Exploring Cognitive Fatigue in Early Multiple Sclerosis

Camille Guillemin

A Thesis Submitted in Partial Fulfilment of the Requirements for the Degree of

Doctor of Philosophy

Faculty of Psychology and Educational Sciences – Université de Liège

2021-2022

LIÈGE université
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PsyNCog

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Abstract

Fatigue is one of the most frequent and disabling symptom of Multiple Sclerosis (MS). Despite its incidence, the underlying mechanisms of MS-related fatigue are not completely elucidated. This is particularly the case of cognitive fatigue (i.e. interfering with mental work) occurring in the early stages of the disease, even in patients showing mild lesion load and disability. The theoretical part of the thesis start with a description of MS disease, with a particular emphasis on cognitive symptoms. The concept of fatigue is introduced and defined. Several models of cognitive fatigue in healthy subjects and in neurological populations are developed, as well as the different methods used to study cognitive fatigue. Finally, the introduction of this work ends with a focus on cognitive fatigue in the context of MS.

In the experimental section, the objectives and hypotheses of this thesis are described, before moving forward with the six studies carried out in this framework, which explores cognitive fatigue in the early stages of MS and in healthy controls from a cognitive, physiological (eye metrics) and cerebral perspectives. Namely, four research questions are considered across the studies:

(i) Is there a link between fatigue and cognition in MS? (Studies 1 & 2)
(ii) What are the effects of long-lasting procedures and cognitive load on cognitive fatigue and which procedure triggers fatigue the most? (Studies 3 & 4)
(iii) Can eye metrics provide an objective measure of fatigue state? (Study 3)
(iv) What are the functional and structural cerebral substrates of cognitive fatigue in the early stages of the disease? (Studies 5 & 6)

Results obtained are further discussed addressing these main questions, the limitations of this work, and future directions that could be taken to expand our findings. Overall, five specific, but not mutually exclusive, causes of cognitive fatigue in early MS were proposed and discussed in the light of our results: decrease in motivation, increased perception of effort, decreased arousal, extra effort due to cognitive deficits and costly brain functional reorganization due to structural alterations.

Résumé

La fatigue est l'un des symptômes les plus fréquents et invalidants de la Sclérose en Plaques (SEP). Malgré sa forte incidence, les mécanismes sous-jacents à la fatigue dans cette pathologie restent largement incompris. Cela est particulièrement le cas pour la fatigue cognitive (i.e. qui interfère avec le travail mental) survenant dès les premiers stades de la maladie, chez des patients ne présentant par ailleurs que peu de troubles cognitifs et d'atteintes cérébrales. Après avoir décrit la pathophysiologie de la SEP, l'introduction théorique de cette thèse développe les différents symptômes cognitifs rencontrés dans cette maladie. Ensuite, une introduction au concept de fatigue est proposée, présentant plusieurs modèles tentant d'expliquer son apparition, à la fois chez les sujets sains et dans le cadre des maladies neurologiques. Les différentes méthodes permettant d'étudier la fatigue de façon expérimentale sont également décrites. Enfin, l'introduction de ce travail se conclut par une attention particulière portée à la fatigue dans le contexte de la SEP.

La section expérimentale est composée des objectifs et hypothèses qui ont motivé ce travail, ainsi que d'une description générale du protocole que nous avons implémenté. S'ensuit la présentation des six études réalisées, visant une exploration approfondie de la fatigue cognitive chez des patients atteints de SEP récente et des sujets contrôles, sur le plan cognitif, physiologique (mesures oculaires) et cérébral. Concrètement, quatre questions de recherche sont abordées :

(i) Y a-t-il un lien entre la fatigue et les performances cognitives dans la SEP ? (Etudes 1 & 2)
(ii) Quels sont les effets de la longueur du protocole ou de la charge mentale sur l'apparition de la fatigue, et quelle méthode est la plus à même d'induire de la fatigue ? (Etudes 3 & 4)
(iii) Certaines variables physiologiques en lien avec les paramètres oculaires permettent-elles d'obtenir une mesure objective de l'état de fatigue ? (Etude 3)
(iv) Quels sont les substrats cérébraux de la fatigue dans la SEP récente, sur le plan fonctionnel et structurel ? (Etude 5 & 6)

Les résultats obtenus sont ensuite discutés sous le prisme de nos questions principales. Les limitations du présent travail et les directions futures qui pourraient être empruntées pour enrichir nos conclusions sont également détaillées. Globalement, cinq causes principales de fatigue cognitive dans la SEP récente sont identifiées et discutées : une perte de motivation, une perception de l'effort exacerbée, une diminution de l'état d'éveil, la nécessité de produire un effort supplémentaire pour compenser les déficits cognitifs, et une réorganisation cérébrale fonctionnelle coûteuse due aux atteintes structurelles.

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Table of Contents

List of Abbreviations

ACC: Anterior Cingulate Cortex

ANS: Autonomic Nervous System

BAWL: Batterie d'Attention William Lennox

BDI-II: Beck Depression Inventory, Second edition

BICAMS: Brief International Cognitive Assessment for Multiple Sclerosis

BF: Bayes Factor

BFS: Brugmann Fatigue Scale

BG: Basal Ganglia

BIDS: Brain Imaging Data Structure

BOLD: Blood Oxygenation Level Dependent

BRBNT: Brief Repeatable Battery of Neuropsychological Tests

BVMT-R: Brief Visuospatial Memory Test Revised

C: Congruent

CF: Cognitive Fatigue

CI: Cognitively Impaired

CIS: Clinically Isolated Syndrome

CNS: Central Nervous System

cogMFIS: Cognitive Subscale of the Modified Fatigue Impact Scale

CR: Cognitive Reserve

CSF: Cerebrospinal Fluid

CVLT: California Verbal Learning Test

DAN: Dorsal Attention Network

DGM: Deep Grey Matter

DMN: Default Mode Network

DMT: Disease-Modifying Therapy

DTI: Diffusion Tensor Imaging

DW: Diffusion-Weighted

EBV: Epstein-Barr virus

EDSS: Expanded Disability Status Scale

EEG: Electroencephalography

EPI: Echo-Planar Imaging

ERP: Event-Related Potential

ESS: Epworth Sleepiness Scale

FA: Flip Angle

FC: Functional Connectivity

FDR: False Discovery Rate

FLAIR: Fluid-Attenuated Inversion Recovery

fMRI: Functional Magnetic Resonance Imaging

FoV: Field of View

FSMC: Fatigue Scale for Motor and Cognitive Functions

FSS: Fatigue Severity Scale

FWE: Family-Wise Error rate

FWHM: Full Width at Half Maximum

GLMM: Generalized Linear Mixed Model

GM: Grey Matter

HADS: Hospital Anxiety and Depression scale

HC: Healthy Controls

HCL: High Cognitive Load

HPA: hypothalamic-pituitary-adrenal

HRV: Heart Rate Variability

I: Incongruent

IPS: IntraParietal Sulcus

IQ: Intelligence Quotient

ITS: Inferior Temporal Sulcus

JLO: Judgment of Line Orientation

KSS: Karolinska Sleepiness Scale

LC: Locus Coeruleus

LCL: Low Cognitive Load

MACFIMS: Minimal Assessment of Cognitive Function in Multiple Sclerosis

MEG: Magnetoencephalography

M-FIS: Modified Fatigue Impact Scale

MPM: Multi-Parameter Mapping

MRI: Magnetic Resonance Imaging

MS: Multiple Sclerosis

MT: Magnetization Transfer

N: Neutral

NACGM: Normal Appearing Cortical Grey Matter

NADGM: Normal Appearing Deep Grey Matter

NAGM: Normal Appearing Grey Matter

NAWM: Normal Appearing White Matter

NEO-FFI: NEO-Five Factor Inventory

NODDI: Neurite Orientation Dispersion and Density Imaging

PASAT: Paced Auditory Serial Addition Test

Pc: Percentile

PCC: Posterior Cingulate Cortex

PD: Proton Density

PET: Positron Emission Tomography

PFC: Prefrontal Cortex

PPMS: Primary Progressive Multiple Sclerosis

PRMS: Progressive Relapsing Multiple Sclerosis

PRS: Pupil Response Speed

PSQI: Pittsburgh Sleep Quality Index

PVT: Psychomotor Vigilance Test

pwMS: People with Multiple Sclerosis

physMFIS: physical subscale of the Modified Fatigue Impact Scale

qMRI: quantitative Magnetic Resonance Imaging

QoL: Quality of Life

RI: Longitudinal Relaxation Rate

R2*: Transverse Relaxation Rate

RF: Radiofrequency

RIS: Radiologically Isolated Syndrome

RNG: Random Number Generation

rmANOVA: Repeated Measures Analyses of Variance

RRMS: Relapsing-Remitting Multiple Sclerosis

RS: Resting State

RTs: Reaction Times

SDMT: Symbol Digit Modalities Test

SMA: Supplemental Motor Area

SPMS: Secondary Progressive Multiple Sclerosis

STAI: State-Trait Anxiety Inventory

STC: Striatio-Thalamo-Cortical

STD: Stimulus Time Duration

STS: Superior Temporal Sulcus

TAP: Test of Attentional Performance

TBI: Traumatic Brain Injury

TE: Echo Time

TLDB: Time Load Dual Back

ToM: Theory of Mind

ToT: Time on Task

TI: Inversion Time

TR: Repetition Time

VAS: Visual Analogue Scales

VBQ : Voxel-Based Quantification

VDM: Volume Displacement Maps

WAIS: Wechsler Adult Intelligence Scale

WM: White Matter

General Introduction

Multiple Sclerosis (MS) is a chronic disease, characterized by the occurrence of demyelinating plaques in the central nervous system (CNS). MS is the first cause of non-traumatic neurological disability in young adults in many countries (Browne et al., 2014), interfering greatly with daily activities and quality of life (Weiland et al., 2015; Young et al., 2021). Among the numerous symptoms affecting people with MS (pwMS), fatigue is one of the most frequently reported (Kluger, Krupp, & Enoka, 2013; Krupp, Alvarez, LaRocca, & Scheinberg, 1988; Penner et al., 2020). Despite its incidence, the underlying mechanisms of MS-related fatigue are not completely elucidated. This is particularly the case of fatigue occurring in the early stages of the disease, even in patients showing mild lesion load and disability. This thesis focuses on the study of cognitive fatigue (namely, fatigue interfering with mental work) in the very early years following the first symptom of MS.

Chapter I describes MS, providing an overview of its pathophysiology, incidence and symptomatology. Following a brief historical introduction, the current knowledge about MS pathophysiology is developed. Then, specificities about MS incidence etiology, and risk factors associated to the development of the disease are provided. Additionally, the different clinical courses characterizing MS are described, along with the large panel of associated symptoms. Finally, this chapter shortly addresses current treatment strategies.

In **Chapter II**, an emphasis on cognitive symptoms is made, describing the neuropsychological processes frequently impaired due to the disease. Cognitive impairments are not seldom in pwMS (Chiaravalloti & DeLuca, 2008) and an in-depth description is truly needed to better understand how they relate to cognitive fatigue. The cognitive symptoms frequently observed in pwMS are described, as well as and their incidence. Then, the different factors identified as influencing cognition are discussed, namely cerebral alterations, associated symptoms (such as depression, sleep disorders and fatigue) and cognitive reserve. Finally, an overview of what is currently known about cognition in early-MS is provided.

In **Chapter III**, the concept of fatigue is introduced. It is challenging to describe the notion of fatigue, which has often been mistaken for other concepts such as boredom or sleepiness (Hockey, 2013; Mairesse et al., 2019). Therefore, a complete definition of what fatigue shall refer to in the present work is developed. Then, the different methods used to study fatigue in research protocols is described, along with some important findings about fatigue mechanisms. To illustrate those findings, several theoretical models of cognitive fatigue in the context of healthy subjects are discussed. Finally, **Chapter III** develops the complex construct of cognitive fatigue in neurological diseases. Fatigue is a prominent symptom of many neurological conditions (Dobryakova, Genova, DeLuca, & Wylie, 2015; Kluger et al., 2013; Penner & Paul, 2017), including Parkinson disease, stroke, and traumatic brain injury (TBI). Due to neurological burden, but also to comorbidities and associated symptoms (such as cognitive impairment, sleep disorder or depression), cognitive fatigue experienced by these patients is multifaceted (Penner & Paul, 2017). After introducing its probable causes, several theoretical models of cognitive fatigue in neurological disorders are presented.

The specificity of cognitive fatigue in MS is brought to light in **Chapter IV**. By reviewing the current literature from the field of neurosciences, this chapter aims at providing a full overview of what is known about the cognitive mechanisms and brain substrates of cognitive fatigue in MS. A description of the few studies investigating cognitive fatigue in the early stages of MS closes the chapter.

The experimental part starts with the presentation of the aims and hypotheses of the present work before moving forward with the six studies carried out in this framework. For each study, the objectives, the protocol used for experimentation and a presentation and discussion are provided.

Due to several confounding factors, the link between fatigue and cognition in pwMS is still unclear. In **Study 1**, this relationship is explored for cognitive and physical fatigue in a sample of pwMS and matched healthy controls (HC), by taking also into account depression, anxiety and disability status. While this first study does not focus on pwMS in the early stages of the disease, the results nevertheless provide evidence of

the interplay between cognition and different fatigue modalities in pwMS, which lays the foundation for the following work.

With **Study 2**, this thesis starts to focus on the early stage of the disease. An overview of the cognitive status of a sample of pwMS with a recent disease history is provided and compared to matched-HC. Additionally, this study investigates whether a full neuropsychological assessment is susceptible to trigger cognitive fatigue in patients and controls, and if such fatigue sensation could affect performance during cognitive testing.

In **Study 3**, the effect of cognitive load on cognitive fatigue is investigated in early pwMS and HC. Participants performed a double-task in two load conditions (High and Low) during two separate sessions. Results on variables assessing subjective fatigue state, objective cognitive performance and eye metrics are discussed to determine how fatigue induction in early MS can be measured and whether physiological markers specific to the disease does exist.

In **Study 4**, the effect of a long-lasting task on subjective fatigue and performance is explored and shortly described. Additional analyses compare the effects of cognitive load and task duration on the triggering of state fatigue in both groups.

Study 5 was designed to investigate functional brain substrates associated to fatigue through a working memory task, with several difficulty levels, carried out after cognitive fatigue induction. We are particularly interested to determine whether cerebral activity correlates with trait fatigue in a disease-specific manner, already during the early years of the disease.

Finally, with **Study 6**, this work shortly describes micro-structural correlates of fatigue obtained in HC and early MS using Multi Parameter Mapping (MPM) quantitative maps within different normal appearing tissue classes.

In the last chapter of this thesis, results from the six studies are integrated and discussed, along with the limitations of this work and further research perspectives.

Chapter I
Defining Multiple Sclerosis

I. A Brief History

The first convincing traces of Multiple Sclerosis (MS) can be found in the early 19th century throughout clinical cases and in reference to graphic medical representations showing patchy lesions of the spinal cord (Compston et al., 2006). Decades later, in 1868, Jean-Martin Charcot describes the disease for the first time (Hayes & Donald Acheson, 2008). After nearly a century of varying nomenclature, such as "insular sclerosis", "disseminated sclerosis" or "polynesic sclerosis", a consensus was found in the mid-1950s with the term "Multiple Sclerosis", following the same-named publication of McAlpine, Compston and Lumsden (Compston et al., 2006). Thanks to a close analysis of hundreds of clinical records, McAlpine and Compston provided a detailed description of the clinical course of the disease, noticing for example the reduction in relapses frequency with disease evolution or some aspects of prognosis (Compston et al., 2006). Since then, diagnosis criteria for MS constantly evolved.

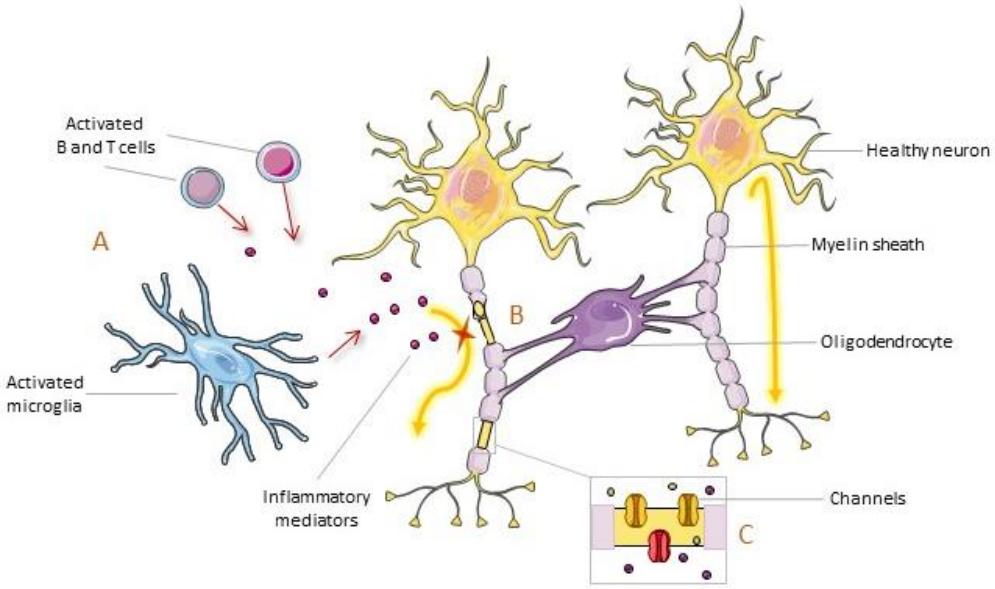
In 1954, Allison and Millar provided the first classification from clinical reports distinguishing "early", "possible" and "probable" MS (Compston et al., 2006; Przybek, Gniatkowska, Mirowska-Guzel, & Członkowska, 2015). In 1983, the Poser criteria introduced laboratory measures (such as Magnetic Resonance Imaging (MRI) and Cerebrospinal Fluid (CSF) examinations) as useful tools to supplement clinical observations and confirm the diagnosis of MS (Poser et al., 1983). Finally, thanks to the development of modern technic and the increasing access to MRI scanners, the McDonald criteria emerged in 2001, and has since become the gold-standard for MS diagnosis (McDonald et al., 2001). These modern criteria introduced the notion of "dissemination in space and time" of gadolinium-enhancing lesions in radiological examination (McDonald et al., 2001) and enabled a faster diagnosis of the disease. With the last revision of these criteria (Thompson et al., 2018), it is now possible to diagnose MS as soon as after the first demyelinating episode, which is particularly important considering that treatments are more effective when started in the early stages of the disease (de Seze & Bigaut, 2021).

II. Pathophysiology

MS is as chronic disease of the Central Nervous System (CNS). It is characterized by inflammatory lesions, called plaques, disseminated in the withe matter (WM) of the brain and the spinal cord. Therefore, MS has long been considered as a disease of the WM. However, it is now acknowledged that grey mater (GM) alterations are also prominent in MS, showing both demyelination and atrophy (Chard & Miller, 2009).

Demyelinating plaques are caused by activated lymphocytes crossing the blood-brain barrier, or the subarachnoid space, and creating an inflammatory cascade leading to alteration of the myelin sheet (i.e. demyelination, Fig. 1), gliosis and axonal loss (Compston et al., 2006; Dendrou, Fugger, & Friese, 2015). Activated T cells (CD4+ and CD8+) and B cells release pro-inflammatory and cytotoxic molecules including antibodies, interferons and cytokines (Calabrese et al., 2015). This cytotoxicity alters the myelin sheath around axons, as well as the surrounding oligodendrocytes. In a healthy neuron, the myelin sheath enable a fast and efficient transmission of neuronal message along the axon throughout saltatory conduction, with electrical impulse traveling from a node of Ranvier to another (Gruchot et al., 2019). In MS, because the myelin sheath is altered, the electrical impulse is slowed down (Gruchot et al., 2019). The homeostatic disturbance will activate CNS-resident cells, and activated microglia will also release neurotoxic inflammatory mediators (Dendrou et al., 2015). In order to compensate from homeostatic imbalance, several ion channels are redistributed along the demyelinated axons. These ions channels, along with excessive concentration of glutamate due to neuronal damage and inhibited reuptake by activated astroglia (Stampanoni Bassi et al., 2017), worsen the ionic imbalance, thus perpetuating neurodegeneration (Dendrou et al., 2015). Increase of glutamate transmission and reduced GABA signaling are thought to result in synaptic hyper-excitation (Rossi et al., 2012; Stampanoni Bassi et al., 2017), leading to excito-toxic neurodegeneration. This imbalance leads to retrograde (toward cell body) and anterograde (toward axon termination, also known as Wallerian) degenerations, leading to neuronal loss (Calabrese et al., 2015; Dendrou et al., 2015).

Figure 1. Inflammatory process in Multiple Sclerosis



In the central nervous system, activated B cells, T cells and Microglia release inflammatory mediators such as antibodies and cytokines **(A).** This inflammation will damage the myelin sheath around axons **(B),** leading to alteration of signal transmission. By comparison, electrical impulse in the healthy neuron travels quickly, jumping along nodes of Ranvier. In the demyelinated axon, the reorganization of ionic-channels repartition **(C)** will worsen homeostatic imbalance and promote neuronal degeneration.

MS white matter plaques are focal, sharply delimitated lesions showing hyper-intensity of signal in T2 FLAIR MRI sequences (Fig. 2) and gadolinium enhanced when they are recent (usually less than 3 months, Brochet, 2017). Plaques are usually small, around 1 to 2 cm, but can aggregate into larger lesions (Fontaine & Lyon-caen, 1996). They appear randomly within the CNS, yet certain areas show greater lesion susceptibility. Lesions to periventricular and cortico-subcortical white matter of the forebrain are commonly observed (Lumsden 1970 and Steiner 1931, both cited by Compston et al., 2006). The optic nerves, midbrain, pons and cerebellum are also often impacted (Field 1979 cited by Compston et al., 2006; Fontaine & Lyon-caen, 1996).

Following acute inflammation, a process of myelin regeneration, known as remyelination, can occur and improves signal conduction and metabolic support

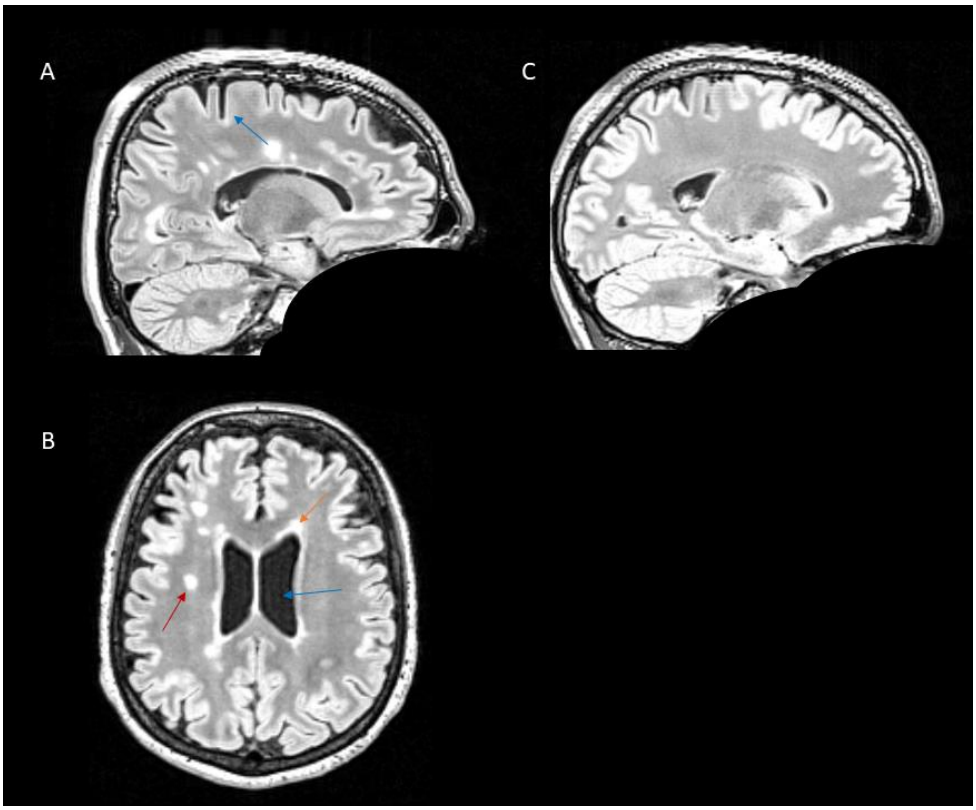
(Lubetzki, Zalc, Williams, Stadelmann, & Stankoff, 2020). Remyelination was often described in animal models, but the exact underlying mechanisms of this process in pwMS is currently not understood due to the difficulty to study this phenomena *in vivo* (Lubetzki et al., 2020). Indeed, conventional MRI sequences used in clinical settings are not specific enough to observe myelin reconstruction. Advanced technics, and especially quantitative MRI, are promising to better understand this process in laboratory environment (Lubetzki et al., 2020). Hence, Magnetization Transfer (MT) sequences are highly sensitive to myelin (Zivadinov, 2007), and a restoration of MT signal in the white matter can be assessed voxelwise. In a longitudinal study, Chen and colleagues (2008) showed that MT signal changed significantly following demyelination and remyelination, and that remyelination process can be at play for at least 3 years following acute demyelination. Likewise, radio-tracers found to bind to myelin have been developed, allowing to observe the processes of myelin loss and repair in pwMS with Positron Emission Tomography (PET, Stankoff et al., 2011). Another PET longitudinal study (Bodini et al., 2016) found high inter-subject variability in terms of myelin restoration, and that remyelination was significantly and inversely correlated to the Expanded Disability Status Scale (EDSS, Kurtzke, 1983), a well-known scale assessing disability status in pwMS. This result demonstrates that patients with more active myelin restoration show preserved abilities, suggesting a neuroprotective role of remyelination process (Lubetzki et al., 2020). The protective effect of myelin repair was further demonstrated with another PET study showing that remyelination is associated to a less severe damage of the surrounding tissue, which could prevent Wallerian degeneration (Ricigliano et al., 2022).

