoon	3.11	1.07	0.70	0.94
PF_in the evening	3.42	1.18	0.65	0.94
MF_in the last 24 hours	2.29	1.13	0.76	0.94
MF_in the last week	2.62	1.13	0.85	0.94
MF_in the last month	2.65	1.13	0.84	0.94
MF_in the last year	2.82	1.14	0.69	0.94
MF_after waking up	2.08	1.06	0.54	0.95
MF_in the morning	2.26	1.11	0.66	0.94
MF_in the afternoon	2.70	1.18	0.77	0.94
MF_in the evening	3.14	1.25	0.71	0.94

Note. Mental Fatigue (MF) and Physical Fatigue (PF); Mean (M), Standard deviation (SD)

As for Controls, a three-factor solution was generated by PCA using the Mineigen criterion (eigenvalues > 1). This three-factor solution presented a clear structure with strong loadings (all > 0.50) and no overlapping items between factors (see Table 12). The first factor was composed of items referring to Mental Fatigue, early called MFi, occurring in the last 24 hours, in the last week, in the last month, in the last year, in the afternoon, and in the evening; the items' loadings on this factor ranged from 0.67 to 0.83, with factor accounting for 28.4 % of their variance. The second factor included items referring to Physical Fatigue, already called PFi, occurring in the last 24 hours, in the last week, in the last month, in the last year, in the afternoon, and in the evening; the items' loadings on this factor ranged from 0.67 to 0.82, with factor accounting for 28.3 % of their variance. The third factor included items referring to mental and physical fatigue occurring immediately after waking up, and in the morning, the items' loadings on this factor ranged from 0.61 to 0.84, with the factor accounting for 17.8 % of their variance. Also in this case, to support the hypothesis that this factor reflects Sleepiness (Si), Pearson's correlations between the three factors and Sleep quality were computed. Results showed significant correlations between Sleep quality, Mental Fatigue ($r = 0.28$, $p < .0001$), and Sleepiness ($r = 0.39$, $p < .0001$; Table 9). Divergent validity was measured by correlating the MFi, the PFi, and the Si scores with the BDI scores and the PSE-MCP scores (calculated as the mean scores across the four subscales of the PSE-MCP). Weak but significant correlations with the BDI ($r = 0.31$, $r = 0.17$, $r = 0.38$, $ps < 0.05$) were found. The correlations with the PSE-MCP mean scores were not significant (see Table 9).

Table 12 Rotated component matrix of the Multi-Temporal Assessment of Fatigue in MS patients

Items	Factor 1	Factor 2	Factor 3
MF_in the last month	**.83**	.38	.21
MF_in the last year	**.79**	.26	.13
MF_in the last week	**.79**	.42	.22
MF_in the last 24 hours	**.72**	.34	.29
MF_in the evening	**.67**	.46	.05
MF_in the afternoon	**.71**	.30	.37
PF_in the last week	.26	**.82**	.24
PF_in the evening	.39	**.74**	-.04
PF_in the last month	.33	**.82**	.11
PF_in the afternoon	.31	**.67**	.29
PF_in the last 24 hours	.19	**.77**	.34
PF_in the last year	.36	**.70**	.15
MF_immediately after waking up	.41	-.03	**.78**
MF_in the morning	.60	.07	**.61**
PF_in the morning	.11	.47	**.73**
PF_immediately after waking up	.09	.28	**.84**

Note. Mental Fatigue (MF) and Physical Fatigue (PF)

To detect potential effects of the sociodemographic and clinical variables on the MtAF, the correlations of the scores on the three factors with the characteristics of MS patients and Controls were first calculated (see Table 9). A mixed pattern of results emerged. Considering MS, Mental Fatigue showed a positive correlation with Sex, Sleep quality, and BDI; Physical Fatigue showed positive correlation with Sex, and BDI and a negative correlation with Education; Sleepiness showed significant positive correlations with Sleep quality and BDI and a negative correlation with Education. None of the factors correlated with Age, Disease duration, and MSA. As for the other correlations, Age showed a positive correlation with

PSE-MCP, Disease duration, and MSA; Education was negatively correlated with Sleep quality and BDI; Sleep quality showed a positive correlation with BDI; BDI and PSE-MCP were negatively correlated; finally, Disease duration was positively correlated with MSA.

Separate simultaneous multiple linear regression analyses were performed assuming the factors indicating Physical Fatigue, Mental Fatigue, and Sleepiness as the dependent variables and variables significantly correlated with them as predictors. The regression models provided a good fit for the data, although the percentages of explained variance were very low (Physical Fatigue, $R^2 = .08$, $F(1, 124) = 3.702$, $p < .01$; Mental Fatigue, $R^2 = .19$, $F(3, 126) = 9.364$, $p < .0001$; Sleepiness, $R^2 = .26$, $F(3, 124) = 14.544$, $p < .0001$; see Table 13).

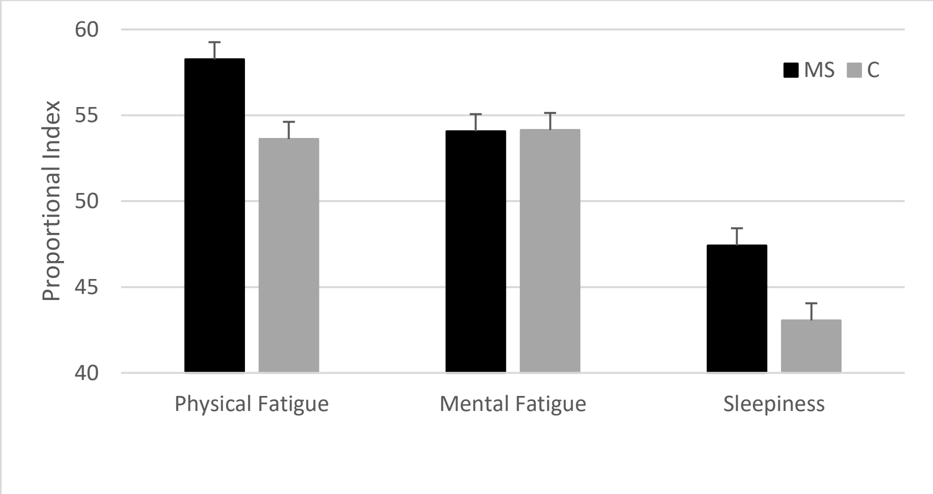
Table 13 Coefficients table of predictors of Physical Fatigue, Mental Fatigue, and Sleepiness in MS patients

		Non-Standardized Coefficients		**Standardized Coefficients**	t	Sig.
		B	SD	Beta		
Mental Fatigue	Sex	.45	.17	.21	2.60	.01
	Sleep Quality	.28	.10	.24	2.80	.01
	BDI	.04	.02	.22	2.49	.01
Physical Fatigue	Sex	.47	.18	.23	2.67	.01
	Education	-.02	.02	-.07	-.81	.42
	BDI	.03	.02	.14	1.56	.12
Sleepiness	Education	-.03	.02	-.11	-1.42	.16
	Sleep Quality	.39	.10	.32	3.89	.00
	BDI	.05	.02	.25	3.09	.00

6.6.4. Group differences in fatigue experience as measured by the Multi-Temporal Assessment of Fatigue

Both the PFi and the MFi scores (6 items each) of the MtAF range from 6 to 30, with higher scores reflecting higher Physical or Mental fatigue. The Sleepiness (4 items) of the MtAF ranges from 4 to 20, with higher scores reflecting higher sleepiness. In order to compare these indexes, proportional indexes were calculated for each participant as (MFi/30)*100, (PFi/30)*100, and (Si/20)*100. The proportional indexes of MS patients and Controls are presented in Figure 1. To compare the intensity of the three different forms of fatigue in MS patients and C, the proportional indexes were submitted to a repeated measures ANOVA 2 (Group: MS vs. C) x 3 (Type of Fatigue: MF vs. PF vs. Si). Results showed a significant main effect of Group, $F (1,401) = 4.390$, $p < .05$, $\eta_p^2 = .01$, indicating that, overall, MS patients were more fatigued than Controls. The effect of Type of Fatigue was also significant $(1,401) = 184.985$, $p <.0001$, $\eta_p^2 = .32$. Post-hoc pairwise comparison indicated that there were significant differences among all three proportional indexes, $ts (402) > 2.04$, $p_s < .05$, with the proportional PFi being the highest and the proportional Si the lowest. Results also showed a significant Group x Type of Fatigue interaction, $F (1,422) = 6.85$, $p<. 01$, $\eta_p^2 = .02$. To better understand this interaction, three different univariate ANOVAs were computed, with each Type of Fatigue as the dependent variable and Group as the independent variable. Results showed that MS patients and Controls had equivalent propositional MFi, F (1,422) < .000, while they differed with respect to proportional PFi and Si, Fs (1,422) > 6.04, ps < .01, η_p^2 = > .01, that were higher in MS patients than in Controls.

Figure 1 Physical Fatigue, Mental Fatigue, and Sleepiness (and standard errors) of MS patients and Controls as indicated by proportional scores.



6.6.5. Assessment of fatigue within a Short and Long-time frame, as measured by the Multi-Temporal Assessment of Fatigue

The mean ratings for items assessing Physical and Mental Fatigue within Short and Long-time frame provided by MS patients and Controls are presented in Table 14.

To assess whether Long-Term Physical and Mental Fatigue differ in MS patients and Controls, a repeated measures ANOVA 2 (Group: MS vs. C) x 2 (Type of Fatigue: MF vs. PF) x 4 (Long-Term Fatigue: last 24 hours vs. last week vs. last month vs. last year) was used.

Table 14 Mean and standard deviation of participants' ratings to items Short and Long-time frame in Mental and Physical Fatigue

		MS		C	
		M	SD	M	SD
PF	**Last 24 hours**	2.53	1.05	2.26	0.90
	Last week	2.69	1.01	2.44	0.87
	Last month	2.79	1.01	2.64	0.88
	Last year	2.93	1.01	2.75	0.95
	In the afternoon	3.11	1.07	2.72	1.00
	In the evening	3.42	1.18	3.28	0.98
MF	**Last 24 hours**	2.29	1.13	2.27	0.97
	Last week	2.62	1.13	2.51	0.94
	Last month	2.65	1.13	2.74	0.94
	Last year	2.82	1.14	2.93	1.03
	In the afternoon	2.70	1.18	2.73	1.00
	In the evening	3.14	1.25	3.05	1.05

Results concerning fatigue within the Long-time frame showed a Group x Type of Fatigue interaction, F (1,401) = 9.839, p<. 005, η_p^2 = .02. Post-hoc analyses indicated that overall Long-Term Physical Fatigue was higher in MS patients than in Controls, F (1, 404) = 7.177, p < .01, η_p^2 = .02, while Long-Term Mental Fatigue was equivalent in the two groups of participants, F (1, 404) = 0. 34. The main effect of Long-Term Fatigue was significant, F (1,401) =124.538, p< .0001, η_p^2= .24. Post-hoc pairwise comparisons indicated that there were significant differences among all the four periods of time, ts (404) > 4.79, ps < .0001, with the rating for fatigue experienced in the last year being the highest and the rating for fatigue experienced in the last 24 hours being the lowest. Long-Term Fatigue significantly interacted with Type of Fatigue, $F(1,401) = 6.263$, $ps < .01$, $\eta_p^2 > 0.2$. Pairwise comparisons indicated that Physical and Mental Fatigue occurred last week, last month, and last year were rated as equivalent, $ts < 1.45$, while Physical Fatigue occurred in the last 24 hours was rated as higher than Mental Fatigue, $t(403) = 1.90$, $p < .05$.

To assess whether Short-Term Physical and Mental Fatigue differ in MS patients and Controls, a repeated measures ANOVA 2 (Group: MS vs. C) x 2 (Type of Fatigue: MF vs. PF) x 2 (Short-Term Fatigue: in the afternoon vs. in the evening) was used. Results showed a main effect of Type of Fatigue, $F(1,402) = 27.563$, $p < .0001$, $\eta_p^2 = .06$, indicating that Physical Fatigue was experienced as higher than Mental Fatigue, and a main effect of Short-Term Fatigue, $F(1,402) = 94.381$, $p < .0001$, $\eta_p^2 = .19$, indicating that Fatigue was, overall, higher in the evening than in the afternoon. Type of Fatigue significantly interacted with Group, $F(1,402) = 7.46$, $p < .01$, $\eta_p^2 = .02$. Post-hoc analyses indicated that Short-Term Physical Fatigue was higher in MS patients than Controls, $F(1,403) = 8.036$, $p < .005$, $\eta_p^2 = .02$, while Mental Fatigue was equivalent in the two groups of participants, $F(1, 403) = 0.494$. Finally, Group x Type of Fatigue x Short-Term Fatigue interaction was also significant, $F(1,402) = 12.958$, $p < .0001$, $\eta_p^2 = .03$. To interpret these three-way interactions, two separate Type of Fatigue x Short-Term Fatigue ANOVAs were computed for MS patients and Controls. Results for MS patients showed a main effect of Type of Fatigue and Short-Term Fatigue, Fs (1,158) > 29.320 ps < .0001, η_p^2 =.16, indicating that Physical Fatigue was experienced as higher than Mental Fatigue and that both types of fatigue were higher in the evening than in the afternoon. Results for Controls showed a main effect of Short-Term Fatigue, F (1,244) = 76.02, p < .0001, η_p^2 = .24, indicating that Fatigue was experienced as being higher in the evening than in the afternoon. The Type of Fatigue x Short-Term Fatigue was also significant, F (1,244) = 11.92, p < .001, η_p^2 = .05. Post-hoc pairwise comparisons indicated that Physical and Mental Fatigue were lower and equivalent in the afternoon, t (244) = .18, while, in the evening, they were higher, and Physical Fatigue was experienced as more severe than Mental Fatigue, t (244) = 3.64, p < .0001.

6.6.6. Group differences in the characteristics of Physical and Mental fatigue

Descriptive statistics of participants' ratings of items assessing internal and external triggers of Fatigue, its effect on different domains, and the strategies effective for its remission are presented in Tables 15, 16, and 17, respectively, as a function of Type of fatigue. MS patients appeared more susceptible, as compared to Controls, to external triggers of both Physical and Mental Fatigue (see Table 15). MS patients were also more affected by Physical Fatigue as compared to Controls, while the effects of Mental Fatigue were overall equivalent in the two groups of participants (see Table 16). Finally, the effectiveness of different strategies in reducing fatigue was rated as equivalent by MS patients and Controls (see Table 17).

Table 15 Descriptive statistics of participants' ratings of items assessing internal and external triggers of Fatigue, as a function of Type of Fatigue

		Physical/mental fatigue usually manifests itself	MS		C		
			M	SD	M	SD	p
Physical Fatigue	Internal Triggers	when I have to concentrate for a short time	2.21	1.11	1.85	0.87	*.001*
		when I have to concentrate for a long time	2.58	1.37	2.25	1.02	*.0001*
		when I slept too little	3.44	1.14	3.32	1.01	*n.s*
		when I slept too much	1.78	0.92	1.78	0.97	*n.s*
		when I am sick	3.26	1.13	2.93	1.06	*n.s.*
		when I feel pain	2.64	1.30	2.25	1.04	*.0001*
		when I find myself in a stressful situation	3.13	1.30	2.65	1.14	*n.s.*
	External Triggers	after a short physical effort	2.43	1.07	2.09	0.93	*.001*
		after a prolonged physical effort	3.50	1.08	3.28	1.02	*n.s.*
		when there are many people	2.30	1.19	1.68	0.89	*.0001*
		when there is a lot of confusion	2.56	1.25	1.98	1.06	*.0001*
		when it is too hot	3.52	1.20	2.69	1.16	*n.s*
		when it is too cold	2.40	1.40	1.71	0.91	*.0001*
		when there is too much humidity	2.49	1.36	2.03	1.10	*.0001*
Mental Fatigue	Internal Triggers	when I have to concentrate for a short time	2.01	1.13	1.77	0.86	*.001*
		when I have to concentrate for a long time	2.84	1.17	2.84	0.98	*.005*
		when I slept too little	3.09	1.24	3.13	1.04	*n.s*
		when I slept too much	1.75	1.02	1.73	0.93	*n.s.*
		when I feel sick	2.75	1.19	2.40	1.02	*n.s*
		when I feel pain	2.51	1.26	2.09	1.02	*.0001*
		when I find myself in a stressful situation	3.29	1.27	2.98	1.13	*.001*
	External Triggers	after a short physical effort	2.11	1.07	1.76	0.84	*.001*
		after a prolonged physical effort	2.82	1.34	2.14	0.97	*.0001*
		when there are many people	2.52	1.30	2.11	1.00	*.0001*
		when there is a lot of confusion	2.74	1.31	2.42	1.14	*n.s*
		when it is too hot	2.97	1.50	2.32	1.15	*.0001*
		when it is too cold	2.16	1.36	1.61	0.83	*.0001*
		when there is too much humidity	2.18	1.32	1.71	0.99	*.0001*

Table 16 Descriptive statistics of participants' ratings of items assessing the physical and mental effects of fatigue, as a function of type of fatigue

When I feel physically/mentally very fatigued							
			MS		**C**		
			M	SD	M	SD	p
Physical Fatigue	**Mental Effects**	I feel sleepy	2.52	0.99	2.60	0.93	*n.s*
		I am easily distracted	2.61	1.12	2.43	0.95	*n.s*
		I am less reactive	2.82	1.06	2.70	0.90	*n.s*
		I feel mentally lethargic	2.49	1.14	2.36	0.94	*.001*
		I have trouble finding the right words	2.34	1.33	2.03	1.02	*.0001*
		I easily forget things	2.60	1.27	2.19	1.04	*.0001*
		It is hard for me to take decisions	2.18	1.20	1.96	0.94	*.0001*
		I am easily irritable	2.93	1.18	2.62	1.09	*n.s*
	Physical Effects	I feel physically slowed down	3.16	1.00	2.97	0.86	*.005*
		I feel physically weak	3.25	1.20	2.95	1.03	*.001*
Mental Fatigue	**Mental Effects**	I feel sleepy	2.48	0.99	2.48	0.98	*n.s*
		I am easily distracted	2.69	1.16	2.66	1.07	*n.s*
		I am less reactive	2.69	1.14	2.62	0.97	*n.s*
		I feel mentally lethargic	2.42	1.14	2.42	1.10	*n.s*
		I have trouble finding the right words	2.38	1.35	2.31	1.18	*n.s*
		I easily forget things	2.65	1.29	2.62	1.15	*n.s*
		It is hard for me to take decisions	2.21	1.25	2.30	1.17	*n.s*
		I am easily irritable	2.92	1.33	2.82	1.14	*n.s*
	Physical Effects	I feel physically slowed down	2.70	1.18	2.43	0.97	*n.s*
		I feel physically weak	2.69	1.14	2.69	1.14	*n.s*

Table 17 Descriptive statistics of participants' ratings of items assessing the effectiveness of different strategies in reducing fatigue, as a function of type of fatigue

The following strategy is effective in alleviating my physical/mental fatigue						
		MS		**C**		
		M	SD	M	SD	p
Physical Fatigue	Usually regresses spontaneously	3.27	1.14	3.35	0.97	*n.s*
	Short physical rest	2.90	0.95	2.78	0.90	*n.s*
	Long physical rest	2.76	1.07	2.78	1.04	*n.s*
	Short daytime sleep	2.31	1.05	2.22	1.00	*n.s*
	Long daytime sleep	2.08	1.11	2.00	1.02	*n.s*
	Slowing down the current activity	2.77	1.02	2.60	0.98	*n.s*
	Stopping the ongoing activity	2.82	1.13	2.51	1.10	*n.s*
Mental Fatigue	Usually regresses spontaneously	3.49	1.15	3.32	1.01	*n.s*
	Short physical rest	2.77	1.07	2.50	0.88	*n.s*
	Long physical rest	2.69	1.13	2.49	1.01	*n.s*
	Short daytime sleep	2.39	1.17	2.10	0.97	*n.s*
	Long daytime sleep	2.09	1.13	1.81	0.94	*n.s*
	Slowing down the current activity	2.67	0.98	2.51	0.98	*n.s*
	Stopping the ongoing activity	2.69	1.15	2.50	1.16	*n.s*

6.7. Discussion

The main objective of this study was to develop a new self-report questionnaire aimed at demonstrating a clear distinction between physical and mental fatigue. Moreover, the study aimed at estimating the presence and severity of fatigue within a short (one day) and long (one year) time frame. Moreover, to highlight the characteristics of fatigue specific to MS, a survey analysis has been performed to investigate internal and external triggers of physical and mental fatigue, its effect on different domains, and effective remission strategies.

Two PCAs were employed to independently assess for Controls and MS patients whether there are inherent clusters that are associated with both physical and mental fatigue. In both groups, findings from the PCA revealed three common factors: physical fatigue, mental fatigue, and a third factor. The third unforeseen factor that surfaced from the PCA was hypothesized to potentially indicate a manifestation of somnolence, as the items loading on it refer to physical and mental fatigue occurring immediately after waking up and in the morning. Moreover, the factor of sleepiness has shown a strong correlation with sleep quality. These findings are consistent with the suggestions made in the literature that fatigue and sleepiness, despite having overlapping signs, are two distinct phenomena and should be assessed as separate entities (Duntley, 2005). Since both fatigue and sleepiness may result from precipitating conditions, like a lack of sleep, they might be mistaken (Duntley, 2005). However, the nature of the third unexpected factor should warrant more investigation. The sleepiness was excluded from further analysis as it was deemed inappropriate to consider it a genuine manifestation of fatigue without further elucidation.

The obtained results provide reassurance regarding the questionnaire's ability to accurately capture the intended constructs of interest, thereby yielding more meaningful assessments of both physical and mental fatigue and instilling confidence in the ability to make overarching assertions regarding variations in fatigue levels among different cohorts. To the best of our knowledge, this is the first study confirming the presence of two independent forms of fatigue through a statistical methodology. The categorization of fatigue into two distinct types based on a statistical analysis aligns with the assertions made by numerous authors in the existing body of literature (e.g., Ford et al., 1998; Gullo et al., 2019; Penner et al., 2009; Schwid et al., 2000).

With respect to the evaluation of physical and mental fatigue within a long- time frames, it was found that both MS patients and Controls rated fatigue experienced last year as the highest and fatigue experienced in the last 24 hours as the lowest. In both groups, physical and mental fatigue experienced in the last year, in the last month, and in the last week were rated as equivalent.

As far as the evaluation of fatigue within a short-time frame is concerned, results indicated that physical fatigue was rated higher than mental fatigue as highlighted by studies in the literature (e.g., Broch et al., 2021; Krupp et al., 2003; Marchesi et al., 2020); however, MS patients reported higher levels of physical fatigue compared to Controls in line with the large amount of evidence present in the literature (e.g., Holtzer & Foley, 2009; Krupp et al., 1988; 1989; Paul et al., 1998).

In both groups, both types of fatigue were rated as higher in the evening than in the afternoon, in line with evidence showing that fatigue peaks in the late afternoon (Powell et al., 2017; Tellez et al., 2006). However, in the Control group, physical and mental fatigue experienced in the afternoon were rated as equivalent, and fatigue experienced in the afternoon was lower compared to fatigue experienced in the evening.

In the MS group, physical fatigue was higher than mental fatigue, in line with the literature (Krupp et al., 2003; Marchesi et al., 2020; Schreurs et al., 2002). In the MS group, physical and mental fatigue experienced by MS patients did not correlate with age, disease duration, or self-reported mobility level, as measured by the MSA. These results are in line with earlier studies showing that fatigue is observed throughout the illness, regardless of age (Ghajarzadeh et al., 2013; Morrison & Stuifbergen, 2016), disease length (Bakshi, 2003; Bisecco et al., 2016; Derache et al., 2013; Gobbi et al., 2014; Yaldizli et al., 2011), or disability status (Pittion-Vouyovitch et al., 2006). It is noteworthy to observe that the findings of the MSA, while not providing a comprehensive evaluation of the patient's disability level, align with existing research (Pittion-Vouyovitch et al., 2006) by demonstrating a lack of association with physical and mental fatigue.

In light of the MSA's development, it is imperative to elucidate certain aspects. The initial goal was to obtain the EDSS from the neurologist responsible for the medical facility, followed by the distribution of an online questionnaire to the respective patient. The study commenced with the enrollment of the control cohort. With the spread of the COVID-19 pandemic, it has become evident that the inclusion of neurologist-assessed disability evaluations within the realm of online data collection was not a viable option. Therefore, an alternative tool capable of replacing the EDSS and gauging the degree of functional deterioration in MS participants has been developed.

In the MS sample, both physical and mental fatigue were correlated with gender, in line with some studies in the literature showing a relationship between gender and fatigue (Broch et al., 2021; Olsson et al., 2005; Schwartz et al., 1996).

Both physical and mental fatigue were correlated with BDI scores, in line with some studies in literature (e.g., Marchesi et al., 2020; Penner et al., 2009).

In line with the literature, sleep quality correlated with mental fatigue (e.g., Chinnadurai et al., 2018).

As for the control sample, in line with the literature, mental fatigue was negatively correlated with age (e.g., Smith et al., 2019; Terentjeviene et al., 2018), and both mental and physical fatigue were correlated with BDI scores (e.g., Patrick et al., 2009; Pittion-Vouyovitch et al., 2006; Strober & Arnett, 2005).

Despite the fact that the results should be interpreted with caution, the MtAF outcome analyses have highlighted for the first time a psychometrically unequivocal distinction between physical and mental fatigue.

Consistent with existing literature, the distinction between two different fatigue constructs is further supported by the disparate associations that each component exhibits with other variables. The findings of the study are extremely important for future research as they provide insight on fatigue in MS and may be considered a baseline from which to develop future research based on common and shared protocols that consider the clear distinction between physical and mental fatigue.

7. ECOLOGICAL ASSESSMENT OF DAILY VARIATIONS OF PHYSICAL AND MENTAL FATIGUE IN MULTIPLE SCLEROSIS

7.1. Introduction

According to the literature, fatigue in MS is a complex and unpredictable phenomenon, and its evaluation is rather challenging as fatigue experience is influenced by several factors. Fatigue evaluation across studies has shown serious flaws, and to date, there is not a benchmarking instrument capable of capturing the several facets of the fatigue experience. The objective of the MtAF discussed in Chapter 6 was to overcome the limits of the self-report instruments used so far in attempting to investigate characteristics of physical and mental fatigue that had been overlooked in earlier investigations. The MtAF outcome analyses have highlighted for the first time a psychometric distinction between physical and mental fatigue.

The assessment of the degree of physical and mental fatigue within a short and long- time frame is not addressed in most fatigue measures, even though this investigation might provide insights to better characterize physical and mental fatigue experiences. Considering these findings, the current study on daily tracking of fatigue aims to detect whether, when, and why fatigue rises, peaks, and regresses.

7.2. Real-time fatigue assessment

Studies conducted on the diurnal pattern of fatigue and its relation to contextual variables seem to suggest that fatigue in MS is not a stable phenomenon but rather varies from morning to night, appearing low in the morning and progressively rising during the day (Claros-Salinas et al., 2010; Kim et al., 2010). Fatigue shows inter-individual differences more pronounced in physical exertion (Heine et al., 2016; Kratz et al., 2017) and appears exacerbated by psychological stress (Mollaoğlu & Üstün, 2009).

In the past few years, studies have begun to investigate the daily trend of fatigue in MS patients through real-time fatigue assessment. Real-time fatigue evaluation occurs when patients are asked to provide an instantaneous response to the question of whether they feel fatigued at a specific time. For instance, Schwid and colleagues (2003) investigated real-time fatigue through the Rochester Fatigue Diary (RFD), which required participants' hourly evaluation of fatigue for 48 hours. Kim and colleagues (2010) devised a real-time fatigue assessment, the Real-Time Digital Fatigue Scores (RDFS), and evaluated its reliability compared to conventional measures such as the FSS and the MFIS (Kim et al., 2010). Their study indicated a strong correlation between the RDFS and the conventional scales and demonstrated the ability of the RDFS to record a daily pattern of fatigue. Moreover, this is the first study to show the usefulness of a wrist-worn device (a digital Actiwatch) combined with a VAS to digitally measure fatigue in MS patients in real time. Their findings showed that fatigue peaked early in the day and gradually rose throughout the day.

Several authors have adopted the Ecological Momentary Assessment (EMA) to investigate real-time fatigue, often in conjunction with handheld electronic devices. The EMA is a recurrent evaluation of variables in real-time, in the current world, while people go about their day-to-day activities. It is a reliable method compared to clinical written interviews utilized in previous studies, which relied on patients' abilities to recollect their symptoms from the recent past (Shiffman, Stone, & Hufford, 2008). It has the advantage of minimizing memory bias and enhancing accuracy in recording instantaneous changes in real life.

In a study on diurnal fatigue, Heine and colleagues (2016) assessed real-time patterns of fatigue and examined the relationship between a real-time fatigue score (RTFS) and three commonly used questionnaires (the CIS, the MFIS, and the FSS) by sending participants four SMS at set times. Their results revealed four distinct diurnal fatigue patterns in MS patients. Two primary profiles, "the stable-high profile" and "the stable-low profile," showed that some MS patients awoke profoundly exhausted and remained fatigued throughout the day. Their study revealed inter-individual differences in daily trends of fatigue and the need for a thorough investigation of inter-individual symptom experiences.

Kratz and colleagues (2017) used the EMA to investigate the daily fluctuation of fatigue in people with MS and the role played by some variables (pain, fatigue, depressive mood, and perceived cognitive function) on fatigue onset. Patients' assessments of pain, fatigue, sad mood, and cognitive performance were collected five times daily at awakening, 11 a.m., 3 p.m., and bedtime using electronic devices that participants had to wear on their wrists continuously for the duration of the research. It was found that fatigue was the most fluctuating of all symptoms, changing from morning to night, and that its daily patterns were different depending on gender and age. The authors also showed that daily fluctuations in fatigue and depressed mood were linked only to same-day emotional well-being.

Powell and colleagues (2017), using the EMA in conjunction with an electronic device, investigated the influence of psychosocial variables (e.g., stress factors, mood, daily activity) in triggering daily fatigue and gathered real-time fatigue measurements in seventy-six participants (RRMS patients and healthy controls). More precisely, during four weekdays, both healthy and MS participants provided self-reported data six times daily, within the time frame of 10 a.m. to 8 p.m. Specifically, fatigue severity was investigated through the assessment of momentary fatigue severity, daily fatigue severity, stressor exposure (work overload, social overload, excessive demands at work, lack of social recognition, work discontent, social tensions, pressure to perform, and social isolation), mood (negative and positive mood), and daily life behaviours. Powell's study findings revealed that the level of fatigue varied greatly from person to person and from day to day, and that fatigue began at a lower level in the early hours of the day and increased steadily until the night in both groups. However, in the RRMS group, fatigue was severe in the morning and increased in the late afternoon, whereas in the control group, fatigue started slowly in the morning and steadily increased until the evening hours. Their analyses revealed that, although many daily life determinants of fluctuations were similar in RRMS and healthy individuals (such as mood and stressful factors such as current employment and a lack of social recognition), physical exertion had a greater impact in individuals with RRMS, while sleep quality appeared to be more relevant in healthy individuals. In both groups, real-world stressors and a negative mood were related to an increase in fatigue, whereas a happy mood was associated with reduced fatigue. Researchers have provided interesting data on the relationship between fatigue and several factors; however, it is impossible to draw definitive conclusions regarding the role played by each factor in the onset of fatigue in MS. To shed light on the association between fatigue in MS and other variables, further studies are required.

The current study attempts to replicate Powell's research by using their methodological approach based on EMA in conjunction with electronic devices. However, unlike Powell's research, the current study aims to investigate on a larger sample of participants the daily physical and mental fatigue patterns and to identify whether daily variations of physical and mental fatigue differ from each other.

Given the scarce literature on the daily trend of physical and mental fatigue, the current study might be highly informative and helpful in identifying effective treatments for fatigue peaks and changes throughout the day in people with MS. The goal of this study is to improve the understanding of this complex and still poorly defined multi-component symptom and to offer opportunities for the development of interventions useful for the management of peak fatigue in MS patients.

7.3. A pilot study

The objective of the pilot study was to evaluate the preliminary viability, feasibility, and practicality of a method that needed to be applied to a larger sample size of both MS and healthy participants. Only healthy participants took part in the pilot study. The pilot study was run between September 2019 and January 2020.

7.4. Methods

7.4.1. Participants

Fifteen healthy adults were recruited to participate in this study, but only 10 of them (N. female = 6) completed the experimental protocol in full.

They had a mean age of 27.3 years (SD = 2.0) and a mean education of 15.08 years (SD = 2.10). Participants were recruited through word-of-mouth. None of them were receiving psychoactive pharmaceutical therapy, had a history of neurological or mental disease, or were currently pregnant. The inclusion criteria were being between 18 and 70 years old and having a willingness to wear a digital clock throughout the course of the experiment. The exclusion criteria were as follows: having less than 8 years of formal education; the presence of neurological or psychiatric diseases or major illnesses that might distort the results of the research, such as diabetes, diabetic therapy, and cardio-vascular dysfunction; a history of mild or severe traumatic brain injury; the use of drugs affecting fatigue state; substance abuse; visual disturbances that might interfere with the experiment's execution; and, for women, being pregnant (as to avoid bias in the results). The exclusion criteria were chosen to enhance the internal and external validity of the fatigue study and to allow for a more accurate assessment free from the interference of unrelated factors (for a comprehensive understanding of the exclusion criteria, please refer to Chapter 6). Before the experiment, participants were given a one-on-one orientation session regarding the study objective and signed an informed written consent form. Participants were not compensated for their participation in the experiment.

Participants were required to fill out the PSE-MCP to detect respondents' perceptions of being able to face problematic life situations and the BDI for depression assessment (for scale descriptions, please refer to Chapter 6). The present study has been approved by the Local Ethics Committee of the University of Federico II with number 80/20 and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki, together with the principles that guide the ethical and methodological practice of online research (Das, Ester, & Kaczmirek, 2011), social and behavioral research, and internet-applied methods and strategies (Hunter et al., 2018; see Appendix 3).

7.4.2. Materials and procedure

Over the course of four continuous weekdays, between 9 a.m. and 11 p.m., participants were prompted to complete the EMA (Powell et al., 2017) eight times a day, alerted by an acoustic alarm. The alarms were delivered by a digital clock provided to participants by the investigator. Participants were required to wear the clock on their non-dominant wrist on a continuous basis throughout the course of the experiment. The digital clock was set in advance to deliver the audio alarms at established times (chosen at random from a pool within six 100-minute time windows). Participants had the option to postpone the completion of the assessment by 5, 10, or 15 minutes if required. During the experiment, participants completed a total of thirty-two assessments.

The original Powell's EMA was supplemented with a few more questions to separately investigate physical and mental fatigue throughout the day (see Table 18). The items from 1 to 8, from 29 to 45, are taken from Powell's EMA. The items from 9 to 28 are taken from the survey which assesses the effects of physical and mental fatigue (see Table 4). The questions A7 and A8 investigate for the first time the overall feeling of physical and mental fatigue. These items have been chosen to better characterize the experience of physical and mental fatigue.

Each assessment included questions evaluating the sleep length, the momentary exposure to stressful factors (work overload, social overload, excessive demands on work, loss of social recognition, discontent at work, social tensions, task pressure, and social isolation), the momentary physical and mental fatigue assessment, the momentary effects of physical and mental fatigue, positive and negative mood, behavioural factors (fasting, sleeping, and exercise), and the daily cumulative physical and mental fatigue. The survey questions are displayed in Table 18. At 9:00 a.m., participants received an alert to answer the first question investigating the participant's sleep quality: *"How long did you sleep last night?".* Participants provided a rating on a 5-point Likert scale (1 = not at all; 5 = very). After filling out the first assessment, participants returned to their activities. The acoustic warning notified participants seven additional times to complete questionnaires during the day. At 11:00 p.m., participants received an alert to answer the last two questions to investigate overall physical and mental fatigue: *"Overall, how physically fatigued did you feel today?", "Overall, how mentally fatigued did you feel today?".* Participants were required to provide a rating on a 5-point Likert scale (1 = not at all; 5 = very).

Table 18 Assessments completed by participants eight times a day

	Question	Description
A1	**How long did you sleep last night?**	**Sleep length**
A2	**From the last alarm**	**Momentary exposure to stressors**
1	I have worked a lot	Work overload
2	I have been involved in complicated social relationships	Social overload
3	I performed my activities in an unsatisfactory way	Excessive requests for work
4	others have underestimated my work	Loss of social recognition
5	I felt unhappy with what I was doing	Discontent at work
6	I found myself at odds with other people	Social tensions
7	I have done tasks where I couldn't afford to be wrong	Task pressure
8	I had to maintain good relationships with other people	Social isolation
A3	**How tired do you feel mentally now?**	**Momentary mental fatigue assessment**
	And for this reason, do you now feel…	**Momentary effect of mental fatigue**
9	I feel sleepy	
10	I feel physically weak	
11	I'm easily distracted	
12	I feel mentally lethargic	
13	I'm less reactive	
14	I feel physically slowed down	
15	I'm easily irritable	
16	I forget things easily	
17	I have trouble finding the right words	
18	It's hard for me to make decisions	
A4	**How tired do you feel physically now?**	**Momentary physical fatigue assessment**
	And for this reason, do you now feel…	**Momentary effect of physical fatigue**
19	I feel sleepy	
20	I feel physically weak	
21	I'm easily distracted	
22	I feel mentally lethargic	
23	I'm less reactive	
24	I feel physically slowed down	
25	I'm easily irritable	
26	I forget things easily	
27	I have trouble finding the right words	
28	It's hard for me to make decisions	
A5	**At the moment you feel…**	**Mood assessment**
29	distressed	Negative mood subscale
30	upset	
31	guilty	
32	irritated	
33	embarrassed	
34	anxious	
35	calm	
36	sad	
37	worried	
38	angry	
39	proud of me	Positive mood subscale
40	energetic	
41	determined	
42	fulfilled	
A6	**In the last 30 minutes you have been doing…**	**Behavioral factors**
43	exercise (yes, no)	
44	ate (yes, no)	
45	slept (yes, no)	
A7	**Overall, how mentally fatigued did you feel today?**	**Overall level of daily mental fatigue**
A8	**Overall, how physically fatigued did you feel today?**	**Overall level of daily physical fatigue**

7.5. Results

Focused group discussions were conducted with 10 participants to identify issues considered relevant from the participants' perspective regarding the experiment. Some participants declared they find it challenging to fill out eight surveys every day during their daily routine and to provide answers promptly at the time of the acoustic sound. Some participants also indicated that they were unable to complete the last self-report because they were sleeping at the time. Moreover, some participants expressed doubts about the exercise-related question (see item 43, Table 18), stating that it could be confusing as it did not specify the distinction between light physical activity and a more structured exercise.

Even though clocks are useful tools for prompting individuals to fill out surveys, there is no way to verify with certainty whether participants answered within the expected time frame.

7.6. Ecological momentary assessment of fatigue in Multiple Sclerosis patients through smartphone

Due to the breakout of the COVID-19 pandemic and the subsequent implementation of limitations, research methodologies have been transitioned to remote modalities to prioritize the safety of participants. To ensure participant safety, in the following study, real-time fatigue was investigated through the EMA, administered remotely by means of participants' mobile phones. In recent years, the widespread availability of mobile technology, smartphone-based apps, and the low cost of these tools have made smartphones useful instruments to continuously gather data through the EMA. Because smartphones are so convenient to carry, numerous researchers have started to develop their own software or have adapted computer programs to conduct EMA through mobile phones. In the last few years, the popularity of this method has grown rapidly, and a wide range of diseases have been studied through the EMA adapted to smartphones (Pearson et al., 2018). In the context of MS research, different studies have made use of ad hoc apps downloaded on patients' smartphones for a variety of purposes. For instance, Newland, Oliver, Newland, & Thomas (2019) employed a phone app to gather data on patients' fatigue, symptoms, and overall quality of life for six days and then again four weeks later to determine participants' overall health. Patients' impairment was assessed using the 12-item WHO Disability Assessment Schedule (WHODAS 2.0; WHO, 2010), pain intensity was assessed using a VAS, fatigue severity was assessed using the PROMIS Fatigue Scale Short Form (PROMIS F-SF; National Institute of Health Patient Reported Outcomes Measurement Information System [NIH], 2007), and cognitive dysfunctions were assessed through the PROMIS Cognitive Abilities and Cognitive Concerns scale (Cook et al., 2016). In the study, the Fatigue App was shown to be a reliable instrument for real-time data collection on fatigue among individuals with MS. The choice to employ a mobile technology platform for the purpose of conducting a clinical research study with the aim of collecting real-time data on various variables has been made based on the demonstrated viability of this approach in prior investigations.

7.7. Method

7.7.1. Participants

A priori power analysis was conducted to determine the number of participants needed using G* Power 3.1.9.4 based on a mixed-factor

ANOVA. At a nominal α level of 0.05, a power (β - 1) of 0.80, an estimated small effect size of f = 0.15, and several measurements ranging from 2 to 5, the required total sample size was between 56 and 90 units. This N was used as a general guideline in the participants' recruitment. The experiment was run between March 2020 and November 2021.

The eligible participants interested in taking part in the experiment provided the experimenter with their phone number and e-mail address and received, through SMS, WhatsApp, or email, according to their preferences, a pdf document with the research details (e.g., the study's procedure and objectives) and a custom URL that directed them to a Google Form portal web page to access and provide their informed consent. In the informed consent, participants were made aware that their information would be used solely for research purposes and that they might withdraw from the study at any time (for more details, see Appendix 3). Participants did not receive financial compensation for their participation.

Eighty-six healthy Italian adults were recruited to participate in this experiment as the control group. Participants were recruited mainly through email, social media posts, word-of-mouth, and the local community, with an effort made to match the age, gender, and education of MS patients. The inclusion criteria for controls were being 18 to 70 years old and having a mobile phone to perform the experiment. The exclusion criteria were as follows: having less than 8 years of formal education; the presence of neurological or psychiatric disease or major illnesses that might distort the results of the research, such as diabetes, diabetic therapy, and cardio-vascular dysfunction; a history of mild or severe traumatic brain injury; the use of drugs affecting fatigue state; substance abuse; visual disturbances that might interfere with the experiment's execution; and, for women, being pregnant (as to avoid bias in the results). Participants unable to use both hands to perform the experiment were excluded. The exclusion criteria were chosen to enhance the internal and external validity of the fatigue study and to allow for a more accurate assessment free from the interference of unrelated factors (for a comprehensive understanding of the exclusion criteria, please refer to Chapter 6). According to the exclusion criteria, data from ten participants was removed. The final sample of healthy participants (Controls) consisted of seventy-six individuals, of whom fifty-eight were female. The cohort of Controls had an average age of 40 years (M = 39.70, SD = 12.13) and, on average, 15 years of educational attainment (M = 15.16, SD = 4.05). As for employment status, physical activity patterns, smoking, and alcohol consumption behaviours, the survey revealed that a significant proportion of participants in the study were employed (78.95%), practiced a sport (40.79%), a relatively moderate portion of subjects assumed alcohol (26.32%), and smoked regularly (23.68%). The descriptive statistics and distributions of demographic characteristics of the final sample of Controls are presented in Table 19.

One hundred and thirty-five MS Italian patients participated in this experiment. Participants were recruited at the Center for MS at the Neurological Clinic of the University of Federico II of Naples, in social virtual groups (i.e., Facebook), and by a snowball sampling strategy. The inclusion criteria for MS patients were having a clinically definite diagnosis of MS, being from 18 to 70 years old, and having a mobile phone to perform the experiment. The exclusion criteria were the same as for Controls. Additionally, MS patients with exacerbations within thirty days of research were excluded (for a comprehensive understanding of the criteria pertaining to the exclusion of participants who have had an exacerbation within a thirty-day timeframe, refer to Chapter 6). Only one hundred twenty-eight MS patients participated in the experiment in full. However, due to the predominant representation of patients diagnosed with RRMS within the sample, a decision was made to exclude a small number of patients who exhibited different subtypes, namely SPMS and PPMS. This exclusion was implemented to maintain sample homogeneity. The final sample upon which the analyses were performed comprises one hundred thirteen RRMS, of whom seventy-nine were female. The cohort of RRMS individuals had an average age of 43 years (M = 42.90, SD = 11.82) and, on average, 14 years of educational attainment, which typically includes at least a high school diploma (M = 14.01, SD = 4.58). As for employment status, physical activity patterns, smoking, and alcohol consumption behaviours, the survey revealed that a significant majority of patients were employed (63.72%), a minority of patients engaged in regular sports activities (17.70%), a relatively small portion of patients consumed alcohol (14.16%), and a substantial portion of participants reported smoking regularly (30.97%). The descriptive statistics on demographic variables of the final sample of RRMS patients are presented in Table 19.

The mean disease duration suggests that participants had experienced MS for a significant length of time (M = 11.73, SD = 7.13). Findings from the MSA revealed that participants in the sample reported mostly full mobility (M = 1.71, SD = 1.43). Specifically, 51.33% of patients reported no mobility limitations, 29.20% reported mild to moderate assistance with walking, and 2.65% reported severe mobility impairment. In the sample, most patients received Dimethyl Fumarate (38.05%), but there was also a significant presence of patients on Interferon Beta-1a (21.24%) and Fingolimod (15.04%), as well as some that were receiving other treatments (7.08%) or had unknown therapy status (15.04%). Regarding the concomitant medication taken by MS patients, it was found that patients reported taking medications for the treatment of MS symptoms (28.32 %) and for the treatment of concomitant diseases (40.71%). The majority of patients (73.45%) did not engage in rehabilitation therapy.

The present study has been approved by the Local Ethics Committee of the University of Federico II with number 80/20 and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki, together with the principles that guide the ethical and methodological practice of online research (Das, Ester, & Kaczmirek, 2011), social and behavioral research, and internet-applied methods and strategies (Hunter et al., 2018; see Appendix 3).

Table 19 Descriptive statistics and distributions of Relapsing-Remitting Multiple Sclerosis (RRMS) patients' and Controls' (C) characteristics

	RRMS	C
N. Total (N. Female)	113 (79)	76 (58)
Age[1]. Mean (SD)	42.90 (11.82)	39.70 (12.13)
Formal education[1]. Mean (SD)	14.01 (4.58)	15.16 (4.05)
Sleep quality. Mean (SD)	1.07 (0.96)	0.41 (0.57)
BDI. Mean (SD)	4.10 (5.12)	2.71 (3.97)
Emotional maturity. Mean (SD)	12.23 (8.51)	10.93 (9.08)
Finalization of the action. Mean (SD)	13.81 (9.33)	12.26 (10.10)
Relational fluidity. Mean (SD)	13.58 (9.30)	12.72 (10.49)
Context analysis. Mean (SD)	14.44 (9.87)	13.54 (11.12)
Employed. N. (%)	72 (63.72)	60 (78.95)
Unemployed. N. (%)	41 (36.28)	16 (21.05)
Practicing sport. N. (%)	20 (17.70)	31 (40.79)
Assuming alcohol. N. (%)	16 (14.16)	20 (26.32)
Smoking regularly. N. (%)	35 (30.97)	18 (23.68)
Disease duration[1]	11.73 (7.13)	/
MSA. Mean (SD)	1.71 (1.43)	/
Full mobility. N. (%)	58 (51.33)	/
Mild mobility impairment. N. (%)	33 (29.20)	/
Severe mobility impairment. N. (%)	3 (2.65)	/
MS therapy. N (%)		
None	4 (3.54)	/
Interferon beta-1a	24 (21.24)	/
Fingolimod	17 (15.04)	/
Dimethyl fumarate	43 (38.05)	/
Other	8 (7.08)	/
Unknown	17 (15.04)	/

[1] years

7.7.2. Materials and procedure

To make the experiment more viable, some changes were made to the pilot study. Fewer assessments were delivered to each participant every day (six rather than eight), and the last alert was moved to 9:00 p.m. rather than 11:00 p.m. Moreover, the question's items "*In the last 30 minutes, I have been doing*" (see A 6 item 43, Table 18) have been modified. Precisely, an additional item to differentiate light exercises (household chores, walking, and rehabilitative activity) from those requiring greater intensity has been included. Furthermore, the questionnaire has been modified to avoid repetitions and make the task easier for the participants (for the survey, see Appendix 6).

Participants received, through SMS, WhatsApp, or email, according to their preferences, a pdf document with the research details and a custom URL that directed them to a Google Form portal web page to provide their demographic information and complete the informed consent. Each participant was scheduled for a preliminary phone interview to provide additional information about the study's procedure, objectives, inclusion, and exclusion criteria, and to determine the start of data collection. Moreover, participants were instructed, confidentially, that they should abstain from engaging in the activity if they were experiencing symptoms of COVID-19 or any physical discomfort.

Socio-demographic data were collected from all participants. Socio-demographic variables such as sex, age, education, marital status, and employment status have been explored. Additional questions were related to self-care practices, such as whether at least one sport was practiced, whether alcohol and smoking were consumed regularly, the quality of sleep, the presence of a disease, and disease treatment. MS patients were required to fill in additional questions related to clinical disease characteristics such as MS phenotype, disease duration, current symptoms, and mobility impairment. Current treatments such as MS treatment, symptomatic treatment, treatment for concomitant disease, and rehabilitation activities were also investigated (for more details, see Chapter 6).

Participants completed the BDI to measure depressive symptoms and the PSE-MCP to detect respondents' perceptions of being able to face problematic life situations (for more details, see Chapter 6). Participants were required to keep their mobile phones on high mode and to take them along during the four days of data collection. Over the course of four continuous weekdays, between 9 a.m. and 9 p.m., participants received six automated SMS messages each day, yielding a total of 24 messages. The SMS notification alerted participants to enter ratings directly from their phones by clicking on the application URL, which directed them to a Google Form portal that enabled recipients to fill out the surveys. Participants had the option to postpone the completion of the survey by 5, 10, or 15 minutes if required. Each participant received messages randomly based on the assigned time window. The participant received an SMS at a time chosen at random from a pool within four 180-minute time windows. The random design reduces the biases associated with fixed-time designs, delivering a representative sample of daily life. SMS were automatically delivered to each participant through the SKEDIT App, a smartphone application that enables the investigator to schedule and deliver messages set up on the investigator's dedicated phone. The survey questions were registered on the Google Form portal web application, and the schedule for delivery of surveys was established (for the surveys, see Appendix 6). The daily assignment for each participant lasted around eighteen minutes. At 9:00 a.m., each participant received a text containing the application URL that directed them to the following question investigating the participant’s sleep length: "*How long did you sleep last night?"*. Participants were required to rate it on a 5-point Likert scale (1 = not at all; 5 = very). Upon completion of the first survey, participants were instructed to complete four identical, consecutive surveys throughout the day. They were notified via SMS, which included the application URL that directed them to each survey. The participants were instructed to evaluate the questions using a 5-point Likert scale (1 = not at all; 5 = very). The last survey was sent at 9:00 p.m. and included the following two questions assessing the overall daily physical and mental fatigue: *"Overall, today, how tired did you feel physically?"; "Overall, today, how tired did you feel mentally?".* The participants were instructed to rate the questions using a 5-point Likert scale (1 = not at all; 5 = very). The collected answers were registered on a cloud server and saved into a spreadsheet as raw data in an Excel file accessible to the researcher for later analysis.

7.8. Statistical analyses

As patients’ level of fatigue and subsequent level of cognitive performance may vary depending on whether they are pharmacologically treated for MS, the above-mentioned analyses were initially run only on MS patients entering pharmacological treatment as a covariate. In any case, neither the covariate nor its interaction with the different independent variables resulted significant. Accordingly, in the following paragraphs, the analyses with Group (MS vs. C) as an independent variable are reported.

Univariate 2 (Group: MS vs. C) ANOVAs were used to assess whether there were differences between MS patients and Controls with respect to Age, Education, Sleep quality, BDI scores, and the scores related to the four dimensions of the PSE-MCP.