To date, it is unclear whether remyelination can also improve disability in restoring demyelinated axons, or if its role is limited to neuroprotection against further worsening (Lubetzki et al., 2020). Additional studies are needed, especially clinical trials targeting remyelination, to elucidate the role of myelin repair in disease progression.

As abovementioned, GM pathology is also involved in MS, and is characterized by both demyelination and atrophy. It is only recently that advanced MRI techniques brought GM pathology to light. Since, it was shown that WM lesions are only the visible

part of the iceberg in MS pathophysiology, and that the normal appearing GM (NAGM) contains many focal lesions as well (Chard & Miller, 2009). Moreover, GM lesions have been shown to correlate with physical and cognitive impairments, and to independently predict disease evolution (Calabrese, Filippi, & Gallo, 2010).

Figure 2. Brain alterations in Multiple Sclerosis



T2 Flair sequences (3T MRI) of an MS patient **(A & B)** and a healthy subject **(C)** of same age and sex. Sagittal **(A)** and axial **(B)** views of the brain reveal hyper-intensities suggestive of plaques (red arrow) and periventricular lesions (orange arrow) as well of signs of atrophy (blue arrows, enlarged ventricles and widened sulci)

The second pathological process, GM atrophy, does not seem to be determined by GM demyelination, as focal demyelination have a limited impact on cortical thickness (Chard & Miller, 2009). Cortical atrophy is present in the early stages of the disease and increases with disease progression (Chard & Miller, 2009). If it is not rare to observe cortical GM atrophy, deep grey matter (DGM) structures are particularly frequently

damaged (Chard & Miller, 2009; Eshaghi, Prados, et al., 2018; Lommers et al., 2021). Among them, the thalami seem especially vulnerable to atrophy (Schoonheim & Geurts, 2019). Compared to HC, pwMS have smaller thalamic volumes, which correlates with disease duration, EDSS score, and score at the Symbol Digit Modalities Test (SDMT, Smith, 1982), a neuropsychological test that is highly sensitive to cognitive impairment in pwMS (Trufanov et al., 2021). In fact, abnormalities in thalami (being functional, morphological, or quantitative) have been linked to numerous clinical outcomes, such as cognitive decline, motor deficits, fatigue and pain (Minagar et al., 2013). The thalamus is a highly connected structure, which receives and projects neurons from/to plenty of cortical and sub-cortical regions. Consequently, the thalamus might be particularly sensitive to retrograde and Wallerian degeneration, but additional mechanisms seem to be at play, as lesions of the thalamic GM were observed, suggesting direct injury of the structure (Minagar et al., 2013).

Interestingly, a recent longitudinal study on a large cohort of pwMS suggested that GM atrophy follows a pattern of progression (Eshaghi, Marinescu, et al., 2018). Their study pointed out that GM atrophy typically started in DGM nuclei (thalamus and pallidum) and the cortex around the midline (the cingulate and precuneus), to progress in more distal cortical regions (Eshaghi, Marinescu, et al., 2018).

Beyond volume loss, microstructure of the NAGM is also affected. MT anomalies of the GM have been found in the early stages of the disease and were correlated to T2w lesion load and EDSS (Davies et al., 2004). Recently, Lommers and colleagues, (2021) showed that GM pathology in MS follows three configurations: (i) GM atrophy in DGM nuclei without significant microstructural changes, (ii) microstructural changes (showing reduction in MT and longitudinal relaxation rate: R1) without significant atrophy in hippocampus and paralimbic cortices and (iii) co-occurrence of the two phenomena in the primary cortices. Consequently, volumetric and microstructural alterations might be driven by different mechanisms.

To conclude on MS pathophysiology, it appears that several mechanisms are at play, affecting both the WM and the GM of the CNS. Despite the growing body of literature investigating GM pathology in MS, its origins are unknown and whether GM damages are preceding, following, or even independent from WM damage (Calabrese

et al., 2015) remains unclear. Due to the high evidence of inflammatory processes in MS, the disease is considered as an immune-mediated disease. However, it is still not clear whether it is an autoimmune condition, or not (Roach, 2004). On the one hand, T-cells are present early in the disease (Dendrou et al., 2015) and positive responses to immune-based therapies in pwMS patients confirm the role of inflammation. However, immunomodulatory therapies are effective in alleviating disease activity, but do not stop disease progression and brain alterations (Dendrou et al., 2015). Moreover, alterations of the GM are observed in the early stages, suggesting that other mechanisms might be at play prior to inflammation of the WM (Chard & Miller, 2009). Consequently, it has been proposed that MS might be a neurodegenerative disorder caused by metabolic dysfunctions (Chaudhuri & Behan, 2004b). To date, this debate is still open.

III. Incidence, etiology and risk factors

In 2013, it was estimated that 2.3 million people live with MS worldwide (Browne et al., 2014). Currently, the website of *"Atlas of MS"* estimates that this number is of 2.8 million ("Atlas of MS," https://www.atlasofms.org/, consulted on April the 1st, 2022). According to this website, MS prevalence in France is currently of about 155/100 000 people and of 104 in Belgium. In France, a recent report (Pivot et al., 2016) showed that MS prevalence varies from 68.1 in the southwest of France (Hautes-Pyrénées) to 296.5 in the northeast (Moselle), which is much higher compared to what was previously reported (Kingwell et al., 2013). No recent peer-reviewed paper updated MS incidence in Belgium since a study conducted in Flanders in 1994 (Dubois, Kobelt, Berg, Capsa, & Gannedahl, 2017; Van Ooteghem, D'Hooghe, Vlietinck, & Carton, 1994). The mean age of disease onset is around 30 years for RRMS and around 40 for PPMS (Rommer et al., 2020).

A particularly intriguing fact about MS is the geographic variations observed regarding its incidence. It has been widely described that MS incidence is distributed along a latitude gradient, with increasing disease rate as distance from the equator increases (S. Simpson, Blizzard, Otahal, Van Der Mei, & Taylor, 2011). Besides, it has

been shown that people migrating to low-risk or high-risk areas of the world respectively decrease or increase their risk of developing the disease, especially if the migration happens during the first 2 decades of their life (Gale & Martyn, 1995). Sunlight exposure, and especially vitamin D level, has often been suggested to be protective against MS and might explain this geographic gradient (Baecher-Allan, Kaskow, & Weiner, 2018; Hayes & Donald Acheson, 2008). Vitamin D has an immune-suppressor effect. More precisely, vitamin D regulates lymphocytes and interleukin-10, and binds to pathogenic T cells to participate to their disruption (Hayes & Donald Acheson, 2008). This provides a neuroprotective effect of vitamin D which could explain why people highly exposed to sunlight are less subject to develop MS.

The exact etiology of MS remains unknown, but several factors might be at play. Among them, genetic susceptibility is undeniable. This is evidenced by family studies showing that first-degree relatives of pwMS and monozygotic twins have an increased risk of developing the disease (Baecher-Allan et al., 2018). Overall, genetics accounts for about 30% of the risk factors to develop the disease and over 100 loci have been associated with its incidence (Baecher-Allan et al., 2018; Dendrou et al., 2015). Consequently, genetic factors might also contribute to geographic disparities in MS incidence (Baecher-Allan et al., 2018; Steele & Mowry, 2014).

Many environmental factors have been identified as potential contributors to MS onset and progression. Among them, cigarette smoking is one of the most studied and has been identified since the 1990s. Smokers show an increased risk to develop MS and also present a more active disease course (Wingerchuk, 2012). Other factors that are currently studied are: Excessive body weight before adult age, night shifts, exposure to organic solvents (Baecher-Allan et al., 2018) and air pollution (Noorimotlagh, Azizi, Pan, Mami, & Mirzaee, 2021).

A viral etiology of MS has often been proposed and one virus that drew particular attention is the Epstein-Barr virus (EBV). EBV infection during adolescence or afterward is a clear risk factor for developing MS (Baecher-Allan et al., 2018). Also, seropositivity rate to EBV is higher in pwMS compared to healthy adults (Steele & Mowry, 2014). In an interesting position paper, Hayes & Donald Acheson (2008) proposed that MS arises from a synergistic occurrence of vitamin D deficiency and EBV

viral infection. EBV may lead to a dysfunction of interleukin-10 production, which could in turn impede the neuroprotective role of vitamin D (Baecher-Allan et al., 2018). How EBV infection contributes to MS development is not known (e.g. if it has a causal role), but it could be related to its effects on the immune system (Baecher-Allan et al., 2018). In any case, since a high proportion of the general population presents a history of EBV infection without developing MS, it is unlikely that EBV infection alone causes the disease (Steele & Mowry, 2014).

A rather new hypothesis regards the implication of the gut microbiome in modulating MS. These past years, research on the role of the microbiota in the Gut-Brain axis has considerably increased (Cryan, O'Riordan, Sandhu, Peterson, & Dinan, 2020). Numerous evidence supports the idea that gut microbiota have a direct effect on the CNS, modulating its physiological state and inflammation (Rutsch, Kantsjö, & Ronchi, 2020). Regarding MS, several studies have pointed out that microbial infections and gut bacteria are linked to the development of the disease (see Rutsch et al., 2020 for a review). More research is definitely needed in this promising field to better understand MS etiology.

Intriguingly, women are more susceptible to develop MS than men, with a female-to-male sex ratio above 2 that keeps increasing (Michel, 2017; Rommer et al., 2020; Steele & Mowry, 2014). Moreover, one study found that women are more frequently subject to cognitive impairment, depression and pain, regardless of disease courses (Rommer et al., 2020). Fatigue is also more frequent in females pwMS compared to males (Rommer et al., 2020). However, other studies suggest that men show a faster progression of the disease (Michel, 2017), which might be explained by the development of more progressive disease courses in men. The reasons behind this imbalanced sex ratio are unknown, but are thought to belong in an interaction of environmental, hormonal and genetic factors (Michel, 2017; Rommer et al., 2020). Since the sex ratio is rapidly changing, environmental factors are, indeed, likely at play (Michel, 2017). Among the numerous possible environmental factors, the increased consumption of tobacco and decreased exposure to sunlight in women (due to urbanization and increasing access to education) are particularly good candidates to explain this phenomenon (Michel, 2017). The implication of hormones, especially

estrogens has often been studied and a mild-level of estrogen was linked to an increased inflammation (Michel, 2017). The drop in relapses frequency during pregnancy and increased risk of relapse during postpartum support this hypothesis (Vukusic et al., 2004).

To conclude, MS most likely arises from a combination of environmental and risk factors, such as low sunlight exposure during childhood, cigarette smoking and viral infection, in persons presenting a genetic susceptibility to develop the disease.

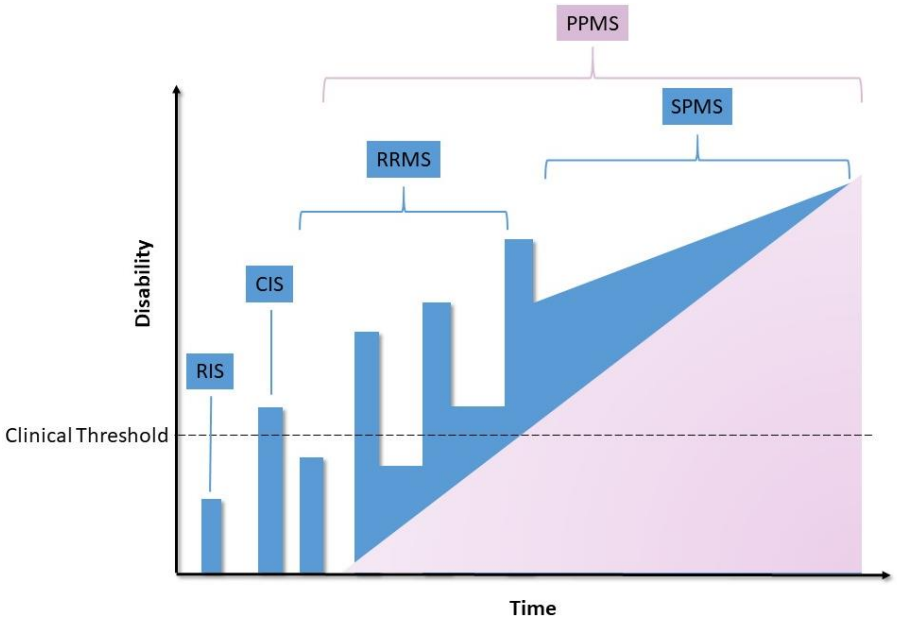
IV. Disease Courses

MS is a heterogeneous disease, with different clinical courses. These clinical courses are defined according to the occurrence of relapses, remission and progression of the symptoms (Compston et al., 2006). Clinical history of MS is determined by three events: Acute episodes with full recovery, acute episodes with partial recovery and chronic progression (Compston et al., 2006). The term *relapse* refers to a sudden exacerbation or apparition of symptoms of varying severity, followed by a period of stability before partial or complete recovery (Compston et al., 2006). The event must last at least 24 hours. New symptoms occurring within a month are considered as belonging to the same relapse (Compston et al., 2006). By opposition, the term *progression* refers to a gradual, systematic increase in clinical status worsening, with occasional steady states and minor temporary improvements (Lublin & Reingold, 1996). It can be identified after 6 to 12 months of progression (Compston et al., 2006). Nevertheless, it is important to mention that relapses can superimpose progression, meaning that the two events are not necessarily independent (Compston et al., 2006).

While gathering these observations, four different clinical courses (Fig. 3) were described (Lublin & Reingold, 1996). The first one is characterized by the occurrence of relapses with remission and is therefore named *Relapsing-Remitting MS* (RRMS). The frequency and severity of relapses are highly variable, and symptoms in the period between two episodes are clinically stable (Compston et al., 2006; Rotstein & O'Connor, 2014). Eventually, the disease will evolve and convert into an irreversible progressive disease course leading to *Secondary Progressive MS* (SPMS). However, a

small proportion of pwMS (about 10%, Lebrun-Frénay, 2017) present an insidious progressive course at disease onset (*Primary Progressive MS,* PPMS). A last progressive course is sometimes described (mainly until 2013) and referred to as *Progressive Relapsing MS* (PRMS) consisting in a progressive evolution at disease onset accompanied by clear acute relapses. This clinical course concerns approximately 5% of all pwMS (Rotstein & O'Connor, 2014). In this case, the period separating two relapses is characterized by a systematic progression. However, since 2013, this clinical course is recognized as belonging to the PPMS disease course (Lublin et al., 2014).

Figure 3. Clinical Courses of MS



Representation of the different clinical courses across time. Radiological Isolated Syndrome (RIS) appears on MRI sequences with no clinical manifestation. Clinically Isolated Syndrome (CIS) corresponds to the first clinical demyelinating episode. Relapsing-Remitting MS (RRMS) characterized by distinct relapses followed by complete or partial recovery. Secondary Progressive MS (SPMS) conversion from RRM with systematic disease progression and Primary Progressive MS (PPMS) with progression from disease onset

With the 2013 revision of MS clinical courses, the concept of *Clinically Isolated Syndrome* has emerged (Lublin et al., 2014). This fifth category corresponds to the first clinical demyelinating episode (i.e. the first relapse). It is a precursor for definite MS, as the majority of patients with CIS will show additional relapses (Rotstein & O'Connor, 2014).

The occurrence of plaques does not completely parallel clinical relapse. Indeed, demyelination can occur without triggering any clinically evident symptom, thus remaining unnoticed (Rotstein & O'Connor, 2014). These under threshold attacks are evidenced incidentally through MRI of the SNC without any history of neurological history evocative of MS (Lebrun-Frénay, 2017), and can occur prior to clinical outburst. MS activity is thus partly silent and the disease can start long before the first clinically assessed relapse. Accordingly, the idea of *Radiologically Isolated Syndrome* (RIS) was proposed, corresponding to the discovery of MS-specific demyelinating plaques in the CNS without any clinical expression (Lublin et al., 2014).

V. The Symptomatology of MS

Due to the spatial dissemination of SNC alterations, the symptoms of MS are heterogeneous across patients and unpredictable (Compston et al., 2006). Symptoms include cognitive impairment, alteration of mood, visual disability, motor symptoms and alteration of the autonomic nervous system (ANS), including bladder, bowel and sexual dysfunctions. However, some symptoms are more frequent than others.

The most frequent presenting symptoms (i.e. at disease onset) are sensory disturbances, visual loss, weakness and ataxia (Rotstein & O'Connor, 2014). *Sensory disturbance* refers to several sensations including numbness, heaviness, sensation of cold or vibration and it often appears in a limb (Robb, Samkoff, & Goodman, 2014). Most of the time, this symptom has an asymmetric presentation, yet, symmetrical presentations can occur and will be suggestive of a lesion in the spinal cord (Robb et al., 2014). *Visual loss* is the second most common presenting symptoms. It usually follows optic neuritis (i.e. inflammation of the optic nerve) and typically affects one eye. Diverse alteration can happen, such as reduced visual acuity, photophobia, alteration of color vision and visual field cut (Robb et al., 2014). In MS, visual acuity loss due to optic neuritis shows, however, a good recovery (Rotstein & O'Connor, 2014). During disease course, visual complains are very common regardless of optic neuritis history (van der Feen et al., 2022). Risk for visual complains increases with disease duration and is more prevalent in SPMS than in other clinical courses (van der Feen et al., 2022).

Weakness at disease onset usually affects the lower limbs and, like sensory disturbance, a bilateral alteration is suggestive of spinal cord injury (Rotstein & O'Connor, 2014). Finally, *ataxia* is suggestive of cerebellar alterations. It can largely impede ambulation and it can be accompanied by other cerebellar symptoms such as nystagmus and dysarthria(Rotstein & O'Connor, 2014).

Alterations of the ANS are not uncommon in MS, even in CIS patients (Crnošija et al., 2016). Both the parasympathetic and the sympathetic systems seem to be affected (Flachenecker, Reiners, Krauser, Wolf, & Toyka, 2001). Among the autonomic dysfunction observed, bladder, bowel and sexual dysfunctions are the more prevalent and have been highly documented. Sudomotor and cardiovascular abnormalities have also been reported (Gunal, Afsar, Tanridag, & Aktan, 2002; McDougall & McLeod, 2003). *Bladder dysfunction* is frequent, affecting up to 70% of patients (Robb et al., 2014). Urinary symptoms comprise urgency, frequency, incontinence and sensation of bladder fullness (Rotstein & O'Connor, 2014). When bladder dysfunction is characterized by a failure to empty the bladder, pwMS are at risk for urinary tract infections and renal dysfunction (Robb et al., 2014). *Bowel dysfunction* is also not rare in MS (yet not as frequent as bladder dysfunction). It relates to both constipation and incontinence and has a deleterious impact on quality of life (QoL) as patients considered bowel symptoms as equally disabling as mobility impairment (Robb et al., 2014). A majority of patient is affected by s*exual dysfunction*. The dysfunction can be either primary (caused by demyelinating lesions), secondary linked to other MS-associated symptoms (such as motor symptoms, fatigue and pain), or tertiary, i.e. due to psychological and emotional state (Robb et al., 2014). Dysfunction include reduced libido, erectile/lubrication disturbances, anorgasmia or dyspareunia (Robb et al., 2014). Sexual dysfunction has an adverse impact on QoL, can occur early in the disease and is likely to be underreported due to the private nature of the symptoms (Robb et al., 2014).

Impaired gait, muscle spasticity and *tremors* are also common and disabling. These symptoms interfere with daily life and movements and can cause social embarrassment (Robb et al., 2014). Physical disability has been linked to cerebellar alterations, including gait and balance impairments as well as reduced walking speed (see Fietsam

et al., 2021 for a review). The high occurrence of plaques in the cerebellum (along with the spinal cord) could partly explain the prevalence of motor impairments in pwMS.

Several MS symptoms are invisible. These symptoms are particularly distressing due to the lack of understanding from others (Parker, Topcu, De Boos, & das Nair, 2021). *Invisible symptoms* are a source of stigmatization, alter confidence in symptom perception, impede help-seeking and lead to social isolation (Parker et al., 2021). These symptoms include *pain, fatigue* and *cognitive impairment*, three symptoms that are highly prevalent in pwMS. Pain prevalence increases with age, disease severity and disease duration (Robb et al., 2014). It impacts QoL and interferes with daily life (Robb et al., 2014). Yet, the underlying mechanisms of pain in MS are not understood. Fatigue and cognitive impairments will not be discussed here, as they will be thoroughly described in further sections of the present thesis. *Heat sensitivity* is another symptom that could be considered as invisible. It refers to worsening or appearance of neurological symptoms due to heat exposure (Marino, 2009). It was proposed that heat has a neuro-blocking effect. Namely, a small increase in body temperatures would be enough to hinder action potential in the demyelinated axon (Guthrie & Nelson, 1995). Heat sensitivity has disabling consequences and is linked to worsen fatigue, cognitive symptoms and pain (Flensner, Ek, Söderhamn, & Landtblom, 2011).

Depression is a symptom of high incidence in pwMS (about 30.5%), which can worsen other symptoms such as fatigue, cognitive impairment and pain sensation (Boeschoten et al., 2017; Charvet, Kluzer, & Krupp, 2014). MS depression has been greatly documented (See Feinstein, Magalhaes, Richard, Audet, & Moore, 2014 for a review). Evidently, depression has a negative impact on QoL, alters social relations and work efficiency (Charvet et al., 2014). The pathogenesis of MS depression can be both primary (due to brain alterations and immunological factors) and secondary to the disease as a reaction to diagnosis and handicap (Charvet et al., 2014; Feinstein et al., 2014). Psychosocial factors of uncertainty, feelings of helplessness, diminution of leisure activities and joy, alteration of social relationships quality, stress and inefficient coping strategies have all been linked to depression in MS (Feinstein et al., 2014). Less attention was brought to *anxiety,* but this symptom is also highly prevalent in MS (about 22%) and has a negative impact on QoL, cognition and fatigue (Boeschoten et

al., 2017; Rooney, Wood, Moffat, & Paul, 2019). *Detecting* and treating depression and anxiety is paramount in pwMS, not only because it can considerably improve the clinical picture, but also because pwMS are at high risk of suicide. Indeed, suicidal attempts are highly related to depression and social isolation (Feinstein & Pavisian, 2017). Suicide rate is particularly high in the 5 years following diagnosis, in men and when age at onset is under 30 years (Feinstein & Pavisian, 2017). Additionally, pwMS showing a co-occurrence of depression and anxiety are more at risk for experiencing thoughts of self-harm and presents more somatic complains (Théaudin & Feinstein, 2015). Psychological well-being in pwMS has been linked to positive illness perception and self-esteem, which could be promoted by psychological interventions (Timkova, Mikula, Fedicova, Szilasiova, & Nagyova, 2021).

Finally, *sleep problems* are also common in psMS, including insomnia, restless leg syndrome, periodic limb movement disorder, circadian rhythm disorders and sleep apnea (see Veauthier, 2015 and Sakkas, Giannaki, Karatzaferi, & Manconi, 2019 for reviews). Particularly, restless leg syndrome (which refers to a sensation of discomfort in legs, especially during rest and in the evening, which can be relieved by movements of the limb) is more severe and five times more frequent in pwMS than healthy subjects (Manconi et al., 2008). If inflammatory processes are likely to cause sleep problems, the secretion of melatonin, the "sleep hormone", could also be involved (Barun, 2013). Indeed, melatonin secretion is altered in MS, which could explain circadian rhythm disruption (Barun, 2013; Melamud, Golan, Luboshitzky, Lavi, & Miller, 2012; Skarlis & Anagnostouli, 2020). Besides, melatonin also seems to have an immune function, though both pro- and anti-inflammatory properties have been observed (Skarlis & Anagnostouli, 2020).

Moreover, fatigue, pain, cognitive and sensory symptoms have been recently linked to productivity loss at work, which concerned 56% of the total sample of worker pwMS (Chen et al., 2018). Similarly, vocational status has been linked to cognition, conscientiousness, depression, disease duration and disability (Benedict et al., 2005; Povolo, Blair, Mehta, Rosehart, & Morrow, 2019). In turn, health-related QoL has been linked to fatigue, depression, and physical disability (Benedict et al., 2005). Some of the associated symptoms, such as cognition, depression and fatigue can be improved

with the appropriate clinical interventions. Consequently, it is crucial to detect them as soon as possible to preserve QoL (Benedict et al., 2005).

To conclude, MS is characterized by a large panel of symptoms, ranging from motor, autonomic, mood and invisible symptoms. Symptoms can be overlapping and interacting and they can increase the risk of developing comorbid conditions. These symptoms are unpredictable and have a severe impact on quality of life. Receiving a diagnosis of MS is highly distressing and leads to incommensurable changes to one person's life. Early in the disease, MS leads to social isolation and unemployment (Simmons, 2010). This diagnosis often occurs early in life, imposing a restructuration and reevaluation of one's personal spheres including domestic, social, employment and life goal pursuit.

VI. Quick Overview of Current Therapies

To date, no curative treatment for MS exists. Current therapies aim at stabilizing or slowing-down disease activity, treating related symptoms and managing acute relapses with corticoids (Doshi & Chataway, 2016).

Treatments targeting disease activity are called Disease-Modifying Therapy (DMT). The first pharmacological treatment was introduced in 1993 with interferon therapies and more than 10 DMT are now available (Montalban et al., 2018), including interferon beta, dimethyl fumarate, fingolimod, natalizumab and alemtuzumab (Doshi & Chataway, 2016). Unfortunately, most pharmacological treatments on the market present frequent side effects (> 1/100), including, amongst others, headache, fever, insomnia, nausea, depression, hair loss, and alterations of liver functions (Doshi & Chataway, 2016). If pioneers DMT were administered with injections, new therapies present an oral administration mode, which has the advantage of being less invasive and avoiding patient hospitalization for treatment (Le Page, Edan, & Veillard, 2017). Selecting the appropriate treatment for a patient can be rather challenging, especially considering the numerous available treatments and their side effects. The choice of the most efficient and safest treatment must be determined for each patient individually (Doshi & Chataway, 2016).

Symptomatic treatment are various, and not necessarily pharmacological. Many MS symptoms can be improved by a pharmacological treatment, such as fatigue (with Amantadine[1]), autonomic symptoms, pain, and spasticity (Doshi & Chataway, 2016). Among the non-pharmacological therapies of MS symptoms, kinesiotherapy is often recommended to pwMS suffering from spasticity, thought data supporting its effectiveness is lacking (Blanchard-Dauphin & Allart, 2017). Fatigue can be improved with exercise, psychoeducation and psychological interventions (Blanchard-Dauphin & Allart, 2017). Effects of yoga practice on mood and fatigue are not robust, as observed in a meta-analysis on studies investigating its effect (Cramer, Lauche, Azizi, Dobos, & Langhorst, 2014). However, it is not associated with adverse events and can be a good recommendation for patients doing few physical exercise (Cramer et al., 2014). Finally, mindfulness interventions show beneficial effects on QoL, mental health, fatigue, balance and pain and are promising interventions for pwMS (Requier et al., in prep; Simpson et al., 2014).

[1] Amantadine seems to significantly alleviate fatigue in pwMS, but presents several side-effects such as nausea, dizziness and insomnia, see Yang, Wang, Deng, & Yu (2017) for a recent meta-analysis.

Chapter II
Cognition in Multiple Sclerosis

I. Cognitive Impairment in pwMS

Cognitive impairments are common in pwMS, with a varying prevalence of 43 to 70% depending on the study (Chiaravalloti & DeLuca, 2008). They occur at any stages of the disease and sometimes following the first demyelinating episode (Chiaravalloti & DeLuca, 2008; DiGiuseppe, Blair, & Morrow, 2018). Cognitive dysfunctions have deleterious consequences on daily life, interfering with vocational status and social relationships (Bobholz & Rao, 2003). The cognitive processes mostly affected are: Processing speed, attention, long-term memory, executive functioning, working memory and social cognition (Brissart et al., 2012; Chiaravalloti & DeLuca, 2008; Dulau et al., 2017). In most of cases, few cognitive domains are altered, with the most frequent impact being on processing speed and memory (Rocca et al., 2015).

A. Cognitive processes affected by MS

Processing Speed

Slowed processing speed is the most frequent cognitive deficit in pwMS (Chiaravalloti & DeLuca, 2008). Information processing speed relies on three different components: Sensorial speed, cognitive speed and motor speed, with one or several that can be altered in pwMS (Costa, Genova, Deluca, & Chiaravalloti, 2017). Increases in processing time in pwMS will affect working memory, learning and executive functioning (Chiaravalloti & DeLuca, 2008). Consequently, processing speed deficits are rarely observed alone and will interfere with many tasks of daily living (Chiaravalloti & DeLuca, 2008). A challenge in interpretation of neuropsychological profile in pwMS is to determine if lower performance on tasks assessing memory and executive functions is due to specific impairment of these processes, or to a global slowing down. Importantly processing speed is a strong predictor of cognitive decline (see, Bergendal, Fredrikson, & Almkvist, 2007 for a eight-year follow-up). Besides, in a large sample of pwMS, measures of processing speed significantly correlated with vocational status and self-reported social participation and satisfaction, well-being, and perception of stigma (Macaron et al., 2020).

Memory

Long-term memory, the ability to learn, maintain and recall information, is impaired in about one pwMS out of two (Chiaravalloti & DeLuca, 2008). While a retrieval deficit was initially postulated, verbal memory impairments appear to be related to a learning deficit (Chiaravalloti & DeLuca, 2008), as pwMS need more learning trials to achieve similar retrieval performances than HC (DeLuca, Barbieri-Berger, & Johnson, 1994; DeLuca, Gaudino, Diamond, Christodoulou, & Engel, 1998). However both acquisition and storage processes seem impaired for visual memory (DeLuca et al., 1998). It has also been proposed that a lower retrieval performance comes from a binding deficit for contextual information[2] at encoding (Thornton, Raz, & Tucker, 2002). Autobiographical memory and future thinking are both often impaired in pwMS, even early in the disease (Ernst, 2020). Finally, procedural learning of motor sequences does not seem to be altered in pwMS, as studies did not find significant differences in learning curve between pwMS and matched HC (Borragán et al., 2022; Tomassini et al., 2011). However, Borragán and colleagues (2022), found that overnight consolidation of learned procedural sequence might be impaired.

Attention

The prevalence of attentional deficits is estimated between 5 and 25% depending on the study (Islas & Ciampi, 2019). Attentional deficits in pwMS are not necessarily generalized and can concern specific processes (Penner, Rausch, Kappos, Opwis, & Radü, 2003). It seems that deficits concern mostly complex attention (such as sustained, divided, and selective attention) and that simple attention (e.g., alterness) is usually preserved (Chiaravalloti & DeLuca, 2008; Islas & Ciampi, 2019). Difficulties in selective and divided attention are expressed mainly as a slowing down of Reaction Times (RTs), but attentional deficits can also alter accuracy in tasks that require a high

[2] The binding process seems nevertheless preserved when based on semantic information.

cognitive effort (Paul, Beatty, Schneider, Blanco, & Hames, 1998). The literature on attention deficits in pwMS can be confusing, because the definition of attention can vary across studies. Indeed many studies describing attentional deficits refer either to cognitive tests assessing processing speed, or working memory or even executive functioning (Chiaravalloti & DeLuca, 2008). As a consequence, description of attentional deficits in pwMS remains elusive.

Working Memory

Studies assessing working memory in pwMS consistently found lower performance in patients compared to controls (see Brissart et al., 2012 for a review). Slowing down of processing speed appears to be a recurrent cause of such dysfunction (Brissart et al., 2012). However, deficits in working memory are also closely related to impairment of processing speed (Chiaravalloti & DeLuca, 2008). Indeed, decreased processing span slows information processing down, while altered information processing speed slows information manipulation during working memory tasks. Accordingly, working memory performance in pwMS can be improved if the time available for processing is increased (Demaree, DeLuca, Gaudino, & Diamond, 1999; Leavitt, Lengenfelder, Moore, Chiaravalloti, & DeLuca, 2011). In pwMS, it seems that the central executive component of working memory is preferably altered, rather than the episodic buffer, phonological loop or the visuospatial scratchpad (Brissart et al., 2012).

Box 1. A Few Definitions...

Autobiographical Memory: The memory for events related to our self.

Future Thinking: Mental projections into future events that can happen to ourselves. This function shows mechanisms, which are highly similar to autobiographical memory.

Together, *Autobiographical memory* and *Future Thinking* are central in one's personal life, as they are involved in problem solving and planning, guiding behavior, promoting self-continuity (they tell us who we are), and also have a social function (Rasmussen & Habermas, 2011).

Working Memory: The immediate retention and manipulation of information for a short duration in order to accomplish a goal.

Executive Functioning: To a set of higher-order cognitive processes enabling a fast adaptation of behavior to environment and goal pursuit. Classically, three distinct processes are described: Mental shifting, information monitoring and updating, and inhibition of response (Miyake 2000). Together, these processes make us able to plan our actions, produce abstract or conceptual thoughts and allocate resources efficiently.

Social cognition: A complex, multi-faceted concept referring to the cognitive abilities fostering social interactions, including the processes of emotion recognition, social conventions integration, empathy and the theory of mind.

Theory of Mind: The ability to understand others by constructing theories (i.e. assumptions) about their feeling, knowledge, thoughts...

Executive Functioning

Though less frequent than deficits in memory or processing speed, impairment of one or more executive processes are not rare in pwMS. This might affect about one patient out of six (Chiaravalloti & DeLuca, 2008; Drew, Tippett, Starkey, & Isler, 2008). Deficits have been observed in the three components of executive functioning (shifting, updating and inhibition), and no typical pattern of deficiency can be drawn (Drew et al., 2008). Verbal fluency deficits are particularly frequent, both in semantic and phonemic conditions. They are actually quite a sensitive measure of cognitive impairment in pwMS (Drew et al., 2008; Henry & Beatty, 2006). However, this test is time-constrained and involvement of processing speed has thus to be taken into account.

Visual Perception

Few data are available on visual abilities in pwMS. Yet, the incidence of deficits in visual perception might be quite high (Marasescu, Cerezo Garcia, & Aladro Benito, 2016; Vleugels et al., 2000). Alterations of visual perception can be related to alterations of the visual system itself (e.g. following optic neuritis) but may also relate to the cognitive processing of visual stimuli (Chiaravalloti & DeLuca, 2008). Actually, Vleugels and colleagues (Vleugels et al., 2000) found that visual perception performances correlate significantly (though weakly) with cognitive status but not with disease duration, MS course or history of optic neuritis. As deficits in visual perception can alter performance on visual modality tasks its assessment should not be neglected.

Social Cognition

Social cognition in pwMS is a field that gained increasing attention in the past years. A recent meta-analysis by Lin et al. (2021) on 45 cross-sectional studies, confirmed that deficits of ToM and facial emotion recognition are both impaired in pwMS. Besides, medium effect sizes observed in this study were not affected by demographics (sex and education), disease duration, EDSS score, severity of depression and several cognitive measures such as working memory (Lin et al., 2021). However, a study from Dulau and colleagues (2017) specifically investigating the association between social cognition and other cognitive domains found a clear link between ToM and executive functioning, working memory and episodic memory. Regarding facial emotions, recognition of fear and anger seem to be mostly impaired, while recognition of happiness seems preserved (Bora, Özakbaş, Velakoulis, & Walterfang, 2016; Lin et al., 2021). Additionally, the deficit in emotion recognition seems to be multimodal, as emotion recognition in vocal bursts has also been evidenced (Montembeault et al., 2022).

Box 2. Assessing Cognitive Impairment in pwMS

Extensive Batteries: Several neuropsychological batteries have been developed to assess cognition specifically in pwMS, two of them are especially used internationally:

The Brief Repeatable Battery of Neuropsychological Tests (BRBNT, Rao, Bernardin & Unverzagt, 1991) is composed of tests assessing processing speed, working memory, verbal and visuospatial memory, and verbal fluency.

The Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS, Benedict et al., 2006), assess the same domains that the BRBNT, with additional measures of visuospatial perception and executive functioning.

Brief Batteries: As a full screening is not always possible in clinical settings, especially because it is time consuming and requires expertise in neuropsychological testing, brief batteries have been developed. The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS, Langdon et al., 2012) is the gold-standard in many countries for a fast screening of cognitive state in pwMS. This battery encompasses the SDMT, the California Verbal Learning Test (CVLT) and the Brief Visuospatial Memory Test Revised

B. The Effects of Disease Duration vs. Disease Course

As a rule, the studies which investigated the effects of disease duration on cognition showed that impairments increase over years in pwMS (Brochet & Ruet, 2019). By means of longitudinal studies (including one with a ten-year follow-up), Amato and colleagues (Amato et al., 2010; Amato, Ponziani, Siracusa, & Sorbi, 2001) found that cognitive impairments are likely to develop and worsen in pwMS, and that SDMT score

is particularly sensitive to cognitive change. However, this observation seems largely driven by increase in age and disease burden rather than disease duration *per se* (Brochet & Ruet, 2019). In a cross-sectional design with pwMS and matched HC from different age groups, Tremblay and colleagues (Tremblay et al., 2020) explored the impacts of MS, age, and disease duration on cognition. They conclude that alterations of cognitive state are mainly driven by age, yet deficits in executive functioning, processing speed and working memory are accentuated by the presence of the disease (Tremblay et al., 2020).

Beyond disease duration and age, disease course also affects cognition. Cognitive impairments are more frequent and severe in the progressive forms of the disease (see for example Ruet, Deloire, Charré-Morin, Hamel, & Brochet, 2013), with a prevalence of cognitive impairment varying from 20% in CIS pwMS to over 75% in SPMS (Charvet, Kluzer, & Krupp, 2014). In comparison to matched HC, PPMS show more severe deficits in a wider range of cognitive functions than RRMS (Brissart et al., 2013; Dulau et al., 2017; Johnen et al., 2017; Ruet et al., 2013). Two recent reviews (Brochet et al., 2022; Johnen et al., 2017) showed that processing speed, verbal learning, working memory and verbal fluency are particularly impaired in PMS compared to RRMS patients, and that impairment in learning and memory cannot be attributed to difference in age (Johnen et al., 2017).

However, one study assessing cognition with a wide range of cognitive tests across HC, RRMS and PMS matched on age, education and time since diagnosis, found no difference in cognitive performance between the two groups of patients (Costa, Deluca, Sandroff, Goverover, & Chiaravalloti, 2018). This suggests that disease course does not affect cognition when controlling for demographics and time since diagnosis, and that cognitive performance is mainly driven by disease severity, rather than clinical course (Costa et al., 2018). Yet, it is important to mention that their study was conducted in patients of approximately 50 years old with a rather long disease duration (average above 12 years in both groups) and that no difference in cognitive scores was obtained between patients and HC for information processing speed.

Results from these studies led to consider that disease course could have an impact on cognition especially in the early stages of the disease, and that, as disease progresses, other factors such as disease severity and aging, are better explicators of cognitive status.

Box 3. Understanding Cognitive Impairments in MS

Pitfalls and methodological issues in research compared to clinic

There is no such test that allows assessing one specific cognitive domain independently from the others. Accordingly, studies assessing cognition by means of one single measure (even if highly sensitive, for instance the SDMT in pwMS), cannot capture the complexity of cognitive functioning. Moreover, other components than the one explicitly studied with the cognitive task can influence performance (e.g. processing speed on executive functioning). Thus, in order to characterize cognitive profiles in pwMS, a good compromise between large neuropsychological testing and long time-consuming protocol is required.

Another problem is that neuropsychological exam in experimental studies, contrary to clinical settings, has to be standardized, in terms of tests used and order of presentation. This type of assessment is necessary to statistical analysis, but this methodology is very distant from a flexible assessment of cognition enriched by qualitative observations as it is performed in clinical settings. Consequently, results from empirical studies can differ from what is actually observed clinically.

Additionally, the definition of what should be considered as a cognitive impairment varies across experimental studies (in clinic, impairment is defined by a convergence of observations including lower than expected cognitive score, usually under percentile 5 or 1). To define cognitive impairment, some studies compare pwMS to a matched HC sample, while others use normative data. For instance, patients might be considered as cognitively impaired if one, two or three scores are above the normative cut-off. Hence, Patti et al. (2009) showed that about 60% of their sample (RRMS with mild impairment as assessed with the EDSS) showed impairment in one test or more (as defined as a Z-Score above 1 or percentile value below 5). This prevalence dropped to about 35% and 20% if cognitive impairment was refereeing to impaired score at 2 or 3 tests, respectively (Patti et al., 2009).Moreover, the definition of the cut-off itself can also vary (i.e. 1.5 vs. 2.0 standard deviation from normative samples for Z-scores; score under 5 vs. 10 for percentiles). This issue leads to discrepancies regarding the prevalence of cognitive impairments in the studied population.

II. Factors influencing Cognition in Multiple Sclerosis

Several factors are influencing cognition in pwMS, such as brain alterations, psychological factors, physiological factors and lifestyle.

A. Cognition and the Brain

As discussed above, MS can lead to a wide range of cognitive symptoms. The links between demyelinating lesions and cognitive deficits have been extensively studied in these past decades (since Rao, Leo, Haughton, St. Aubin-Faubert, & Bernardin, 1989). Pioneering studies repeatedly (yet not systematically) found a link between T2w lesion volume and cognitive impairment at diverse cognitive tests. Yet, longitudinal studies rose conflicting results regarding the prognostic value of lesion load on cognitive functioning evolution (See Rocca et al., 2015 for a review). Later, the effects of lesion localization on cognition have been studied, leading to the conclusion that WM tracts disruption are at least partly responsible for clinical outcomes (Rocca et al., 2015). However, abnormalities within plaques alone do not fully explain the severity of cognitive impairment (Benedict, Amato, DeLuca, & Geurts, 2020). More recently, advanced imaging technics have provided insightful results on the determinants of cognitive state in pwMS. With the development of Diffusion Tensor Imaging (DTI) and voxel-based statistics, the study of normal appearing WM tracts provided more evidences of a disconnection syndrome in pwMS (Rocca et al., 2015). Hence, tract-based analyses linked alterations of the corpus callosum and WM tracts connecting prefrontal regions with deficits in working memory, attention and processing speed (Rocca et al., 2015).

Regarding grey matter pathology, recent studies also implicated cortical GM lesions in determining cognitive state. Actually, cortical GM lesions volume seems to be more predictive of cognitive evolution than WM lesions (Calabrese et al., 2012). Interestingly, GM lesions in the hippocampus seem particularly frequent in pwMS, which could partly explain the high prevalence of memory impairments in this population (Roosendaal et al., 2008). Accordingly, volumetric and functional connectivity measures of the hippocampus have been linked to memory (González Torre et al., 2017). Moreover, both cortical GM and DGM volumes and thickness are linked to cognition (see for example Matías-Guiu et al., 2018). In a recent volumetric

study (Stellmann et al., 2021) cortical thinning in the left inferior insula, superior frontal gyrus, medial temporal cortices and the right intraparietal sulcus has been associated with cognitive impairment in attention, memory, spatial processing and executive functioning domains, depending on the exact region. Among DGM structures, the thalamus seems particularly targeted, and its alterations (atrophy and diffusivity changes) are linked to cognition (Benedict et al., 2020). Indeed, thalamic atrophy is a relevant biomarker of cognitive impairment in pwMS (Houtchens et al., 2007; Trufanov et al., 2021). It is worth noting that third ventricle width is also a good predictor of cognitive state and is often used as a proxy measure of global atrophy (Benedict et al., 2006, 2004). Due to its close position to the thalamic nuclei, enlargement of the third ventricle could, in fact, reflect thalamus atrophy (Benedict et al., 2006). Finally, alterations of GM tissues microstructure have also been linked to cognition in pwMS. For instance, working memory score was linked to mean diffusivity in the cerebellum, while fractional anisotropy was linked to working memory and processing speed (Moroso et al., 2017).

Besides structural alterations within the CNS, cognition in pwMS is also determined by functional cortical reorganization (Rocca, De Meo, & Filippi, 2016). Several evidences for cerebral compensatory mechanisms in pwMS have been provided by functional MRI (fMRI) studies, both in terms of increased brain activity and connectivity (Rocca et al., 2015). For instance, Penner and colleagues (2003) found that, while performing three attention tasks of varying difficulty (alertness, incompatibility and working memory), pwMS with mild cognitive impairment showed increased cerebral activity compared to healthy subjects (i.e. increased signal intensity and width of regions recruited), especially in frontal and posterior parietal regions. Importantly, this pattern of increased recruitment decreased with task complexity, and was not observed in patients that were cognitively impaired (i.e. patients who performed poorly at the tasks). This study provides evidences that compensation throughout increased brain activity (in intensity and topography) is observed in pwMS with preserved cognitive abilities, but that this compensatory mechanism is task-dependent and can collapse in patients with cognitive impairment. Bonnet et al. (2010) found similar results in their fMRI study using a Go/noGo task of varying complexity. They observed

that maintenance of cognitive performance in RRMS patients was obtained throughout a reorganization of cerebral activity, with decreased functional connectivity between the dorsolateral prefrontal cortex and the cerebellum, but increased connectivity with medial frontal regions (Bonnet et al., 2010). As in the study from Penner et al. (2003) they found that this cerebral reorganization collapsed in the more complex task, leading to performance decrement in pwMS compared to HC (Bonnet et al., 2010). Results suggests that the recruitment of regions associated with higher order cognitive processing is needed in pwMS to perform the task due to decreased ability to resort to automated strategies (Bonnet et al., 2010). Assessment of cerebral Resting State (RS) connectivity in pwMS also suggest that altered pattern of activation in several networks (including the Default-Mode Network, DMN) are related to cognitive impairments (Bonavita et al., 2011; Sjøgård et al., 2020; Tona et al., 2014). Yet these alterations are not clearly understood since studies appear to rise conflicting results (reduced vs. increased connectivity was found depending on the study and/or the brain regions). Functional reorganization in pwMS has been linked to brain alterations relating to demyelinating plaques but also in normal appearing brain tissues (Rocca et al., 2016). It has been proposed that, in the early stages of the disease, increased cerebral activity and connectivity promote maintenance of performances, but as cerebral alteration adds up, functional reorganization does not sufficiently prevent from cognitive decline (Rocca et al., 2015). In turn, these functional reorganizations can become maladaptive, leading to cognitive impairment and other clinical manifestations such as fatigue and mood disturbance (Rocca et al., 2016).

To conclude, numerous brain measures have been linked to the severity and prevalence of cognitive impairment in pwMS. However, though very useful to understand the underlying mechanisms of neuropsychological impairments, these variables alone are not sufficient to fully explain cognitive deficits in pwMS. This observation brings us to the next sections, which will discuss the impact of other concomitant factors.