The main issues of interest in this Experiment are as follows:

- Whether there are differences in Sleep length during the nights of the four days of data collection between MS patients and Controls. This issue was addressed by means of a univariate 2 (Group: MS vs. C) ANOVA. The dependent variable was the mean scores to the question *“How long did you sleep last night?”.*
- Whether there are differences in daily Physical and Mental Fatigue between MS patients and Controls. This issue was addressed by means of a 2 (Group: MS vs. C) x 2 (Type of Fatigue: MF vs. PF) mixed factor ANOVA. The dependent variables were the mean scores to the questions "*Overall, today, how tired did you feel physically?"; "Overall, today, how tired did you feel mentally?”.*
- Whether there are differences in momentary assessments of Physical and Mental Fatigue between MS patients and Controls. This issue was addressed by means of a 2 (Group: MS vs. C) x 2 (Type of Fatigue: MF vs. PF) x 4 (Assessments: Assessment 1 vs. Assessment 2 vs. Assessment 3

vs. Assessment 4) mixed factorial ANOVA. The dependent variables were the mean scores for the items *"How tired do you feel physically now?"; "How tired do you feel mentally now?".*

- Whether there are differences in the assessment-to-assessment variability of Physical and Mental Fatigue between MS patients and Controls. This issue was addressed by means of a 2 (Group: MS vs. C) x 2 (Type of Fatigue: MF vs. PF) x 3 (Variability: From Assessment 1 to 2 vs. From Assessment 2 to 3 vs. From Assessment 3 to 4) mixed factor ANOVA. The dependent variable for this analysis was the mean Variability, calculated as the difference, in absolute value, between each assessment and the preceding one, averaged across four days. For instance, assuming that the mean scores of a participant to the item "*How tired do you feel physically now?"* are 2, 2, 0, 1 in the four assessments, his/her Variability scores will be 0 (as the absolute value of the difference between 2 of the second assessments and 2 of the first assessments), 2 (as the absolute value of the difference between 0 of the third assessments and 2 of the second assessments), and 1 (as the absolute value of the difference between 1 of the fourth assessments and 0 of the third assessments (see Figure 2). These values can be assumed as a measure of the extent to which the rating of fatigue changes from one assessment to the next, regardless of whether it increases or decreases.
- Whether there are differences in the momentary exposure to Stressors between MS patients and Controls. This issue was addressed by means of a 2 (Group: MS vs. C) x 4 (Assessment: Assessment 1 vs. Assessment 2 vs. Assessment 3 vs. Assessment 4) mixed factorial ANOVA. The dependent

variable was the mean scores on items of the following questions: "*From the last alarm …*"

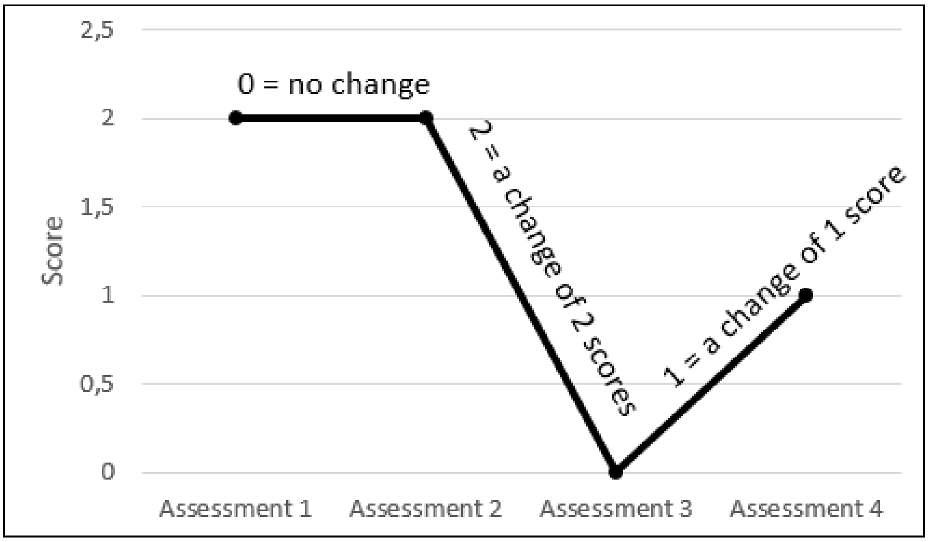
- *"I have worked a lot".*
- *"I have been involved in complicated social relationships".*
- *"I have performed my activities in an unsatisfactory way".*
- *"Others have underestimated my work".*
- *"I have felt unhappy with what I was doing".*
- *"I have found myself at odds with other people".*
- *"I have done tasks where I couldn't afford to be wrong".*
- *"I have maintained good relationships with other people".*

▪ Whether there are differenced in the momentary effects of fatigue between MS patients and Controls. This issue was addressed by means of a 2 (Group: MS vs. C) x 4 (Assessment: Assessment 1 vs. Assessment 2 vs. Assessment 3 vs. Assessment 4) mixed factorial ANOVA. The dependent variable was the mean score on items of the following question: "*Do you now feel...*"

  - *"I feel sleepy".*
  - *"I feel physically weak".*
  - *"I am easily distracted".*
  - *"I feel mentally lethargic".*
  - *"I am less responsive".*
  - *"I feel physically slowed down".*
  - *"I am easily irritable".*
  - *"I forget things easily".*
  - *"I have trouble finding the right words".*

– *“It is hard for me to make decisions”.*

Figure 2 Example indicating how assessment-to-assessment ratings of fatigue can be transformed into Variability scores



For all ANOVAs, when necessary, follow-up analyses were run, and the relevant pairwise contrasts were reported. A $p \leq 0.05$ was considered statistically significant.

Separate correlational analyses for MS patients and Controls, were used to assess the relations among the different measures of Physical and Mental Fatigue collected in this experiment (e.g., daily Physical and Mental Fatigue, Physical and Mental Fatigue Variability) and to detect the potential effects of exposure to stressors and of the sociodemographic and clinical variables on these measures.

The statistical analyses were conducted through IBM SPSS AMOS (version 22).

7.9. Results

7.9.1. Descriptive statistics of the samples of participants

The descriptive statistics on demographic and clinical variables of the sample of MS patients and Controls are presented in Table 19. Mean Age and Education were equivalent in Controls and in MS patients, Fs (1, 189) < 3.27. Sleep quality was significantly better in Controls as compared to MS patients, F (1, 189) = 31.33, $p < 0.0001$, $\eta_p^2 = .14$. The analyses of the responses to the BDI items indicated marginally higher scores in MS patients as compared to Controls, F (1, 189) = 4.1, $p < 0.05$, $\eta_p^2 = .02$. Scores from the four subscales of the PSE-MCP were equivalent in Controls and MS patients, Fs (1, 189) < 0.23.

7.9.2. Differences in Sleep length between MS patients and Controls

The mean ratings of Sleep length of MS patients and Controls across days of data collection are presented in Table 20. Results showed that MS patients and Controls rated their Sleep length as equivalent, F (1, 189) = 0.39.

7.9.3. Differences in daily Physical and Mental Fatigue between MS patients and Controls

The mean ratings of daily Physical and Mental Fatigue of MS patients and Controls across days of data collection are presented in Table 20. Results showed a main effect of Group, F (1, 185) = 8.76, $p < .005$, $\eta_p^2 = .04$, indicating that MS patients rated their Daily Fatigue as higher than Controls. The effect of Type of Fatigue was also significant, F (1, 185) = 22.50, $p < .0001$, $\eta_p^2 = .11$, indicating that Physical Fatigue was rated as higher than Mental Fatigue.

Table 20 Mean ratings and standard deviations of Sleep length and Daily Physical and Mental Fatigue of MS patients and Controls across days of data collection

	MS		**Controls**	
	M	SD	M	SD
Sleep length	2.91	0.65	2.97	0.43
Daily Physical Fatigue	2.76	0.81	2.42	0.70
Daily Mental Fatigue	2.50	0.96	2.16	0.96

7.9.4. Differences in the momentary assessments of Physical and Mental Fatigue between MS patients and Controls

The mean ratings of Mental and Physical Fatigue of MS patients and Controls across assessments are presented in Table 21. Results showed a main effect of Fatigue $F(1, 165) = 4.62$, $p < .05$, $\eta_p^2 = .03$, indicating that participants rated Physical Fatigue as higher than Mental Fatigue. The Group x Type of Fatigue interaction was also significant, $F(1, 165) = 7.12$, $p < .01$, $\eta_p 2 = .04$. Post-hoc analyses indicated that Controls rated Mental Fatigue as higher than Physical Fatigue, $F(1, 55) = 825.13$, $p < .0001$, $\eta_p^2 = .94$, while MS patients rated Physical Fatigue as higher than Mental Fatigue, $F(1, 110) = 942.46$, $p < .0001$, $\eta_p^2 = .89$. The main effect of Assessment, $F(1, 165) = 94.79$, $p < .0001$, $\eta_p^2 = .36$, and the Group x Assessment interaction, $F(1, 165) = 7.12$, $p < .01$, $\eta_p^2 = .04$, were also significantly. Post-hoc analyses indicated an overall gradual increase in fatigue from the first to the last assessments; mainly MS patients, $ts > 1.96$, $ps < .01$, reported this increase, while Controls rated fatigue almost equally across assessments.

7.9.5. Differences in assessment-to-assessment Variability of Physical and Mental Fatigue between MS patients and Controls

The mean Variability of Physical and Mental Fatigue of MS patients and Controls across assessments is presented in Table 21. Results showed a main effect of Group, $F(1, 187) = 537.15$, $p < .0001$, 10.59, $p < .001$, $\eta_p^2 = .74$, indicating that the Variability was higher for Controls than for MS patients.

Table 21 Mean ratings and standard deviations of Physical and Mental Fatigue of MS patients and Controls across assessments

	MS		**C**	
	M	SD	M	SD
Physical Fatigue				
Assessment 1	2.21	0.91	1.80	0.57
Assessment 2	2.38	0.94	1.97	0.67
Assessment 3	2.38	0.92	2.19	0.75
Assessment 4	2.57	0.88	2.29	0.66
Variability Assessment 2-1	0.48	0.47	0.70	0.58
Variability Assessment 3-2	0.51	0.56	0.38	0.39
Variability Assessment 4-3	0.55	0.52	0.78	0.58
Mental Fatigue				
Assessment 1	1.93	0.79	1.87	0.66
Assessment 2	2.11	0.85	2.09	0.68
Assessment 3	2.11	0.84	2.33	0.72
Assessment 4	2.23	0.83	2.38	0.75
Variability Assessment 2-1	0.44	0.42	0.73	0.58
Variability Assessment 3-2	0.46	0.49	0.40	0.40
Variability Assessment 4-3	0.49	0.44	0.78	0.54

7.9.6. Differences in momentary exposure to Stressors between MS patients and Controls

The mean ratings of MS patients and Controls concerning Stressors exposure across assessments are presented in Table 22. Results showed that MS patients and Controls were equally exposed to Stressors across the four different assessments. Furthermore, the exposure to stressors did not vary across assessments.

7.9.7. Differences in Momentary Effects of fatigue between MS patients and Controls

The mean ratings of MS patients and Controls concerning the Effects of fatigue across assessments are presented in Table 22. Results showed that the Momentary Effects of fatigue were equivalent in MS patients and Controls. The main effect of Assessments was however significant F (1, 165) = 17.08, $p < .0001$, $\eta_p^2 = .09$. Post-hoc pairwise comparisons indicated a significant difference among Assessments, ts >2.85, except between Assessment 1 and Assessment 2, and between Assessment 2 and Assessment 3, ts < 1.48.

Table 22 The mean ratings of MS patients and Controls concerning the presence of Stressors and the Effects of fatigue across Assessments

	MS		C	
	M	SD	M	SD
Stressors				
Assessment 1	1.80	0.422	1.85	0.49
Assessment 2	1.81	0.436	1.80	0.42
Assessment 3	2.01	0.484	1.81	0.43
Assessment 4	1.82	0.446	2.01	0.48
Effects				
Assessment 1	1.74	0.67	1.70	0.66
Assessment 2	1.73	0.66	1.74	0.67
Assessment 3	1.76	0.67	1.73	0.66
Assessment 4	1.85	0.71	1.76	0.67

7.9.8. Correlational analyses

A mixed pattern of results emerged (see Table 23). Considering MS patients, Daily Physical and Mental Fatigue showed a strong positive correlation, and both were positively correlated with Sleep quality, BDI, Physical Fatigue, Stressors exposure, and Mental Fatigue Variability; they were also negatively correlated with PSE-MCP and Sleep length. Daily Physical Fatigue was positively correlated with MSA. Physical and Mental Fatigue Variability showed a strong positive correlation; they were both negatively correlated with Sleep length. Physical Fatigue Variability was also negatively correlated with PSE-MCP. With respect to Controls, the only correlations of interest are the negative correlations between Daily Mental Fatigue and Physical and Mental Fatigue Variability.

Table 23 Correlations between Daily Physical and Mental Fatigue, Physical and Mental Fatigue Variability and the characteristics of MS patients and Controls

		1	2	3	4	5	6	7	8	9	10	11	12
1	Age		**-.457****	-0.217	0.105	0.079	0.108	0.212	0.117	0.099	-0.182	**.530***	
2	Education	**-.333****		0.187	0.121	**-.300***	-0.195	-0.183	-0.097	0.094	**.258***	0.039	
3	Sleep quality	-0.068	-0.162		0.025	0.114	-0.166	-0.108	-0.131	-0.136	0.138	0.15	
4	BDI	-0.1	-0.172	**.384****		**-.408****	-0.179	-0.091	-0.079	0.106	0.105	-0.22	
5	PSE-MCP	0.174	.278*	-0.121	**-.414****		0.227	0.059	-0.052	-0.059	-0.058	0.368	
6	Sleep length	0.118	0.125	**-.492****	**-.292****	**.262***		0.077	0.12	-0.071	-0.198	-0.195	
7	Physical Fatigue Variability	0.064	-0.05	0.138	0.121	**-.247***	**-.240***		**.812****	-0.023	**-.389****	0.143	
8	Mental Fatigue Variability	0.046	-0.038	0.165	0.144	-0.207	**-.230***	**.732****		-0.083	**-.338****	0.238	
9	Daily Physical Fatigue	0.071	-0.174	**.388****	**.311****	**-.235***	**-.310****	**.344****	**.410****		**.543****	-0.012	
10	Daily Mental Fatigue	-0.137	-0.111	**.419****	**.405****	**-.302****	**-.470****	**.311****	**.488****	**.724****		0.43	
11	Stressors exposure	0.118	0.008	**.410****	0.087	-0.026	-0.212	0.236	0.271	**.371****	**.427****		
12	Disease duration	**.415****	0.014	-0.065	-0.179	0.068	0.004	**.204***	0.082	-0.072	-0.168	-0.054	
13	MSA	**.264****	-0.071	-0.03	0.035	-0.004	0.15	0.021	-0.003	**.252****	-0.107	-0.073	0.166

Note. Numbers in the bottom left half and numbers in the top right half represent correlations in the groups of MS patients and Controls, respectively. $^{*}p<.05$; $^{**}p<.01$

7.10. Discussions

The purpose of the current study was to identify daily changes in physical and mental fatigue and to detect whether they differ in MS patients and Controls. To this purpose, the methodology employed in this study closely aligns with the approach utilized by Powell et al. (2017). This involved the implementation of a comprehensive assessment strategy utilizing EMA over a period of four consecutive days.

In accordance with earlier results (e.g., Powell et al., 2017), the results of the present study showed that MS patients rated their daily overall physical and mental fatigue as higher than Controls. Results concerning the momentary assessments of physical and mental fatigue indicated that MS patients rated physical fatigue as higher than mental fatigue, in accordance with the literature (e.g., Krupp et al., 2003; Marchesi et al., 2020; Schreus et al., 2002), while Controls rated mental fatigue as higher than physical fatigue. A gradual increase in overall fatigue from the morning to the evening was reported by MS participants, in accordance with the literature showing that fatigue rises across the day and is usually at its worst later in the day (e.g., Claros-Salinas et al., 2010; Kim et al., 2010; Powell et al., 2017). In contrast, Controls reported similar levels of fatigue across assessments. Assessment-to-assessment variability of physical and mental fatigue indicated that the fatigue variability was higher for Controls than for MS patients. Finally, as far as the exposure to stressors is concerned, both MS patients and Controls were equally exposed to stressors, and exposure to stressors did not vary across assessments.

The assessment of sleep quality (gathered during the collection of demographic data) and sleep length (gathered in the experiment) provided interesting insights into the role of sleep in the perception of fatigue. Indeed, the results of this study indicated, in line with earlier findings (e.g., Merlino et al., 2009), that sleep quality was significantly better in Controls than in MS patients. Furthermore, daily physical and mental fatigue in MS patients positively correlated with sleep quality and negatively correlated with sleep length, suggesting that the better and longer the night's sleep, the lower the experience of physical and mental fatigue. In a similar vein, results indicated that, although there were no differences in sleep length during the four days of data collection between MS patients and Controls, the variability in physical and mental fatigue in MS patients was negatively correlated with sleep length, suggesting, once again, that the longer the night's sleep, the lower the variability in physical and mental fatigue. Overall, these results highlight that sleep is an important contributor to predisposing MS patients to experience general fatigue (Trojan et al., 2007).

As far as the PSE-MCP is concerned, although MS patients and Controls reported equivalent scores, the correlational analysis indicated that, in MS patients, daily physical and mental fatigue negatively correlated with self-efficacy levels. It may be hypothesized that, as a result of the inherent unpredictability of MS, individuals diagnosed with this condition may perceive their disease as being difficult to control (Bandura, 1977). Accordingly, this psychological factor may potentially influence various health outcomes, such as the experience of fatigue (Bradley et al., 1984).

The crucial role of self-efficacy in the development of fatigue has been widely acknowledged in literature, as strategies aimed at mitigating physical fatigue revolve around the utilization of energy conservation techniques, which serve to foster a sense of self-efficacy (Mathiowetz, Finlayson, Matuska, Chen, & Luo, 2005). The way in which individuals perceive and cope with fatigue could potentially influence the intensity of their fatigue symptoms, as suggested by Bol et al. (2009).

In line with literature demonstrating a correlation between fatigue and higher degrees of physical impairment (Bergamaschi et al., 1997; Pittion-Vouyovitch et al., 2006; Schreurs et al., 2002), the results of the present study showed that, in MS patients, daily physical fatigue positively correlated with the scores obtained on the MSA. The MSA, although not encompassing a comprehensive assessment of the patient's disability, offers valuable insights into the patient's subjective perception of their mobility status. Individuals diagnosed with MS who experience physical impairments commonly associated with mobility may encounter heightened challenges in executing various tasks, consequently leading to a heightened sense of physical fatigue compared to individuals without the condition (Bergamaschi et al., 1997; Colosimo et al., 1995; Krupp et al., 2003; Marchesi et al., 2020; Pittion-Vouyovitch et al., 2006; Schreurs et al., 2002).

Overall, the results of the present study suggest that sleep quality and perception of self-efficacy are crucial factors in fatigue development. The results of the present investigation contribute to a multifaceted conceptualization of fatigue in MS and suggest that these factors should always be included in research on fatigue in MS.

8. THE IMPACT OF PHYSICAL AND MENTAL FATIGUE ON ATTENTIONAL PROCESSES IN MULTIPLE SCLEROSIS

8.1. Introduction

The literature review (see Chapter 5) highlighted a complex picture, and very heterogeneous approaches have been found in the examined studies on the relationship between fatigue and cognitive functions. For instance, several studies examined the impact of a protracted, continuous task on performance decline or performance changes at various time periods; others evaluated performance in a cognitive task before and after the loading task to determine the impact of an induced fatigue state on subsequent performances; still others evaluated objective fatigue by comparing performances at the beginning and conclusion of a cognitively demanding activity. The analysis of these research studies makes it clear that cognitive tasks that should serve merely as fatigue-inducing tasks have, in several cases, been used to evaluate subjects' cognitive performances. Moreover, several studies evaluate trait (a steadier fatigue state) and state fatigue (changes in fatigue over time) through the same appraisal tool (Ayache et al., 2018). The available fatigue measurements are not designed to assess at the same time trait fatigue and state fatigue (DeLuca et al., 2008; Genova et al., 2013). Also, most studies investigating the relationship between fatigue and cognitive functions have assessed fatigue broadly or have focused on mental fatigue, neglecting the investigation of physical fatigue. Those that looked at both physical and mental fatigue examined the results of separate physical and mental fatigue subscales of self-report tools, primarily with respect to the impact of fatigue on day-to-day patients 'activities. Furthermore, some studies lacked depression screening, which is crucial to identifying overlapping symptoms between fatigue and depression as well as coping strategies and personality traits. The investigation of these factors is crucial, as it contributes to clarifying the role of mood and personality traits in fatigue assessment and the impact of fatigue on cognitive abilities.

The objective of the present experiment is to provide new insights into the effects of two distinct forms of fatigue in MS, physical and mental, on attentional processes. Specifically, the main objective of the current study was to investigate whether physical and mental fatigue differentially impact attentional functions in MS patients. Overcoming the limits of the experimental approaches employed in earlier investigations was a fundamental goal of this work. A new and more accurate approach consisting of specific steps capable of systematically studying the relationship between fatigue and cognitive functions has been employed in the present research. A superordinate purpose of this work is to demonstrate the clear separation of physical and mental fatigue. In this research, physical and mental fatigue have been assessed separately to provide insight into the differences between these two components of fatigue in relation to cognitive performance. For a comprehensive assessment of fatigue, the current work investigates both subjective fatigue through two tools, i.e., the VAS and the MtAF, as measures of state and trait fatigue, and objective fatigue. In the current experiment, the VAS has been administered multiple times to assess the change in fatigue over time, whereas the MtAF has been employed only once before performing the experimental tasks to evaluate a steadier fatigue state. Both measures clearly discriminated between physical and mental fatigue. A key feature of the current experiment is the clear distinction between inductive tasks and tasks aimed at evaluating cognitive performance. Indeed, participants had been physically and mentally fatigued through a physical and cognitive inductive task and, subsequently, underwent a cognitive task to evaluate the impact of physical and mental fatigue on attentional processes.

8.2. Method

8.2.1. Participants

The study was conducted between June 2020 and August 2021. The eligible participants interested in taking part in the experiment provided the experimenter with their phone number and e-mail address and received, through SMS, WhatsApp, or email, according to their preferences, a pdf document with the research details (e.g., the study's procedure, objectives, participant inclusion, and exclusion criteria) and a custom URL that directed them to a Google Form portal web page to access and provide their informed consent. In the informed consent, participants were made aware that their information would be solely used for research purposes and that they had the option to withdraw from the study at any time. (For more details, see Appendix 3). Participants did not receive financial compensation for their participation.

Sixty-one healthy Italian adults were recruited to participate in this experiment as the control group. They were recruited mainly through email, social media posts, word-of-mouth, and the local community, with an effort made to match the age, gender, and education of MS patients. The inclusion criteria for Controls were being 18 to 70 years old and having access to a computer to perform the experiment. The exclusion criteria were as follows: having less than 8 years of formal education, the presence of neurological or psychiatric disease or major illnesses that might distort the results of the research, such as diabetes, diabetic therapy, and cardio-vascular dysfunction, a history of mild or severe traumatic brain injury, use of drugs affecting fatigue state, substance abuse, visual disturbances that might interfere with the experiment's execution, and, for women, being pregnant (as to avoid bias in the results). Moreover, participants with upper-limb disabilities or who were incapable of using both hands and who could not have access to a computer or who lacked basic computer skills to run the experiment were equally excluded. The exclusion criteria were chosen to enhance the internal and external validity of the study and to allow for a more accurate assessment free from the interference of unrelated factors. (For a comprehensive understanding of the exclusion criteria, please refer to Chapter 6). According to the exclusion criteria, data from nine participants was removed. The healthy participant sample (Controls) consisted of fifty-two individuals, of whom thirty-three were female. Participants had a mean age of 41 years (M = 41.46, SD = 14.08) and a notable degree of educational attainment (M = 17.13, SD = 3.82). Regarding participants' employment status, physical activity patterns, and alcohol and smoking consumption behaviours, the survey reveals that more than half of participants in the study were employed (65.38%), a high percentage practiced a sport (42.31%), and a low percentage of participants reported assuming alcohol (15.38%) and smoking regularly (7.69%).

Eighty MS Italian patients were recruited to participate in this experiment at the Neurological Clinic of the University of Naples Federico II, in social virtual groups (i.e., Facebook), and by a snowball sampling strategy. The inclusion criteria for MS patients were having a clinically definite diagnosis of MS, being from 18 to 70 years old, and having access to a computer to perform the experiment. The exclusion criteria for the MS group were consistent with those of the control group. Furthermore, MS patients who experienced exacerbations within a 30-day timeframe prior to the commencement of the research study were deemed ineligible for inclusion. (For a comprehensive understanding of the criteria pertaining to the exclusion of participants, refer to Chapter 6). Only fifty-eight MS patients participated fully in the experiment. However, due to the predominant representation of patients diagnosed with RRMS within the sample, a decision was made to exclude a small number of patients who exhibited different subtypes, namely SPMS and PPMS. This exclusion was implemented to maintain sample homogeneity. The final sample upon which the analyses were performed comprised fifty-four RRMS, of whom 36 were female. The cohort of RRMS participants had a mean age of 43 years (M = 43.89, SD = 11.04) and, on average, 15 years of educational attainment (M = 15.81, SD = 4.80). Regarding participants' employment status, physical activity patterns, alcohol, and smoking consumption behaviours, the survey has revealed that a significant majority of RRMS participants were part of the workforce (74.07%), a relatively modest portion of patients were actively engaged in physical activities (24.07%), a low percentage of participants reported assuming alcohol (11.11%), and a relatively modest portion of RRMS patients reported to smoke regularly (24.07%).

Regarding RRMS clinical characteristics, the mean disease duration suggests that the patients had experienced MS for a significant length of time (13.13 years). As for MSA, on average, RRMS patients reported average full mobility (M = 1.46, SD = 1.42). Specifically, participants reported full mobility (68.52%), mild mobility impairment (29.63%), and severe mobility impairment (1.85%).

As for MS treatment, some patients were managing their condition without the use of disease-modifying medications (24.07%), a substantial portion of patients followed a drug therapy characterized by Dimethyl fumarate (38.89%), and a smaller portion of patients assumed Interferon beta-1a (20.37%). Regarding the concomitant medication taken by MS patients, it was found that patients reported taking medications for the treatment of MS symptoms (14.81 %) and for concomitant diseases (48.15%). The majority of patients (77.78%) did not engage in rehabilitation therapy. The descriptive statistics and distributions of RRMS patients' and Control's characteristics are presented in Table 24.

The present study was approved by the Local Ethics Committee of the University of Federico II with number 80/20 and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki, together with the principles that guide the ethical and methodological practice of online research (Das, Ester, & Kaczmirek, 2011), social and behavioral research, and internet-applied methods and strategies (Hunter et al., 2018; see Appendix 3).

Table 24 Descriptive statistics and distributions of Relapsing-Remitting Multiple Sclerosis (RRMS) patients' and Control's (C) characteristics

	RRMS	C
N. Total (N. Female)	54 (36)	52 (33)
Age[1]. Mean (SD)	43.89 (11.04)	41.46 (14.08)
Formal education[1]. Mean (SD)	15.81 (4.80)	17.13 (3.82)
MoCA 5 min. Mean (SD)	12.19 (1.55)	/
Sleep quality. Mean (SD)	0.96 (0.95)	0.29 (0.54)
BDI. Mean (SD)	3.37 (4.23)	3.54 (5.68)
Emotional maturity. Mean (SD)	12.20 (9.19)	12.77 (7.11)
Finalization of the action. Mean (SD)	14.25 (10.61)	15.15 (8.41)
Relational fluidity. Mean (SD)	13.20 (9.67)	15.60 (8.63)
Context analysis. Mean (SD)	14.35 (10.68)	17.63 (9.85)
Employed. N. (%)	40 (74.07)	34 (65.38)
Unemployed. N. (%)	14 (25.93)	18 (34.62)
Practicing sport. N. (%)	13 (24.07)	22 (42.31)
Assuming alcohol. N. (%)	6 (11.11)	8 (15.38)
Smoking regularly. N. (%)	13 (24.07)	4 (7.69)
Disease duration[1]	13.13 (7.47)	/
MSA. Mean (SD)	1.46 (1.42)	/
Full mobility. N. (%)	37 (68.52)	/
Mild mobility impairment. N. (%)	16 (29.63)	/
Severe mobility impairment. N. (%)	1 (1.85)	/
MS therapy. N (%)		
None	13 (24.07)	/
Interferon beta-1a	11 (20.37)	/
Fingolimod	5 (9.26)	/
Dimethyl fumarate	21 (38.89)	/
Other	4 (7.41)	/
Unknown	0 (0.00)	/

[1]years

8.2.2. Materials

In the current investigation, participants performed the N-Back task (Kirchner et al., 1958), motor exercises, watched a film designed to induce relaxation, and completed the Attention Network Test (ANT; Fan et al., 2002).