B. Depression, Anxiety & Fatigue

Depression and anxiety, two symptoms of high prevalence in pwMS, have been linked to cognition. MS patients with associated symptoms of depression and anxiety are more at risk for cognitive impairment than patients free from those symptoms (Kalron, Aloni, & Allali, 2018). Anxiety seems to have a negative impact on processing speed, working memory, visuo-spatial memory, verbal learning abilities and social cognition (Genova et al., 2020; Morrow, Rosehart, & Pantazopoulos, 2016; Vissicchio et al., 2019; Whitehouse et al., 2019). In turn, depressive symptoms have been negatively associated with processing speed, executive functioning, attention, memory and social cognition (DiGiuseppe et al., 2018; Genova et al., 2020; Golan et al., 2018; Kalron et al., 2018; Morrow et al., 2016; Niino et al., 2022; Nunnari et al., 2015) However, some studies did not find a link between depression and cognition in pwMS (see Arnett, Barwick, & Beeney, 2008 for a review). This could come from the relatively small sample sizes used in those studies, or the fact that depression might relate to cognition when it is severe only (Arnett et al., 2008; Golan et al., 2018).

Unfortunately, most studies exploring the effects of mood disturbances on cognition used cross-sectional paradigms, with an extensive number of correlations, sometimes with limited sample size and without controlling for demographic variables. Besides, cognitive domains of interest and neuropsychological assessment vary across studies. These methodological issues limit our understanding of the effects of mood disorder on cognition. Most particularly, because longitudinal studies in that field are scarce, it is still unclear whether cognitive impairments precedes mood disorder (due to their negative impact on quality of life and social interactions, or in relation to brain alterations), if mood disorders are a risk factor for cognitive impairment, or if the two phenomena interact with each other. A study from Hildebrandt & Eling (2014) in RRMS patients highlighted that baseline performance in executive functioning and memory significantly predicted depression after a follow-up of one year, and that depression was never improved suggesting that neurodegeneration is involved in mood alterations. In turn, in a heterogeneous sample of pwMS (RRMS and PWMS patients), Christodoulou and colleagues (2009), found that high negative affects (including depressive mood and anxiety) predict cognitive change after the same amount of time, especially in episodic

memory. Additional longitudinal studies are needed to better understand how cognition and mood relate to each other, but it is likely that the two symptom interact.

The relationship between reported fatigue in everyday life and cognitive deficits, however, has been less studied and is still debated. In a study comparing a sample of cognitively impaired (CI) pwMS with cognitively preserved patients, Heesen and colleagues (Heesen et al., 2010) observed that both depression and fatigue were higher in the CI group. While depression was strongly correlated to memory, fatigue was found to be associated to attention (Heesen et al., 2010). Besides attention (Heesen et al., 2010; Anna Pokryszko-Dragan, Zagrajek, et al., 2016), fatigue has been linked to processing speed (Andreasen et al., 2019; Diamond, Johnson, Kaufman, & Graves, 2008; DiGiuseppe et al., 2018) and verbal memory (Anna Pokryszko-Dragan, Zagrajek, et al., 2016). However, these results are challenged by other studies which did not find a link between fatigue and cognition, or found that this link was mediated by other factors, such as depression, disability and pharmacological treatment (Golan et al., 2018; Hildebrandt & Eling, 2014; Jougleux-Vie et al., 2014; Morrow, Weinstock-Guttman, Munschauer, Hojnacki, & Benedict, 2009; Parmenter, Denney, & Lynch, 2003). The relationship between, fatigue and cognition in pwMS is further described in **Chapter IV**.

In conclusion, depression, anxiety and fatigue are frequent symptoms of MS that are thought to interfere with cognition. Further studies are needed in this field to better understand how these variables interact with each other, and with cognition itself.

C. Cognitive & Brain Reserves

The last determining factor of cognition that will be discussed is reserve. Initially proposed by Stern (2002), the theory of Cognitive Reserve (CR) has enjoyed a plethora of evidences from studies on Alzheimer's disease, Parkinson's disease, traumatic brain injuries and stroke (see for example Hindle, Martyr, & Clare, 2014; Nelson, Jester, Petkus, & Andel, 2021 for Parkinson's disease and Alzheimer's disease, respectively). This theory was proposed following the recurrent observation that brain damage does not necessarily lead to cognitive deficits and clinical manifestations (Stern, 2002). Concretely, the notion of reserve refers to the capacity of the brain to compensate the

effects of neurological alterations to maintain adequate functioning. It is thought that this reserve can be nourished during the lifetime thanks to a nurturing and stimulating environment as well as physical and cognitive exercising (Stern, 2009). Two distinct concepts are described: *Active Reserve*, which is a functional, evolving reserve that depends on environment and nourishing activities, and *Fixed Reserve*, which refers to the genetically determined inborn capacities and is also referred to as *Brain Reserve* (Stern, 2009). The two concepts can be understood as *"What you've got, and how you use it"* (Sumowski et al., 2013, cited by Brochet, 2018).

With respect to Multiple Sclerosis, it is becoming clear that reserve plays a role in the evolution of cognitive functioning. Indeed, high intracranial volume (which is an estimate of maximal lifetime brain volume) and intellectual enrichment both lessen the effects of cerebral changes on clinical measures (Sumowski & Leavitt, 2013). In fact, pwMS with lower brain and/or cognitive reserves show a high correlation between MRI-estimated disease burden and cognitive impairments (Sumowski & Leavitt, 2013, see however Bonnet et al., 2006 in which, on the contrary, cognitive performance in early MS correlated to cerebral alterations in patients with high cognitive reserve only). In a longitudinal study (Modica et al., 2016), decreased performance at the SDMT after a 3-year follow-up was observed in pwMS with low CR score only (compared to HC and pwMS with medium and high reserve), and high CR was shown to protect pwMS against the effects of DGM atrophy on processing speed. It has been shown that patients with high premorbid Intelligence Quotient (IQ) might not be considered as cognitively impaired according to conventional cognitive testing, yet show decreased abilities compared to their premorbid state (Feinstein, Lapshin, O'Connor, & Lanctôt, 2013). Consequently, CR seems to attenuate the impacts of cognitive decline, leading to sub-threshold cognitive impairment in some patients (Feinstein et al., 2013). In a 2-years longitudinal study, Rocca and colleagues (2018) show that CR explains a significant part of variance in verbal memory and verbal fluency abilities when controlling for cerebral atrophy. However, in this study, CR did not predict the evolution of cognitive score from baseline (Rocca et al., 2018). These results suggest that the protective role of CR may decrease as disease progresses. The effect of CR was further confirmed by a recent meta-analysis (Santangelo, Altieri, Gallo, & Trojano, 2019, with a synthesis of 72

studies) showing that CR proxies (education, vocabulary knowledge and CR questionnaires) significantly attenuate the effects of brain damage and physical disability on cognition, yet this was confirmed for only two cognitive processes: lexical access and cognitive flexibility.

Some evidence for an effect of brain reserve on disease evolution has also been observed. For instance, estimated brain reserve (total intracranial volume) has been shown to modulate the effects of brain alterations on verbal memory (Ifantopoulou et al., 2019) and cognitive efficiency (Sumowski et al., 2014, 2013). However, Sumowski and colleagues (2013) proposed that CR (i.e. lifestyle) have an independent and superior protective role against disease evolution compared to brain reserve (i.e. genetic factor).

Research on cognitive reserve is highly promising and could lead to intervention targeting a protection of cognitive decline through cognitive enrichment. Consequently, there is an urgent need to identify whether cognitive enrichment after disease onset (i.e. not only in early life) is effective in increasing cognitive reserve, and for how long. Further studies are also needed to determine which activities best protect again brain alterations, and if it is generalized to every cognitive domain or not (studies described above suggest that only a few of them may benefit from reserve). With regard to the type of cognitive activities which most likely protects against cognitive decline, Sumowski and colleagues (2016), found that among several leisure activities during early adulthood (reading & writing, art & music and games & hobbies), only literacy activities predicted hippocampal volumes and were the best predictor for memory performance.

III. Clinical Management of cognitive deficits

The effectiveness of pharmacological treatments are difficult to estimate as cognition is rarely a primary outcome of randomized control trials of DMT drugs, and effects on cognitive deficits are often assessed retrospectively in post-hoc analysis (Ruet, 2015). Overall, current studies suggest an effect of DMT drugs on the evolution of processing speed, working memory and attention (as assessed with the SDMT and the Paced Auditory Serial Addition Test: PASAT, Benedict et al., 2020; Gronwall, 1977).

Symptomatic treatments have also been proposed (i.e. treatments directly targeting the symptom), such as acetylcholinesterase and stimulant drugs, but studies assessing their efficacy are scarce and no robust data are supporting their effectiveness so far (Ruet, 2015). Overall, evidences for the effects of drugs on cognitive impairment in pwMS are insufficient, and cognitive rehabilitation interventions provides more convincing results (Benedict et al., 2020).

These neuropsychological interventions can be classified into two approaches (Benedict et al., 2020): the *Restorative Approach* (training of one particular cognitive domain throughout repetition) and the *Compensatory Approach* (relying on preserved cognitive domains and the use of strategy to compensate the deficit). Studies assessing the effectiveness of cognitive restoration extensively relies on computerized programs, and lead to encouraging results. Indeed, a recent meta-analysis (Lampit et al., 2019) observed that computerized cognitive training show a small to moderate effects on attention/processing speed, memory and executive functioning (effects on working memory were not significant, though assessed by solely four studies). However, the benefits of cognitive training appeared to vanish with time if a booster session was not administered (Lampit et al., 2019).

The first published study supporting the effect of the compensatory approach in pwMS used context and imagery strategy-based encoding and showed effectiveness in improving verbal learning abilities for at least six months (Chiaravalloti, Moore, Nikelshpur, & DeLuca, 2013). Since, other studies have brought additional evidences for the effects of this approach, mostly in RRMS. Studies assessing its efficacy in PMS are scarce, but there are encouraging evidences suggesting that these technics are also effective in this disease courses (R. H. B. Benedict et al., 2020).

Another treatment strategy raising promising results (yet requiring further investigations) is the multidisciplinary approach, combining cognitive rehabilitation with another type of intervention, such as psychoeducation, cognitive behavioral therapy, transcranial direct stimulation and aerobic exercises (R. H. B. Benedict et al., 2020; Sokolov, Grivaz, & Bove, 2018). For instance, a recent study found that, compared to cognitive training alone, adding transcranial direct current stimulation during training sessions (1.5 mA for 20 min on dorsolateral prefrontal cortex) enhanced the

improvement observed on complex attention and reaction times variability (Leigh Charvet et al., 2018). Studies investigating the effects of physical exercise on cognition also show promising results, but several limitations should be addressed, including small sample sizes and type and dose of exercises included in protocol (Sokolov et al., 2018).

To conclude, non-pharmacological approach showed promising results in the clinical management of cognitive impairment in pwMS. Considerable efforts have been made to improve methodology and collect more robust data. Several practical points still need clarifications, such as intervention duration and frequency required for optimized efficiency, as well as the need of a booster session. From a clinical point of view, other factors influencing cognition such as depression, anxiety and fatigue, should be taken into account in psychological interventions.

IV. Early Multiple Sclerosis

Studying the specific case of early MS raises insightful observations. Due to the limited brain alterations following onset, it promotes a better understanding of the temporal dynamics of MS underlying neuropathology (see for instance Koubiyr et al., 2021). Focusing on early MS also limits the impact of interacting factors such as physical disability and severe depression.

But what should we understand by early MS? According to Chard & Miller (2009), it is challenging to define what early MS is, especially because the pathological process of the disease might start years before its first clinical manifestation. Nevertheless, they suggested a cut-off of 5 years since the first clinical manifestation to consider the disease as being in its early stage, whatever the subsequent clinical course, but emphasize that this should be understood as “clinically early” and not “pathologically” (Chard & Miller, 2009). Most studies referring to early-MS have used this arbitrary duration of 5 years.

As developed in the first chapter, grey matter pathology, and not only alterations of the WM, are already visible in early MS (Chard & Miller, 2009). MRI studies

investigating brain alterations found diffuse alteration of NAWM microstructure, frequent occurrence of cortical lesions and reduced cortical thickness and volumes (Granberg et al., 2017; Koubiyr et al., 2018; Nygaard et al., 2015).

During the first years of the disease, cerebral reorganization is already at play. A monitoring of structural and functional connectivity evolution from the first clinical manifestation (CIS[3]) to 1 and 5 years following disease onset showed that structural connections first diminished within the first year and increased after 5 years (Koubiyr et al., 2021). After 5 years, this enhanced connectivity was reflected by an increased structural clustering associated to a decrease of characteristic path length, suggesting that a reorganization onto more constrained connectivity occurred (Koubiyr et al., 2021). Moreover, structural-functional coupling increased over the five years and was negatively associated with cognitive and clinical worsening, suggesting a decreased plasticity ability to reconfigure functional connectivity due to structural constraint and alterations (Koubiyr et al., 2021). Indeed, in their preliminary study, CIS patients show decreased structural-functional coupling compared to HC after one year, especially in the sensorimotor, salience and visual networks, along with preserved cognitive performances suggestive of compensatory mechanisms due to functional reorganization (Koubiyr et al., 2019).

Despite functional reorganization, cognitive impairments are already observed at disease onset in some cases. The prevalence of CI in CIS and early MS varies from 12 to 57% depending on the study, the criteria used for cognitive dysfunction and the cognitive domain studied (Grzegorski & Losy, 2019; Bardia Nourbakhsh, Nunan-Saah, et al., 2016). Most of the time, CI is not the sole clinical manifestation of CIS, yet cognitive relapses (acute or subacute cognitive symptom without any other clinical manifestation) can occur in rare cases (Grzegorski & Losy, 2019). CI in CIS and early RRMS follows the same pattern of dysfunction than later in the disease, affecting memory, attention, processing speed and executive functioning (Kiraç, Ekmekçi,

[3] As a reminder, CIS refers to patient with only one clinical manifestation (first clinical episode), and are by definition in the early stages of the disease, yet the presence of MS might have to be confirmed.

Yüceyar, & Kocaman, 2014). Information processing speed and memory seem especially impaired in the early stages of the disease (Deloire, Ruet, Hamel, Bonnet, & Brochet, 2010; DiGiuseppe et al., 2018; Khalil et al., 2011). As for general cognition, prevalence of deficits in specific cognitive domains greatly varies. For instance, DiGiuseppe and colleagues (2018) found that almost one patient out of three present a deficit in processing speed within the first year following diagnosis, while another study assessing cognition in CIS and early RRMS showed that processing speed was altered in 13.6 and 16.3% of the patients, respectively (Khalil, Enzinger, et al., 2011). In this last study, processing speed in CIS was linked to MT ratio in the cortex, suggesting that early microstructure changes of NAGM occur in relation to CI, while in RRMS, processing speed was associated to cortical volume and T2-lesion load (Khalil, Enzinger, et al., 2011). Lesion location following the first demyelinating episode seems also critical, especially for memory deficits, as demyelination in Broca's area, right frontal lobe and splenium have been linked to lower scores in verbal memory, and lesions to the deep WM to spatial learning (Reuter, Zaaraoui, Crespy, Faivre, Rico, Malikova, Confort-Gouny, et al., 2011). Atrophy has also been linked to cognitive deficits in CIS patients, as for example in the study of Štecková and colleagues (2014), showing that several cognitive measures correlates with thalamic atrophy in CIS patients. Consequently, several markers of brain integrity are linked to cognitive deficits in CIS patients, comprising diffuse and focal alterations, which suggest that different pathophysiological mechanisms might be at play.

Finally, assessing cognition early in the disease is crucial because it can predict disease evolution. Hence, information processing speed and memory performance at disease onset can predict EDSS score assessed 5 and 7 years later (Deloire et al., 2010). Besides, cognitive deficits are likely to worsen during the first years of the disease (Glanz, Healy, Hviid, Chitnis, & Weiner, 2012; Hankomäki, Multanen, Kinnunen, & Hämäläinen, 2014; Reuter, Zaaraoui, Crespy, Faivre, Rico, Malikova, Soulier, et al., 2011). Therefore, they should be carefully monitored. Among the neuropsychological tools available to track evolution of cognitive deficits, the SDMT seems particularly sensitive to detect changes in longitudinal evaluations (Deloire et al., 2006; Glanz, Healy, Hviid, Chitnis, & Weiner, 2012).

Chapter III
Fatigue

I. What is it that we call Fatigue?

A. The History of Fatigue

Perhaps one aspect of fatigue that is consistently acknowledged in our society is its negative impact and aversive dimension. However, no universal deffinition of fatigue exists. This chapter will describe this concept and provide a definition that should suit the present work.

According to Robert Hockey (2013), the cultural perception of fatigue evolved drastically following the Industrial Revolution. During the pre-modern era, it is very likely that fatigue was considered as a natural sensation occurring in daily life, just like sleepiness or hunger. While fatigue was, indeed, experienced by our ancestors, there is no evidence suggesting that it would have been perceived as an aversive cause of complaint (Hockey, 2013). In fact, the first medical description of fatigue as a symptom can be found at the end of the 19th century, with the apparition of the expression *"neurasthenia"* (Léotard, 2021). Already, confusion emerged regarding fatigue symptoms, since neurasthenia was used as an umbrella expression referring to many conditions and etiology, including a symptom of psychosis, depression or fatigue (Torres-Harding & Jason, 2005). Later, several illnesses with fatigue as a primary outcome and overlapping symptoms have been described in soldiers (during the American Civil War and the First World War), including the DaCosta's syndrome, neurocirculatory neurasthenia and the effort syndrome. These syndromes included symptoms of fatigue, headaches, palpitation, disturbed sleep, fainting, pain, breathing difficulties and more (Torres-Harding & Jason, 2005). If these symptoms were initially attributed to cardiovascular malfunction, the lack of physiological evidence led to the conclusion that they had a psychosomatic or psychogenic etiology (Torres-Harding & Jason, 2005). Back then, already, the psychological dimension of fatigue was suggested.

In the early 20th century, fatigue was considered as the disease of modern age (Hockey, 2013). A particular attention was brought to this topic following the observation that factory workers showed decreased performance when fatigue arises (Torres-Harding & Jason, 2005). Consequently, scientific publications exploring fatigue fundamentally increased from 1900, reaching a peak in the 1930-1940's (Hockey, 2013). According to Hockey (2013), the Industrial Revolution led to major changes in the work

environment. If work demand and effort were already high in the pre-modern era, the industrialization (i.e. factory work) led to an increased work rate, decreased support and control over work as well as a decreased reward and recognition of work. Importantly, work goal shifted from a task oriented to a time oriented process, and began to be externally paced, with the frequency and duration of breaks not being self-managed anymore (Hockey, 2013). This high work demand combined to a loss of control most likely triggered the evolution of fatigue perception, which is now seen as aversive in our culture (Hockey, 2013).

Following this widespread interest in exploring fatigue, characterized by numerous theoretical framework and lots of empirical studies, the mid-20th century showed a progressive decrease in fatigue-related publications (Hockey, 2013). However, since the 80's, a renewal of interest is observed, with an increasing body of literature exploring the effects of sleep deprivation on fatigue, but also (and maybe most importantly regarding the present thesis), investigating fatigue as a clinical outcome of neurological diseases (Hockey, 2013).

B. Fatigue: A Multi-Faceted Concept

Fatigue is non-specific. It can be a natural physiological signal indicating the need to rest or interrupt a task, but it can also become pathological, interfering with daily activities. Fatigue can be a reflection of physiological state, can be triggered by medication (for instance antihistaminic drugs) or by lifestyle (night shifts, lack of physical exercises, substance abuse…), but can also be caused by a medical condition or psychiatric disorder (Torres-Harding & Jason, 2005). In some cases, fatigue can even have no apparent etiology (Torres-Harding & Jason, 2005). Whatever the cause, fatigue can take several forms. It can be differently defined depending on its origin (central vs. peripheral), the modality it will affect (cognitive *vs.* physical), the way it will be expressed (subjective *vs.* objective[4]) and its transitory or persistent nature (state *vs.* trait).

[4] The distinction between subjective fatigue and objective fatigability as being two different processes is still debated. Indeed, for some authors, these are two different constructs and are not necessarily concomitant (see for instance Hockey, 2013 or Burke et al., 2018), for some others,

Origin of fatigue: Peripheral vs. Central

One dichotomy that has been widely proposed in fatigue's taxonomy is whether it is a peripheral or central mechanism. This classification differentiates fatigue according to its origin, as arising from the muscle (peripheral) or the central nervous system (central). According to Chaudhuri & Behan (2000), peripheral fatigue is *"the inability to sustain a specific force output or work rate during exercise"* (p. 34) that is limited to physical/motor work and can be a symptom of neuromuscular or peripheral circulatory disorders. In contrast, central fatigue is *"the failure to initiate and/or sustain attentional tasks [...] and physical activities [...] requiring self motivation"* (Chaudhuri & Behan, 2000, *p. 35*) and can arise without any muscle failure or cognitive disability. Consequently, peripheral fatigue will limit motor tasks only, while central fatigue can alter both motor and mental functioning. The possibility of central origin in motor fatigue was confirmed by several studies throught the demonstration that transcranial stimulation of the motor cortex can restore force decrement (Leavitt & DeLuca, 2010).

Modality of fatigue: Physical vs. Cognitive

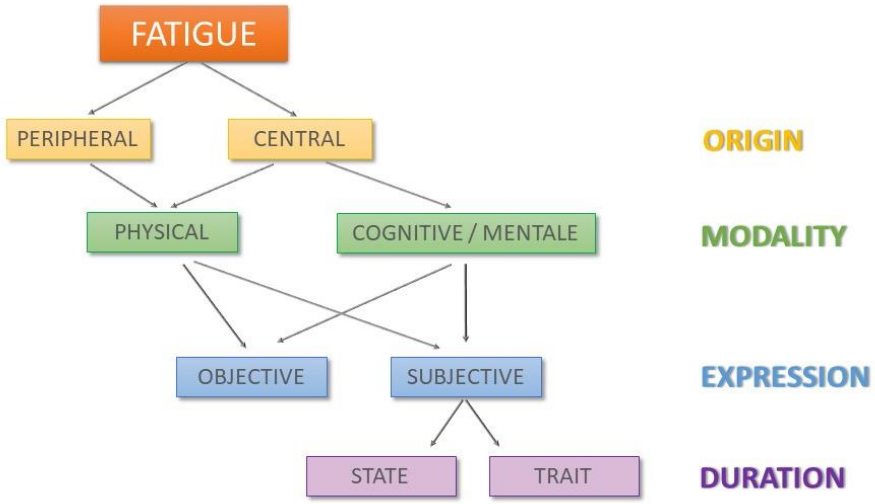
Fatigue can be classified according to the affected modality. *Physical Fatigue* refers to the exhaustion of the body, as physically perceived or measured (for instance, reduction in volitional muscle activation, Dotan, Woods, & Contessa, 2021), while *Cognitive Fatigue* (sometimes also referred to as *Mental Fatigue)* corresponds to a lack of mental energy. The latest will be further defined in this chapter, as this thesis focuses on the cognitive aspects of fatigue.

This duality is often pointed out in fatigue definitions, as for example the definition from the MS council (1998), describing fatigue as *"a subjective lack of physical and/or mental energy".* Differentiating the two modalities is crucial, because the two domains: Show distinct interactions with other symptoms (such as depression); are not necessarily concomitant; and might rely on different mechanisms (Penner et al., 2009). However, the two mechanisms may interact. This is suggested by evidences of physical performances alteration (reduced endurance) subsequent to cognitive fatigue

subjective and objective fatigue are measures of the same mechanism (see for example Bafna & Hansen, 2021). In this thesis, the former hypothesis is favored.

induction, possibly due to a higher perception of exertion (see Van Cutsem et al., 2017 for a review). Yet, the effects of cognitive fatigue on physical performances are still debated, as they might be driven by decreased motivation rather than fatigue itself (McMorris, 2020; McMorris, Barwood, Hale, Dicks, & Corbett, 2018).

Figure 4. The taxonomy of fatigue



Fatigue is a multifaceted concept of varying definitions. It can be defined according to its origin, the affected domain, its clinical/behavioral manifestations or its duration.

From a psychological point of view, psychosocial fatigue can also be described and measured, referring to social disengagement due to fatigue (for instance, decreased participation to social events). However, this last classification can be seen as controversial, since it highly interacts with physical and cognitive factors (Daphne Kos et al., 2005) and should be seen as relevant mostly for clinical purpose (i.e. the impact of fatigue on daily living and QoL).

Expression of fatigue: Subjective vs. Objective

Whatever the modality affected (physical or cognitive), fatigue can have a subjective and/or an objective expression. Subjective fatigue is usually reported by means of self-assessment questionnaires, scales and interviews, referring to how someone "feels" fatigued. Objective fatigue is mainly behaviorally assessed throughout the decrement in performance (cognitive or motor), following or during a fatiguing task, and would be

more accurately called *"fatigability"*. Due to its objective and measurable nature, behavioral fatigability was preferably studied in research protocols, while in the medical context, assessment of subjective fatigue is predominant as it directly relates to patients' experience and complaints (DeLuca, 2005).