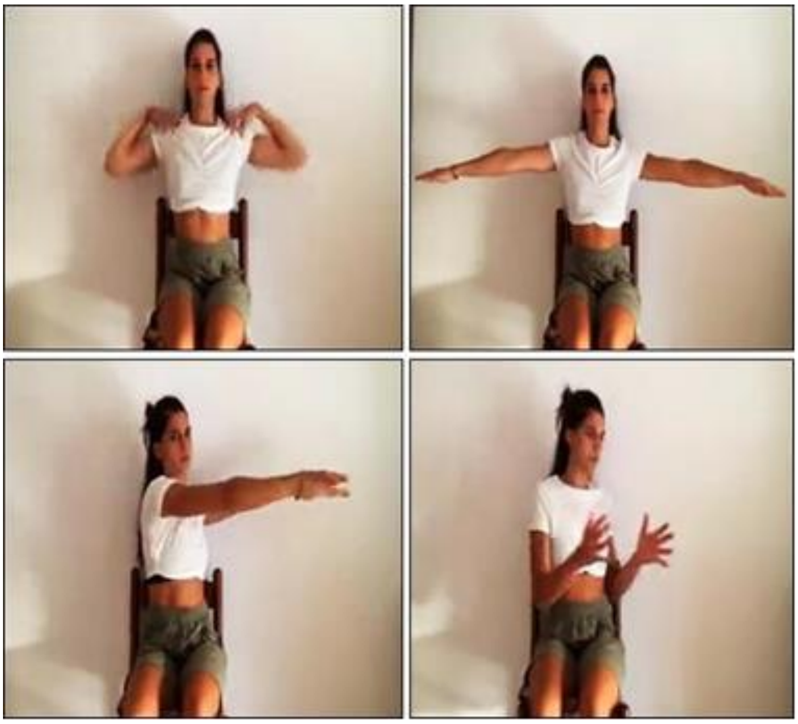
N-Back (1-back and 2-back) task. The N-Back is a continuous performance task that is often used in psychology and cognitive neuroscience to gauge the capacity to keep, update, and modify data in a temporary memory store. The N-Back enables manipulation of the load factor and makes the task simpler or more difficult. The 1-back and 2-back were selected to control high and low cognitive burdens, respectively. Within each group, the test presentation sequence (1-back or 2-back) was randomly chosen and counterbalanced. The participant is questioned about whether an existing item and one that was given "n" back are the same. Participants in the 1-back and 2-back tests completed a trial test in advance to familiarize themselves with the task. A through Z were shown as white letters on a black backdrop in the middle of the screen for 500 ms, followed by a 2500 ms interstimulus period. The viewing angles of the letters were 2.4° (h) and 2.4° (w). The 1-back test session consisted of two blocks of 64 letters displayed on the computer screen. The stimulus presentation was not self-paced, and each block consisted of 16 target stimuli and 48 distractor trials, all presented in random order. If the target letter was immediately followed by the identical target letter (e.g., B-B), participants had to push a pre-defined key on the computer keyboard to the target letter using either the left hand, the right hand, or both hands.

The 2-back test session consisted of two blocks of 64 letters appearing on a computer screen. The display of the stimuli was not self-paced, and each block had 12 target stimuli and 52 distractor trials in a randomized sequence. In this instance, if the target letter matched the one shown in the two trials before, participants had to push a pre-defined key to the target letter with either the left hand, the right hand, or both hands (e.g., B-P-B). No response was necessary for non-targets, and the participants' response window covered the period (3000 ms) between the start of the stimulus and the display of the following stimulus. Both the median reaction time (RT) and the percentage of correctly answered questions were measured for each activity.

Motor exercises. The subjects' physical fatigue was induced through physical activity. The participants were required to perform a sequence of moderate exercises shown by the video guide for 15 minutes without any equipment. The video-guided training, devised by a skilled doctor of motor sciences, Antonio Casale (Professor of Motor Sciences at the Comprehensive Institute of San Lazzaro of Savena, Bologna, Italy; personal trainer at Body Line Club of Bologna), made participants physically exhausted while allowing them to execute it safely.

The video was preceded by detailed instructions related to the sequence of exercises, and participants were invited to interrupt the experiment at any time if they felt uncomfortable. To keep the viewers engaged, a voice guide explained the exercises performed by a seated subject. The sequence of exercises chosen for this experiment involved only the upper limbs to allow participants with mobility problems of the lower limbs to perform the exercises safely while sitting at the desk of their computer (see Figure 3).

Figure 3 Sequence of the exercises performed by participants in the Motor Condition Load



Video (neutral loading condition). Participants were required to watch a documentary displayed on the computer screen. The video presented to the subjects lasted fifteen minutes and was a documentary about nature.

Attention Network Test (ANT). The ANT was developed to assess the independence and functioning of the three network attentive skills: alerting, orienting, and conflict resolution. This test was created to be brief (approximately 20 minutes), rapid, and simple to administer in a variety of fields. To perform the test, participants were required to be seated in front of a computer monitor at a normal 60-cm distance from it. Participants were required to maintain focus on a point of fixation, often indicated by a cross located in the middle of the display. Three different kinds of potential stimuli that might occur above or below the site of fixation were offered in this exam. These stimuli were made up of five arrows that are horizontally aligned and may face either right or left. The center line, to which the subject must pay attention, serves as the goal, while the two lines to the right and left serve as distractions. The three possible stimuli were displayed: neutral, where only the target is oriented (indifferent whether right or left); congruent, where the target and the distractions are oriented in the same direction, regardless of whether right or left; and incongruent, where the target is oriented in the opposite direction to the distractions, regardless of whether right or left.

Additionally, before the start of each trial, four different cues were randomly displayed across the flankers' conditions: the no cue condition, in which the occurrence of the stimulus is not prompted by the appearance of an alert signal; a central cue, consisting of an asterisk appearing at the location of the central fixation cross; a double cue condition, in which the occurrence of the stimulus is preceded by the presence of two asterisks, one above and one below the fixation point, appearing at the two possible target locations; and a spatial cue condition in which the presence of the stimulus is prompted by the appearance of an alert (an asterisk) signal suggesting the exact location in which the stimulus will act.

A single arrow or line subtended a visual angle of 0.6 at this distance, while the center arrow and its four flankers subtended a total visual angle of 2.8. The asterisk used for cueing has a subtended visual angle of 0.3. The spatial cue, the double cue, and the center arrow were all shown either 0.9 above or below the central fixation cross. The subjects must be answered as fast and precisely as possible by using the left and right keys on the computer keyboard.

The participants' response times (RT) and accuracy (ACC) are recorded. These results enable the calculation of the three attentive networks using the formula provided by the test's designers (Wang et al., 2004): Alerting: RT for no cue - RT double cue; Orientation: RT for the center cue - RT for the spatial cue; Executive Control: RT (incongruent flanker) – RT (congruent flanker).

The three networks' accuracy-related efficiencies are assessed using the same formulas but substituting the percentage values for the reaction time values of precision. In the test, there are four blocks: the first is a learning block consisting of 20 practice trials (all possible combinations among flankers and cue types were randomly repeated eight times in each block). The individual performed 96 trials in each of the next three experimental blocks without receiving any feedback. The subjects had the option of taking a 60-second break between the second and the last one. Each trial included the following series of activities: for a random variable amount of time (between 400 and 1600 milliseconds), a fixation cross was displayed in the center of the screen. It was then followed by one of the four types of alert cues, which was displayed for 100 milliseconds. The warning cue was then followed once more by the fixation cross, which was displayed for 400 milliseconds. Finally, the central arrow and one of the three types of flankers were displayed, and they remained observable until the participant responded or until 1700 ms had elapsed (see Fig. 8.2). By hitting the left or right key on the computer keyboard in accordance with whether the center target arrow was pointing left or right, participants needed to determine the direction of the arrow. At the beginning of the test, participants were asked to specify if they used either the left hand, the right hand, or both hands to perform the test. Measuring the effectiveness of alerting, orienting, and conflict resolution using a single experimental paradigm has various benefits (see McDowd & Shaw, 2000, for a review). First off, by mixing up the different warning signals (no cue, central cue, double cue, and spatial cue), it lessens the chance that participants will develop a habit of paying attention to either spatial cues or alerting cues, which is what would be expected if they were presented in the same task context. It is more likely to encourage the trial-by-trial elicitation of orienting and alerting effects when different warning signals are mixed together within a single task (Festa-Martino et al., 2004). Second, the no-cue condition enables one to evaluate the value of nonspatial warning signals without using any spatial information due to the fact that any cue that is delivered before the target stimulus might reasonably serve as a warning signal for its impending presentation. To determine the impact of alerting, only reaction times for targets preceded by nonspatial, neutral alerting signals and those targets without any cues are compared. Finally, altering flanker congruency and cue type in the same tasks, as it is done in the ANT, allows for a comparison of the ways that alerting and orienting signals affect conflict resolution (Rueda, Fan, & Posner, 2003).

Fatigue evaluation. To evaluate state physical and mental fatigue, participants rated their fatigue on a VAS. The VAS is a viable and trustworthy tool for measuring self-reported fatigue in MS. Participants described their level of physical and mental fatigue on a scale of [0–10]. This measurement allows for an estimation of the degree of fatigue driven by the various tasks throughout the blocks.

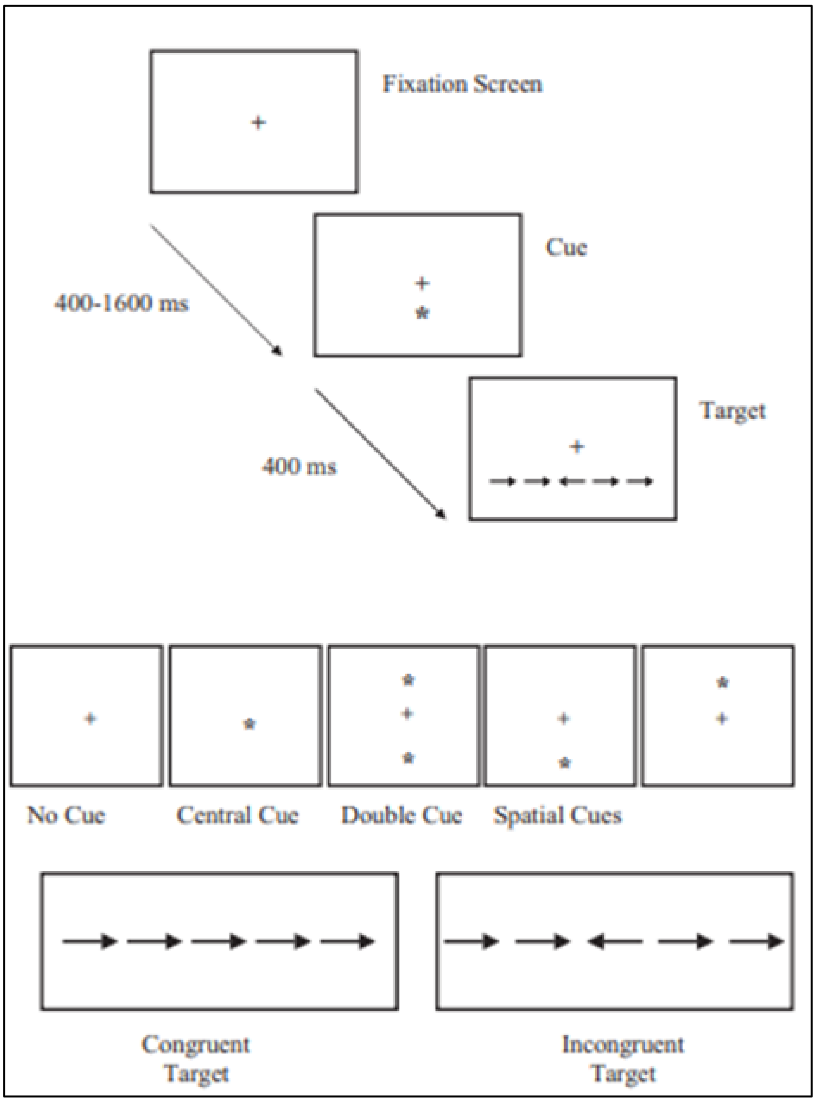
To evaluate trait physical and mental fatigue, participants completed the MtAF. The MtAF estimates the presence and severity of physical and mental fatigue. (See MtAF, Chapter 6).

Mood and Self-esteem. The BDI and PSE-MCP were administered to detect respondents' perceptions of being able to face problematic life situations and measure depressive symptoms. (For more details, see Chapter 6).

Cognitive profile. To assess MS patients' cognitive profiles, participants underwent the evaluation through the MoCA 5-min (Nasreddine, 2021), which takes five minutes over the telephone. The MoCA 5-minute protocol is a brief and highly reliable screening tool for mild cognitive impairment. The MoCA 5-minute protocol is a shortened version of the original MoCA and consists of tasks that have proven to be more sensitive to mild cognitive impairment and have been developed to allow even faster screening and evaluation, even remotely, as it is possible to administer by phone. It assesses several cognitive domains (attention, concentration, executive functions, memory, language, and orientation) and shows the advantage of much greater sensitivity in the early stages of deterioration compared to the Mini Mental State Examination (MMSE;

Folstein et al., 1975). The MoCA 5-minute score ranges from 0 to 30.8. (For more details, see Appendix 7).

Figure 4 Schematic representation of cue and flanker types used in the Fan et al. (2002) Attention Network Test and of the sequence of events included in each trial.



Source Leskin, L. P., & White, P. M. (2007). Attentional networks reveal executive function deficits in posttraumatic stress disorder. Neuropsychology, 21(3), 275.

8.2.3. Procedure

A preliminary phone interview was planned to provide participants with more study details and to perform the MoCA 5-minute telephone version. Moreover, participants were instructed, confidentially, that they should abstain from engaging in the activity if they were experiencing symptoms of COVID-19 or any physical discomfort.

Participants were provided with an application URL via email, SMS, or WhatsApp, based on their preferences. This URL directed them to a Google Form web page where they provided their demographic information and completed the informed consent. Socio-demographic data were collected from all participants. Socio-demographic variables such as sex, age, education, marital status, and employment status were explored. Additional questions were related to self-care practices, such as whether at least one sport was practiced, whether alcohol and smoking were consumed regularly, the quality of sleep, the presence of a disease, and disease treatment. MS patients were required to fill in additional questions related to clinical disease characteristics such as MS phenotype, disease duration, current symptoms, and mobility impairment (for more details, see Chapter 6). MS treatment, symptomatic treatment, treatment for concomitant disease, and rehabilitation activities were also investigated.

Furthermore, participants completed the MtAF, the BDI, and the PSE-MCP. Participants' answers were gathered on a cloud server and automatically entered as raw data in an Excel file.

Participants received a PDF document via email after three days containing the experiment's details pertaining to their assigned experimental conditions, along with a customized URL to participate in the experiment within the next seven days. The experiment was devised by means of PsychoPy, a multiplatform software suite that can operate natively on Microsoft Windows, GNU/Linux, and Apple Mac OS X. It was run remotely through the Pavlovia/PsychoPy platform (www.pavlovia.org).

Participants were randomly allocated to one of three conditions: (i) the cognitive loading condition, requiring participants to perform the N-Back task; (ii) the motor loading condition, requiring participants to perform a physical workout following a video tutorial; and (iii) the neutral loading condition, requiring participants to watch a relaxing video clip.

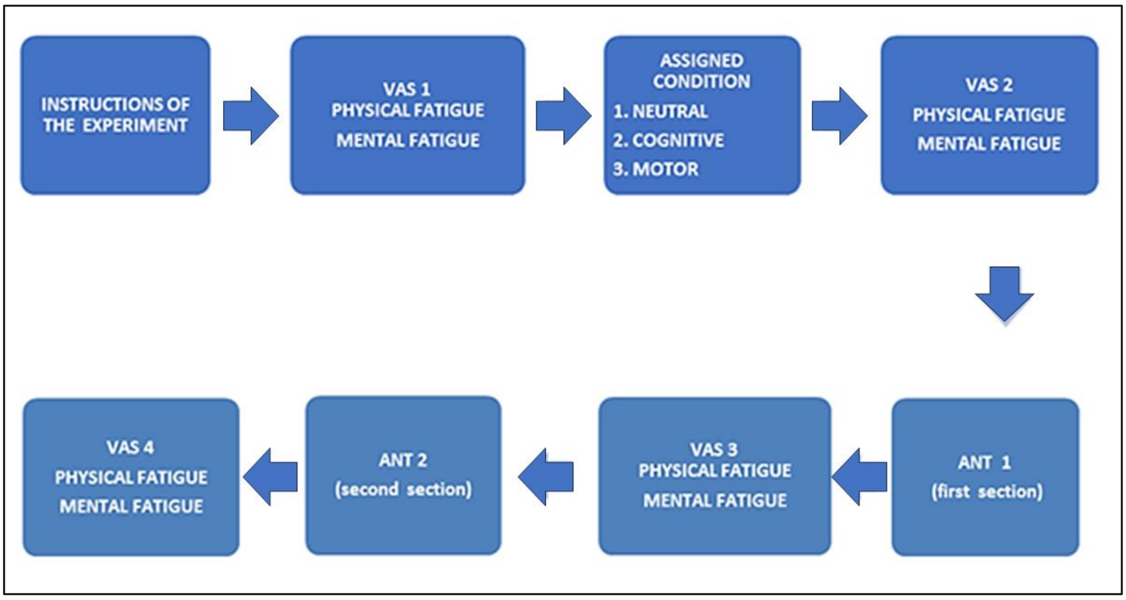
When tapping the custom URL, the following sequence of events occurred (see Figure 5):

1. Instructions for the entire experiment and a description of physical and mental fatigue (to avoid any biases in the ratings during the experiment) were displayed on the computer screen on sequential pages that the participants could scroll freely.
2. Two VAS, assessing physical and mental fatigue, respectively, were presented.
3. The assigned experimental conditions were performed, each lasting about 15 minutes (motor, cognitive, and neutral). In the cognitive loading task, half of the participants completed the 1-back condition first, followed by the 2- back condition; the other half performed the two tasks in the opposite order.
4. Two VAS, assessing physical and mental fatigue, respectively, were presented.
5. The first trial of the ANT was performed.

6. Two VAS, assessing physical and mental fatigue, respectively, were presented.
7. The second trial of the ANT was performed.
8. The last two VAS, assessing physical and mental fatigue, respectively, were presented.

Participants moved through these events by clicking the space bar on the keyboard. The entire experiment lasted about forty minutes. Once the experiment was complete, the obtained data were stored on the Pavlovia Platform for statistical analysis.

Figure 5 Experiment flow



8.3. Statistical analyses

Univariate 2 (Group: MS vs. C) x 3 (Loading Condition: cognitive vs. motor vs. neutral) ANOVAs were used to assess whether there were differences between MS patients and Controls randomly assigned to the three loading conditions with respect to Age, Education, Sleep quality, BDI scores, and the scores related to the four dimensions of the PSE-MCP. One main purpose of the present experiment was to assess whether there were differences between MS patients and Controls in Alerting, Orienting and Conflict Resolution, and whether these differences varied as a function of the loading condition (cognitive loading, motor loading, neutral loading). The dependent variables for this task are RTs and Accuracy. Accordingly, three different multivariate MANOVAs were computed on mean RTs and Accuracy rates.

Precisely, a 2 (Group: MS vs. C) x 3 (Loading Condition: cognitive vs. motor vs. neutral) x 2 (Trials: no cue vs. double cue) MANOVA was computed on mean RTs and Accuracy rates to assess the effect of the MS Group and the Condition on Alerting, a 2 (Group: MS vs. C) x 3 (Loading Condition: cognitive vs. motor vs. neutral) x 2 (Trials: central cue vs. spatial cue) MANOVA was computed on mean RTs and Accuracy rates to assess the effect of MS Group and the Loading Condition on Orienting, and a 2 (Group: MS vs. C) x 3 (Loading Condition: cognitive vs. motor vs. neutral) x 2 (Trials: congruent vs. incongruent) MANOVA was computed on mean RTs and Accuracy rates to assess the effect of the MS Group and Loading conditions on Conflict Resolution.

Although not relevant for the purposes of the present experiments, the performances of participants in the N-Back task were also analysed. The dependent variables for this task are the mean RTs for correctly identified targets, the percentage of correctly identified targets (Hits), the percentage of responses to non-targets (false alarms; FA), and d-prime (d'), a signal-detection parameter reflecting the sensitivity of participants to discriminate between items previously presented n trials ago and non-target items. To assess whether there were differences between MS patients and Controls and whether these differences were affected by task difficulty, four separate repeated measures 2

(Group: MS vs. C) x 2 (N-Back: 1- back vs. 2- back) ANOVAs were used for each dependent variable.

Another main purpose of the experiment was to assess whether there were differences between MS patients and Controls in changes in Physical and Mental state Fatigue as measured by the VAS during the experiment (4 assessments) as a function of the loading condition (cognitive loading, motor loading, neutral loading). To this purpose, a 2 (Group: MS vs. C) x 3 (Loading Condition: cognitive vs. motor vs. neutral) x 2 (Type of Fatigue: MF vs. PF) x 4 (Assessment: VAS_1 vs. VAS_2 vs. VAS_3 vs. VAS_4) MANOVA was computed.

As patients' level of fatigue and subsequent level of cognitive performance may vary depending on whether they are pharmacologically treated for MS, the above-mentioned analyses were initially run only on MS patients entering pharmacological treatment as a covariate. In any case, neither the covariate nor its interaction with the different independent variables resulted significant. Accordingly, in the following paragraphs, the analyses with Group (MS vs. C) as an independent variable are reported.

For all MANOVAs, when necessary, follow-up analyses were run and the relevant pairwise contrasts were reported. A $p \leq 0.05$ was considered statistically significant. Separate correlational analyses, for MS patients and Controls, were used to assess the relations among the different measures of Physical and Mental Fatigue collected in this experiment (e.g., physical and mental fatigue, from the MtAF and physical and mental fatigue from the VAS) and to detect potential effects of the sociodemographic and clinical variables on these measures.

The statistical analyses were conducted through IBM SPSS AMOS (version 22).

8.4. Results

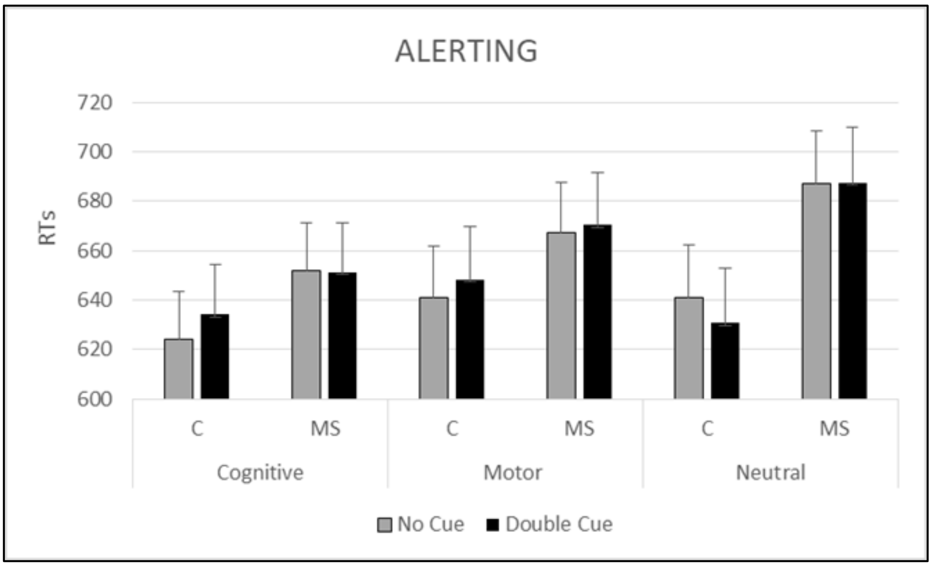
8.4.1. Descriptive statistics of the samples of participants

The descriptive statistics on demographic and clinical variables of the final sample of MS patients and Controls are presented in Table 24. Mean Age, Education, BDI, and PSE-MCP scores were equivalent in MS patients and Controls. Sleep quality was, however, found to be worse in MS patients than in Controls, $F\ (1, 105) = 21.92$, $p < .0001$, $\eta_p^2 = .17$).

8.4.2. Effects of Multiple Sclerosis and fatigue-induction tasks on attention networks

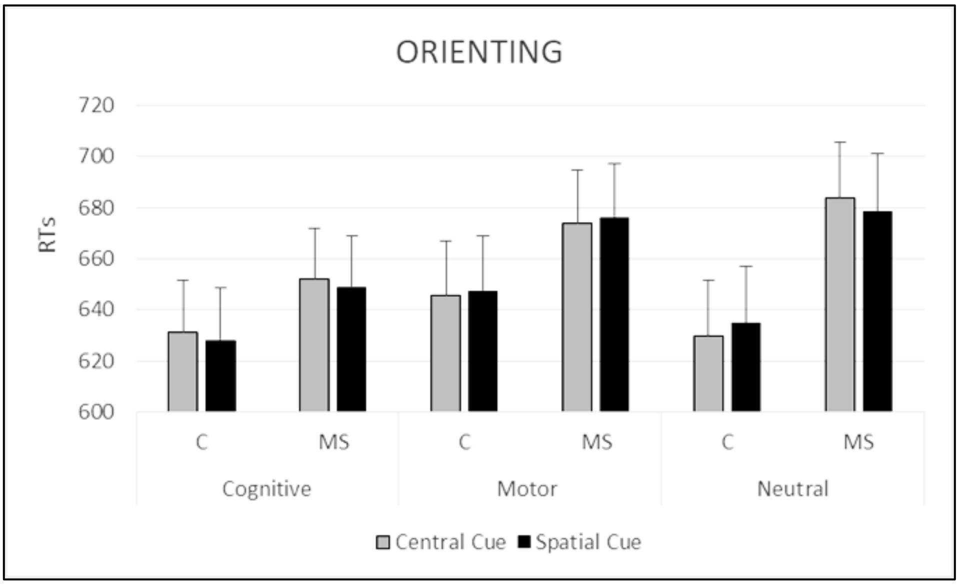
All the trials in which an error occurred or for which the response latency was shorter than 200 ms were excluded from the analysis. Concerning Alerting, only a marginally significant main effect of Group was found, $F\ (1,100) = 3.74$, $p < .05$, $\eta_p^2 = .04$, indicating that MS patients were overall slower than Controls (see Figure 6).

Figure 6 Mean RTs of MS patients and Controls in the No Cue and Double Cue trials, as a function of Loading Condition. Bars indicate standard errors



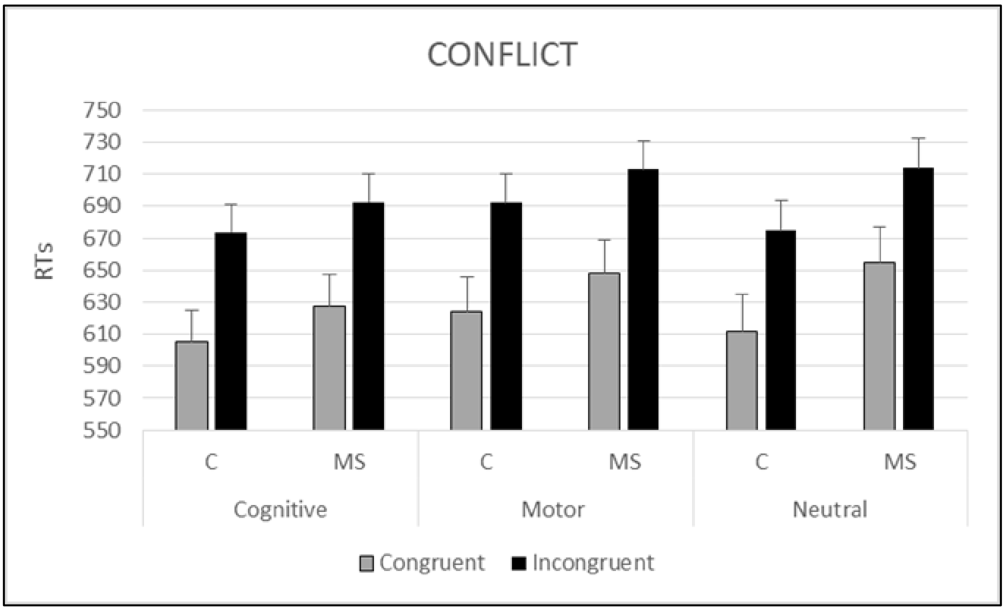
Similar results were obtained with respect to Orienting, that is, only a significant main effect of Group was found, $F(1,100) = 4{,}03$, $p < .04$, $\eta_p^2 = .04$, indicating that MS patients were overall slower than Controls (see Figure 7).