One major difficulty to obtain a universal definition of fatigue lies in the observation that subjective and objective measures do not correlate well (DeLuca, 2005). Measures of subjective feeling and actual performance decrement are not concomitant in many examples and even seem unrelated sometimes (Penner & Paul, 2017, see for also Linnhoff, Fiene, Heinze, & Zaehle, 2019 for a review in MS). One possible explanation is that fatigue sensation arises prior to any performance decrement, reflecting an increased effort to maintain task goal (Hockey, 2013). This will be further developed below in this chapter.

According to Penner & Paul (2017), distinguishing subjective fatigue and objective fatigability is essential to our understanding of fatigue symptoms. In fact, they suggest that the two phenomena might be preferably triggered by different mechanisms. Accordingly, altogether with Kluger, Krupp & Enoka (2013) they proposed that performance fatigability relates to peripheral and central factors, while self-perceived fatigue is mostly determined by homeostatic factors, environmental factors (e.g. medication, poor sleep) and psychological factors (Penner & Paul, 2017).

Box 4. Peripheral, Central and Homeostatic Factors

Peripheral Factors refers to the muscular-skeletal system and peripheral nerves, comprising loss of muscle force, peripheral neuropathy and myopathy.

In contrast, **Central Factors** refers to factors directly linked to the central nervous system functioning integrity.

Homeostatic Factors are linked to the regulation of the organism and maintenance of a steady state. It includes inflammatory reaction, regulation of physical activity and neuroendocrine changes.

Duration of fatigue: Trait vs. State

One last distinction useful for the present work is whether fatigue is transient or persisting (Kluger et al., 2013). As no existing tool enables an objective measurement of persisting fatigue, this classification is meaningful for subjective fatigue only (physical or cognitive). State fatigue refers to a transient state of fatigue sensation that is caused by, and usually accompanies/follows, sustained effort (effort-dependent fatigue,

Genova et al., 2013). Trait fatigue, however, is a persisting sensation, that is not necessarily caused by a specific event (effort-independent fatigue, Genova et al., 2013). It is a more stable state experienced in everyday life and it is not necessarily relieved by rest. Excessive trait fatigue is most of the time pathological and it is a complaint of many illnesses, including neurological conditions.

C. Fatigue, Sleepiness and Boredom

If a universal definition of fatigue does not exist yet, we can however discuss what fatigue is not. Sleepiness and boredom are two states that could be confused with fatigue (actually, in some studies, these terms are used interchangeably). These three states present overlapping signs, but they must be considered as distinct phenomena (see Table. 1).

Fatigue and sleepiness can be confused because it can both emerge from precipitant factors such as sleep deprivation (Duntley, 2005). Sleep is a primary need that serves restorative functions, though its exact mechanisms are not completely understood. Sleepiness is a physiological state urging the need to sleep, which arises with increasing sleep pressure (for instance following sleep deprivation) and is modulated by the circadian clock. Sleepiness is expressed by a high propensity to fall asleep or difficulties to maintain wakefulness. In contrast to sleepiness, fatigue is relieved by rest, and not sleep per se (Mairesse et al., 2019). Sleepiness can be easily detected, because it goes along with numerous characteristic signs such as heavy eyelids, yawning and nodding off (Duntley, 2005). Fatigue, however, is not characterized by such signs. Similarly, sleepiness can be objectively measured (with sleep latency for example), while objective measure of fatigue only rely on dynamic evolution of performance due to fatigability (Mairesse et al., 2019). While sleepy people usually report fatigue sensation, it is clear that fatigue can be experienced without any sign of sleepiness (Duntley, 2005). Consequently, it is much likely that the two phenomena emerge from distinct neurophysiological mechanisms (Duntley, 2005). Sleepiness state depends on the balance between activity of the wakefulness-promoting and the sleep-promoting pathways. The wake-promoting pathways starts in cholinergic and monoaminergic regions of the midbrain (including the laterodorsal tegmental nuclei, locus coeruleus, raphe nuclei…) and splits into a dorsal pathway innervating the thalamus and a ventral

pathway to the hypothalamus, basal forebrain and the cortex (Scammell, Arrigoni, & Lipton, 2017). In turn, sleep is promoted by different routes depending on the ongoing sleep stage. Non-Rapid Eye Movement sleep is principally promoted by GABAergic neurons of the preoptic nuclei inhibiting the activity of the wake pathway (Scammell et al., 2017). According to Duntley (2005), increased wakefulness throughout the activation of the corresponding pathway may not improve the function of regions responsible for fatigue state. To date, no consensus exists regarding the fatigue pathway, but Duntley's hypothesis relies on evidences showing that fatigue may arise from change in activity in the basal ganglia and its connections with the cerebral cortex (Chaudhuri & Behan, 2000), suggesting that change of cortical activity (for example in the cingulate) may trigger fatigue without affecting sub-cortical circuity of sleep pathways (Duntley, 2005).

Table 1. Proposal for differentiation between Fatigue, Sleepiness and Boredom

	FATIGUE	*SLEEPINESS*	*BOREDOM*
COGNITIVE SIGNS	Sometimes	Yes	Yes
LOW MOTIVATION	Sometimes	No	Yes
INDUCED BY SLEEP DEPRIVATION	Yes	Yes	No
INDUCED BY SUSTAINED TASK	Yes	Sometimes	Sometimes
CHARACTERISTIC SIGNS	None	Yawning, nodding off	Mind-wandering
RELIEVED BY	Rest	Sleep	Changing task/goal

The three states, though presenting overlapping signs, must be considered as distinct. All of the three can be characterized by decreased cognitive performance (such as vigilance drop or slower reaction times), but these states are not necessarily co-occurring. This table presents some contrasting characteristics of these states. For characteristics signs, the difference between fatigue and boredom is more tentative and need to be formally assessed.

Boredom is another psychological state, which highly overlaps with fatigue sensation. Studies assessing the effects of cognitive fatigue extensively used long-lasting protocols to induce fatigue, relying on the hypothesis that performance will inevitably decrease at some point (i.e. if the task is long enough). However, performance

decrement observed with time on task might also be attributed to a disengagement from the task due to boredom. According to Meyers (1937 cited by Hockey, 2013) boredom refers to a failure to find interests in a task, leading to a decreased spontaneous or voluntary attention. Boredom is highly linked to motivation and the conflict between maintaining or avoiding a specific task, but conversely to fatigue, it does not reflect an increased effort to remain engaged in the task (Hockey, 2013). Accordingly, boredom often arises in environmental context of low stimulation, leading to a state of underload (Hockey, 2013; Pattyn, Neyt, Henderickx, & Soetens, 2008).

Hence, one alternative way to think about boredom, is to discriminate active and passive fatigue as proposed by Hancock and Desmond (2001). While *active fatigue* derives from an increased effort to adjust behavior to task demand in situations of overload, *passive fatigue* is caused by prolonged monotonous task, leading to a context of underload and triggering boredom (Pattyn, Van Cutsem, Dessy, & Mairesse, 2018). Despite this clear conceptual differentiation, discriminating between the two phenomena in empirical studies is challenging, as both mechanisms can be at play in long-lasting protocols (Hockey, 2013). In fact, Hockey (2013) argues that boredom is a component of a wider spectrum of fatigue state, and that boredom, just like fatigue, is an externally imposed situation and motivates individuals to change the environment or the ongoing task. Yet, in the context of this thesis, the two states will be considered as distinct. If boredom and fatigue may be considered as reflecting a unique mechanism in healthy subjects, this may not be the case for pathological fatigue. As it will be argued in this thesis, fatigue in neurological conditions does not necessarily arise from task engagement. It is thus a construct essentially different from boredom.

D. Defining Cognitive Fatigue

The present work is centered on the cognitive aspects of fatigue. So, what is cognitive fatigue? Fatigue can refer to many different constructs, depending on the field of study. This is why it is needed to provide a clear description of what one should understand by *"cognitive fatigue"* in this thesis.

Agyemang and colleagues described cognitive fatigue as the *"inability to maintain an optimal level of performance throughout a sustained cognitive task"* (Agyemang, Berard,

& Walker, 2021, *p.1*). However, this definition is not specific enough and could relate to boredom, sleepiness or even cognitive impairment. For Tanaka and colleagues, *"Mental fatigue can be defined as a psychobiological state caused by prolonged periods of demanding cognitive activity and manifests as a reduced efficiency in cognitive performance"* (Tanaka, Ishii, & Watanabe, 2014, *p.60*). Though more specific, this definition can be seen as incomplete, because it lacks the important notion that fatigue is a subjective state that can arise without any performance alteration. By contrast, according to Van As and colleagues, cognitive fatigue is *"a complex psychobiological state resulting from cognitive effort exertion and is characterized by feelings of low energy, low positive affective states and a reduced motivation to exert effort"* (van As et al., 2021, *p.2*). In this definition, the subjective aspect of fatigue is at the forefront, but the idea of behavioral alterations or interference with the ongoing task does not appear. The definition of Slimani and colleagues, however, seems more complete, as they define cognitive fatigue as *"a psychobiological state induced by prolonged periods of demanding cognitive activity"* which *"has subjective, behavioral and physiological manifestations"* (Slimani, Znazen, Bragazzi, Zguira, & Tod, 2018, *p.1*). In the present thesis, this last definition will be preferred in the context of "physiological" normal fatigue.

Regarding *pathological* cognitive fatigue (which should be understood here as a symptom of neurological diseases), the definition will slightly differ. According to the MS Council (1998), fatigue in MS refers to *"a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities"*. Thought highly relevant in clinical settings, the idea that the symptom can be perceived by caregivers will be secondary here. Maybe one definition which encompasses all the complexity of this symptom is the one provided by Bakshi (2003), according to whom fatigue is *"an abnormal sense of tiredness or lack of energy, out of proportion to the degree of effort or level of disability, that significantly interferes with routine physical or intellectual functioning"* and is *" an unusual and abnormal form of fatigue that differs from the fatigue experienced by healthy individuals after exertion"* (Rohit Bakshi, 2003, *p.2019*). This definition is particularly elegant, because it suggests that fatigue is by essence a subjective state, which can lead to deleterious impacts on functioning in everyday activities. Besides, the notion of effort is present, distinguishing

fatigue from boredom and sleepiness, but is not constraining, complying with the special case of pathological fatigue. Similarly, the level of disability is taken into account, suggesting that physical and cognitive deficits can be concomitant but do not fully explain fatigue symptom. Finally, and importantly, it emphasises that pathological fatigue is fundamentally different from the normal physiological state experienced by healthy subjects. Therefore, this definition should be kept in mind when referring to cognitive fatigue in pwMS and other neurological disorders.

II. The Markers of Fatigue and How to Study Them

A. Subjective Fatigue

As described earlier, subjective fatigue can be thought in terms of trait fatigue and state fatigue. The former can be assessed by means of interviews, fatigue diaries and fatigue scales. Numerous fatigue scales have been developed and validated, assessing for instance the severity of fatigue symptom (Fatigue Severity Scale, FSS, Krupp, LaRocca, Muir-Nash, & Steinberg, 1989) or the proportion to rest following diverse daily activities (Brugmman Fatigue scale, BFS, Mairesse et al., 2019). Some scales also enable a multimodal assessment of fatigue, as it is the case for Fatigue Scale for Motor and Cognitive Functions, Penner et al., 2009) and the BFS which encompasses a cognitive and a physical score. The Modified Fatigue Impact Scale (MFIS, Ritvo et al., 1997) is also a widely used scale with cognitive, physical and psychosocial components. These are just a few examples of widely used scales, many more exists. Quality of fatigue scales varies drastically and one should be aware of their psychometric characteristics (such as internal consistency, specificity and sensibility) when selecting one of them. One specific pitfall is the measurement of overlapping symptoms between fatigue and depression (for instance, decreased participation in social events), with some scales being highly correlated to depression score, thus presenting a low specificity. The choice should also be driven by the population studied and the question to answer. For instance, the FSS and the FSMC are two scales that have been originally designed to assess fatigue in Multiple Sclerosis, specifically (Krupp et al., 1989; Penner et al., 2009), and are therefore often recommended to study fatigue in this disease. Finally, some scales present the advantage of providing clinical cut-off (like the FSMC) or normative

data (M-FIS, Strober et al., 2020) to detect abnormal fatigue. Thought these tools come with some limitations, fatigue scales are very useful to assess fatigue incidence in general or specific populations. They are also valuable in experimental designs to screen fatigue symptoms in participants and refine results interpretation in fatigue studies.

Regarding state fatigue, available tools are much more limited. Classically, evolution of fatigue state is assessed by means of Visual Analogue Scales (VAS). VAS are used to assess different current subjective states (pain, mood, motivation, effort…) and can be applied to fatigue assessment (Lee, Hicks, & Nino-Murcia, 1991). These scales consist on a horizontal line representing a continuum between two extrema, as for example "no pain/unbearable pain" or "feeling fresh / exhausted" and individuals are required to rate their current state by indicating where they situate themselves on the continuum. VAS are usually used to assess fatigue evolution with time on task or after induction of a fatiguing task compared to a control task. VAS are highly valuable because they quantify a subjective state and can demonstrate the effects of fatigue induction on perceived state. This is important because, as explained in the previous section, fatigue is a subjective, self-experienced sensation by essence. However, VAS might be difficult to interpret in some cases. Two methods of analyses can be considered: Using the *"raw score"* of the scale (usually from 0 to 100) to reflect fatigue state at a given time, or derive a *"delta score"* which will take into account baseline fatigue state of the participants (delta = current score – baseline score). Depending on the method used for analysis, outcomes might significantly differ. Indeed, as VAS are by definition highly subjective, assessment in a sample of volunteers will often lead to great inter-subject variability and puzzling results[5]. Hence, one major problem with

[5] Consider that two participants obtained a score of 80/100 at a VAS assessing fatigue following fatigue induction, with a high score reflecting high fatigue. Now, consider that participant 1 had a score of 50/100 at baseline (i.e. before fatigue induction) while participant 2 had a score of 20/100. Which participant was more affected by fatigue induction? Can we consider that they both experience the same level of fatigue? Similarly, in the situation where two participants showed an increase of 10 points on the VAS scale following fatigue induction, but that participant 1 increased from 10 to 20/100 while participant 2 increased from 80 to 90. Can we consider that the task had the same effects on both participants?

VAS scales is that, paradoxically, they are not linear (i.e., an increase in 10 points will not have the same implication depending on where we are situated in the continuum).

To conclude, assessing fatigue by means of self-report scales and questionnaires is crucial, because fatigue is a subjective symptom. However, these tools present several limitations and may be difficult to interpret in research settings. Consequently, objective signs of cognitive fatigability are often preferred in research protocols.

B. Objective Fatigability

According to Christodoulou, almost every cognitive performance can be considered to assess fatigue (Christodoulou, 2005). Yet, the vast majority of studies used slowness of RTs and decreased accuracy to assess fatigability, often in attentional and executive tasks. Two different approaches have been classically used to measure fatigability: the *Time on Task* approach (ToT, or *continuous work method*) and the *probe task* approach (Hockey, 2013). The former aims at assessing the effects of a prolonged, continuous task on performance decrement or variations, while the latter investigates the effects of induced fatigue state on subsequent performances.

The Time on Task Approach

The ToT approach derives from the work curve, initially proposed by Kraepelin in 1902 (Hockey, 2013), and consist in assessing performance evolution during a continuous task at different time points. The idea behind the work curve is that performance will necessarily drop as a function of time spent in a task and that this could be mathematically described (Hockey, 2013). One of the most famous applications of the work curve is the work provided by Arai (1912, cited by Hockey, 2013). Arai administered herself a set of difficult arithmetic problems (multiplication of four by four digits) over continuous 12-hour periods from 11:00 to 23:00, during four repeated days. To assess fatigability, she reported the time she needed to perform each problem. Impressively, she performed these arithmetic problems without exposing them in front of her eyes, thus highly relying on her working-memory abilities (Hockey, 2013). As the effects of practice were already suspected by then, she trained herself to solve such problems prior to her experimental investigation. The results of this experiment show clear evidence of a ToT effect on performance, as the time needed to resolve a problem

almost doubled after 12 hours (Hockey, 2013). Two important observations can also be mentioned: Performance completely recovered after a night of sleep, and the effects of ToT gradually diminished from day 1 to day 4, suggesting that a practice effect still occurs. Since this early work, assessments of performance fatigability with ToT protocols were extensively carried out. Some of them will be presented in the following paragraph.

In a study assessing the effects of cognitive fatigue on attention, a visual attention task was administered for 3 hours without interruption (Boksem et al. 2005). This protocol lead to decreased performance, as evidenced by increased RTs and decreased accuracy (i.e. increased miss and false alarm rates) with time on task. Similar results were found by Lorist and colleagues (2008; 2005) with an attention and flexibility task of 2 hours, during which RTs and accuracy were gradually altered. Wang and colleagues (2014) administered a computerized Stroop task (Stroop, 1935) of 3 hours to assess performance decrement in 17 healthy young adults. Their results show that both mean and variability of RTs increased with ToT with a significantly greater effect size for the later. To assess the effects of breaks on cognitive fatigue, Gilsoul and colleagues (2021) also administered a computerized Stroop task (of 160 minutes in this case) in groups of young, middle-age and older healthy participants. As a function of time spent on the task, participants showed slower RTs with increased amount of extreme RTs (highly deviating above average), especially in younger and middle-aged people, and when no breaks were provided. In studies assessing the effects of long-driving sessions on fatigability, performance decrements are also observed. For instance, Guo and colleagues (2018) showed that participants performing a driving simulation for 90 minutes make more deviations from lane during the last 30 minutes. Hopstaken and colleagues (2015a) administered an N-Back working memory task (Kirchner, 1958) of varying difficulty (1 to 3-Back) for 2 hours.

Box 5. Hit, Miss, Correct Rejection and False Alarm

When ones should decide if a stimulus is a *Target* (i.e. stimulus to be detected) or a *Distractor* (i.e. irrelevant stimulus to be ignored), four types of answers can be provided:

A **Hit** corresponds to the correct detection of a target stimulus

A **Miss** corresponds to the absence of detection of a target

A **Correct Rejection** corresponds to the absence of response following a distractor

And a **False Alarm** corresponds to the erroneous response to a distractor

After 2H, motivation was ingeniously manipulated by informing the participants that the remaining duration of the task will depend on their performance (i.e. if they performed better than earlier, the task will last only 5 minutes. Otherwise, it could last for up to 40 minutes). Yet, task length was actually not depending on their performance and was set to another 18 minutes. Results clearly show that accuracy decreased with ToT for the easiest and the middle difficulty conditions (1 & 2-Back) but was fully restored following motivation manipulation (Hopstaken et al., 2015a). Accuracy for the most difficult task (3-Back) showed an overall improvement during the whole session, and no significant ToT was observed for RTs, regardless of task difficulty (Hopstaken et al., 2015a). These results support a strong link between decreased performance and task disengagement in cognitive fatigue, and suggest that motivation is a variable of high relevance (at least for tasks with low load level). If ToT protocols usually rely on tasks of long duration (i.e. over an hour), fatigability is also observed in designs with shorter task length. Borragán, Salma and colleagues (2017) succeeded in inducing performance fatigability with a dual task of 16 minutes only. Cognitive load was manipulated in their experiment by adjusting the time available to process stimuli. Results showed that performance decrement (drop in accuracy) was occurring more rapidly in condition of high cognitive load (i.e. when the time to process stimuli was short). Indeed, accuracy significantly decreased after only 8 minutes of performing the task in the high cognitive load condition, while it decreased after 16 minutes in the slow, low cognitive load session (Borragán et al., 2017).

As pointed out by Borragàn (2016), the ToT method is particularly convenient because it reduces the amount of variables to be controlled for (e.g. work load, control task…). In fact, this method was usually preferred in laboratory studies, since it enables a control for the homogeneity of work amount during successive time periods (Hockey, 2013). In turn, probe tasks were preferably used for field-studies, assessing the effects of fatigue in real life situations, where a ToT protocol is not easily set up (Hockey, 2013). Practically, the probe approach consists on assessing the effects of fatigue with a "probe" task administered before, after or during a *"loading task"* that is fatiguing. Difference in performance in repeated probe tasks (for instance before vs. after fatigue induction) enable assessing objective fatigue effects of the loading task. The probe task

approach derived from the need to develop a reliable, short and convenient test to assess fatigue during a working day in different industrial settings (Hockey, 2013). Of course, due to the complexity of fatigue symptom, such test does not exist and probably never will, especially if it is based on performance decrement only. However this approach has been often used as for instance to assess the effects of sleep deprivation or medication on cognitive fatigue (Hockey, 2013). Importantly, the probe approach refers to the idea that cognitive fatigue is transferable and can generalize to any cognitive task (i.e. from the loading task to the probe task). As we will see in the following paragraph, this might not be completely accurate.

The Probe Approach

One challenging issue often met in the probe approach is to find a suitable control task. Some studies assess performance at a cognitive task prior to and following the loading task. However, this method presents several limitations, including the confounding effect of practice contaminating the results on the repeated task. Another method is to recruit two groups: a group who will perform a fatigue-induction task and another who will perform a control task for the same amount of time (usually, watching videos, reading magazines...). This is the case of the study from van der Linden and colleagues, in which half of their sample completed a cognitively demanding planning task during two hours and a control group which had free time in the lab for 2 hours instead (van der Linden, Frese, & Meijman, 2003). A short-term memory task (forward digit span) was administered prior to and following the loading task in both groups, to assess the effects of fatigue induction. Both groups exhibited a similar increased performance at the digit span following the loading task, reflecting practice effect. However, compared to controls, participants in the fatigued group showed decreased performance at executive control tasks (the Wisconsin Card Sorting Test and the Tower of London) administered at the end of the protocol (van der Linden et al., 2003). Indeed, fatigued participants showed increased planning time and displayed more perseverations than control participants. These results are interpreted by the authors as indicating that cognitive fatigue alters executive functioning rather than short-term memory (van der Linden et al., 2003), but this could also indicate that cognitive fatigue is not contaminating task of different cognitive processes, as their loading task was relying on

executive processes. In their above-mentioned study, Guo et al. (2018) opted for a similar design. Half of their sample performed the fatiguing 90 minutes driving simulation, while the other half performed a control task which consisted on watching movies for the same amount of time (Guo et al., 2018). A Go/noGo task was administered prior to and following driving simulation and video watching. Only participants in the fatigue group displayed an alteration of performance (increased RTs and miss rate, but false alarm rate did not change) following the load task, as watching videos did not influence performance. In a study from Klaassen and colleagues (2014), each participant completed two sessions in counterbalanced order: A fatiguing session consisting in performing cognitively demanding tasks during 1.5 hours (working memory N-Back, Stroop, arithmetic and puzzle tasks) and a control session of same duration during which participants watched videos or read magazines. In both sessions, participant performed a working memory task after the loading task. Results show that accuracy was lower following the fatiguing session compared to the control session, while RTs did not differ across sessions (Klaassen et al., 2014). In the study from Esposito and colleagues (2014), participants were invited for two testing sessions: a fatiguing session during which participants were trained with a helicopter flight simulator during four hours, and a control session during which they could leave the lab and engage in any non-effortful activity they wanted for the same amount of time. The probe task was an N-Back task administered in the morning and in the evening, in both sessions. Performance obtained at the N-Back task did not differ across session, which was interpreted by the authors as related to the increased subjective effort reported by participants in the fatigue session compared to control (Esposito et al., 2014). In other words, the authors suggest that performance was maintained due to a compensatory effort provided in fatigued participants. However, this result could also be in favor of a domain specific alteration of performance in cognitive fatigue. In a recent study from Gergelyfi and colleagues (Gergelyfi et al., 2021), participants were administered a working memory task following a modified Stroop task of 90 minutes (non-verbal number and arrow Stroop task) or a control task of the same duration (reading magazines) in two separated sessions. During the working memory task, motivation was manipulated through different monetary incentives. Accuracy at the working memory task was lower following fatigue induction compared to the control

condition, and higher reward led to better performances. Importantly, the effects of fatigue induction on accuracy were not modulated by reward manipulation, suggesting that motivation was not sufficient to restore accuracy following fatigue induction (Gergelyfi et al., 2021). To test the interacting effects of fatigue and motivation on lower order processes, a simple reaction time task was also administered in both sessions with reward manipulation, prior to and following the working memory task. Again, higher rewards were leading to better performances (shorter RTs), but this effect was not modulated by fatigue condition. Yet, the simple effect of fatigue condition was not significant for this task and participants showed a greater practice effect in the fatiguing condition compared to the control condition (greater decrease in RTs following the working memory task). The last study that will be presented in this section is the one from Borragàn and colleagues (2016) that provides an example of increased performance following fatigue induction, which might be counterintuitive at first sight. In their paradigm, high and low cognitive fatigue was induced during two separated sessions using a dual task with varying cognitive load (i.e. the high cognitive load condition led to high fatigue, and the low cognitive load to low fatigue). A serial reaction time task was administered after fatigue induction, during which participants displayed faster RTs following the high cognitive load compared to the low cognitive load sessions. This gain in RTs was due to a faster acquisition of the sequence to be learned. As discussed by the authors, this is a nice example of how cognitive fatigue can facilitate automatic procedural learning through decreased cognitive control (Borragán et al., 2016).

Concluding Remarks

Both the ToT and probe methods present advantages and inconvenients. The selection of one or the other mainly depends on the question. Ideally, both can be implemented in the same protocol to get a wider picture of the mechanisms at play. In the present thesis, the two approaches will be used in the same sample of participants.

As pictured in this section, behavioral results suggestive of performance fatigability show discrepancies across studies. Some studies found evidences for an effect of cognitive fatigue on reaction times or/and accuracy (Gilsoul & Collette, 2018; Lorist, 2008), others did not (Hopstaken et al., 2015a). Some studies are suggestive of a

generalization of the effects of cognitive fatigue across tasks (Guo et al., 2018), others are not (van der Linden et al., 2003). Finally, some studies proposed a restorative effect of motivation in fatigued participants (Hopstaken et al., 2015a), while others found that motivation is not sufficient to counteract fatigue consequences (Gergelyfi et al., 2021). To better understand the mechanisms at play, physiological markers of cognitive fatigue have been extensively explored in association to its objective and subjective behavioral manifestations.

C. Physiological Measures of Fatigue

Eyes, Skin & Heart Measures

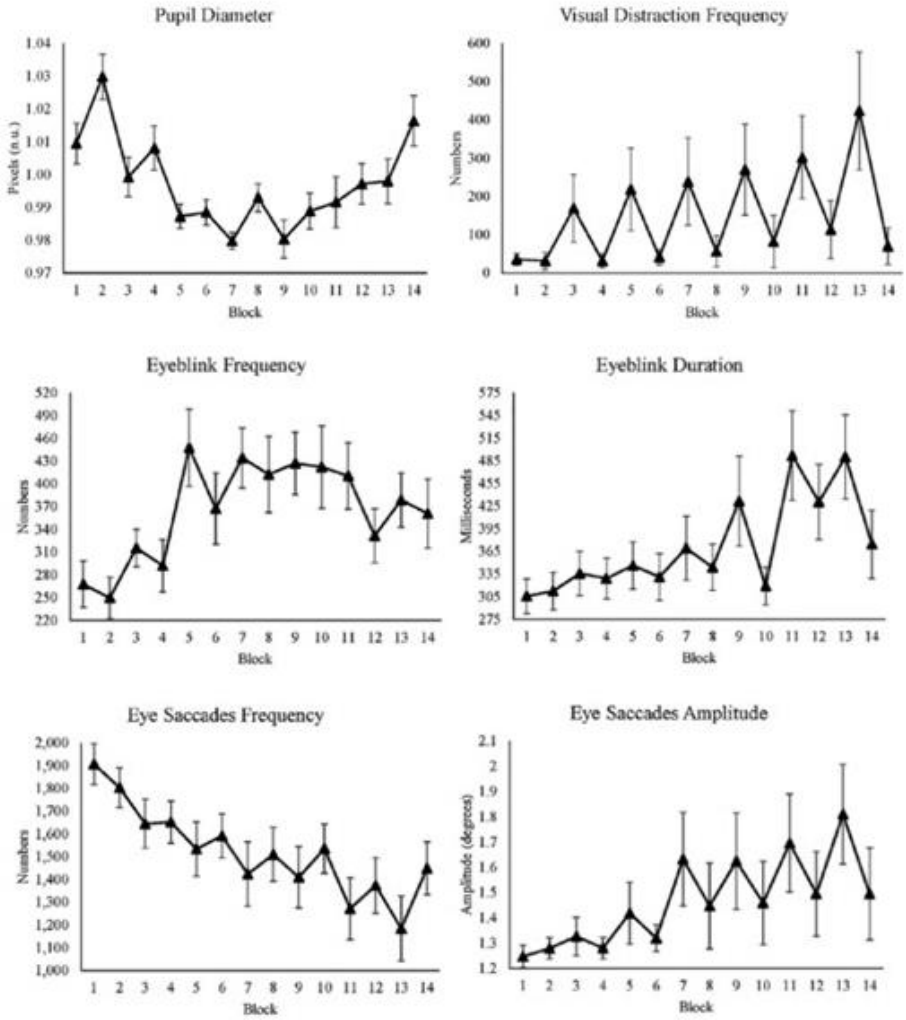
In the past years, eye metrics variable have gained increased interest in the field of fatigue. Measures such as blinks, eye movements, eyelids closure and pupil variations seem to be promising indicators of cognitive fatigue (see Bafna & Hansen, 2021; Cori, Anderson, Shekari Soleimanloo, Jackson, & Howard, 2019 and Rodriguez et al., 2018 for reviews). With increasing fatigue, a decrease in variables of pupil dilation (mean, peak, range) and saccade velocity (mean and range) and an increase in blink count and frequency was observed (Bafna & Hansen, 2021). For instance, it was shown that pupillary light reflex is reduced and delayed in fatigued participants (Bafna & Hansen, 2021; Rózanowski, Bernat, & Kamińska, 2015). Pupil measures are particularly interesting because they relate to mental effort and task engagement (Zénon, 2019). Consequently, they have been used to test the link between fatigue and motivation. In a study from Hopstaken and colleagues (2015), stimulus-evoked pupil dilation diminished as a function of time in a fatigue inducing protocol. Following motivation manipulation, pupil size was restored to its baseline measure and stimulus-evoked dilation rose again, along with accuracy and subjective task engagement. In a recent study from Herlambang and colleagues (Herlambang, Taatgen, & Cnossen, 2019), eye metrics were extensively used to assess the effects of motivation on fatigue induction. In their design, participants were administered a working memory task of 2.5 hours with blocks alternating between providing reward or not. As expected, accuracy decreased in the non-reward blocks only while it remained high in the reward condition. Time on task, but not reward, had an effect on subjective fatigue, while subjective effort was linked to reward only. Regarding eye metrics, several measures

indicated that participants showed a disengagement from the task during the non-rewarding blocks, to favor engagement during reward blocks (Herlambang et al., 2019). Indeed, as displayed in Figure 5, participants exhibited less visual distractions, less saccades, less and shorter blinks in rewarding blocks (Herlambang et al., 2019). Regarding pupil size variations, the authors suggest that pupil first decreases due to a learning effect of the task leading to diminishing workload and exploration, and then increases again with task engagement and reward expectation (Herlambang et al., 2019). Overall, this study suggests that participant regulated mental effort to favor performance during the rewarding blocks, and might have rested during the non-reward condition. However, several time*reward interactions were observed in this study, including in eye variables, suggesting that motivation throughout reward manipulation does not allow a full recovery of physiological state. Unfortunately, these interactions are not discussed by the authors.

Skin conductance and heart rate measures are also used to physiologically assess fatigue. With time on task, decreased heart rate and increased heart rate variability (HRV) have been liked to fatigue (Mascord & Heath, 1992), while the opposite pattern is observed when mental effort increases, suggesting that fatigue might be related to lower effort investment (Gergelyfi, Jacob, Olivier, & Zénon, 2015). Skin conductance is highly sensitive to sympathetic activity due to changes in sweating activity. Electrodermal activity has been linked to arousal, cognitive fatigue and effort (Heaton et al., 2020; Pakarinen, Pietila, & Nieminen, 2019) and can discriminate between chronic fatigue syndrome and depression (pre-stimulus skin conductance is lower in patients with chronic fatigue syndrome compared to depressed patients and controls, Pazderka-Robinson, Morrison, & Flor-Henry, 2004). In a study from Gergelyfi and colleagues (2015), eye metrics, electrocardiograms and skin conductance were recorded during a fatiguing protocol (2 hours of Sudoku tasks) to explore how cognitive fatigue relates to task disengagement due to a drop in motivation. While subjective fatigue increased and performance in a working memory task decreased, blink rate and HRV increased, reflecting induction of cognitive fatigue. However, skin conductance and pupil response were constantly sensitive to reward manipulation during the whole experiment, and reward was not sufficient to restore performance. Consequently, this

study suggests that cognitive fatigue is not caused by task disengagement, as physiological markers of motivation remained sensitive to reward incentives during the whole task (Gergelyfi et al., 2015).

Figure 5. Example of eye measures in fatigue protocol



Effects of motivation and time on task on diverse eye metrics related to pupils, blinks and saccades. Odd blocks provided no reward, even blocks are rewarded. Adapted from Herlambang et al. (2019)

Noteworthy, measures of pupil, heart rate and skin conductance have one common point: They all relate to the activity of the ANS. As already mentioned, ANS symptoms

are highly frequent in pwMS, and we will discuss later a recent hypothesis linking pathological fatigue in pwMS with ANS alterations.

Electroencephalography & Magnetoencephalography

Studies providing Electroencephalography (EEG) and Magnetoencephalography (MEG) data are plentiful in the field of cognitive fatigue. Due to its high temporal resolution and its convenience for long-lasting protocols, EEG are particularly suitable for ToT protocols. Boksem and colleagues (2005), found that several event-related potential (ERP) components are linked to performance decrement in cognitive fatigue. More precisely, performance change with ToT was accompanied by a decrease in error related negativity (i.e. large negative shift in amplitude following a mistake) and N2 (i.e. negative shift prior accurate answer) amplitude, suggestive of impaired action monitoring in fatigued participants. Besides, contingent negativity activation amplitude (negative shift between warning and stimulus, reflecting anticipation and preparation) was also reduced, reflecting a decreased response preparation when cognitive fatigue rose (Boksem et al., 2005). In a very interesting EEG study, Wang and colleagues (2016) found evidences of a compensatory mechanism to maintain performance during fatigue induction. In their study, late ERP component (i.e. between 640 and 1272ms) recorded in anterior frontal scalp mirrored performance. During the first half of the experiment (approximately 80 minutes) the amplitude of this ERP gradually increased while performance at the task was maintained. Afterwards, the amplitude decreased progressively until the end of the task and was accompanied by performance decrement. Consequently, this result suggests that a compensatory neural activity occurs, reflected by late ERP component located in frontal regions of the brain, but that such mechanism is limited and can be disrupted in prolonged cognitive tasks, leading to performance alteration (Wang et al., 2016).

MEG investigations received particular attention by the team of Watanabe, leading to a series of studies published by their lab. For instance, they found that alpha power in the visual cortex decreased following fatigue induction during rest (eyes closed), especially following a 2-back fatiguing task compared to a 0-back task. This suggests that over-activations consecutive to fatigue induction are load-dependent (Ishii et al., 2013). These results were replicated in another study showing that the decreased alpha-

frequency band power in the visual cortex observed following fatigue induction was associated with decreased performance (Tanaka, 2015). Additionally, in a small sample of healthy subjects (n=10), they found that fatigue induced by a short auditory attentional task (10 min) led to increased event-related synchronization of beta-frequency band in the right middle frontal gyrus, and that this increase was correlated to self-perceived boredom and sleepiness. This result was interpreted by the authors as reflecting a decline in brain arousal level during cognitive fatigue (Tanaka et al., 2014).

Magnetic Resonance Imaging & Positron Emission Tomography

Finally, MRI and Positron Emission Tomography (PET) studies also provide insightful results to our understanding of cognitive fatigue. Neuroimaging studies assessing the effects of cognitive fatigue in healthy subjects evidenced the implication of fronto-parietal areas and deep grey matter nuclei in fatigue genesis, yet with conflicting results. For instance, in a $H_2{}^{15}O$ PET study, using a fatiguing visual attention task, Tajima and colleagues (2010) found that subjective fatigue correlated significantly and positively with regional cerebral blood flow in the medial orbitofrontal cortex, while performance remained stable. In another PET study, Paus and colleagues (1997) showed that the induction of an auditory vigilance task of one hour led to decreased activity in the thalamus and the putamen as well as cortical frontal (ventrolateral, dorsolateral and orbitofrontal cortex), parietal, and temporal areas. In a study from Lim and colleagues (2010) the administration of a 20-minute attention task (Psychomotor Vigilance Test: PVT) resulted in a decreased speed in RTs and increased subjective fatigue with ToT, along with decreased fronto-parietal network activation during post-task rest fMRI, which correlated to performance decline. Additionally, baseline rest activity was predictive of subsequent effect of ToT on performance. Namely, increased activity of the right middle frontal gyrus and the thalamus before the task were positively and negatively associated with subsequent performance decrement, respectively (Lim et al., 2010). In Persson et al. (2013), the neural correlates of interference control depletion were explored, showing that executive resource depletion (as expressed behaviorally by reduced ability to resolve interference following a fatiguing working memory task) were accompanied by a shift in activity from left to right. Namely, Blood Oxygenation Level Dependent (BOLD) signal during the task decreased in the left inferior frontal gyrus,

striatum and cerebellum, but increased in the right hemisphere, including in the inferior frontal gyrus, the insula and the temporal cortex (Persson et al., 2013). Increased fronto-parietal activations with ToT was also observed by Lim and colleagues (2016). In their study, healthy participants performed a mentally demanding symbol decoding task in the scanner. With ToT, a shift was observed from left to bilateral brain activity, and activity steadily increased in several brain areas including in the left middle frontal gyrus and the bilateral paracentral gyrus. Additionally, they observed that the deactivation of regions belonging to the DMN gradually decreased with ToT (increased activation with ToT). The authors interpret the discrepancies in terms of hyper/hypo activations in fronto-parietal regions between the present study and their previous one (Lim et al., 2010) as being most likely a consequence of the cognitive task used for fatigue induction (Lim et al., 2016). Indeed, they suggest that simple decision-making tasks (binary target vs. non-target decision) will lead to decreased recruitment of the above-mentioned regions, while more complex processing, such as in the present study, will lead to an over activation when fatigue arises (Lim et al., 2016). In the same vein, Anderson and colleagues (2019) recently pointed out that most neuroimaging studies assessing the effects of cognitive fatigue on cerebral activity did so during effortful cognitive task. Yet, as cognitive fatigue might be task-specific, so might be its neural correlates. Consequently, results from specific fMRI studies might not be generalized to every cognitive task. To test this hypothesis and seek for task-general correlates of cognitive fatigue, Anderson et al. (2019) administered four different cognitive tasks in healthy older individuals during repeated fMRI sessions. Using a data-driven representational similarity analysis, they found that the right insula and the right putamen were relevant functional hubs reflecting subjective cognitive fatigue across tasks (Anderson et al., 2019). Additionally, bilateral caudate, left middle frontal gyrus, right inferior frontal gyrus and right parietal gyrus based networks were found to be implicated in not all, but the majority of the tasks. These results suggest that, if some cerebral substrates of cognitive fatigue are task-specific, some task-generalized pattern can be found.

The decreased deactivation of the DMN observed by Lim et al. (2016) was also noted by others during fatiguing tasks. For instance, Gergelyfi and colleagues (2021)

found that changes in activation in regions of the DMN due to fatigue induction were correlated to subjective fatigue. More precisely, they found that, while performing a working memory missing number task, subjective fatigue positively correlated with activity of task negative regions (i.e. decreased deactivation in regions not implicated in the task, including in the DMN). Conversely, subjective fatigue negatively correlated with activity of task positive brain regions (i.e. decreased activity in regions activated to perform the task). Moreover, during RS sessions, connectivity between seed regions of DMN significantly and positively correlated to subjective fatigue (Gergelyfi et al., 2021). Consequently, it appears that DMN activity mirror subjective feeling of fatigue, both during task and during rest (Gergelyfi et al., 2021).

To conclude this section, it appears that fatigue can be studied with a plethora of tools and methods. Due to several factors (such as task length and motivation) objective fatigability does not necessarily mirror subjective feeling. Physiological measures of fatigue partly bridge the gap between these two measures and provide valuable information about the underlying mechanisms of cognitive fatigue. However, neuroimaging studies led to results that seem discrepant at first sight and to date, no consensus was reached to describe fatigue's underlying mechanisms. In the future, increased knowledge on the reasons behind those discrepancies might, hopefully, provide a full picture of the mechanisms at play. To meet this ultimate goal, several theoretical models of cognitive fatigue have been proposed and evolved across years. Some of them will be described in the next section.

III. The Theory of Fatigue in Healthy Subjects

A. Energy Depletion

As mentioned earlier, the Industrial Revolution lead to the Golden Ages of fatigue research, as it is called by Hockey (2013). In 1927, the Fatigue Laboratory of Harvard was created to better understand this phenomenon and attempt to provide a suitable and universal definition of fatigue and its contributing factors (Torres-Harding & Jason, 2005). The awareness that fatigue was actually a common symptom among workers arose, and led to the postulation that fatigue might be triggered among employees

working over 100% of their capacity (Torres-Harding & Jason, 2005). This assumption refers to the *energy depletion* theory of fatigue, which was very popular in the 20th century. This theory postulates that the increased consumption of energy due to a highly demanding task will inexorably lead to the depletion of resources available. When resources are drained, fatigue will arise and performance will drop, just like a motor will stop without fuel. As the reader may already acknowledge at this point, such resource depletion model seems too simplisitc to be accurate.

Hockey (2013) postulates that after the Industrial Revolution, factory-based work lead to a growing body of energy-based metaphors to describe our behavior, comparing the human body to a machine. Expressions such as "mental breakdown", "everything is on track", "running out of stream", or "recharging my batteries" are actual reflection of this view (Hockey, 2013). This metaphor of the human machine coined the early theoretical construct of cognitive fatigue. However, the resource depletion theory is probably over-simplistic, because such state of complete resource emptiness has never been observed, even though brain metabolism can slightly change due to effort (Hockey, 2013). What is more, as it has often been mentioned in this thesis, the subjective sensation of fatigue is not necessarily accompanied by performance decrement. This suggests that some compensatory mechanisms might be at play, and that fatigue might be the direct consequence of the increased effort provided to maintain performance.

B. Effort or the Compensatory Control Model

In the view of Hockey (2013), fatigue should rather be conceptualized in terms of control. According to Hockey, fatigue is an emotion, which is *"triggered by an automatic response to significant environmental events, leading to a set of changes designed to resolve the problem"* (Hockey, 2013, *p.21*) and that *"rather than interfering with our ability to carry out tasks by wearing down our energy or resources, fatigue makes us aware of the opportunity costs of current activities, and of the attraction of neglected needs and alternative goals"* (Hockey, 2013, *p.4*). In his view, goal pursuit is clearly central. Hockey claims that a sustained cognitive task will lead to different consequences, behaviorally and subjectively, depending on engagement in the task and the effort provided (Table 2).

Table 2. The effects of fatigue during sustained cognitive task

FATIGUE MODE	*SUBJECTIVE STATE*	*PERFORMANCE DECREMENT*	*AFTER-EFFECTS*
ACCEPTANCE	Minor (transient) fatigue	Yes	No
RESISTANCE	Increased effort and fatigue	No	Yes
STRAIN	Sustained high effort and fatigue	Slight	Yes

Effects of fatigue on subjective state, performance and after-effects (prolonged fatigue) depending on task's engagement and effort provided. Adapted from Hockey (2013, *p.15*)

According to Hockey (2013), effort is the key filling the gap between subjective feeling of fatigue and objective fatigability. When confronted to a sustained cognitive task, one should simply *accept* to interrupt engagement in the ongoing task when transient fatigue arises, leading to performance decrement but preserving from goal-directed cost and aversive after-effects. Alternatively, one could *resist* against fatigue sensation, considering that goal-pursuit is crucial, thus providing extra-effort to comply with task demand. This fatigue mode preserve performance, but the increased effort provided will lead to increased fatigue, both during and following the task. In the last fatigue mode, the effort that has to be provided is so consequent due to task's *strain,* that performance cannot be perfectly maintained. Additionally, subjective fatigue will be high and will persist after the task (after-effects), leading to an aversive state for the task.

Box 6. What is Effort?

As is the case for fatigue, effort is a complex state, and would deserve an entire thesis to be fully described. Effort can be defined as an ***increased mental or physical activity to comply with goal-pursuit*** *(Inzlicht, 2018). For André and colleagues (2019), effort is associated to voluntary attention and will and refers to three interconnected constructs:*

Effort is a ***mechanism*** *integrating information about the task constraints, the possible reward, and the current state of the subject.*

Effort is an ***output****, modulating neuronal activity to select pertinent information, in relation to the Salience Network.*

Effort is a ***feeling*** *emerging during effortful tasks and reflecting the cost associated with maintaining goals.*

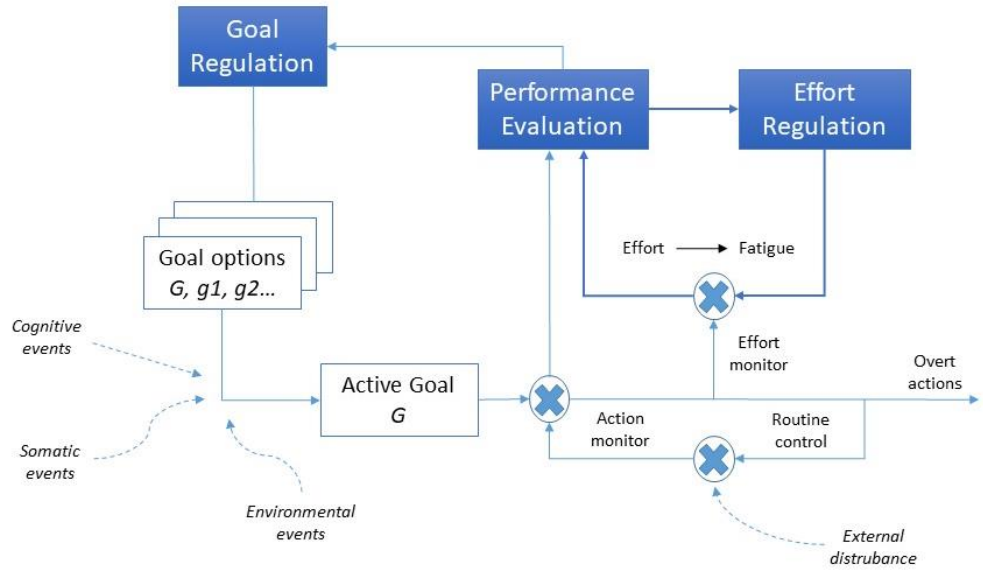
Consequently, Hockey proposes that effort, and not task demand or duration, is the main cause of cognitive fatigue. Effort is modulated by task's goal, and will depend on the cost-benefice balance of current goal compared to other alternative goals, such as, for instance, primary needs (Hockey, 2013). Following this hypothesis,

Hockey developed a new model to theorize fatigue, the *Compensatory Control Model*, which he gradually polished over the years, leading to its *Motivational Control Model*. Originally, the Compensatory Control Model was designed to bring a picture of cognitive performance under stress. It was composed of two systems leading to two options when confronted to a demanding cognitive task: Increasing effort to maintain performance, or reducing effort and allow performance decrement (Hockey, 2013). During the latter, the importance given to task goal is decreased to agree with lower performances.