Figure 7 Mean RTs of MS patients and Controls in Central Cue and Spatial Cue trials, as a function of Loading Condition. Bars indicate standard errors



As concerns Conflict Resolution, results showed a significant main effect of Group, F (1,100) = 3.35, $p < .05$, $\eta_p^2 = .03$, indicating that MS patients were overall slower than Controls. The main effect of Trials was also significant, F (1,100) = 190.08, $p < .0001$, $\eta_p^2 = .66$, indicating that, overall, participants were slower in responding to incongruent trials than to congruent trials (see Figure 8).

Figure 8 Mean RTs of MS patients and Controls in Congruent and Incongruent trials, as a function of Loading Condition. Bars indicate standard errors



8.4.3. Effects of Multiple Sclerosis on performance in the N-Back task

The Mean percentage of Hits and FA, mean d,’ and mean RTs to correct responses of MS patients and Controls are presented in Table 25 as a function of task difficulty. As concerns Hits, results showed a main effect of N-Back, F (1, 37) = 5.16, $p < .02$, $\eta_p^2 =.12$, indicating that participants correctly identified more targets in the 1- back condition than in the 2-back condition. As for FA, no significant main effect or interaction was found. With respect to d’, a marginally significant effect of Group was found, $F(1,37) = 4.43$, $p < .05$, $\eta_p^2 = .10$, indicating that Controls were better at discriminating between items previously presented n trials ago and non-target items as compared to MS patients. Finally, results concerning RTs to correct responses showed a main effect of Group, $F(1, 37) = 4.41$, $p < .03$, $\eta_p^2 = .10$, indicating that MS patients were slower at responding as compared to Controls.

Table 25 Mean percentage (and standard deviations) of Hits (%) and FA (%), mean d', and mean RTs (sec) to correct responses of MS patients and Controls as a function of task difficulty (1-back, 2-back)

	MS		**C**	
	1-back	**2-back**	**1-back**	**2-back**
Hits (%)	20.02 (28.62)	12.52 (14.26)	28.31 (22.90)	21.89 (17.15)
FA (%)	1.39 (0.60)	1.56 (1.36)	1.18 (0.43)	1.28 (0.67)
d' (mean)	1.08 (1.02)	0.88 (0.45)	1.49 (0.83)	1.34 (0.88)
RTs (mean)	0.42 (0.03)	0.43 (0.42)	0.41 (0.02)	0.42 (0.03)

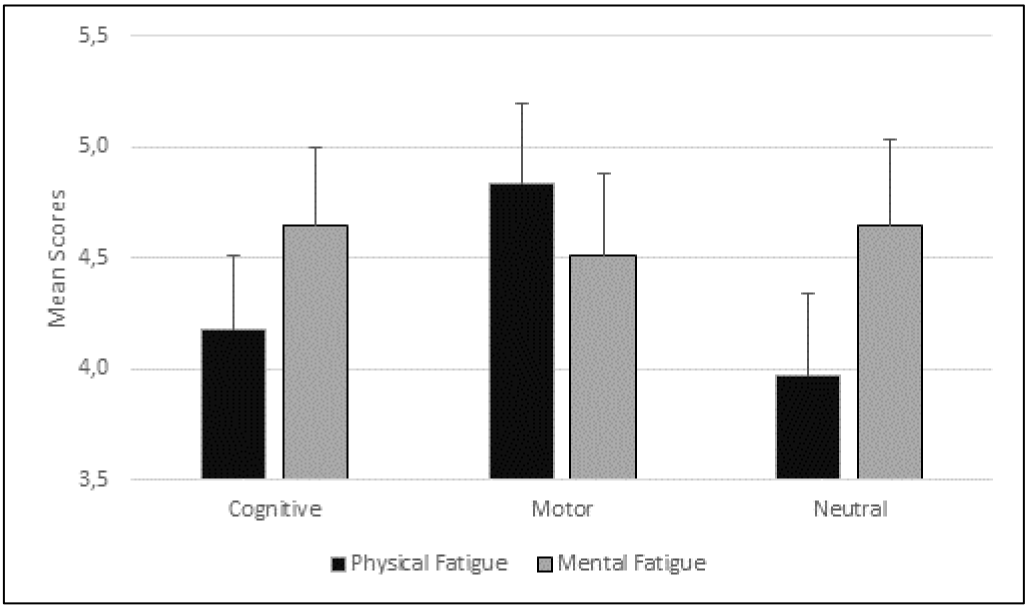
8.4.4. Effects of Multiple Sclerosis and fatigue induction on changes in VAS for Physical and Mental Fatigue

Mean VAS scores and standard deviations for Physical and Mental Fatigue provided by MS patients and Controls during the four assessments are presented in Table 26 as a function of Loading Condition. Results showed a main effect of Type of Fatigue, $F(1, 100) = 8.29$, $p < .005$, $\eta_p^2 = .08$, indicating that participants experienced more Mental than Physical Fatigue. There were also significant Type of Fatigue x Loading Condition, $F(2,100) = 10.18$, $p < .0001$, $\eta_p^2 = .17$, and Type of Fatigue x Assessment, $F(1,100) = 4.63$, $p < .05$, $\eta_p^2 = .04$, interactions. As for the first interaction, post-hoc pairwise comparisons indicated that participants who performed the Cognitive Loading task, t (38) = 2.81, p<.01, and participants in the Neutral Loading condition, t (31) = 3.31, p<.005, reported, overall, more Mental than Physical Fatigue; inversely, participants who performed the Motor Loading task, t (34) = 2.73, p<.01, reported, overall, more Physical than Mental Fatigue (see Figure 9).

Table 26 Mean VAS scores and standard deviations for Physical and Mental Fatigue provided by MS patients and Controls during the four assessments, as a function of Loading Condition

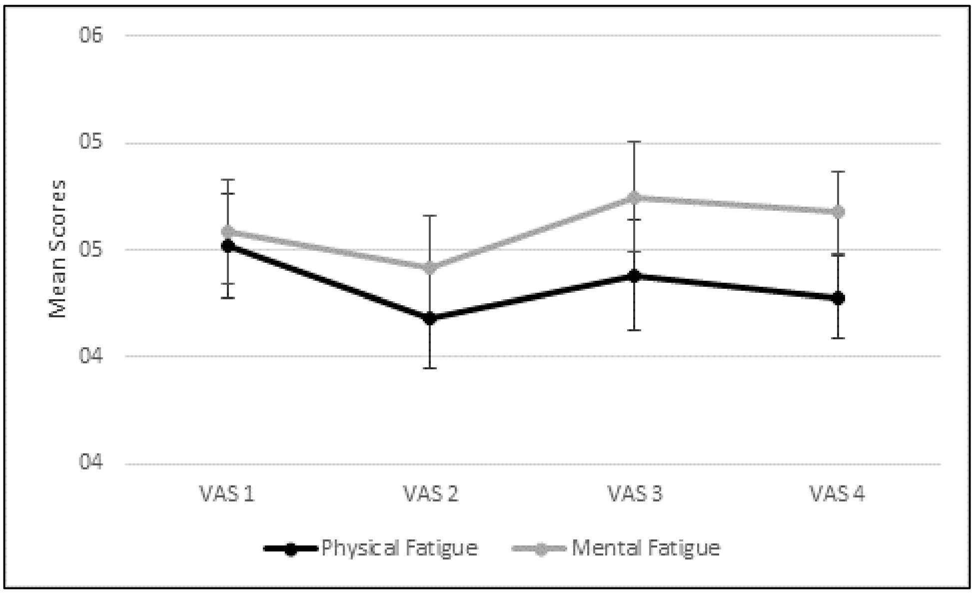
Loading Condition	Assessment	Physical Fatigue				Mental Fatigue			
		MS		C		MS		C	
		M	SD	M	SD	M	SD	M	SD
COGNITIVE	VAS 1	4.80	2.73	3.89	2.69	5.10	2.57	4.47	2.72
	VAS 2	4.53	2.82	3.22	2.09	4.90	2.71	4.12	2.15
	VAS 3	4.87	2.83	3.63	2.77	4.86	2.76	4.37	2.75
	VAS 4	4.82	0.00	3.66	1.63	5.09	0.00	4.26	1.40
MOTOR	VAS 1	4.83	2.33	4.93	1.98	4.17	2.46	4.12	1.87
	VAS 2	5.06	2.62	4.76	2.22	4.19	2.53	4.59	2.21
	VAS 3	5.00	2.61	4.53	1.97	5.06	2.58	5.24	2.28
	VAS 4	5.39	1.42	4.20	1.31	4.51	1.20	4.22	1.51
NEUTRAL	VAS 1	4.88	2.94	3.75	2.24	5.06	3.07	4.56	2.39
	VAS 2	4.03	2.83	3.44	2.16	4.38	2.80	4.25	2.52
	VAS 3	4.50	3.16	3.69	2.52	5.38	2.83	3.56	2.58
	VAS 4	4.19	2.86	3.25	2.57	5.75	3.32	4.25	2.74

Figure 9 Mean VAS scores for Physical and Mental Fatigue, as a function of Loading Condition. Bars indicate standard errors



With respect to the second interaction, post-hoc pairwise comparisons indicated that Physical and Mental Fatigue, as assessed by the VAS, were rated as equivalent during the first two assessments, ts (105) < 1.64, while, during the third and fourth assessments, Mental Fatigue was rated as higher than Physical Fatigue, ts (105) > 2.52, ps < .05 (see Figure 10).

Figure 10 Mean VAS scores for Physical and Mental Fatigue, as a function of Assessment. Bars indicate standard errors



The main effects of Group, Loading Condition and Assessment were not significant. However, a significant interaction among Group, Type of Fatigue, Assessment and Loading Condition was found, $F(2,100) = 4.19$, $p < .02$, $\eta_p^2 = .08$. To better explain this pattern of results, two separate Group x Assessment x Loading Condition ANOVAs were run for Physical and Mental Fatigue. Results showed, for Physical Fatigue, only a significant effect of Group, $F(1, 100) = 4.11$, $p < .05$, $\eta_p^2 = .04$, indicating that MS patients reported experiencing more Physical Fatigue than Controls. With respect to Mental Fatigue, the results failed to show any significant main effect or interaction.

8.4.5. Correlational analyses

A mixed pattern of results emerged (see Table 27). Considering MS patients, Physical Fatigue and Mental Fatigue, as measured by the MtAF, and Physical Fatigue and Mental Fatigue, as measured by the VAS, showed large, significant positive correlations among each other. Both forms of fatigue, measured by the MtAF and the VAS, were significantly correlated with Sleep quality and the BDI. Interestingly, they did not correlate with Disease duration, MSA, and MoCA 5-minute protocol scores. With respect to Controls, the correlations among the different forms of fatigue, measured by the MtAF and the VAS, did not emerge. There were only significant negative correlations between Physical and Mental Fatigue, as measured by the VAS and PSE-MCP scores.

As for demographic characteristics, Age was negatively correlated with Physical and Mental Fatigue, as measured by the MtAF, in the group of MS patients and only with Physical Fatigue in the group of Controls. Furthermore, in the group of MS patients, it negatively correlated with Sleep quality and MoCA 5-minute scores, while in the group of Controls, it negatively correlated with PSE-MCP scores.

Table 27 Correlations between Physical Fatigue and Mental Fatigue, as measured by the MtAF, and Physical Fatigue and Mental Fatigue, as measured by the VAS, and the characteristics of MS patients and Controls

		1	2	3	4	5	6	7	8	9	10	11
1	Age		-0.195	-0.004	-0.178	-.579**	-0.195	-.300*	0.216	0.015		
2	Education	-0.022		0.096	0.222	0.137	0.091	-0.102	0.039	0.054		
3	Sleep quality	-.338*	-0.11		0.097	-0.114	-0.044	0.027	0.272	0.235		
4	BDI	-0.23	-0.208	.386**		-0.033	0.193	0.242	0.175	0.184		
5	PSE-MCP	-0.115	-0.155	0.048	-0.129		0.261	0.251	-.423**	-.360*		
6	Mental Fatigue	-.328*	-0.15	.462**	.381*	-0.08		.755**	-0.041	0.061		
7	Physical Fatigue	-.382*	-0.215	.487**	.457**	-0.073	.830**		-0.157	-0.082		
8	VAS_Physical Fatigue	0.025	-0.005	.351*	.361**	-0.295	.520**	.445**		.820**		
9	VAS_Mental Fatigue	-0.126	-0.043	.441**	.431**	-0.176	.541**	.589**	.846**			
10	Disease duration	.585**	0.083	-0.238	-0.251	-0.257	-0.116	-0.065	-0.06	-0.195		
11	MSA	0.066	0.059	-0.134	-0.125	-0.209	-0.022	-0.193	-0.165	-.304*	0.257	
12	MoCA 5-min	-.390**	0.046	-0.022	0.087	0.112	0.037	0.057	-0.018	-0.016	-0.215	-.373**

Note. The numbers in the bottom left half and the numbers in the top right half represent correlations in the groups of MS patients and Controls, respectively*p<.05; **p<. 01.

8.5. Discussion

The aim of the present experiment was to provide new insights into the effect of physical and mental fatigue on attentional processes, as measured by the ANT, in MS patients. Specifically, state physical and mental fatigue, as measured by the VAS, were assessed at baseline, after inducing physical or mental fatigue or after a neutral task, halfway through, and at the end of the ANT. Participants' trait physical and mental fatigue were also measured through the MatF a few days before participating in the experiment.

The present investigation focused on attentional functions, as evidence in the literature indicates that attention, and specifically the alerting component, is one of the most affected cognitive functions in MS and a cognitive domain more associated with fatigue (Hanken et al., 2014). Such evidence has been confirmed by studies showing that inflammation, which is characteristic of MS, alters noradrenergic modulation (De Rodez Benavent et al., 2017), which is known to be involved in arousal and the allocation of attention (Alnaes, et al., 2014).

In the current study, the ANT has been employed to investigate attentional processes, as it is a rapid and easily performable task that provides reliable estimates of the efficiency of alerting, orienting, and conflict resolution.

The results of the present study are quite inconclusive. The main findings can be summarized as follows.

In line with abundant evidence in the literature, MS patients were slower at performing the ANT as well as the N-Back Task (e.g., Ishigami, Fisk, Wojtowicz, & Klein, 2013; Neumann et al., 2014) as compared to Controls. As for the overall rating of state fatigue, as measured by the VAS, both MS patients and Controls experienced more mental than physical fatigue. Participants in the cognitive and neutral loading conditions reported more mental fatigue, while those in the motor loading task reported more physical fatigue. The findings align with existing literature that supports the notion that cognitive tasks requiring heightened cognitive exertion are indicative of mental fatigue (Van der Linden et al., 2003), whereas tasks demanding physical exertion are indicative of physical fatigue (Steege et al., 2015). In the context of a neutral task, it is plausible that mental fatigue may have arisen either due to engagement in a monotonous task (Hockey et al., 2003) or, alternatively, as a consequence of participating in a cognitive activity that demands relatively prolonged concentration in relation to attentional processes (Aldughmi et al., 2017; Lundberg et al., 2010).

State physical and mental fatigue, as assessed by the VAS, were rated by participants as equivalent during the first two assessments, but during the third and fourth assessments, mental fatigue was rated by participants as higher than physical fatigue. The overall experiment lasted about forty-five minutes, of which twenty minutes were dedicated to performing the ANT. It is plausible to hypothesize that there may have been an escalation in mental fatigue during the latter phase of the experiment, aligning with existing literature that demonstrates the tendency for prolonged cognitive tasks to elicit a cognitive exertion capable of influencing the subjects' mental fatigue levels (e.g., Genova et al., 2013; Slimani et al., 2018).

In the MS sample, a significant relationship was found between trait physical and mental fatigue, as measured by the subscales of the MtAF, and state physical and mental fatigue, as measured by the VAS. As discussed in Chapter 3, state fatigue is defined as the momentary, transient subjective perception of fatigue or task-related fatigue, whereas trait fatigue corresponds to a steadier fatigue state.

As far as we know, this is the first study evaluating trait and state fatigue by examining the physical and mental fatigue constructs in a systematic way.

In line with the literature (e.g., Amtmann, Bamer, Kim, Chung, & Salem, 2018; Bol et al., 2009; Ford et al., 1998; Induruwa et al., 2012; Kaminska et al., 2011;

Kos et al., 2008; Pittion-Vouyovitch et al., 2006), the results of the present experiment showed significant correlations between trait and state physical and mental fatigue (as measured respectively by the MtAF and the VAS) and sleep quality and BDI scores. However, in line with literature studies, the correlations between trait and state physical and mental fatigue, as measured by the MtAf and the VAS, respectively, and disease duration, MSA, and general cognition (MoCA 5-min) were not significant (e.g., Baski et al., 2000; Bryant et al., 2004; Fisk et al., 1994; Johnson et al., 1997; Paul et al., 1998; Walker et al., 2012).

In accordance with the literature, physical and mental fatigue measured through the MtAF are negatively correlated with age (Al-Mulla et al., 2011). This pattern of results adds to the already controversial results on the topic (e.g., Codella et al., 2002).

9. GENERAL DISCUSSION

9.1. A journey into the complex world of fatigue

The aim of the present Thesis was to examine fatigue in MS, as it is a prominent symptom of the disease that negatively affects the well-being of patients (Penner et al., 2020). Despite countless studies on the issue, the underlying processes of MS-related fatigue are not fully recognized, and no effective therapies for managing fatigue have been identified.

The overall objective of this research was to provide a broad understanding of the multidimensionality of fatigue and to investigate its relationship with attentional functions in MS patients. Moreover, the superordinate purpose of this work was to demonstrate a clear distinction between physical and mental fatigue, whose nature is still unclear. Differentiating between the two modalities is crucial due to their distinct expressions, interactions with various symptoms, and impact on health. Differentiating between the physical and mental aspects of fatigue in individuals with MS could offer valuable insights into the differential efficacy of treatments on specific dimensions of a patient's fatigue because managing and recovering from physical and mental fatigue may require different strategies and interventions. Distinguishing between physical and mental fatigue can help individuals enhance and promote their overall well-being.

In order to achieve these goals, three studies were run: the first study, discussed in Chapter 6, aimed at discriminating between physical and mental fatigue; the second study, discussed in Chapter 7, aimed at assessing whether and, if so, to what extent physical and mental fatigue fluctuate within a short time frame (from morning to evening during 4 days); and the third study, discussed in Chapter 8, aimed at evaluating the impact of experimentally induced physical and mental fatigue on the attentional functions of alerting, orienting, and conflict resolution.

Before summarizing and discussing the main results of the studies presented in this Thesis, some important shortcomings need to be acknowledged. Initially, the studies were planned to be conducted in person using specific behavioural, physiological, and diagnostic tools, along with neuropsychological tests. However, in light of the COVID-19 pandemic, the original research endeavour has undergone a reinterpretation and alteration of its fundamental purposes, necessitating its transition to an online platform. This adaptation introduced a multitude of variables that extend beyond the confines of experimental control, preventing the possibility of making conclusive inferences based on the collected data. For instance, as a result of the temporary cessation of various activities, the process of recruiting MS patients posed a significant challenge and required the exploration of alternative approaches for patient enrolment. Accordingly, not only patients who were associated with the Neurological Clinic of the University of Federico II were selected to participate in the studies, but also MS patients recruited from social virtual groups (such as Facebook), through word-of-mouth, and by utilizing a snowball sampling strategy. As a result, it was not possible to verify the accuracy of the information provided by all MS patients regarding the characteristics of their illness. This was also the case for the disability evaluation, a very important aspect to take into consideration when studying MS, conventionally assessed by means of the EDSS. The MSA was then derived from the EDSS to collect a self-reported estimate of the degree of functional deterioration. The MSA, although not providing a comprehensive assessment of the patient's disability, was meant to offer valuable insights into the patient's subjective perception of their mobility status. Furthermore, it has been impossible to ascertain whether participants, both MS patients and Controls, diligently adhered to the researcher's instructions. Finally, only RRMS patients were enrolled in the studies discussed in the present Thesis, thus limiting the possibility of generalizing the results to all types of MS. Initially, it was planned to recruit patients affected by different phenotypes of MS; however, due to the challenges encountered during the enrolment process, this goal could not be achieved.

It is worthy to underline that online experiments, however, have proven to be an effective means of reaching a large and diverse population, particularly during times of emergency such as the COVID-19 pandemic. Furthermore, in numerous instances, online experiments have demonstrated their ability to facilitate reliable data collection. For instance, the use of the specific online mode in the daily fatigue assessment experiment ensured reliable data collection by allowing verification of participants' timely responses.

Despite the above-mentioned limits, a global picture of results can be drawn. The main findings of the three studies discussed in the current Thesis are summarized as follows:

Distinction between physical and mental fatigue. One relevant finding concerns the emergence of two discernible constructs related to physical and mental fatigue (Chapter 6). To the best of our knowledge, this is the first time that a clear distinction between physical and mental fatigue has been psychometrically documented in MS patients.

Interestingly and unexpectedly, a third factor emerged from the CFA. It has been accounted for as corresponding to sleepiness as it was loaded by the items assessing physical and mental fatigue experienced shortly after awakening and during the early hours of the day; furthermore, this factor is robustly correlated with the overall sleep quality. The inherent characteristics of this third unanticipated factor necessitate further scrutiny and examination; therefore, it would be unfounded to postulate that the third factor under consideration aligns with a manifestation of fatigue. Due to this rationale, the third factor has not been incorporated in subsequent analyses.

The MtAF should be further developed to become a useful clinical tool to be used by professionals dealing with MS fatigue as well as fatigue affecting other forms of chronic and/or neurodegenerative pathologies.

Differential levels of physical and mental fatigue in MS and Control. Across experiments, patients reported experiencing more overall fatigue than Controls, regardless of whether fatigue was measured as a trait by means of the MtAF (see Chapter 6) or as a state by means of the Likert scale and the Visual analogue scale (see Chapters 7 and 8). This finding is largely in line with the extensive scientific literature (e.g., Mills and Young, 2008). The new insight emerging from the results of the studies discussed in the present Thesis consists of a trend for MS-related selective increases in physical fatigue. Indeed, across experiments and independently on whether fatigue was measured as a trait or as a state, mental fatigue was found to be equivalent in MS patients and Controls, while physical fatigue was significantly more pronounced in MS patients as compared to Controls. This finding contributes to supporting the distinct nature of physical and mental fatigue, over and above the results of the PCA.

Effects of physical and mental fatigue on attention. As for the effects of physical and mental fatigue on attentional processes in MS, the results of the study discussed in Chapter 8 are quite inconclusive. In line with the abundant experimental literature (Claros-Salinas et al., 2013), results indicated that MS patients were slower as compared to Controls in performing the ANT; however, they showed an equivalent effect to Controls. The Orienting and Alerting effects were not significant, neither in MS patients nor in Controls. Furthermore, the Executive Control effect was equivalent across fatigue-inducing conditions (neutral, mental, and motor). There are several plausible hypotheses that could account for this pattern of results. For instance, as indicated earlier in this Chapter, as the experiment was run by means of an online platform (e.g., Pavlovia), it was impossible to ascertain whether participants, both MS patients and Controls, adhered to the researcher's instructions. Furthermore, it is possible to speculate that the lack of effects of fatigue on MS participants' performance may be due to the ANT not lasting long enough (in the experiment discussed in Chapter 8, the ANT lasted approximately twenty minutes). Indeed, some studies showed that performances deteriorate significantly as the temporal extent of the cognitive task escalates (Sandry et al., 2014). Initially (before the occurrence of the COVID-19 pandemic), the intention was to assess the impact of physical and mental fatigue on attentive abilities through a cognitive test of extended duration. However, due to challenges in recruiting participants during the COVID-19 pandemic who could commit to a long-lasting remote experiment, it was determined that the experiment should be limited to a maximum duration of one hour.

With regards to the methodology implemented in the experiment, it is important to emphasize that the chosen approach was developed specifically to address the limitations observed in prior studies. In contrast to previous studies, the aforementioned experiment incorporated a clear differentiation between inductive tasks, encompassing both motor and cognitive aspects, and tasks specifically designed to evaluate cognitive performance. Additionally, two distinct fatigue assessment tools were utilized, one for evaluating state fatigue and the other for assessing trait fatigue, to better characterize the experience of fatigue. Furthermore, across experiments, a consistent focus has been placed on the investigation of sleep quality, self-efficacy, and mood disturbances, as they play a pivotal role in the comprehensive understanding of the intricate nature of fatigue.

Physical and mental fatigue within a short and long-time frame. Although perceiving different levels of fatigue, both MS patients and Controls reported having experienced more overall fatigue in the past (one year ago) than in the present (the last 24 hours; see Chapter 6). This result may indicate the existence of a covert strategy to preserve an optimistic view of present and future health. It would be extremely informative to conduct a longitudinal study aimed at monitoring subjective perceptions of fatigue over the long term.

A gradual increase in overall fatigue from the morning to the evening was reported by MS participants, in accordance with the literature showing that fatigue rises across the day and is usually at its worst later in the day (e.g., Claros-Salinas et al., 2010; Kim et al., 2010; Powell et al., 2017). (See Chapter 7).

Determinants of mental and physical fatigue in MS. Across studies, evidence for a correlation between self-efficacy (as assessed by the PSE-MCP), general cognitive functioning (as assessed by the MoCA 5-min protocol), functional deterioration (as assessed by the MSA), and physical and mental fatigue was fragmented, thus preventing a clear conclusion. However, worse sleep quality was observed in MS patients than in Controls, and significant correlations between sleep quality and physical and mental fatigue were consistent across experiments. These findings are of particular importance as they suggest that enhancing restorative sleep may help patients manage fatigue.

Significant correlations between the findings of BDI scores and physical and mental fatigue were consistent across experiments in line with the literature (Penner et al., 2009; 2008), suggesting that despite depression and fatigue being different constructs, they might share similar pathophysiological processes and neurological correlates (Gobbi et al., 2014) and should be considered in all research endeavours.

In conclusion, despite its not negligible limitations, the research line discussed in the present Thesis provides insight on MS fatigue and may be considered a baseline from which to start and develop future investigations based on common and shared protocols that consider the clear distinction between physical and mental fatigue.