The revised model, integrating the concept of fatigue, is much more complex and elaborated (Figure 6). In this model, three central executives are at play (referred to as *Executive Functions* by Hockey): *Goal regulation*, that manage between the current goal and alternative options, and which is regulated by *Performance Evaluation.* The later send outputs to the last executive, *Effort Regulation*, which monitor the amount of effort to be provided to attain performance. As optimal performance can be costly due to effort, it will be maintained if the active goal is important enough, or if benefits override the costs. In this model, selection of the current goal *G* leads to the inevitable exclusion of the other competing ones (*g1, g2…)*. The *Goal Regulation* system select and maintain the current goal throughout top-down control and inhibition of competitors. Under routine condition, the loop between goal regulation and performance works without any executive control and is not disturbed. In some cases, cognitive (i.e. the task is new or challenging), somatic (the subject feel fatigued, is hungry…) or environmental (external disturbance) events may challenge the execution of current task goal *G* throughout bottom-up distractions. A negative feedback loop detects deviations from goal by the *Action monitor* which compares the output with expectancies. If the task is well-learned, small adjustment can be made automatically in this lower loop, initiated by the *Routine control*. Otherwise, the upper loop will be involved. Conflicting events are detected by the *Performance Evaluation* system, which is the core feature of motivational control as it regulates activity. After detecting threats to goal pursuit, it sends output to the *Goal Regulation* controller to reinstate goal. Additionally, when the *Performance Evaluation* system perceives that an additional effort will be needed to maintain performance, it will activate the *Effort* Regulation

system which in turn will lead to subjective fatigue. According to Hockey (2013), this mechanism is at play during tasks of high load, when performance is maintained throughout increased effort. However, if the cost of effort becomes too high compared to benefices, it will not be increased (*Effort monitor*). In this case, effort will remain at the same level or decrease, allowing performance decrement or interruption of the ongoing task to pursue an alternative goal.

Figure 6. Hockey's Motivational Control Model of Executive Control, Effort & Fatigue



Three *Executive Functions* regulate goal maintenance, performance and effort. Effort produced will trigger fatigue. Adapted from Hockey (2013, *p. 144)*

From a neuroscientific point of view, Hockey (2013) proposes that the prefrontal cortex (PFC) is the main region responsible for the *Goal Regulation* system. Indeed, the PFC seems to be involved in goal selection, management and maintenance (Miller & Cohen, 2001). This hypothesis is corroborated by studies showing an involvement of frontal regions during fatigue induction. For instance, Hockey's view is strongly supported by the study of Wang et al. (2016) described above, in which late components ERPs in frontal areas reflected compensatory mechanisms to maintain performance. According to André and colleagues (2019), the cerebral substrates of effort are probably

located in the Saillance Network, which identify relevant signals to maintain homeostasis and make decision. This network comprises the orbital frontoinsular cortex the dorsal Anterior Cingulate Cortex (ACC), the anterior insula and the superior temporal gyrus (André et al., 2019). The ACC is also implicated in effort regulation according to Hockey (2013). This region belongs to the limbic system and has been linked to conflict deflection, outcomes evaluation of actions and maintenance of high effort response to task (Hockey, 2013). Consequently, the ACC may play a major role in *effort regulation* and *performance evaluation*. However, as mentioned by Hockey (2013) his model of fatigue does not aim to describe actual cerebral substrates of fatigue, but rather provides a theoretical psychological model.

To conclude, the Motivational Control Model of Hockey takes into account many internal and external factors leading to effort control and fatigue. As such, it offers rich support to explain behavior from a psychological point of view. In the next section, the mechanisms leading to decision for goal maintenance or substitution will be further developed.

C. Cost Versus Benefit & Dopamine

How do we decide which concurring goal should be favored? What drives the production of extra effort to maintain performance? From a psychological point of view, one major hypothesis is that goal-directed behaviors are determined by the internal evaluation of the energetic cost associated with an action and the consequent reward expected. As pointed out by Boksem & Tops (2008), reward seeking is essential from an evolutionary perspective. Hence, survival is very costly. For instance, chasing for food all day, looking for an appropriate mate, escaping from a potential predator will consume lots of energy. Yet, these behaviors are highly motivated, because they will lead to a reward or avoid unfortunate events. The cost-benefit model of goal-directed behaviors fundamentally rely on potential rewards and avoidance of punishment (Boksem & Tops, 2008), echoing the early works of Skinner on operant conditioning. According to Boksem & Tops (2008), three main processes are linked to reward: the pleasant feeling of receiving the reward (*"liking"*), motivation to obtain the reward (*"wanting"*) and the integration of behaviors leading to the reward (*"learning"*). To integrate these three components, our brain has evolved a much elaborated system

assessing the rewarding value of an action, which involves the dopaminergic neurons of the midbrain, the orbitofrontal cortex, the basolateral amygdala, the ACC and the nucleus accumbens (Boksem & Tops, 2008). These interacting structures evaluates potential aversive and rewarding consequences of an action (i.e. cost *vs.* benefit) and promote goal directed actions (Boksem & Tops, 2008).

Consequently, Boksem & Tops (2008) proposed that fatigue sensation emerges from evaluation of the cost vs. benefit balance to expend or conserve energy. Accordingly, energy will be consumed only in situations that are worthy (i.e; when the benefits outperform the costs). If the task is prolonged and the goal not attained, energy depletion may exceed the predicted benefits, leading to fatigue sensation and a drive to interrupt the ongoing task (Boksem & Tops, 2008). However, if the motivation to complete task happens to be enhanced, the benefit suddenly increases and an extra effort will be provided. This is in line with results from the literature showing that performance recovers (at least partially, if not completely) when a motivational incentive is provided. Here, we can see how Hockey's model and the one of Boksem & Tops are closely related: Both relating to concurring goals, increased energy/effort, and considering fatigue as a signal to interrupt the task.

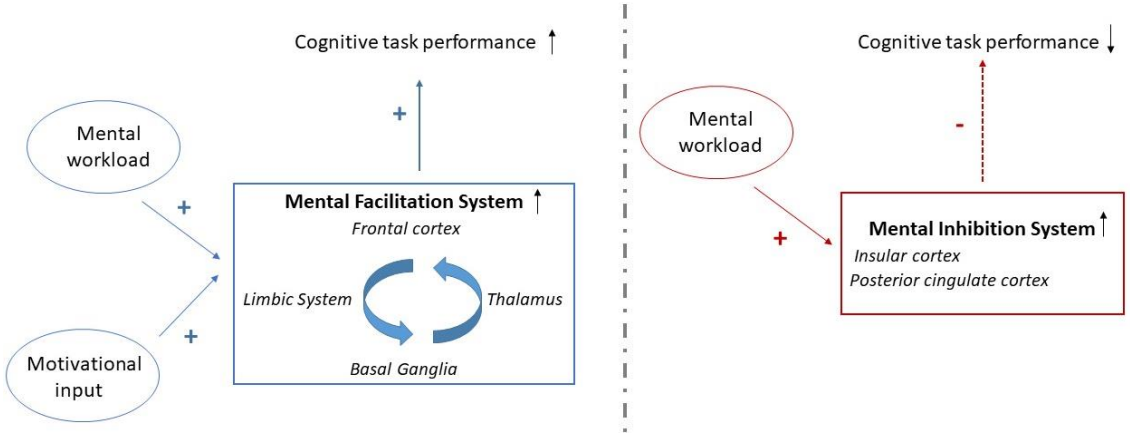
Regulation of motivation in continuous task might be mainly achieved by the dopaminergic system. In fact, dopamine has also been linked to cognitive fatigue and effort. According to Chaudhuri & Behan (2000, 2004), a reduction of the dopaminergic drive in the striato-thalamo-cortical loop might cause cognitive fatigue. In fact, basal ganglia alterations might be the primary cause of fatigue in neurological populations, such as Parkinson disease and MS (this model of pathological fatigue will be further describe in the last section of this chapter). In the same vein, Dobryakova and colleagues (2015) suggested that in neurological disease, a dopamine imbalance will lead to cognitive fatigue throughout a disruption between the striatum and frontal areas. In healthy subjects, it is thus possible that a down regulation of dopamine pathways relates to cognitive fatigue, as these pathways are projecting to the above-mentioned regions associated with the cost vs. benefit balance (ACC, orbitofrontal cortex, insula and basolateral amygdala, Boksem & Tops, 2008). Specifically, Boksem & Tops (2008) proposed that perception of increasing effort and unreachable reward

leads to a down regulation of dopaminergic activity in the nucleus accubens and the midbrain, leading to decreased activity in their efferent regions and adaptation of goal-directed behavior.

D. The Dual Regulation System

Another model of cognitive fatigue that is highly related to the notion of effort and motivation is the one proposed by Ishii and colleagues (2014). In their view, cognitive fatigue is regulated by two competing systems for cognitive performance: an *inhibition system* and a *facilitation system*. When fatigue arises due to work load, the mental facilitation system will be activated to maintain performance (figure 7, left panel). This system comprises the limbic system, basal ganglia, thalamus and frontal cortex that are interconnected and activated throughout a facilitating loop. Any motivational input (such as increased reward) will enhance the facilitation. However, and simultaneously, work load will also activate the inhibition system (Figure 7, right panel), composed by the insular cortex and the Posterior Cingulate Cortex (PCC), leading to performance decrement.

Figure 7. The Dual Regulation System of Cognitive Fatigue (Ishii et al., 2014)



In this model, two competing systems will determine if cognitive performance increases or decreases with work load when fatigue arises (Ishii et al., 2014)

As a consequence, it is the balance between the two systems that will determine if performance is preserved or decreased (Ishii et al., 2014). When workload is high, a motivational input can boost the facilitation system to increase task engagement and

preserve performance. On the contrary, the inhibition system has a protective role against homeostasis disruption and will urge the need to rest. As will be described later, this dual regulation system is particularly relevant to explain the process of pathological fatigue.

Evidence for the facilitation system is found in the fatigue and motivation literature, implicating the striato-thalamo-cortical loop and the limbic system as above described. In turn, evidence from the inhibition system mostly derives from a previous model proposed by the same team (Tanaka & Watanabe, 2012), involving the insular cortex and PCC, but this assumption would benefit from further supporting data. However, several studies found that these two regions are implicated in fatigue sensation and mental effort (Ishii et al., 2013; Otto, Zijlstra, & Goebel, 2014; Cook, O'Connor, Lange, & Steffener, 2007). This is consistent with studies implicating the insular cortex with monitoring of bodily state (Craig, 2002) and the PCC with self-reflection and self-monitoring (Johnson et al., 2002; Vogt & Laureys, 2005).

VI. Fatigue in Neurological Diseases: Specificities and Theoretical models

A. Fatigue as a Major Symptom of Neurological Diseases

In the general population, it is estimated that 5 to 45% of patients from primary care report debilitating fatigue (Kluger et al., 2013). In the neurological population, this prevalence rises to 27-91% (Kluger et al., 2013). Indeed, fatigue is a major symptom of numerous neurological diseases including in TBI, stroke, Parkinson disease and MS. Fatigue prevalence is estimated between 45 and 73% in TBI, 36 and 77% in stroke, 28 to 58% in Parkinson disease and between 38 and 83% in MS (Kluger et al., 2013). According to Kluger and colleagues (2013) this prevalence is much more aggravated than what would be expected according to age, disability and chronicity of the disease. Pathological fatigue is more severe than the physiological fatigue experienced in everyday life by healthy subjects, as it is more persistent, not necessarily relieved by rest and is disproportionate in comparison to the effort provided (Rohit Bakshi, 2003). Pathological fatigue is debilitating, interfering with leisure activities, social duties and vocational status, and if often considered by patients as their worst symptom (Kluger

et al., 2013). Moreover, fatigue is an invisible symptom, and patients might feel hopeless when trying to explain this sensation to their relatives. This will lead to the difficult decision between accepting to be "seen" and alert others about the symptom, or remain "invisible" and endure advert consequences (Newton, Griffith, & Soundy, 2020; Parker et al., 2021).

If fatigue in healthy subjects is a complex phenomenon, it is even more the case for fatigue in neurological diseases. As will be addressed in this section, numerous factors are related to and interacting with fatigue sensation in neurological diseases.

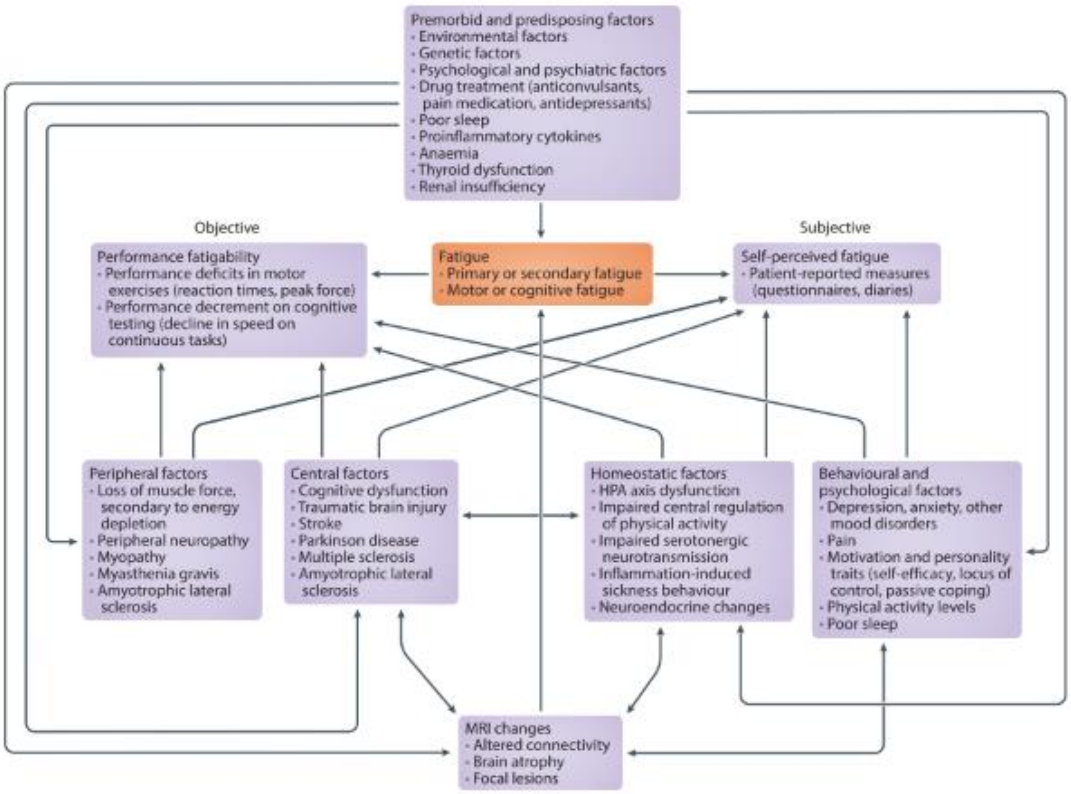
B. Primary, Secondary & Comorbid Fatigue

In the context of neurological diseases, the differentiation between primary and secondary fatigue should be specified. *Primary fatigue* refers to fatigue symptoms emerging from the disease itself (e.g. from tissue damage), independently from other factors. For instance, in MS, primary fatigue can emerge as a consequence of focal and diffuse brain damages, leading to disruption in structural and functional connectivity, from cytokine release and inflammatory processes, and/or from neuroendocrine dysregulation (Penner & Paul, 2017). In turn, *Secondary fatigue* results from concomitant factors associated to the disease. These include sleep disorders (Attarian, Brown, Duntley, Carter, & Cross, 2004; Braley & Chervin, 2010; Mills & Young, 2011; Riccitelli et al., 2021; Veauthier, 2015), depression (Bakshi et al., 2000; Corfield, Martin, & Nyholt, 2016), reduced physical activity (Kos, Kerckhofs, Nagels, D'hooghe, & Ilsbroukx, 2008), pain (Amtmann et al., 2015) and pharmacological treatments. A third category, *Comorbid Fatigue* is sometimes described and refers to fatigue occurring in the context of a disease, though neither primary nor secondaty causes can be identified (Penner & Paul, 2017).

Accordingly, Penner & Paul (2017) developed a model of the causes and consequences of fatigue in neurological disease (Figure 8). In their model, performance fatigability is mainly driven by peripheral and central factors, such as decreased muscle force or brain atrophy. Subjective fatigue is principally resulting from homeostatic factors, such as hypothalamic dysfunction and impaired central regulation of physical activity (energy and neural feedback), as well as other secondary factors such as sleep

disorder and psychological factors (Penner & Paul, 2017). However, all these factors are interacting and can be a cause of both objective and subjective fatigue, as well as physical and cognitive fatigue. It might be challenging to accurately identify the primary and secondary causes of fatigue symptoms, but this examination is crucial to propose personalized treatment options. For instance, detecting and treating mood and sleep symptoms may alleviate fatigue. Regarding primary fatigue, many theoretical models have attempted to explain its main underlying mechanisms. Some of them will be described in the next section, focusing on cognitive fatigue.

Figure 8. Causes and consequences of fatigue in neurological diseases, by Penner & Paul (2017)



Fatigue in neurological diseases is complex, and is caused by primary and secondary factors, namely peripheral, central, homeostatic and psychological along with premorbid and predisposing factors. Consequences can be objective (fatigability) or subjective. HPA: hypothalamic-pituitary-adrenal. Adapted from Penner & Paul (2017, *p.664*)

C. The Theory of Cognitive Fatigue in Neurological Diseases

Tissue Damage and Compensation

One possible explanation for fatigue in neurological diseases that has been proposed is the recruitment of compensatory functional reorganization and increased brain recruitment as a consequence of tissue damage (Kos et al., 2008; Manjaly et al., 2019). This hypothesis is closely related to theoretical models associating fatigue in the healthy population to an increased effort to perform the task. Over recruitment of cerebral activity has been observed in neurological illnesses, both in terms of additional regions recruitment and increased activity of regions associated to the task or to physiological fatigue (Manjaly et al., 2019; Scheibel, 2017). For instance, Tartaglia and colleagues (Tartaglia, Narayanan, & Arnold, 2008) found that pwMS show increased fMRI activity in several brain regions during a simple motor task compared to controls, including frontal areas, premotor and supplemental motor area (SMA). Such over-activations have been linked to cognitive fatigue level in pwMS (see for example DeLuca, Genova, Hillary, & Wylie, 2008 and Engström, Flensner, Landtblom, Ek, & Karlsson, 2013). Control-related activations are enhanced in TBI patients compared to controls (Scheibel, 2017), which could reflect an increased effort to perform the task in relation to fatigue (Kohl, Wylie, Genova, Hillary, & DeLuca, 2009). Yet, to date, the causality and temporality of such link is not clear. One possibility is that higher brain activity is detected by self-monitoring mechanisms (i.e. metacognition of interoception, network function and effort) leading to building-up of fatigue sensation (Manjaly et al., 2019). For instance, it has been show that fatigue induction with cognitive tasks in pwMS leads to subsequent increase in fMRI activations during a motor task in the bilateral cingulate and the left primary sensory cortex in (Tartaglia et al., 2008), two regions which are associated to metacognition (Manjaly et al., 2019).

Cytokine and Endocrine Influences

The influence of cytokine and endocrine levels on fatigue have often been proposed, especially regarding MS. Starting from the observation that production of pro-inflammatory cytokines will always lead to fatigue sensation (for instance, during any common infections, following vaccination or as a side effect of immunomodulatory drugs), the inflammatory origin of MS fatigue has been suggested (Manjaly et al., 2019).

Indeed, this is consistent with studies showing that fatigue complaint in pwMS is exacerbated during a relapse (see for instance Hanken et al., 2019). However, studies assessing inflammatory markers in pwMS did not demonstrate a consistent association between inflammation and fatigue level (Penner & Paul, 2017). It is very likely that immune dysfunction is at least partly related to MS-fatigue, but this factor alone does not fully explain fatigue symptom. Hence, fatigue can be severe even distant from a relapse and without any inflammation (Krupp, Christodoulou, & Schombert, 2005).

In turn, increased pro-inflammatory cytokines level may cause a deregulation of the HPA axis. Such dysregulation was extensively linked to chronic fatigue syndrome, and has been proposed to explain fatigue in stroke and MS (Stulemeijer, Fasotti, & Bleijenberg, 2005). The HPA axis regulates stress by releasing corticosteroid hormones from the adrenal gland. This response to stress enables a mobilization of available energy in emergency situations to promote fight or flight responses. When this reaction becomes chronic, it is maladaptive and lead to energy depletion and dysregulation of immune functions (Klimas, Fletcher, Maher, & Lawrence, 2005). Implication of the HPA axis in MS fatigue led to conflicting results, and to date, no reliable biomarker of fatigue has been identified (Penner & Paul, 2017).

The Striato-Thalamo-Cortical Loop and Dopamine Imbalance

One very influential theory of cognitive fatigue in neurological disease relates to basal ganglia alterations and neurotransmitter disturbances, including dopamine. According to Chaudhuri and Behan (2000, 2004), cognitive fatigue in neurological disorders can be a consequence of BG alterations and their disconnection from prefrontal cortex and the thalamus. The basal ganglia (BG) is composed of six sub-cortical structures: The caudate & putamen (forming the striatum), the subtantia nigra, the pallidum, the subthalamic nucleus and the amygdala. The BG are highly connected to the limbic system and show numerous afferent and efferent connections forming feedback loops, thus conferring an important role of BG in cognitive functioning (Chaudhuri & Behan, 2000). Among the functional loops involving the basal ganglia, the *associated* loop integrating Striatio-Thalamo-Cortical loop (STC) fibers seems particularly implicated in central fatigue, and structural alterations within the loop or change in thalamic activity would predispose to fatigue (Chaudhuri & Behan, 2000). Such alterations

would interfere with cognitive performance, sustained attention and motivational drive through dopaminergic pathways (Chaudhuri & Behan, 2000). Evidences from several neurological diseases, including Parkinson disease and MS, support this hypothesis, as BG are particularly targeted in both conditions (Chaudhuri & Behan, 2000). In MS, there exists evidence that cerebral correlates of subjective fatigue are linked to the STC loop, including atrophy and lesions located in the frontal lobes, thalamus or BG as well as within WM tracks connecting those regions (Kluger et al., 2013).

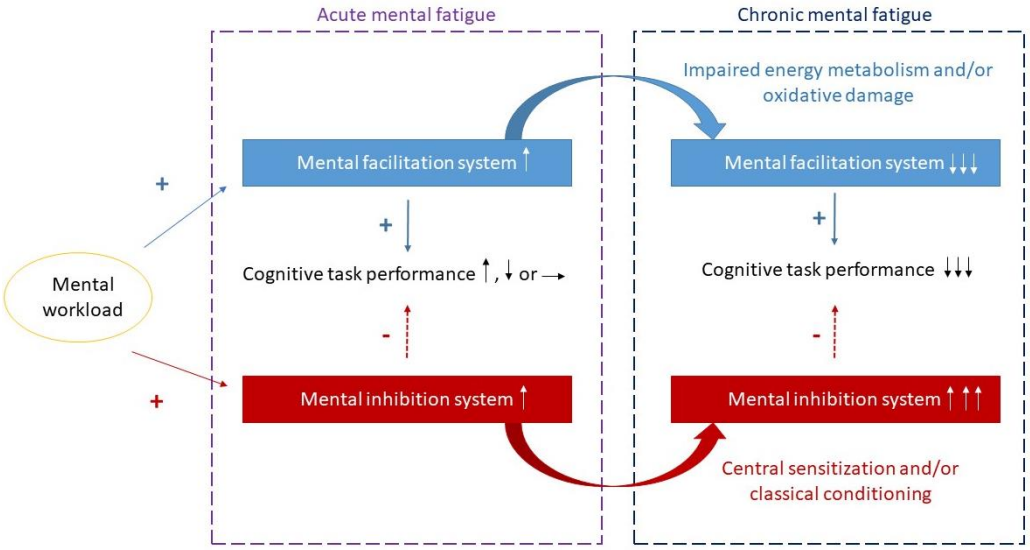
Interestingly, several regions from the STC loop are also implicated in dopaminergic pathways (the substantia nigra, amygdala, striatum, and prefrontal cortex). As mentioned earlier, the reward system is highly related to fatigue in healthy subjects. Consequently, it is relevant to question the role of dopamine in the pathophysiology of fatigue. According to Dobryakova and colleagues (2015) cognitive fatigue in neurological disorders may result from a dopamine imbalance. Hence, dopamine medications seem to improve fatigue symptom and structural alterations within the dopaminergic mesocorticolimbic pathway (*"reward pathway"*, from the ventral tegmental area to the striatum, limbic areas and orbitofrontal, prefrontal and cingulate cortices) is linked to fatigue in several clinical populations (Dobryakova et al., 2015). For instance, fatigue in MS and in TBI was associated with WM pathology of the ventromedial prefrontal cortex and/or the internal capsule (Dobryakova et al., 2015). In stroke, fatigue is associated with infarcts in the striatum (Tang et al., 2010). From a functional perspective, fatigue associated to neurological disease has been linked to abnormal activation and connectivity (both increased and decreased, depending on the study) of regions belonging to the mesocorticolimbic pathway (Dobryakova et al., 2015).