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APPENDICES

Author	Sample	Sample Size	Age Mean (SD/range)	Education Mean (SD/range) or %	MS phenotype	Disability status Mean (SD/range)	Disease Duration Mean (SD/range)	MS Related Medications	Inclusion Criteria	Exclusion Criteria	Control group	Sample Size	Age Mean (SD/range)	Education Mean (SD/range) or %	Depression	Baseline NT
Claros-Salinas et al., 2010	MS	20	39.70 (9.40)	NP	NP	NP.	8.19 (7.15)	NP	NV NH	NP	HC STROKE	76 (HC) 22 (STROKE)	HC 37.20 (11.70) STROKE 45.70 (8.30)	NP	NP	NP
Andreasen et al., 2010	MS	60	PF 43.0 (27–53) SF 39.0 (24–52) NF 39.0 (23–53)	PF 13 (9-16) SF 13 (10-16) NF 15 (9-16)	RR (NP)	EDSS <3.5	PF 5.0 (1-14) SF 3.5 (0-16) NF 3.0 (0-9)	IMM.MOD	RR EDSS<3.5 RHNF	MMI DEM ATTACK 4 WEEK CHANGE TREAT D/A/ PRE	HC	18	40 (23-54)	15 (11-16)	MDI	NP
Bryant et al., 2004	MS	56 (28) (Chiaravalloti et al., 2002) (26) De Luca et al., 1994)	45.19 (1.50) (Chiaravalloti et al.,2002) 38.00 (2.50) (De Luca et al., 1994)	15.22 (14.90) (Chiaravalloti et al., 2002) 14.60 (0.48) (De Luca et al., 1994)	NP (Poser et al.,1983)	AI 1.85 (0.45) (Chiaravalloti et al., 2002) EDSS 1.8 (0.30) (De Luca et al., 1994)	10.65 (1.78) (Chiaravalloti et al., 2002) 5.78 (1.57) (De Luca et al., 1994)	NP.	NP.	ND PD LD D/A	HC	39 13 (Chiaravalloti et al., 2002) 26 (De Luca et al., 1994)	41.18 (2.17) (Chiaravalloti et al., 2002) 35.00 (2.0) (De Luca et al., 1994)	14.90 (0.51) (Chiaravalloti et al., 2002) 15.80 (0.29) (De Luca et al., 1994)	BDI	WAIS-R Digit Span (digit span) SRT (verbal learning) WMS (Logical Memory) BOSTON NAMING TEST (object naming impairment) COWAT (verbal fluency) STROOP (selective attention) TMT(visuomotor) WCST (problem solving)
Holtzer et al., 2009	MS	20	40.55 (8.60)	15.85 (2.30)	RR (Mc Donald et al., 2001)	ISS 7.20 (4.8)	NP.	NP	NV NH	HT MMI DEP STEROID CHOLINESTERASE	HC	20	39.90 (9.10)	16.25 (1.70)	BDI-II	WASI verbal IQ WASI performance IQ
De Luca et al., 2008	MS	15	40.80 (7.40)	15.60 (1.90)	RR PP (Poser et al., 1983)	NP.	6.4 (4.9)	NP	ATTACK FREE 30 days CORTICOSTEROID FREE	D/A PRE ND PD CORTICOSTEROID ATTACK 4 WEEKS	HC	15	35.40 (10.1)	15.80 (2.30)	NP	SDMT (processing speed) TMT A and B (processing speed) PASAT (processing speed) WRAT-3 (General Intelligence) WAIS-III (Working memory) HVLT (verbal memory)
Krupp & Elkins et al., 2000	MS	45	45.00 (6.80)	14.80 (2.60)	RR PP SP (Poser et al.,1983)	EDSS 3.80 (1.70)	NP.	IMM.MOD. ANTDEP ANTISPASTICITY ANTICHOLINERGIC	NP.	ANTDEP-DMT- ANTISPASTICITY/ANTICHOLINERGIC (NOT CONSTANT DOSAGE 1 MONTH BEFORE THE EVALUATION) BENZ D/A DEP PD, MMI HI	HC	14	41.80 (6.60)	15.10 (1.90)	CES-D PANAS	BRB: SRT (verbal memory) SPART (visuospatial memory) COWA (verbal fluency) TOH (conceptual planning) DIGIT SPAN (attention) COWA (verbal fluency)
Schwid et al., 2003	MS	20	49.8 (range 30-61)	M75% H 85%	RR SP PP (Poser et al., 1983)	EDSS 3.80 (1.50) MMSE 29.60 (0.70) MSFC -1.10 (0.5)	NP	NO RESTRICTION IN MEDICATION	NP	ATTACK 3 MONTHS STABLE	HC	21	47.2 (10.7)	M 52% H 81%I	CMDI-Mood	NP
Neumann et al., 2014	MS	30	44.70 (7.10)	NP.	RR SP PP (McDonald et al., 2001)	EDSS 3.80 (1.20)	9.0 (6.7)	NP	MS (McDonald criteria, 2001) FSMC≥22	ND PD ESS≥10 BDI ≥20	HC	15	43.6 (11.0)	NP	BDI-II	NP
Paul et al., 1998	MS	39	45.5 (6.7)	14.9 (2.5)	NP (Poser et al., 1983)	AI 4.10 (2.50)	12.2 (4.8)	NP	MS (Poser et al., 1983)	ND PD D/A HI MMI VI	HC	19	42.4 (16.6)	15.1 (2.1)	MDI	NP
Lehmann et al., 2012	MS	42	MS F 47.7 (7.6) MS NOT F 45.3 (8.6)	MS F 11.0 (1.6) MS NOT F 11.2 (1.5)	RR (McDonald et al., 2001)	EDSS MS F 2.83 (1.39) EDSS MS NOT F 4.30 (2.68)	NP	IMM.MOD.	RRMS (McDonald criteria,2001)	CORTICOSTEROIDS FOUR WEEK MODAFINIL ATTACK 4 WEEK	HC	11	42.7 (9.6)	11.5 (1.7)	BDI	Mehrfachwahl–Wortschatz Intelligenztest (lexical decision task)
Bailey et al., 2007	MS	14	58.29 (12.64)	12.86 (3.48)	CP (McDonald et al., 2001)	EDSS 7.68 (0.37)	27.21 (range 8-59)	NP	MS (Mc Donald criteria,2001)	D/A PD ND ANX DEP LD DYSLEXIA VI	HC	17	60.18 (16.08)	13.00 (3.04)	HADS	Spot the Word test (verbal intelligence)
Gossman et al., 2014	MS	31	42.5 (11.4)	NP	RR (Mc Donald et al., 2001)	EDSS 3.6 (2.1)	10.39 (9.18)	NP	NP	PD MMI CORTICOSTEROID SIX WEEK ATTACK SIX WEEK	HC	10	42.8 (10.6)	NP	BDI BDI psy BDI som	NP
Spiteri et al., 2019	MS	40	46.75 (7.53)	11.5 (1.7)	RR PP SP (NP)	EDSS 3.5 (1.5)	14.1 (8.8)	NP	NV (>4)	PD ND	HC	22	41.73 (12.52)	12.1 (1.4)	BDI	NP
Fiene et al., 2018	MS	15	43.20 (14.97)	NP	RR SP (McDonald et al., 2001)	EDSS 3.54 (1.94)	9.63 (8.57)	IMM.MOD.	WEIMuS≥ 9 (cognitve subscale) ATTACK 3 MONTHS BDI ≤ 19	PD ND	/	/	/	/	BDI	NP
Chinnadurai et al., 2016	MS	50	33.6 (10.6)	9.4(4.0)	RR SP PP (Polman et al., 2011)	EDSS 4.6 (81.9)	6.0 (7.4)	NP	MS (revised Mcdonald criteria 2010)	PD D/A MMI VI V AC <20/100 HI	HC	50	33.6 (9.6)	10.6 (4.2)	CES-D	NP
Sandry et al., 2014	MS	32	48.23 (9.66)	15.77 (2.33)	RR SP PP PR (Polman et al., 2011)	AI 2.44 (2.53)	11.91 (7.05)	NP	ATTACK 30 days CORTICOSTEROID FREE	PD MMI D/A HI LD	HC	24	37.74 (11.09)	16.13(1.96)	CMDI	DST (attenzione) SDMT (processing speed) PASAT-2/3 (attention information processing speed) CVLT-II (memoria) LDFR BVMT-R (visuospatial learning) JLO (visuospatial ability)
Aldughmi et al., 2017	MS	52	46.8 (10.1)	NP	RR SP (NP)	MMSE 28.7 (1.6) FSQ 79.7 (13.9)	12.5 (7.6)	NP	MMSE≥24 18>AGE> 60 RR SP AMB	D/A ND LD UNTREAT SLEEP DIS VI MMI ATTACK within 4 weeks CORTICOSTEROID	/	/	/	/	BDI	NP
Bruce et al., 2010	MS	87	47.05 (9.05)	14.25 (2.00)	RR SP (McDonald et al., 2001)	EDSS 4.5 (1.57)	10.86 (7.98)	NP	AGE<61 IMM. MOD	ND D/A ATTACK 4WEEKS : MOTOR IMPAIRMENT VI LD CARB <90% accuracy	HC	24	47.38 (12.00)	15.08 (2.24)	CMDI	NP
Greim et al., 2007	MS	79	36.70 (8.60)	NP	RR (NP)	EDSS 2.51 (1.89)	6.70 (4.30)	NP	4.5≤MRC≤ 5 forearm hand muscles	NOT STABLE	HC	51	35.2 (12.6)	NP	BDI	NP
Berard et al., 2018	MS	32	40.09 (9.21)	14.86 (1.92)	RR (NP)	EDSS 1.83 (1.18)	4.35 (3.09)	NP	NP	ATTACK 28 DAYS ND PD	HC	32	42.22 (11. 63)	15.42 (2.00)	NP	NAART NB
Walker et al., 2012	MS	70	40.37 (8.80)	14.81 (1.98)	RR (McDonald criteria et al., 2001)	EDSS 1.83 (1.18)	4.35 (3.09)	IMM.MOD.	RRMS (McDOnald riteria, 2001)	PD ND	HC	72	40.69 (11.83)	15.10 (1.93)	BDI-FS	NAART NB
Beatty et al., 2003	MS	17	48. 5 (5.4)	16.2 (2.2)	RR SP	EDSS 2.9 (2.3)	14.2 (7.4)	IMM.MOD	MS (McDonald et al., 2001; Poser et al., 1983)	HI CI D/A LD MMI PD ATTACK 30days	HC	12	46.4 (14.0)	16.7 (2.0)	CMDI	NB Least Recall LNST SDMT PASAT
Kos et al. 2004	MS	50				EDSS 6.4 (1.2)			FSMC ≥ 22	np	HC	21	/	/	/	PASAT,2 PASAT3
Claros Salinas , 2013	MS	32	46.8 (8.6)		RR PP SP	3.6 (1.6)	7.7 (5.4)	Betaferon Rebif Avonex Copaxone Cortison pulses Tysabri Mitoxantrone Imurek	MS (McDonald et al., 2001) FSMC score ≥ 22 on the FSMC	ND PD BDI>29	HC	20	39.1 (10.9)	NP	/	NP
Hanken et al., 2016	MS	46	27.13 (7.71)		RR PP SP	LF: 3.7 (1.8) HF: 4.7 (1.1)	LF: 13.5 (8.8) HF: 10.9 (7.8)	NP	NP	ND PRE HI	HC	52	RF 27.13 (7.71) RP 26.19 (16.42) PL 23.75 (2.70)		BDI	

Author	Methods to investigate objective fatigue	Fatigue examined	Operazionalized fatigue	Subjective scale of fatigue	Objective measure of fatigue (mental/ cognitive/ physical motor)	Inducing task (cognitve/motor)	Task to evaluate cognitive performance	Parameter	Relationship between subjective fatigue (state/trait) and objective performances (Yes/No)	Objective Fatigue (Yes/No)	Depression	Depression as covariate	Impact of fatigue on cognitve functions (YES/NO)	Function
Claros-Salinas et al., 2010	Cognitive fatigue over an extended period of time	Subjective cognitive fatigue Objetive cognitve fatigue	NP	VAS	Performances at three different time points of the day in three TAP subtests		GO/NoGo (selective attention) TAP-M(divided attention REACTION TIME TASK(tonic alertness)	RT Accuracy	NP	YES (cognitive performances decreased over time)	NP	NO	YES	Attention and Alertness
Andreasen et al., 2010	Cognitive fatigue over an extended period of time	Subjective cognitive fatigue Objective cognitive fatigue (cognitive fatigability)	Cognitive fatigue processing speed performances at baseline (DSC-I) Cognitive fatigability processing speed performances across two test blocking	FSS	Performances across two test blocking of DSCII-DSC		WAIS- III WMS-III **DSC-I** (processing speed)(baseline cognitive fatigue) **DSC II-I** (processing speed)(cognitive fatigability) COPY (grapho-motor speed) LM I (memory) LM II (memory) M R (perceptual organization) V (Verbal IQ) 9-HPT (motor speed)	Processing Speed	YES (subjective trait-fatigue and cognitive performances)	NO (cognitive performances in processing speed improved in second test blocking	No participant fulfilled diagnostic criteria for depression MDI-FSS significant correlation(r = 0.40; P = 0.01)	NO	YES	Processing Speed:
Bryant et al., 2004	Cognitive fatigue during sustained mental effort	Subjectve fatigue Objective cognitive fatigue	Cognitive fatigue failure to maintain performance level over the course of a sustained working memory task	NP (Chiaravalloti et al., 2002) FAI (trait-fatigue) (DeLuca et al., 1994)	Performances in first versus second half of each of four continuous testing blocks of PASAT		PASAT(attention, information processing speed)	Percent dyad score CR	NO (subjective trait-fatigue and cognitive performance)	YES .(across the four trials percent dyads declined earlier in time; percent dyads analysis)	BDI MS>HC (p<0.001) MS (CP/CI) BDI-PASAT (number correct) not significant correlation MS (CP/CI) BDI-PASAT (percent dyads correct) not significant correlation	NO	YES	Working memrry
Holtzer et al., 2009	Cognitive fatigue over an extended time	Subjective fatigue	Cognitive fatigue as strong performance decrements in cognitive demanding tasks over time,	FSS	Increase in cerebral activity across time based on objective performance.		DIR (primary visual task) DIGIT SPAN TASK (secondary verbal interference task)	RT Accuracy	YES (subjective trait faigue and performances in the condition where executive demands are maximized)	YES (performance was slower and less accurate (DIR) and increased executive demands across the three task conditions.)	BDI-II MS>HC (p<0.05) BDI-FSS significant correlation BDI-II-DIR (alone condition) significant correlation (RT= =.669 p< 0.05)	NO	YES	Executive Functions
De Luca et al., 2008	Cognitive fatigue over an extended period of time	Objective cogniitive fatigue (within-run across-run)	Cognitive fatigue decreased performance during acute but sustained mental effort Cognitive fatigue increase in cerebral activity across time	NP	Performance across four blocks of modified SDMT (fatigue across-run) Performance in second compared to first half in each of four blocks of modified SDMT (fatiigue within each run) Cerebral activity during mSDMT across time		SDMT (processing speed)	RT, Accuracy BOLD response	NP	NO	NP	NO	NO	Processing speed
Krupp & Elkins et al., 2000	Cognitive fatigue after challenging mental or physical exertion	Subjective physical and mental fatigue Objective cognitive fatigue	Cognitive fatigue decline in cognitive performance over a single testing session	FSS VAS	Performance in NB before and after cognitive demanding task	ALFA-ARITHMETIC (A-A) Test CONTINUOUS COGNITIVE TASK (RT)	BRB: SRT (verbal memory) SPART (visuospatial memory) COWAT (verbal fluency) TOH (conceptual planning) DIGIT SPAN (attention)	NTP	NO (subjective fatigue and cognitive performance)	YES (performances worsened following cognitive task)	CES-D MS> HC (p=0.006)	NO	YES	Verbal memory visual memory and conceptual planning:
Schwid et al., 2003	Cognitive fatigue during sustained mental effort	Subjective physical and cognitive fatigue Objective cognitive fatigue	Cognitive fatigue decline in cognitive performance during a test requiring sustained attention	RFD FSS MFIS MFIS-C	Per cent decline in performance using the ratio of the number of correct responses for the first 20 items of the PASAT (of 60 items total) to the last 20 items, or the first five trials (of 15 trials total) to the last five trials for the DOT (1st method) The slope of the linear regression of the number of correct responses per each 10 items of the PASAT versus the number of the decile, or the number correct per trial for the DOT versus the number of the trial (2nd method).		PASAT (attention, information processing speed) DOT (working /attention)	Accuracy	YES (moderate association between subjective trait-fatigue (FSS) and fatigability)	YES (performances decline over time ;PASAT)	CMDI :Partecipant not fulfilled diagnostic criteria for depression (CMDI-Mood)-PASAT (2 method) not associated (r=0.20 p=0.39)	NO	YES	Information processing speed
Neumann et al., 2014	Cognitive fatigue after challenging mental or physical exertion	Subjective motor and cognitive fatigue Objective cognitive fatigue	NP	FSMC	Performance in TAP alertness test before and after cognitive load and after a one hour resting time.	NB (attention, word recognition, verbal fluency, memory,calculation, visuospatial, reasoning abilities)	TAP (alertness test)	RT	YES (subjective trait-fatigue and cognitive performance)	Yes (increased RT after cognitive load)	BDI minimal Depression Severiity	NO	YES	Alertness
Paul et al., 1998	Cognitive fatigue after challenging mental or physical exertion	Subjective motor and cognitive fatigue Objective motor and cognitive fatigue	NP	PHYSICAL FATIGUE SCALE COGNITIVE FATIGUE SCALE	Performance in WORD LIST LEARNING and GORDON DISTRACTIBILITY TASK , GRIP STRENGHT and after a cognitive work battery lasted 30 min.	Cognitive work battery LETTER and CATEGORY FLUENCY TEST FAMOUS FACES TESTS WAIS-R VOCABULARY Wais-R Comprehension Tests (from the Wechsler Adult Intelligence Test-Revised (Wechsler, 1981)	GRIP STRENGHT (force) WORD LIST LEARNING((memory) GORDON DISTRACTIBILITY TASK (vigilance)	Accuracy Percent change (force exerted)	NP	NO (no changes in cognitive performance after 30 min task)	MS≈HC (P>0.05)	NO	NO	Memory Vigilance Force
Lehmann et al., 2012	Cognitive fatigue during sustained mental effort	Subjective fatigue Objective cognitive fatigue (fatigability)	NP	FSMC VAS	Performance decline from first to second half of a 10 min 2-back task		N-BACK (2-back task ;working memory)	RT Accuracy (HITS)	YES (state fatigue and working memory)	NO (no fatigability during task esecution)	BDI MS sleep problem >MS no sleep problem (p< 0.05).	NO BDI COV for the analyses on fatigability MS patients with fatigue still performed worse than healthy subject	NO	Working memory
Bailey et al., 2007	Cognitive fatigue over an extended period of time	Subjective cognitive fatigue Objective cognitive fatigue	Cognitive fatigue decline in performance over time	FSS FRS	Performance decline over time across the first, second, third pairs of blocks in the N-back test.		N-back 0-back (attention) 1-back (working memory)	RT Accuracy	NO (subjective fatigue and fatigability)	YES (accuracy decreased overtime; 0--back accuracy decrease on the second than the first presentation; N-back)	HADS MS>HC (t= 2.55, p<0.016) HADS- FRS (overtime) not a significant correlation HADS- N-BACK (0-BACK/1-BACK)not a significant correlation	NO	YES (moderately	Working memory
Gossman et al., 2014	Cognitive fatigue during sustained mental effort	Subjective fatiigue Objective cognitive fatigue	NP	FSMC VAS	Performances of the first and second 15 minutes period in the TAP		TAP (vigilance)	Accuracy	YES (subjective state-fatigue and fatigability)	YES (decrease in accuracy in the TAP)	BDI MS> HC (p=0.004).	NO BDI COV To control for a potential effect of depressive symptoms on fatigue. Fatigue correlated with the number of omissions made in the second half of the vigilance test, even when controlling for depression	YES	Vigilance
Spiteri et al., 2017	Cognitive fatigue after challenging mental or physical exertion	Subjective cognitive fatigue Objective cognitive fatigue (fatigability)	Effort-independent fatigue (traitfatigue Effort-dependent fatigue (state fatigue)	FSMC VAS	Performance in ALERTNESS TEST before and after a cognitive demanding task	N-BACK	ALERTNESS TEST (from the Test-battery of Attentional Performance (visual reaction task)	RT	NO (subjective trait as well as state-fatigue and cognitive performance)	YES (RTs increased after n-back task)	BDI- FSMC significant correlation (r = 0.57, p <0.000).	NO	YES	Alertness
Fiene et al., 2018	Cognitive fatigue over an extended period of time	Subjective fatigue Objective cognitive fatigue	Cognitive fatigue as subjective exhaustion and fatigue-related objective alertness decrements with time-on-task.	WEIMUS NUMERICAL RATING SCALE	Performance across three blocks of SRT and auditory oddball paradigm		SRT and P300 (auditory oddball paradigm)	RT P300 amplitude and latency	YES (subjective state-fatigue and fatigability)	YES (RT increased; lower amplitudes and prolonged latencies of the P300)	BDI Minimal Depression Severity	NO	YES	Processing speed
Chinnadurai et al., 2016	Cognitive fatigue during sustained mental effort	Objective cognitive fatigue	NP	/	Performance in 60 and 180 sec version of STROOP TASK, SDMT, serial addition task and ratio between first and last 50 items in P300 oddball paradigm task		STROOP (modified version) (sustained attention and informationprocessing speed) mSDMT (modified version) (concentration and sustained attention)SDMCAT test (to increase cognitive load) SAT (attention, calculation information processing speed) 30SAT (to measure effect of increasing cognitive load) Additionallly P300 (esame potenziali evocati) latency/amplitude	CR P300 amplitude and latency	NP	YES (performance decline in cognitive tests and more prolongedlatency in P300)	CES-D MS>HC (p<0.0001)	NO	YES	Attention , information processing sped
Sandry et al., 2014	Cognitive fatigue over an extended period of time	Subjective cognitive fatigue Objective fatigue (fatigability)	NP	FSS MFIS VAS	Performance across four testing blocks of mSDMT and N-back		mSDMT (processing speed) (high cognitive load/low cogitive load) N-BACK (2-back, 0-back) (working memory)(high cognitive load/low cogitive load)	RT Accuracy	NO (subjective state-fatigue and cognitive performance)	NO (RT improved across blocks, no changes in accuracy)	CMDI MS> HC (p<0.05)	NO	NO	Processing Speed Working memory task
Aldughmi et al., 2017	Fatigability during sustained mental effort	Subjective physical and cognitive fatigue Objective cognitive fatigue (fatigability)	Performance fatigability is defined as a measure of change in the performance of a physical or a cognitive task over time	NFI-MS VAS	- Performance throughout the test (CPT test) -percent change in meters walked between the first and sixth minute (6-MWT) -percent change in force exerted between the first and the last trial (GRIP STRENGHT TEST)		6-Minute Walk Test (6MWT) GRIP STRENGHT TEST (physical fatigability) CPT (sustained attention)	Response speed variability score (CTP) Percent change in meters walked (6-Minute Walk test) Percent change (force exerted)	YES (subjective fatigue attentional task) NO (subjective fatigue and physical task)	YES	MS BDI minimal to mild depression BDI-NFI/MS significant association (physical: r = 0.426, P = .002; cognitive: r = 0.458, P = .001) BDI-NFI/MS summary scale score significant association (r= 0.470, P ≤ .001).	YES BDI COV After controlling for depression, significant association between physical quality of life and overall perceived fatigue physical remained unchanged. Quality of lifea significant predictor, explaining 34.3% of the variance in the NFI-MS summary scale score.	YES	Attention
Bruce et al., 2010	Cognitive fatigue over an extended period of time	Subjective fatigue Objective fatigue	NP	FIS	Performance across three blocks of CARB		CARB (RT, RT variability (RTV:executive function) SHIPLEY INSTITUTE OF LIVING SCALE (intellectual functioning) The VISUAL ELEVATOR TEST (information processing speed and mental flexibility) SDMT (attention, processing speed) SRT (learning and memory)	RT, RT variability	YES (subjective trait-fatigue and cognitive performance)	NO (shorter RT and smaller variability over time)	CMDI MS> HC CMDI-FIS (social) significant correlation (r=.42, p< .001) CMDI-FIS significant correlation (r=.26, p< .05)	NO	YES	Executive function
Greim et al., 2007	Cognitive fatigue over an extended period of time performance during a fatiguing task	Subjective mental and physical fatigue Objective mental and physical fatigue	NP	LIKERT MFIS	Performance decrement in muscle strenght (fist-tightening strength 10th trial 10th trial reduction in % of the initial value and levels of VIGILANCE TEST		VIGILANCE TEST (Objective Mental fatigue) (sustained and focus attention) VIGORIMETER TEST (Objective Physical fatigue)	Omission, RT Percent change(in fist tightening strength)	YES (reversed relationship between subjective fatigue and objective performance decline	YES (lower levels of performance regarding omission mistakes and reaction time in the VIGILANCE TEST the fist-tightening strength significantly decreased from the 1st trial to the 10th ; VIGORIMETER TEST)	MS BDI- MFIS (total score) significant correlation (r=0.51; p< 0.01 MFIS MSDEP> MS NOT DEP (depressed MS patients:M=49.8; SD=13.1, not depressed MS patients: M=32.6, SD=16.8; P=0.003)	NO	YES	Attention Strenght
Berard et al., 2018	Cognitive fatigue during sustained mental effort	Subjective cognitive fatigue Objective cognitive fatigue	Cognitve fatigue decreased performance as a result of sustained cognitive effort	FSS MFIS	Performance in first third versus last third of PASAT		PASAT-3" PASAT-2 (information-processing speed and working memory, sustained attention)	Total number of CR Total dyad score Percent dyad score	No (subjective trait-fatigue and fatigability)	YES (performance decline using the percent dyad scoring method)	NP	NO	YES	Attention
Walker et al., 2012	Cognitive fatigue during sustained mental effort	Subjective cognitive fatigue Objective cognitive fatigue	Cognitive fatigue decreased performance with sustained cognitive effort	FIS FSS	Performance during first compared to second half in PASAT and CTIP		PASAT (information processing speed working memory CTIP (information processing speed)	RT CR Total correct Total dyad Percent dyad	YES (correlation PASAT negative correlation between subjective trait-fatigue and fatigability	YES (performance decline overtime using the percent dyad scoring method)	BDI-FS minimal severity	YES BDI-FS COV. given that cognitive performance can also be impacted by mood, depression (BDI-FS) was also covaried Significant interaction for PASAT and CTIP.	YES	Working Memory
Beatty et al., 2003	Cognitive fatigue over an extended period of time	Subjective fatigue Objective cognitive fatigue	Physical fatigue reduction in force, rate or persistence of motor responses over time or following exposure to some event	FSS	Performance in NB and 25ft walk before and after workday		25-ft. timed walk Battery of cognitive tests LEAST RECALL (verbal memory) LNST (short term memory) SDMT (processing speed) , PASAT (information processing speed attention)	Time to Walk 25-ft CR	NO (subjective state-fatigue and objective fatigue)	NO (no performance decline from first to second testing block)	MS= HC not significant differences CMDI- FSS significant correlation (p<.05; p<0.001) CMDI (mood)- PASAT/ LIST RECALL significant correlation (-0.02; -0.23) CMDI (evaluative)PASAT/L NST significant correlation (-0.20; -0.38) CMDI (vegetative)- LNST/PASAT significant correlation (-0.13; -.36)	NO	NO YES (walked more slowly)	Processing Speed Attention Memory
Kos et al., 2004	Cognitive fatigue during sustained mental effort	Subjective fatigue Objective cognitive fatigue	NP	FSS MFIS	Performance in the first ten items compared to the last ten items in PASAT		PASAT-3" PASAT-2 (information-processing speed and working memory , sustained attention)	CR	No (subjective trait-fatigue and fatigability)	YES (performance decline in the PASAT test)	NP	NO	YES	Information-processing speed Working memory Sustained attention
Claros Salinas et al., 2013	Cognitive fatigue after challenging mental or physical exertion	Subjective trait and state fatigue Objective fatigue	Cognitive fatigue decline of cognitive performance over a single testing session. In	FSMC RATING SCALE	Performance in TAP subtests before and after physical and cognitive load (NB) for 2.5 hours	NB (attention, word recognition, verbal fluency, memory,calculation, visuospatial, reasoning abilities) ERGO FIT 3000 treadmill	Three subtests TAP-M/version mobility (alertness, selective attention, divided attention)	RT	YES (subjective trait as well as state-fatigue and fatigability)	YES (RT increased after cognitive load)	BDI-II minimal severity	NO	YES	Alertness Attention
Hanken et al., 2016	Cognitive fatigue during sustained mental effort	Subjective trait and state fatigue Objective fatigue	NP	FSMC FSS VAS	Performance in first 5 min compared to last 5 min of a 20 min VISUAL VIGILANCE TASK		VISUAL VIGILANCE TASK	RT Accuracy	NP	YES (RT increased with time-on-task)	BDI- VIGILANCE TASK not significant correlation	NO	YES	Vigilance

Author	Sample	Sample Size	Age (SD /range)	Education Mean (SD/range) or %	MS phenotype	Disability status (SD/range)	Disease Duration (SD/range)	MS Related Medications	Inclusion Criteria	Exclusion Criteria	Control group	Sample Size	Age Mean (SD/range)	Education Mean (SD/range) or %	Depression scale	Baseline NT	Fatigue Investigated	Operazionalized fatigue	Subjective fatigue scale	Task to evaluate cognitive performance	Depression	Depression (COV /CONF)	Impact of fatigue cognitve functions
Denney et al., 2004	MS	71 RR 39 PP 32	RR 44.0 (9 .7) PP 49.9 (8.1)	PP 3.8 (1.0) RR 3.3 (1.3)	RR, PP (McDonald et al., 2001)	EDSS 4.3 (NP)	8.7 (NP)	NP	NP	D/A MR HI, ND	HC	40	44.9 (8.8)	4.1 (1.3)	CES-D	NP	UNSPECIFIED	NP	FSS	TOL (executive function) PALT (verbal learning and memory) STROOP (information processing speed) WSCT(executive functions)	CES-D MS >HC (F=12.2, df=2, 107, p<.001);	YES CES-D COV (Differences between MS and HC occurred on several measures. When differences with respect to fatigue and depressionwere statistically controlled, the only differences that remained significant involved measures relating to the speed of information processing)	YES Information processing speed
Diamond et al., 2008	MS	48 MS DEP 21 MS NOT DEP 26	MS DEP 49.1 (3.63) MS NOT DEP 47.6 (5.21)	MS DEP 15.8 (2.34) MS NOT DEP 16.4 (2.98)	RR, SP, PP, PR (Poser et al., 1988)	EDSS MS DEP 4.90 (1.10) EDSS MS NOT DEP4.80 (1.27)	MS DEP 14.70 (5.0) MS NOT DEP 17.80 (9.78)	IMM. MOD FATIGUE TREAT	DD > 2 years 1.5 <EDSS > 6.0	DEP ADHD D/A, ATTACK 30 days	HC	30	44.9 (NP)	15.9 (NP)	CES-D	NP	UNSPECIFIED	NP	MFIS	CVLT (memory, verbal fluency) DIGIT SPAN (memory) COWAT (verbal fluency) ROCFT (visual-perceptual.motor skills) VTSAT (processing speed working memory attention)	CES-D- VTSAT significant correlation (r= .396, p = .001)	YES	YES Processing Speed
Di Giuseppe et al., 2018	MS	107	35.8 (9.5)	13.7 (2.3)	RR (Polman et al.,2011)	EDSS median 1.75 (range 0.0-5.0)	NP	IMM.MOD	NP	PD ND	/	/	/	/	HADS		UNSPECIFIED	NP	FSS	JLO (visuospatial perception) COWAT (verbal fluency) CVLT (Verbal memory) BVMT-R (visuospatial memory) PASAT (working memory) SDMT (processing speed) DKEFS (executive function)	high HADS-scores - SDMT PASAT significant correlation (r = −0.397 P < .001; r = −0.254, P = .009).	NP	YES Processing speed
Golan et al. 2016	MS	699	46.1 (10.5)	14.5 (2.7)	RR, SP, PP (NP)	EDSS 2.70 (2.0)	7.3 (6.4)	IMM. MOD	BENZ FREE ANALG FREE CORTICOSTEROID FREE	NP	/	/	/	/	BDI	NP	COGNIITIVE FATIGUE	Cognitive fatigue: the subjective feeling of difficulty concentrating and thinking clearly.	M-FIS	CCTB (CogD): memory (verbal and nonverbal) executive function visual-spatial processing, verbal function, attention, information processing speed, motor skills. Go-No-Go (vigilance and alertness)	BDIM-FIS moderately associated(r = 0.66, p < 0.0001). BDI -CCTB- MFIS weakly correlated (p ⩽ 0.01; p ⩽ 0.001.)	YES BDI EDSS, CONF (No residual correlation between subjective cognitive fatigue and objective cognitive function)	NO
Morrow et al., 2009	MS	CROSS-SECTIONAL ANALYSIS 465 LONGITUDINAL STUDY 65	CROSS SECTIONAL ANALYSIS 45.80 (9.10) LONGITUDINAL STUDY 46.40 (47.0 8.80)	CROSS-SECTIONAL ANALYSIS 14.20 (2.30) LONGITUDINAL STUDY 14.0 (14.0 2.20)	SP, PP, RR (Polman et al., 2005)	CROSS-SECTIONAL ANALYSIS EDSS 3.0 (1.0 - 8.0) LONGITUDINAL STUDY EDSS 3.0 (1.0–6.5)	CROSS-SECTIONAL ANALYSIS 10.4 (8.0, 8.3) LONGITUDINAL STUDY 11.7 (9.0, 8.8)	IMM. MOD	NP	NP	HC	70	46.5 (9.1)	14.4 (2.0)	BDIFS	NP	COGNITIVE FATIGUE	Cognitive fatigue: the subjective feeling of difficulty in concentrating and thinking clearly	FSS	MACFIMS DKEFS (executive functions) SDMT (processing speed) PASAT (processing speed/ working memory) CVLT2 (auditory verbal episodic memory) BVMTR(visual spatial memory) COWAT (verbal fluency) JLO (visual spatial perception)	BDIFS- FSS (r = 0.44, P < 0.001) significant correlation (cross-sectional analyses) BDIFS- FSS (CHANGE) significant correlation (r = 0.34, P = 0.001 (longitudinal analyses)	NO	NO
Weinges Evers e al., 2010	MS	109 MS F 53 MS NOT F 56	MS F 41.0 (8.0) MS NOT F37.0 (9.0)	MS F 14.7 (2.6) MS NOT F 15.80 (3)	RR	EDSS 1.5 (0–5.5)	5.87 (4.80)	NP	ATTACK FREE CORTICOSTEROID FREE	NP	/	/	/	/	BDI	NP	UNSPECIFIED	NP	FSS	TAP (attention alertness working memory) BRB-N: SRT (short-term and long term verbal memory) SPART (short-term and long-term visuospatial memory) SDMT (attention, information-processing speed and working memory) PASAT (sustained and complex attention, information-processing speed and working memory) WLG (semantic verbal fluency) FST (motor and visual function)	BDI. MSF > MS NF (p<0.001) BDI-FSS signiifcant correlation (r= 0.49 p= < 0.001)	NO BDI COV (The correlation between alertness and FSS was independent of education, BDI and EDSS)	YES Alertness
Simioni et al., 2007	MS	106	34.1 (9.3)	L 13.2 % M 62.3% H 24.5 %	EARLY RR, CIS (Mc Donald et al., 2001)	EDSS 1.8 (0.4)	2.60 (1.80)	IMM.MOD ANTIDEP	ATTACK FREE NO CORTICOSTEROID 0<EDSS>2.5 3 months > DD > 5 years	MS DIAGNOSIS NOT CONFIRMED	/	/	/	/	HAD-D QSP	NP	UNSPECIFIED	NP	FAI	RAVLT(long- term memory) BADS (executive functions) TMT (attention and processing speed)	HAD-D MS CD > MS WCD (HAD-D 37% vs 11%, p = 0.004) (FAI 70% vs 46%, p = 0.03). HAD-D- FAI - significantl associated (p = 0.02)	YES Impaired cognition was associated with anxiety (p = 0.05), depression (p = 0.004), fatigue (p = 0.03), handicap (p <0.001) and a lower QoL (p <0.001). After adjustment for QoL, handicap, depression, anxiety and fatigue were no longer associated with the presence of cognitive deficits.	YES Memory Executive functions Attention
Jougleux-Vie et al., 2014	MS	50	NP	12 (2.0)	RR, PP, SP (Mc Donald et al., 2005)	EDSS 3.0 (2.0- 5.0)	13.0 (8.0)	IMM.MOD ANTDEP HYPNOTIC ANTIEPILETIC	NP	PD ND D/A, CORTICOSTEROID FREE	/	/	/	/	BDI II		UNSPECIFIED	Fatigue as a chronic fatigue that has occurred during at least six months and for more than half of that time	FIS	BCcogSEP SRT (memory) 10/36 Spatial Recall Test (visual learning) SDMT (attention and inf. processing speed) PASAT (attention and inf. processing speed and working memory) WORD LIST (semantic and phonemic verbal fluency) GOnoGO (response inhibition)	BDI- FIS TOT/ COGN/PHYSI significant correlation (p<0.0001 ; p <0.0001*p=0.0006*)	YES BDI CONF (After adjusting confounding factors, neither fatigue complaint nor memory complaint was correlated with SRT performance)	NO
Mattioli et al., 2011	MS	255 MS DEP 65 MS NOT DEP 190	40.0 (11.3) MS DEP 43.45 (12.15) MS NOT DEP 39.96 (10.88)	MS DEP L 56% M 34% H 10% MS NOT DEP L 44% M 39% H 17%	NP	EDSS MS DEP 3.35 (2.33) EDSS MS NOT DEP 2.37 (1.193)	MS DEP 9.45 (5.98) MS NOT DEP 8.52 (6.27)	IMM.MOD.	CORTICOSTEROID FREE	NP	HC	166	41.5 (11.3)	L 28% M 43% H 29%	BDIFS		UNSPECIFIED	NP	FIS	SRT (memory) SDMT (attention) PASAT (attention and working memory) COWA P COWA C (executive functions verbal fluency)	BDI MS> HC (p=0.002) BDI-FS- NP not a significant correlation BDI-FS-FIS significant correlation (p = 0.007) BDI IMP-BDI NOT IMP not a significant correlation	NO	YES Memory, executive function, attention
Nunnari et al., 2015	MS	60	39.35 (10.56)	13.80 (3.80)	PPMS RRMS (McDonald et al., 2001)	EDSS 2.40 (1.40)	6.3 (5.2)	IMM.MOD	NP	AGE >63 YEARS D/A CORTICOSTEROID FREE PD ND	MS				BDI-II		UNSPECIFIED	NP	FSS	BRB-N: SRT (verbal learning memory) SPART (visuospatial learning) SDMT (attention) PASAT-2 PASAT-3 (processing speed working memory) SPART-D (long term visuospatial memory) SRT-D (long term visuaspatial memory) WLG (verbal fluency)	BDI-II -FSS significant correlation (=0.40, <0.01) BDI-II - SDMT /PASAT/SPART negatively related (SDMT =−0.58, <0.0001), PASAT (PASAT-3: =−0.57, < 0.0001; PASAT-2: =−0.52, <0.0001), and SPART (= −0.50, <0.0001).	NO	YES Verbal memory (weak correlation)
Rotstein et al., 2012	MS	49	42.70 (10.70)	M 97.9%	NP	EDSS median 3.5 (0-7.5)	8.7 (8.5)	STIMULANT FATIG. TREAT IMM.MOD ANTIDEP	NP	VI	MS				BDI-FS (fast screen)	NP	UNSPECIFIED	NP	MFIS	PVT (alertness)	BDI-FS-PVT not a significant correlation	YES MFIS correlated with PVT reaction time (p<0.05),a stepwise regression model, fatigue (MFIS) showed the strongest correlation with PVT reaction time (p<0.05) . Mood,was not associated with impaired objective alertness	YES Alertness
Heesen et al., 2012	MS	50	43.70 (10.0)	NP	SP RR (Poser et al., 1983)	EDSS MS CP 3.0 (1.6) EDSS MS CI 4.40 (1.80) CAMBS	MS CP 9.9 (3.8) MS CI 11.6 (6.5)	IMM. MOD		ENDOCRINE ABNORMALITIES DISEASE AFFECTING HPA axis BENZODIAZEPINE PD ANTDEP NEUROLEPTICS ATTACK FREE STEROID FREE	MS				ADS (german version of CESD)		Subjective cognitive fatigue	NP	MFIS LIKERT SCALE	PASAT (processing speed) AVLT (memory) TAP (attention) RWT (executive functions) WST (general intelligence)	ADS MS CI> CP (p=0.04) ADS-AVLT tot strongly associated (r=-.32 p<0.05) ADS-AVLT delayed significant association (r=-0.45 p<0.001)	NO	YES Attention
Archibald et al., 2010	MS	35	39.50 (9.20)	13.50 (2.90)	RR SP (Kurtzke et al., 1988)	EDSS RR 2.7 (1.0) EDSS SP 4.0 (1.0)	RR 10.6 (6.9) SP 13.1 (6.6)	NP	CLINICALLY DEFINITE MS (Kurtzke, 1988) EDSS mild to moderate	ATTACK CORTICOSTEROID within 4 weeks D/A PD LD SEIZURES HI ND NEUROLEPTICS FREE	HC	35	38.0 (13.0)	14.10 (2.30)	BDI		UNSPECIFIED	NP	VAS	WMS-R Attention/ Concentration Index (memory span) CVLT (learning and retention of new information) SALTHOUSE TASK (Zero-intercept and slope indices)	BDI MS > HC RR (p < .05)	NO BDI VAS COV (On the CVLT Sternberg and Salthouse did not account for performance differences)	NO
Wilting et al.,2015	MS	79	MS F 34.5 (20-58) MS NOT F 30 (17-54)	MS F L 3 M 20 H 15 MS NOT F L 0 M 14 H 25	RR (Polman et al.,2010)	EDSS MS F 1.50 (0-5.5) EDSS MS NOT F 0.50 (0-3.5)	MS F 2 (0-10) MS NOT F 2 (0-10)	IMM.MOD	NP	22< FSMC <27 SLEEP DISTURBANCE DEP MOOD DISORDERS	HC	40	28 (21-54)	L 0 M 6 H 12	HADS	NB	UNSPECIFIED	NP	FSMC	PASAT-3 RWT SDMT TAP TMT VLMT, WMS-R	NP	No	YES Information processing (trend towards a reduction in MSF group)
Parmenter et al., 2003	MS	30 H 15 LF 15	HF (15) 43.00 (13.08) LF(15) 46.57 (6.48)	NP	NP (Poser et al.,1983)	EDSS H F 4.68 (2.18) EDSS LF 4.60 (1.81)	HF 11.73 (9.32) LF11.64 (5.96)	MS TREATMENT	CLINICALLY DEFINITE MS (Poser et al., 1989)	NO CHANGE TREAT TOO COGNITIVELY IMPAIRED	MS				CES-D	NP	UNSPECIFIED	NP	FSS FIS POMS	TOL (executive functions) WCST (executive functions) STROOP (information processing speed) PALT(memory)	CES-D HF -LF not significantly difference	NO	NO
Pokryszko-Dragan et al., 2016	MS	86	39.5 (19-60)	NP	CIS RR SP (Polman et al., 2010)	EDSS3.03 (1.42) MSSS	8.57 (8.4)	NP	NP.	DISEASE AFFECTING FATIGUE OR COGNITIVE FUNCTIONS DMT	HC	40	38.8 (23-60)	NP	NP	NP	SUBJECTIVE FATIGUE	NP	FSS MFIS	BRBNT ERP (event-related potentials) P300	NP	NP	YES Processing Speed Attention Memor

ABBREVIATION FOR PREVIOUS TABLES

10/36 SRT	10/36 Spatial Recall Test
6MWT	6-Minute Walk Test
9HPT	9 Hole Peg Test
A-A-TEST	Continuous cognitively effortful task
ACCURACY	Total correct responses
ACROSS-RUN FATIGUE	The effects of fatigue examined across time (across each run)
ADS	Allgemeine Depressions Scale
AI	Ambulation Index
AMB	Able to ambulate without assistance
ANALG	Analgesic
ANTDEP	Antidepressant
ANTICHO	Anticholinergic medication
ANTISPASTICITY/ANTICHOLINERGIC	Antispasticity Anticholinergic Agent
ANX	Anxiety
ATTACK	Clinical attack (exacerbation) (e.g., within 4 weeks, 30 days, 28 days, 3 months)
AVLT	Auditory Verbal Learning Test
BADS	Behavioural Assessment of the Dysexecutive Syndrome
BCcogSEP	Modified version of the “Brief Repeatable Battery of Neuropsychological tests for Multiple Sclerosis”
BDI	Beck Depression Inventory
BDI som	BDI somatic component
BDI-FS	Beck Depression Inventory-Fast Screen
BDI psy	BDI psychological component
BENZ	Benzodiazepine
BLOCK- SPAN	Block-Span from german version of Wechsler Memory Scale-Revised (WMS-R)
BRBNT	Brief Repeatable Battery of Neuropsychological Tests
BUSCHKE SRT	Buschke Selective Reminding Test;
BVMT-R DR	Brief Visuospatial memory test – revised delayed recall
BVR	Benton Visual Retention
CR	Number of correct responses
CI	Cognitive impaired
CAMBS	Multiple Sclerosis Basic Score
CARB	Computerized Assessment of Response Bias (o measure response time and response variability)
CBT	Cognitive behavioural therapy
CCTB	Computerized cognitive testing battery
CES	Center for Epidemiologic Studies
CES-D	Center for Epidemiological Studies – Depression
CFS	Chronic fatigue syndrome
CHANGE TREAT	Change of medical treatment
CHOLINESTERASE	Cholinesterase
CII	Cognitive Impairment Index
CIS	Clinical isolated syndrom
CONF	Confounding factor
CMDI	Chicago Multiscale Depression Inventory
COPY	Digit Simbol Copy
COV	Covariata
MDI	Multiscale Depression Inventory
CMDI-Mood	Chicago MultiscaleDepression Inventory
COWA	The Controlled Oral Word Association Test
COMPOSITE NP	Composite Neuropsychological Performances
COWA-C	Controlled oral word associations for categories
COWA-P	Controlled oral word associations for phonemes
COWAT	Controlled Oral Word Association Test
CP	Cognitive preserved
CPT	Continuous Performance Test
CTIP	Computerized Test of Information Processing
CVLT-II LDFR	California verbal learning test – II long delay free recall

D/A	Drug/or Alcol abuse
DD	Disease duration
DEM	Dementia
DEP	Depression
DOT	Digit Ordering Test
Digit-Span	Digit-Span from german version Wechsler Memory Scale-Revised (WMS-R)
DIR	Delayed item recognition
DIR ALONE	Dir adminestered alone
DIR RT CI	Complete interference (dual task condition)
DIR RT PI	Partial Interference (dual task condition)
DIVIDED ATTENTION SUBTEST (TAP)	Test for Attentional Performance
DKEFS	Delis-Kaplan Executive Function System Sorting Test
DMT	Disease Modifying Therapy
DSC-I	Digit Symbol-Coding I
DSC-II	Digit Symbol-Coding II
DST	Digit span total
DST	Digit Symbol Test (Wechsler-Adult-Intelligence Scale)
DYAD	The proportion of correct responses generated immediately following another correct response.
DYSLEXIA	Dyslexia
EDSS	Expanded Disability Status Scale
ERP	Event-related potentials
ESS	Epworth Sleepiness Scale
F	Fatigued
FATIGUE TREAT	Fatigue treatment
FINEMF	Adequate fine motor functions
FIS	Fatigue impact scale
FRS	Fatigue Rating Scale
FSMC	Fatigue Scale for Motor and Cognitive Functions
FSQ	Functional Status Questionnaire
FSS	Fatigue Severity Scale
FST	Faces Symbol Test
FTT	Finger tapping test
GNDS	Guy's neurological disability scale
GO-NO-GO	Selective attention task
H	High
HADS	The Hospital Anxiety and Depression Scale
HC	Healthy control
HF	High fatigue
HI	Head injury
HIGH-LOW	Highest fatigue early in the day
HRSD	Hamilton Rating scale for Depression
HT	Hand tremor
HVLT	Hopkins Verbal Learning Task
ICCs	Intraclass correlation coefficients
IMM.MOD.	Immunomodulatory therapy
IMM.SOPP FURTHER DISEASE	Immune soppressive therapy for further disease
INEXP.	Impossibilitati a fare esperimento =INEXP.
ISS	Incapacity Status Scale (functional disability)
JLO	Judgment of line orientation
KEDSS	Kurtzke Expanded Disability Status Scale
KFS	Krupp Fatigue Scale
L	Low
LD	Learning disability
LF	Low fatigue
LNST	Letter-Number Sequencing Test
LNST	Letter-Number Sequencing Test
LM-II	Logical Memory II
LOW-HIGH	Highest fatigue later in the day
M	medium
MACFIMS	Assessment of Cognitive Function in Multiple Sclerosis

MB	Metal in the body
MS DEP	Depressed MS
MS NOT DEP	Not Depressed MS
MDI	Multiscale Depression Inventory
MEHRFACHWAHL– WORTSCHATZ INTELLIGENZTEST	Lexical decision task for frequent and infrequent words
METHOD1	Decline in performance from the start to the end of the test
METHOD2	Slope of declining performance
MFIS	Modified fatigue impact scale
MMI	Major Medical Illness
MMSE	Mini Mental State Examination
MOTOR IMPAIRMENT	Motor Impairment
mPVSAT	Paced Visual Serial Addition Test
MR	Mental Retardation
MR	Matrix Reasoning
MRC	Med. Research Council
mSDMT	Modified version of the Symbol Digit Modalities test
MSSS	Index of disability progression
MS F	MS Fatigued Multiple Sclerosis Patients
MS NOT F	MS Not fatigued Multiple Sclerosis Patients
MSFC	Multiple Sclerosis Functional Composite Measure
MWT-B	Mehrfachwahl-Wortschatz-Test
NAART	North American Adult Reading Test
NB	Neuropsychological Battery
N-BACK	N-Back test
ND	Neurological disabilities
NF	Non-fatigued
NFI-MS	Fatigue Scale (physical, cognitive, and sleep quality)
NH	Normal hearing
NO PARESIS UL	No paresis upper limb
NP	Not provided
NTP	Neuropsychological test performances
NV	Normal vision
ODDBALL PARADIGM TASK	In oddball task subjects detect rare target stimuli in a series of standard stimuli
PALT	The Paired Associates Learning Test
PANAS	The Positive and Negative Affect Schedule
PASAT 2	Paced auditory serial addition test 2
PASAT 3	Paced auditory serial addition test 3
PD	Psychiatric disorders
PDQ	Perceived Deficit Scale
PF	Primary fatigued
PL	Placebo
POMS	Profile Mood States
PP	Primary-Progressive
PR	Progressive Relapsing
PRE	Pregnant
PSQI	Pittsburgh Sleep Quality Index
QSP	Questionnaire de Santé du Patient (for mood disorders evaluation)
RAVLT	Rey's Auditory Verbal Learning Test
RF	Right frontal
RFD	Rochester Fatigue Diary
RH	Right handness
RHNF	Right hand normal function
ROCFT	Rey–Osterreith Complex Figure Test
RP	Right parietal
RR	Relapsing-Remitting
RR MS F	MS fatigued Relapsing-Remitting
RR MS NF	MS not fatigued Relapsing-Remitting
RT	Reaction time

RWT	Word fluency test
RWT	Regensburger Word Fluency Test
S	Suicide
SAT	Serial Addition Test
SCF	Subjective cognitive fatigue
SDMT	Symbol Digit Modalities Test
3DSAT	Three digit serial addition test
SDMCAT	Symbol Digit Modality Cum Addition test
SED MED	Sedating medication
SF	Secondary fatigued
SILS	Shipley Institute of Living Scale
SP	Secondary Progressive
SpaRT	Spatial Recall Test
SPM	Raven's Standard Progressive Matrices
SRT	Spatial Recall Test
SRT	Selective Reminding Test
STABLE	Stable during the study
STROKE	Cerebrovascular accident
STROOP	The Stroop Color-Word Interference Test
SVRT	Selective Verbal Reminding Test
TAP-M	Battery for Attention Performance
TIME-OF-DAY	from morning to afternoon
TMT	Trail Making Test
TMT-A	Trail-Making-Test A
TMT-B	Trail-Making-Test B
TOH	The Tower of Hanoi Test
TOL	The Tower of London
UNTREAT SLEEP DIS	Untreated sleep disorders
V	Vocabulary
V AC	Visual acuity
VAS	Visual analogue scale
VF	Verbal fluency
VI	Visual impairment
VLMT	Verbal Learning and Memory Test
WASI	Wechsler Abbreviated Scale of Intelligence
WAIS III	Wechsler Adult Intelligence Scale
WEIMUS	Würzburger Fatigue Inventory
WGL	Word Generation List
WITHIN-RUN FATIGUE	Performance each run (WITHIN-F: first half of each run vesus second half)
WMS-R	Wechsler Memory Scale-Revised
WMS-III	Wechsler Memory Scale-III
WRAT	Wide Range Achievement Test 3 Reading subtest
WORD LIST	Reading Subtest
WRMS	Walter REED Mood Scale
WSCT	The Wisconsin Card Sorting Test
WST	The ''Wortschatztest" (vocabulary test)

Ethical permission

The studies have been approved by the Local Ethics Committee of the University of Federico II with Approval Id# 80/20 and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki, together with the principles that guide the ethical and methodological practice of online research (Das, Ester, & Kaczmirek, 2011), social and behavioral research, and internet-applied methods and strategies.

The study participants received comprehensive information about the research goals, methods, potential risks, and benefits. Participants were provided with informed consent and research information through an online platform. This was facilitated by a custom URL that directed participants to a web-based portal hosted by Google Forms. Informed consent was obtained, emphasizing the voluntary nature of participation. Participants were provided with information regarding the utilization of their data, including the possibility of publication, and they explicitly consented to sharing their data. This approach adheres to ethical guidelines and safeguards data integrity. The data collection and handling procedures were designed with a strong adherence to ethical principles. The data underwent processing using commonly used standard software. The data was securely recorded and labeled with unique codes to ensure anonymity. Strict measures were implemented to ensure the preservation of data confidentiality during the study, with the primary objective of safeguarding the privacy of participants. The measures implemented consisted of secure data storage with limited access and de-identification. Access to the data was limited to authorized personnel to uphold confidentiality. The study was conducted with a strong commitment to maintaining ethical standards and safeguarding the rights and well-being of participants. Comprehensive measures have been implemented in collaboration with ethical oversight to ensure the credibility, integrity, and ethical soundness of this research.

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* Indicates required question

Informed consent

I DECLARE THAT I AM AWARE THAT:

Each participant is free to ask for clarification on the data collection procedure and on any aspect of the experiment; each participant is free to leave the session at any time; any refusal to participate or abandonment of the session does not entail any negative consequences for the participant; the personal data collected will not be transmitted to people not directly involved in the research; the personal data collected will be processed anonymously; the results will be presented in aggregate form and with all necessary caution to avoid the identifiability of the participants; the research is conducted in compliance with the Declaration of Helsinki; the data collected will be used exclusively for the purposes of the research; the research results may be the subject of scientific publication e therefore disseminated through specific sector magazines and provide theoretical support to experts; this research has a scientific purpose only and will never be used for commercial purposes; the results of the research cannot be disseminated without respecting absolute anonymity, therefore, the names of the participants in the experiment will never be reported in any communication. *

☐ YES, I DECLARE

I ALSO DECLARE: *

TO BE OF ADULT	☐
THAT YOU HAVE CAREFULLY READ ALL POINTS OF THE DECLARATION AND/OR INFORMATION DOCUMENTS	☐
TO GIVE YOUR CONSENT TO PARTICIPATE IN THE RESEARCH	☐

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Data controllers and related purposes The AOU Experimental Center, Federico II University Hospital, in collaboration with the Suor Orsola Benincasa University, commissioned the study that has been described to you, each for the areas of its competence and in accordance with the responsibilities provided for by the rules of good clinical practice (Legislative Decree 211/2003). The data collected, in particular those on health, will be processed in accordance with Legislative Decree 30 June 2003, n.196 "Code regarding the protection of personal data" which has the aim of guaranteeing respect for the rights, fundamental freedoms, as well as the dignity of natural persons.Your data is essential for carrying out the study: refusal to provide it will not allow you to participate

Your answer

Nature of the data The doctor and the investigator who will follow you in the study will identify you with a code: the data concerning you collected during the study, with the exception of your name, will not be transmitted to third parties, but recorded, processed and stored together with this code. Only your doctor and authorized individuals will be able to link this code to your name

Your answer

Processing methods The data, processed using tools including electronic ones, will be disseminated only in a strictly anonymous form, for example through scientific publications, statistics and scientific conferences. Your participation in the study implies that, in compliance with the regulations on clinical trials, the staff of the Suor Orsola Benincasa University, involved in the experiment which carries out the monitoring and verification of the study, will be able to know the data concerning you, contained also in your original clinical documentation, in ways that guarantee the confidentiality of your identity.

Your answer

I consent to the processing of my personal data for research purposes within the limits and in the manner indicated in the information provided to me with this document *

◯ YES, I AGREE

I also declare: *

☐ that I have carefully read all points of the declaration and any attachments and/or information documents

☐ to give their consent to participate in the research

Back Submit Clear form

The Mobility Self-Assessment (MSA)

1	Fully walking, despite having obvious neurological deficits in various areas (motor, cerebellar sensitive, visual, sphincteric) of mild or moderate degree, not interfering with my autonomy.
2	Autonomous, walking without help and without stopping, for about 500 meters.
3	Autonomous, with minimal limitations in the full daily activity and walking possible, without stops and without help, for about 300 meters.
4	Not entirely autonomous, with modest limitations in the full daily activity and walking possible, without stops and without help for about 200 meters.
5	Not entirely autonomous, with obvious limitations in the full daily activity and walking possible, without stops and without help, for about 100 meters.
6	Need of steady assistance on one side (stack, clamps) to walk 100 meters without stopping.
7	It needs constant bilateral assistance, to walk 20 meters without stopping.
8	Not able to walk for more than 5 meters, even with help, mostly confined to the wheelchair, but managing to move from there on its own.
9	Only able to move a few steps. You are forced to use the wheelchair and may need help to move from it.
10	Compulsory in bed, not for the whole day or on a wheelchair. Usually, efficient use of one or both upper limb

Below a screenshot of the first page of the questionnaire:

pQLSd2kXV4e1b-_col-MW6SqsOUPkX-oB0rPrgN1dNb-fl1zuWmA/viewform

PART I - PERSONAL DATA

Sign in to Google to save your achievements. Find out more

*Required field

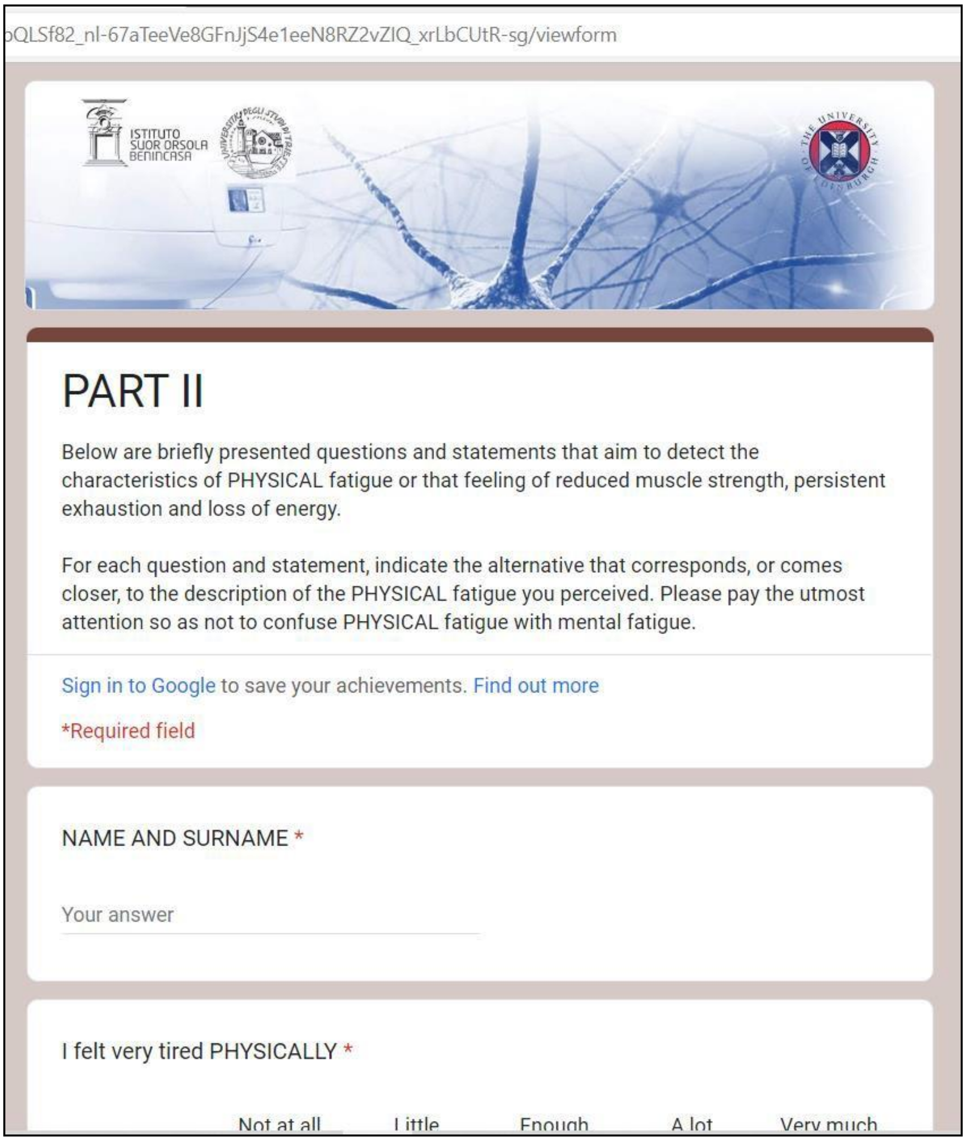
MULTIDIMENSIONAL ASSESSMENT OF FATIGUE
Before proceeding with the submission of applications, we consider it appropriate to clarify what is meant, in this research, by the term fatigue. By this term we mean a subjective feeling of extreme fatigue or lack of energy. Fatigue can occur on a physical (or motor) level, on a mental level, or both. Physical fatigue is characterized by the feeling of reduced muscle strength, persistent exhaustion, loss of energy; Mental fatigue is characterized by difficulty sustaining mental activities for a long time, such as reading, learning, concentrating, memorizing, studying. It is important not to confuse fatigue with drowsiness resulting, mainly, from lack of sleep.
It should be noted that some people tend to tire more easily on a mental level, others tend to tire more frequently on a physical level, others experience physical and mental fatigue in their daily lives at the same time.

Instructions for completing the questionnaire This questionnaire

provides several ways of answering. Some questions will have to be answered by choosing one of several alternatives, while other questions will have to answer by choosing the numerical value that corresponds, or closer to describing its status. Please answer the

Multi-temporal Assessment of Fatigue Test (MtAFT)	
The questionnaire in “Google Form” format is accessible interactively at the following URL:	https://forms.gle/U9K9AofLZMPFQQSm6

Below a screenshot of the first page of the questionnaire:



pQLSf82_nl-67aTeeVe8GFnJjS4e1eeN8RZ2vZIQ_xrLbCUtR-sg/viewform

ISTITUTO SUOR ORSOLA BENINCASA

PART II

Below are briefly presented questions and statements that aim to detect the characteristics of PHYSICAL fatigue or that feeling of reduced muscle strength, persistent exhaustion and loss of energy.

For each question and statement, indicate the alternative that corresponds, or comes closer, to the description of the PHYSICAL fatigue you perceived. Please pay the utmost attention so as not to confuse PHYSICAL fatigue with mental fatigue.

Sign in to Google to save your achievements. Find out more

*Required field

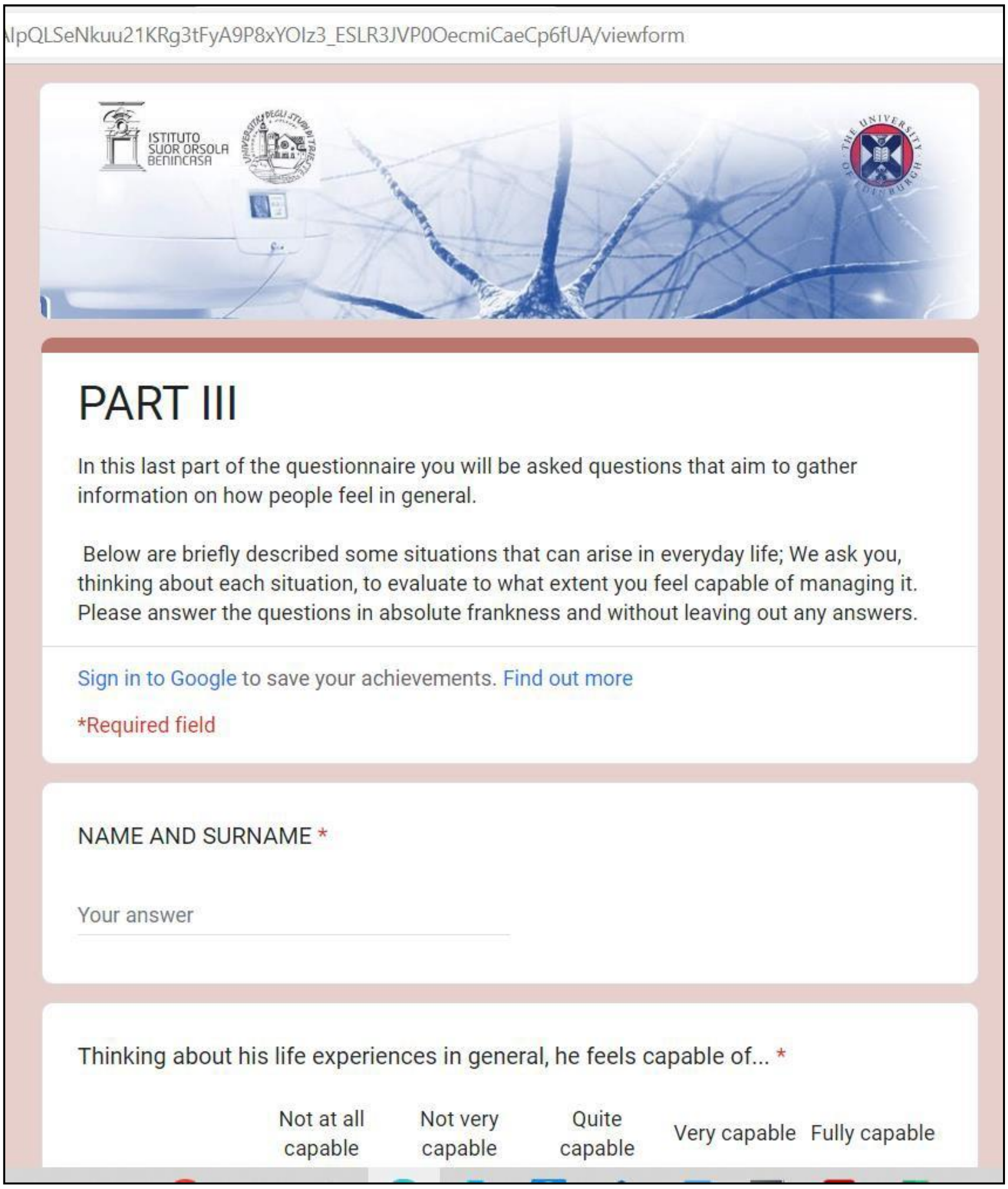
NAME AND SURNAME *

Your answer

I felt very tired PHYSICALLY *

Not at all | Little | Enough | A lot | Very much

BDI and PSE-MCP	
The questionnaire in "Google Form" format is accessible interactively at the following URL:	https://forms.gle/xBthLxxCcJG3kwpy8
Below a screenshot of the first page of the questionnaire:	



lpQLSeNkuu21KRg3tFyA9P8xYOIz3_ESLR3JVP0OecmiCaeCp6fUA/viewform

PART III

In this last part of the questionnaire you will be asked questions that aim to gather information on how people feel in general.

Below are briefly described some situations that can arise in everyday life; We ask you, thinking about each situation, to evaluate to what extent you feel capable of managing it. Please answer the questions in absolute frankness and without leaving out any answers.

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*Required field

NAME AND SURNAME *

Your answer

Thinking about his life experiences in general, he feels capable of... *

Not at all capable	Not very capable	Quite capable	Very capable	Fully capable

CLINICAL DATA MS	
The questionnaire in "Google Form" format is accessible interactively at the following URL:	https://forms.gle/S2ea9dzkmoMyquk39
Below a screenshot of the first page of the questionnaire:	

PwAQM4c6eL_YisJ-6s6LUgFtvaQ__LgiaQ/formResponse

Analisi della stanchezza nei pazienti affetti da SM - Demografia, Anamnesi, Consenso informato - Consenso al trattamento dei dati personali e sensibili

martinivalentina80@gmail.com (non condiviso)
Cambia account

*Campo obbligatorio

Demografia

NOME E COGNOME *

La tua risposta

RECAPITO TELEFONICO (CELLULARE) *

La tua risposta

INDIRIZZO E-MAIL *

The questionnaire in “Google Form” format is accessible interactively at the following URL:	https://forms.gle/B8imAdNQan58FQMQA

Below a screenshot of the first page of the questionnaire:

Sc7fThZ2EIYyKF_Xbhq1DTPf-Lku-k4Boxv_qo2UQV0gKE_Kg/viewform

Analysis of daily variations of fatigue

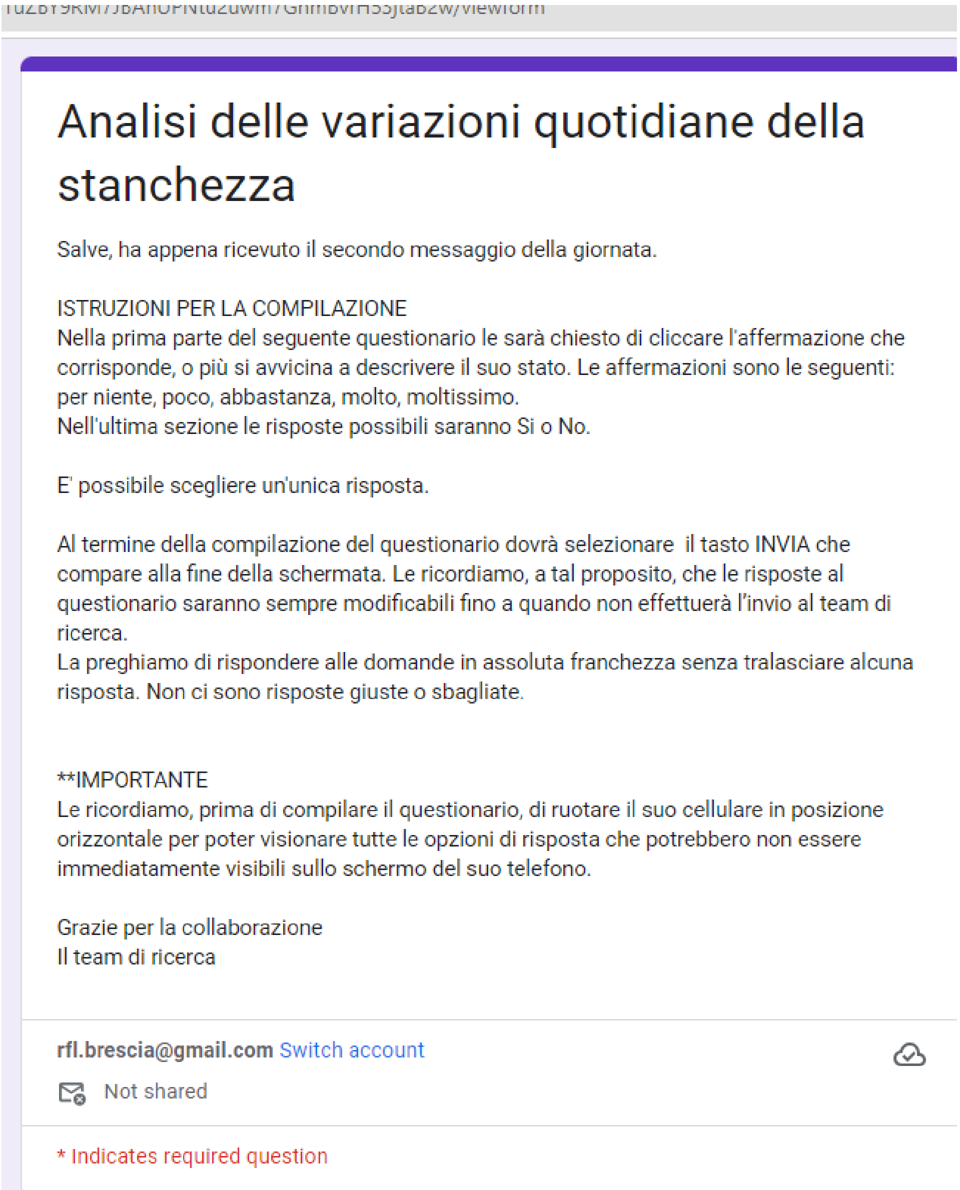
Good morning, you have just received the first message of the day.

Before proceeding with the submission of applications, we consider it appropriate to clarify what is meant, in this research, by the term fatigue. By this term we mean a subjective feeling of extreme fatigue or lack of energy. Fatigue can occur on a physical (or motor) level, on a mental level, or both. It is important not to confuse fatigue with drowsiness resulting, mainly, to lack of sleep
Physical fatigue is characterized by the feeling of reduced muscle strength, persistent exhaustion, loss of energy; Mental fatigue is characterized by difficulty sustaining mental activities for a long time, such as reading, learning, concentrating, memorizing, studying. It should be noted that some people tend to tire more easily on a mental level, others tend to tire more frequently on a physical level, others experience physical and mental fatigue in their daily lives at the same time.

COMPILATION
INSTRUCTIONS To answer this first question you will be asked to click on the statement that matches, or comes closest to describing your status. The statements are as follows: not at all, little, enough, very, very much. It is possible to choose only one answer.
At the end of completing the questionnaire, select the SEND button that appears at the end of the screen. We remind you, in this regard, that the answers to the questionnaire will always be editable until you send them to the research team.
Please answer the questions in absolute frankness without leaving out any answers. There are no right or wrong answers.

Thank you for your cooperation.
The research team

Recurrent questions through the day	
The questionnaire in “Google Form” format is accessible interactively at the following URL:	https://forms.gle/yzydSo83Gc2niv5CA
Below a screenshot of the first page of the questionnaire:	



Analisi delle variazioni quotidiane della stanchezza

Salve, ha appena ricevuto il secondo messaggio della giornata.

ISTRUZIONI PER LA COMPILAZIONE
Nella prima parte del seguente questionario le sarà chiesto di cliccare l'affermazione che corrisponde, o più si avvicina a descrivere il suo stato. Le affermazioni sono le seguenti: per niente, poco, abbastanza, molto, moltissimo.
Nell'ultima sezione le risposte possibili saranno Si o No.

E' possibile scegliere un'unica risposta.

Al termine della compilazione del questionario dovrà selezionare il tasto INVIA che compare alla fine della schermata. Le ricordiamo, a tal proposito, che le risposte al questionario saranno sempre modificabili fino a quando non effettuerà l’invio al team di ricerca.
La preghiamo di rispondere alle domande in assoluta franchezza senza tralasciare alcuna risposta. Non ci sono risposte giuste o sbagliate.

**IMPORTANTE
Le ricordiamo, prima di compilare il questionario, di ruotare il suo cellulare in posizione orizzontale per poter visionare tutte le opzioni di risposta che potrebbero non essere immediatamente visibili sullo schermo del suo telefono.

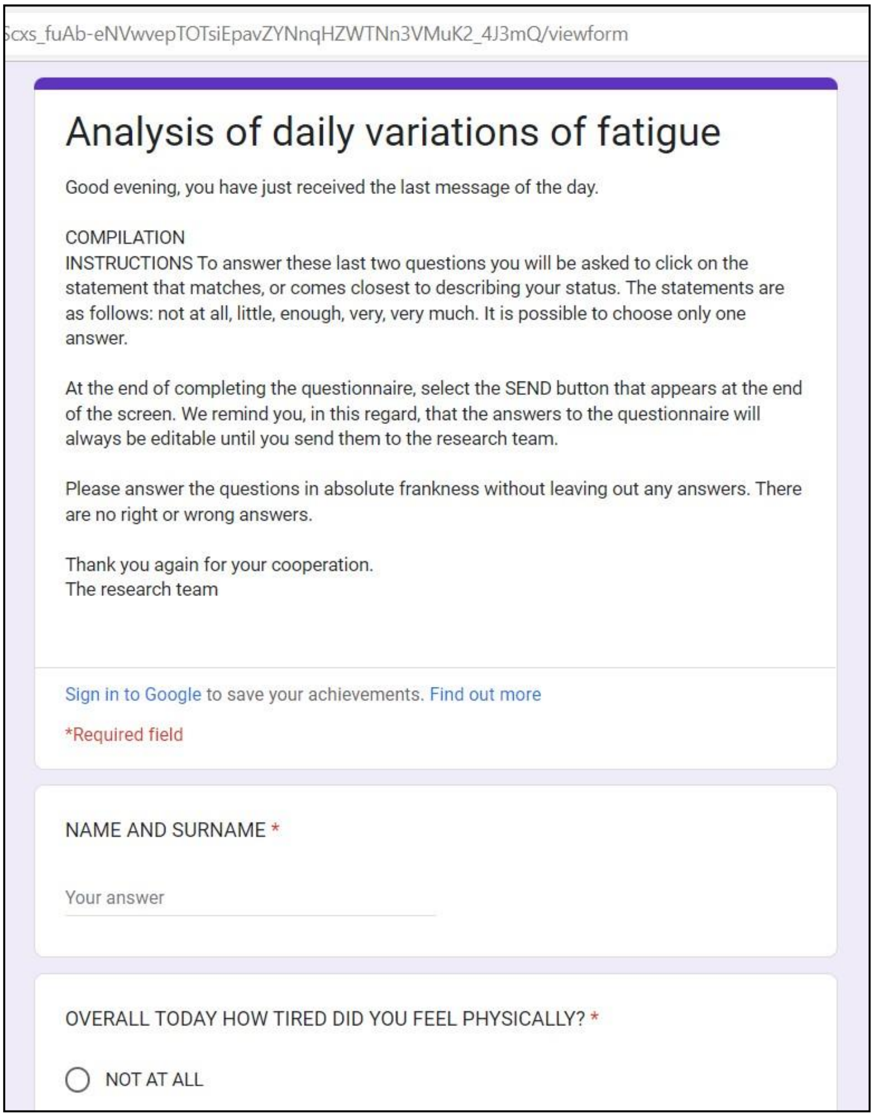
Grazie per la collaborazione
Il team di ricerca

rfl.brescia@gmail.com Switch account

Not shared

* Indicates required question

Last question of the day	
The questionnaire in "Google Form" format is accessible interactively at the following URL:	https://forms.gle/DFeYHeYhmuCZZ9y8A
Below a screenshot of the first page of the questionnaire:	



Scxs_fuAb-eNVwvepTOTsiEpavZYNnqHZWTNn3VMuK2_4J3mQ/viewform

Analysis of daily variations of fatigue

Good evening, you have just received the last message of the day.

COMPILATION
INSTRUCTIONS To answer these last two questions you will be asked to click on the statement that matches, or comes closest to describing your status. The statements are as follows: not at all, little, enough, very, very much. It is possible to choose only one answer.

At the end of completing the questionnaire, select the SEND button that appears at the end of the screen. We remind you, in this regard, that the answers to the questionnaire will always be editable until you send them to the research team.

Please answer the questions in absolute frankness without leaving out any answers. There are no right or wrong answers.

Thank you again for your cooperation.
The research team

Sign in to Google to save your achievements. Find out more

*Required field

NAME AND SURNAME *

Your answer

OVERALL TODAY HOW TIRED DID YOU FEEL PHYSICALLY? *

NOT AT ALL

Montreal Cognitive Assesment (MoCA), 5-minute protocol
'Mini MoCA'

NAME: Date:
Education in years: ID:

1. Attention, 'Immediate recall of 5 words'

Read the list of 5 words - 1 second per word
(Subject must repeat the words immediate in the 1st trial and then again in the 2nd trial)

	Face	Velvet	Church	Daisy	Red
1st trial					

2. Executive Functions/Language, '1-minute verbal fluency'

Name maximum number of words in one minute that begin with the letter F.

3. Orientation, '6-item date and geographic orientation

Assure that the subject can't see a calender or a watch

Ask Date _______ Month ________ Year _______
Day __________ Place __________ City ____________

4. Memory, 'Delayed recall and recognition of 5 words learned in item 1'

	Face	Velvet	Church	Daisy	Red
2nd trial after 5 min.					

Administered by date/sign.:____

Scoring system

1st domain, attention
1 point for each word correctly recalled in first trial
__/5

2nd domain, Executive Function/language
0,5 point for each correct output (multiply number of words with 0,5)
___/9

3rd domain, orientation
1 point for each correct response
__/6

4th domain, memory
2 points for each of the word spontaneously recalled AND
1 point for each word by cued recall or recognition but not spontaneously recalled (look in the MoCA Instructions)
___/10