Conditioning and Sensitization

The last model of fatigue that will be presented in this section is an extension from the dual regulation system model (Ishii et al., 2014) presented above. In this model, repeated and prolonged workload will lead to a dysfunction of the mental facilitation system (Figure 9). Namely, energy decrement or repeated oxidative stress will lead to reduced activity of the facilitation system. In turn, the inhibition system can be over activated throughout sensitization and classical conditioning due to a maladaptive over

expression of alarm signal to interrupt the task. Hence, according to Ishii and colleagues (2014), classical conditioning is observed in the context of fatigue, resulting from the repetition of fatigue signal in the system, and leading to a lowering of the threshold for fatigue sensation (i.e. sensitization). In this case, fatigue sensation will be exacerbated, even in a context with low cognitive demand. According to Ishii and colleagues (2014) alterations of the dual regulation system (dysregulation of the facilitation, inhibition or both systems) will leed to chronic fatigue and drastic performance decrement.

Figure 9. The dual regulation system and chronic fatigue



In case of repeated mental workload, chronic fatigue can be triggered by impaired energy metabolism, oxidative damage, central sensitization or conditioning. Adapted from (Ishii et al., 2014).

Chapter IV
Fatigue in Multiple Sclerosis

I. The Fatigue Problem in MS – Incidence, Associated Factors & Impact

As already mentioned, the incidence of fatigue in pwMS varies between 38 and 83% depending on the study[6] (Kluger et al., 2013). By means of an international online survey, Weiland and colleagues (2015) found that about two thirds of their large sample of pwMS (n = 2138) presented a clinically significant fatigue (i.e. FSS score above or equal to 4). In this study, several Stable and Modifiable factors associated to fatigue severity were identified (Weiland et al., 2015). Compared to non-fatigued patients, fatigued pwMS were older, had a longer disease duration, a lower education level, QoL, physical health, and mental health and a higher number of comorbidities. Other stable factors associated to severe fatigue were being a woman, being separated, divorced or widowed, having several children and being unemployed or retired due to disability. Patients with a progressive course were four times more at risk to report severe fatigue than RRMS patients. In the latter, fatigue was associated with disease activity (i.e. increasing, stable or decreasing activity as determined by relapse rate during the last 12 months in comparison to average rate across the past 5 years). Regarding the modifiable factors that could be targeted and may reduce fatigue symptom, fatigue severity was positively associated to smoking, alcohol consumption, DMT (currently or previously prescribed), low level of physical activity, unhealthy dietary habits and overweight or obesity. Additionally, social isolation (having less than 6 close relationships) was associated to fatigue. The result highlight the fact that fatigue in pwMS interacts with numerous life spheres, including domestic, social and professional activities (Penner et al., 2020). Consequently, it is not surprising to observe that about one over three patients consider fatigue as being their worst, most bothersome symptom (Krupp et al., 1988; Penner et al., 2020).

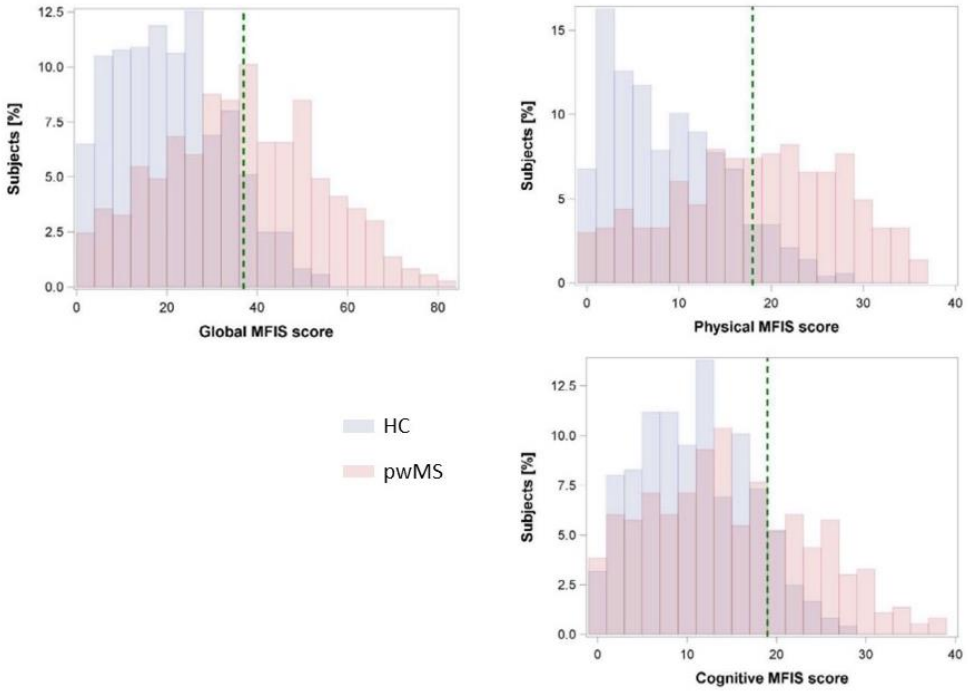
In a longitudinal study, Lerdal and colleagues (2007) were interested in the evolution of fatigue in pwMS. By collecting three FSS reports within two years, they found that more than a third of their sample (38%) presented a persistent fatigue (FSS score above or equal to 5, at every time points), and another 37% presented sporadic

[6] Most studies on MS-fatigue did not provide a differentiation between cognitive and physical fatigue symptoms. In this chapter, when the modality of fatigue is not specified, it will refer to a global fatigue score / symptom.

fatigue (FSS score above or equal to 5, at one or two time points). Overall, only 25% of their sample never presented significant fatigue across the 3 years. Among patients who reported severe fatigue, intensity of fatigue varied between two time points in about half of them. This suggest that fatigue is not a static symptom and should be monitored (Lerdal et al., 2007).

When taking a closer look at fatigue prevalence depending on the modality affected, Broch and colleagues (Broch et al., 2021) found that in a sample of 1454 patients, 77% had mild to severe *cognitive fatigue*, and 82% for *physical fatigue* (as assessed by the FSMC). Additionally, physical fatigue was more prevalent than cognitive fatigue in patients above 40 years old, but this difference was not observed in younger patients. In this study again, fatigue was associated with female gender, older age and worse disease severity. Report from another study which included a control group (Marchesi et al., 2020) showed a prevalence of 31.4% for cognitive fatigue and of 53.8% for physical fatigue in pwMS. As for cognitive impairment, prevalence of fatigue in pwMS seem to be highly variable depending on the assessment tool and the cut-off used. Yet, in this study, pwMS presented higher scores in both sub-scales compared to HC (Figure 10), and fatigue was higher in PMS compared to RRMS, in both modalities. In their study, cognitive fatigue in RRMS was associated to female gender, depression and disability, while it was associated to age and depression in PMS. Regarding physical fatigue, the subscale was associated with age, depression and disability in RRMS, but also with several brain variables (normalized brain volume, WM volume and thalamic volume). In PMS, physical fatigue was associated to disability and normalized WM volume only. The observation that the two subscales correlates to distinct explanatory variables suggests that the two modalities are triggered by different mechanisms.

Figure 10. Distribution of M-FIS global, physical and cognitive scores in HC and pwMS



Healthy Controls (blue) obtained lower scores for each scale compared to pwMS (red). The dashed lines represent clinical cut-off for fatigue as proposed by the authors. Adapted from Marchesi et al., 2020.

Overall, and as mentioned in the previous chapter, fatigue symptom in pwMS is associated to numerous features characterizing the disease. Among them, factors of secondary fatigue are highly predominant, including sleep disorders, anxiety and cognitive impairments (Berard, Smith, & Walker, 2019; Braley & Chervin, 2010; Hu, Muhlert, Robertson, & Winter, 2019; Rooney et al., 2019; Strober & Arnett, 2005). Depression is often described as the major one. As above mentioned, scales of depression and fatigue are often correlated, partly due to overlapping signs between the two (such as lack of energy, sleep problems, interference with social duties…), but these two symptoms are nevertheless distinct. In a recent study from Sparasci and colleagues (2022), fatigue and depressive mood in pwMS showed a great overlap, as 94.8% of the depressed patients also had severe fatigue according to the FSS. Yet,

fatigue without depressive symptom was present in 43.6% of their sample, and 25.4% of the sample had a co-occurrence of fatigue and depression.

Impact on Employment

Clearly, MS has a negative impact on vocational status. Several studies observed that pwMS show a deterioration of work status compared to controls (see for instance Jaworski et al., 2020) and unsurprisingly, fatigue is a strong predictor of such deterioration. In a recent study, Jaworski and colleagues (2020) found that about one patient out of four in their sample had a deterioration of employment status (decreased working hours or occurrence of negative work events) within the three past years, and that this deterioration was predicted by several factors, including fatigue (score at the FSS). In the early stages of the disease, fatigue is already associated to a deterioration of professional duties in RRMS, as assessed by disease-related absenteeism and loss of productivity (Sainz de la Maza et al., 2022).

Impact on Quality of Life

Similarly, QoL of pwMS is also deteriorated, and highly related to fatigue. In a cross-sectional study assessing QoL in a very large sample (n = 5695) of pwMS from any age and disease course, Young and colleagues (2021) attempted to provide a comprehensive model of factors associated to QoL. The final model explained above 80% of the variance of the QoL score. In this model, fatigue clearly was the predominant explanatory factor, mostly due to its indirect effects on QoL throughout other variables including self-efficacy, perceived health, and pain (Young et al., 2021). Similarly, Rodgers and colleagues (2021), found that fatigue strongly mediates the effects of depression on QoL, and this was the case for both physical and cognitive domains of fatigue.

To conclude, it clearly appears that fatigue is a major symptom of MS, due its high prevalence and drastic consequences on daily living. This chapter will further develop important findings regarding cognitive fatigue in pwMS, from a behavioral and cerebral (structural and functional) point of view. The current knowledge on cognitive fatigue in the early stages of the disease will be developed at the end of this chapter.

II. Empirical Studies on Subjective Cognitive Fatigue and Fatigability

A. Is Subjective Fatigue Linked to Cognition in pwMS?

Spontaneously, it seems very likely that subjective fatigue and cognitive performance are strongly related. Numerous studies attempted to evidence a link between trait fatigue and cognition in pwMS, and this search was often unsuccessful. However, some studies (though often with smaller sample size) do suggest a link between the two. In this section, we will review findings supporting both hypotheses.

Trait Fatigue Does Not Predict Cognition

In a retrospective study, Morrow and colleagues (2009) assessed the link between scores obtained at the MACFIMS and fatigue severity (FSS) with a cross-sectional and a longitudinal approach (follow-up > 1.5 years). In both approaches, no correlation was found between fatigue severity and cognition (Morrow et al., 2009). Golan and colleagues (2018) assessed the link between cognitive scores from a computerized neuropsychological battery as well as scales of depression and cognitive fatigue. Both scales were correlated to processing speed, executive function, attention and memory. However, when evaluating the concurrent effects of both symptoms on cognition in a same model, only depression was independently correlated to cognitive scores. Similar findings were observed in another study assessing the effects of subjective fatigue on verbal memory, showing that subjective fatigue is associated to memory complaint, but does not predict objective memory score when controlling for depression, pharmacological treatment and EDSS (Jougleux-Vie et al., 2014).

Trait Fatigue Does Predict Cognition

Niino and colleagues (2014) assessed the correlations between cognitive scores obtained at the BRBNT battery and measures of depression, anxiety and fatigue in a sample of pwMS and HC. In the patients group, all cognitive tests correlated significantly with apathy and depression, while fatigue score was correlated to verbal fluency only (word list generation test). However, when assessing the effects of group, apathy, depression and fatigue on cognition in the same model (by means of multiple regression analyses), fatigue significantly predicted several cognitive scores. Namely, fatigue was associated to verbal memory, processing speed (SDMT) and the word list generation test (Niino et al., 2014). Similarly, Pokryszko-Dragan and colleagues (2016),

assessed the link between fatigue and cognition using the same neuropsychological battery. Depression and anxiety were not considered in their study, but fatigue was considered as multidimensional (cognitive vs. physical fatigue). Scores at the SDMT and the PASAT were both correlated to all measures of fatigue, whatever the modality (physical or cognitive). Moreover, global fatigue scores remained associated to cognitive performance when controlling for MS-related variables (disease duration, disability and disease severity), but unfortunately, this last analysis was not performed on physical and cognitive subscales. These results are supported by a study from Andreasen and colleagues (Andreasen et al., 2019) using a comprehensive neuropsychological assessment (SDMT, trail making test, working memory, visual and verbal memory tasks, executive functioning and attention tests). Results showed that, when controlling for depression, disability, age and sex, total score at the FSMC remains significantly associated to the SDMT and the trail making test part A (assessing processing speed). The cognitive sub-score of the FSMC was also predictive of the SDMT when controlling for the same confounding variables. Similarly, Heesen and colleagues (2010) assessed the link between fatigue and depression questionnaires and several cognitive measures, namely the PASAT, verbal memory, attention (alertness, divided attention and shifting) and verbal fluency. While depression was significantly correlated to the SDMT, the verbal memory task, as well as alertness and shifting performance, fatigue was correlated to every measure studied, except for the PASAT and the delayed recall of the memory task. Overall, depression showed higher correlations with memory scores, while fatigue was strongly correlated to measures of attention (Heesen et al., 2010). When assessing the effects of fatigue depending on its modality, the same pattern of correlations were observed for both sub-scales, thought correlations were somewhat stronger for cognitive fatigue. However, one strong limitation of this study is the lack of correction for multiple testing.

To conclude, studies raised conflicting results regarding the link between general fatigue and cognition. When a link was found, fatigue was mostly related to task assessing processing speed. Yet, this is also the cognitive domain that has been most extensively studied. Additionally, only few studies assessed the effects of ***cognitive***

fatigue specifically. Thus, to date, the relationship between cognitive fatigue and cognitive performances in pwMS is still not clear.

B. Effects of Prolonged Cognitive Effort on Performance and Subjective State, and the Link between the Two

The first study to explicitly mention the effects of prolonged task on performance fatigability in pwMS is one from Jennekens-Schinkel and colleagues (1988). In this study, RTs at a simple attention task were recorded before and after a 4H neuropsychological assessment. After the task, RTs in pwMS significantly increased in comparison to HC, providing the first evidence for a fatigue susceptibility in pwMS as assessed by performance fatigability. Since, many studies have explored the effects of prolonged cognitive effort in this population. Some of them are described below.

Bailey and colleagues (2007) assessed the effects of cognitive fatigue induction on subjective state and performance of pwMS with an advanced progressive clinical course (mean disease duration: 27.21 years) and HC. Participants performed an N-Back task (0- and 1-Back, in two separate sessions and 15 to 20 minutes each, depending on participant's response speed) prior to and following the accomplishment of diverse cognitive tests for executive functioning (the loading task, see Chapter III, section II). For the 0-Back, pwMS showed decreased performance with time on task, while a ceiling effect was observed in HC. This suggests that pwMS present an increased performance fatigability even in attentional tasks of low complexity and relatively short duration. Regarding the 1-Back (which is a bit more complex and rely on short-term memory) pwMS obtained lower accuracy compared to HC, especially during the second presentation of the task (following the executive functioning tasks). Hence, pwMS decreased their performance at the 1-Back following fatigue induction, while HC did not. In turn, this result shows that fatigue induction with a loading task can alter performance on a subsequent task. Accordingly, pwMS were more sensitive to fatigue induction compared to control, and this was demonstrated by both the ToT and the probe methodological approach. Regarding subjective fatigue, it increased similarly in both groups in the 0-Back session. However, during the 1-Back, pwMS showed an

enhanced fatigue increase compared to controls, again supporting that pwMS present an increased sensitivity to fatigue induction. Finally, in this study, increased subjective feeling did not correlate with performance decrement, for both groups and both conditions.

Box 7. The PASAT and The N-Back

Two Cognitive Tasks that Are Extensively Used

PASAT: The PASAT is an attention and processing speed task that also rely on working memory and arithmetic abilities. In this test, the subject is asked to add the last two digits (1 to 9) of a continuing auditory series of 61 items (60 answers are thus expected). The task difficulty can be manipulated by changing the pace at which stimuli are presented. Usually, the 2 seconds and 3 seconds conditions are used. The first one is more difficult as it is more time-constrained.

N-Back: the N-back is a working memory task in which the subject is presented with a series of letters (usually administered visually). The subject is asked to determine if the current letter is the same as the one presented N positions before (e.g. the previous one for the 1-Back, the second last in the 2-Back, etc). In some cases, a 0-Back is administered. In this version of the task, participants are usually required to detect a target letter in a series of stimuli. This version does not involve working memory but relies on attentional processes.

In an attempt to determine if subjective fatigue is caused by cognitive load, specific cognitive processes, or task's length, Sandry and colleagues (2014) administered a processing speed and a working memory task in pwMS and HC, in different cognitive load levels. Results showed that pwMS presented higher subjective fatigue than HC, especially as time on task increased and preferably during the processing speed task. However, cognitive load did not influence fatigue sensation. Hence, pwMS presented a stepper increase in subjective fatigue during the processing speed task, whatever the cognitive load, suggesting that MS fatigue depends on task's length rather than cognitive load. Interestingly, when splitting the pwMS group according to their trait fatigue score (Fatigued MS vs. non-Fatigued MS), no between-group difference was observed regarding evolution of subjective state. Most patients presented a high fatigue complaint, so the non-Fatigued sample was relatively small (Sandry et al., 2014). However, this result was supported by an additional analysis showing that trait fatigue score, including MFIS cognitive sub-score, was not correlated to state fatigue (Sandry et al., 2014). This result suggests that trait fatigue and actual fatigue susceptibility are not necessarily related in pwMS.

Interestingly, Claros-Salinas and colleagues (2013), provided evidence that physical effort, as well as cognitive effort, can have a deleterious impact on cognitive performance. In their study, pwMS and HC performed attention tests prior to and

following a 2.5-hour session of either treadmill training or various cognitive tests. In both sessions, pwMS showed increased RTs at the tonic alertness task, while HC remained constant in this test. In both conditions, patients' subjective feeling of fatigue increased, though the increase was worse following neuropsychological testing. Again, subjective fatigue evolution did not correlate with objective performance decrement.

In a study from Agyemang and colleagues (2021), an analysis of the cumulative error rate obtained during the administration of the PASAT (in its 2 and 3 seconds version) was performed in pwMS and HC. Again, this study suggests that pwMS present an increased susceptibility to cognitive fatigue, as they obtained a higher error score than healthy subjects as a function of time. This was especially true when the slower version (3-seconds) of the test was administered, as the faster version (2-seconds) was highly challenging for both groups. Interestingly, cumulative error rate increased steadily in pwMS, showing no specific breakthrough. According to the author, this finding might reflect increased cognitive effort in pwMS during the task (i.e. due to cognitive impairment), leading to increased performance fatiguability.

For that reason, one study challenges all the results described above. Borragán and colleagues (2018) were interested in exploring if pwMS show an increased fatigue susceptibility when cognitive status is taken into account. In their study, cognitive fatigue was induced by means of a dual task (the Time Load Dual Back), in which the cognitive load of the task was adapted to the abilities of each participant. By doing so, pwMS showed similar performance decrement that HC with time on task, as well as similar level of perceived fatigue. Thus, the increased susceptibility to cognitive fatigue previously observed in pwMS compared to HC might, in fact, relate to methodological settings. Indeed, in cases where cognitive fatigue is iduced with an identical protocol in patients and healthy subjects, pwMS might need an increased effort to perform the task if they are cognitively impaired, leading to increased fatigue. However, the sample size in this study was limited, and the MS group comprised patients with mild impairment only and these results, though highly interesting, need further confirmation.

In order to clarify the conflicting results obtained in the literature, one meta-analysis (Loy, Taylor, Fling, & Horak, 2017) aimed to summarize findings on performance fatigability and subjective fatigue. This study found that perceived fatigue

and fatigability are, indeed, positively associated through a medium effect size, such that pwMS that report higher fatigue state also show high performance decrement. However the authors stipulate that this link is not strong enough to assume that these two processes reflect the same construct, and emphasis on the need to assess both variables independently (Loy et al., 2017).

To summarize, studies assessing the effects of prolonged cognitive effort in pwMS clearly show that this population exhibit a higher susceptibility to cognitive fatigue. Both subjective feeling and performance decrement show a steeper aggravation with time on task, compared to control. Interestingly, physical effort can also trigger enhanced cognitive fatigue in pwMS. While most studies did not evidence a clear link between subjective feeling of fatigue and performance decrement, a recent meta-analysis suggests that the two measures are indeed correlated. Importantly, one recent study suggests that the increased fatigue susceptibility observed in pwMS might be due to the extra effort provided to complete the fatiguing task compared to healthy subjects.

III. Structural Brain Correlates of Cognitive Fatigue in pwMS

As one can consider from the previous section, behavioral studies alone, though very useful, are not appropriate to elucidate the underlying mechanisms of cognitive fatigue in pwMS. In this section, we will describe current knowledge about the structural substrates of cognitive fatigue in pwMS.

A. Global Brain Measures

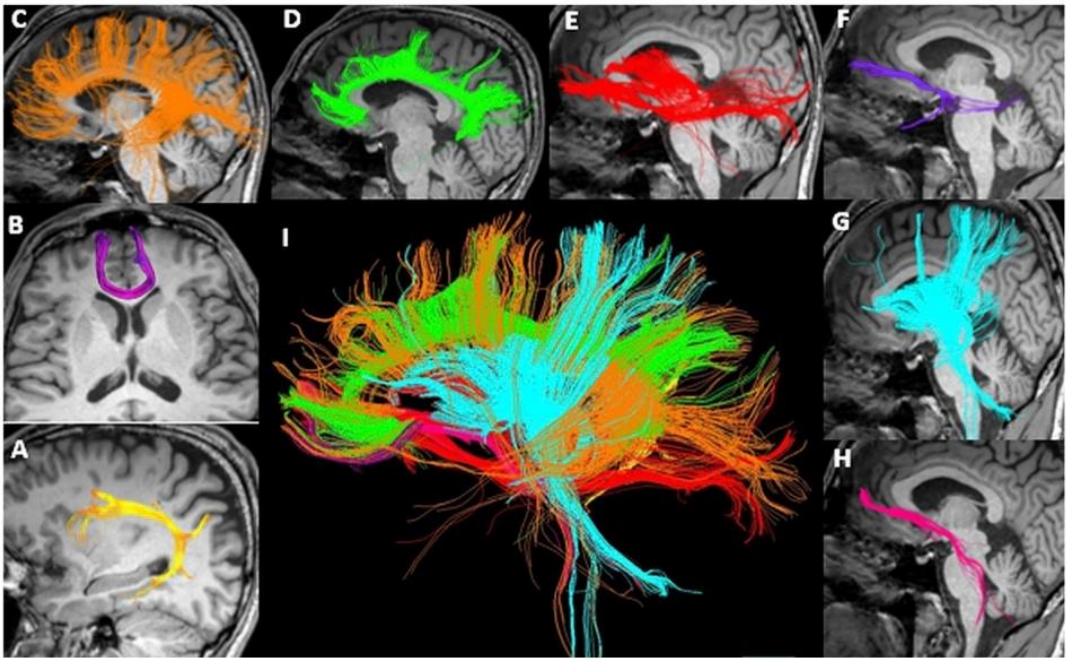
Global measures of brain integrity, such as brain volume, global cortical thinning, WM volume or cortical and WM lesion burden are not related to fatigue score most of the time (see Palotai & Guttmann, 2020 for a review). However, some studies did find a link between global brain measures and fatigue. For instance, in a longitudinal study, Sanders and colleagues (2016) found that patient with cognitive fatigue at baseline showed increased brain atrophy (i.e. parenchymal loss and enlargement of lateral ventricles) compared to non-fatigued patients after a follow up of approximately 1.5 years. Regarding lesion load, its association with fatigue is debated, with no evidence in early research work, contrary to more recent studies (see ARM, Ribbons, Lechner-

Scott, & Ramadan, 2019 for a review). Tedeschi and colleagues (2007) found that, in a large sample of mildly disabled patients, fatigued pwMS had higher T1 and T2 lesion volume compared to non-fatigued patients. However, when entering lesions volume, abnormal WM, NAWM and NAGM fractions as well as disease-related and demographic variables in the same model for multivariate analysis, only WM and GM fractions were significantly and negatively associated to fatigue severity. Nevertheless, studies finding a link between global brain measures and fatigue are rare. As a consequence, regional measures of brain pathology might be stronger predictors of fatigue symptom (Maria A. Rocca et al., 2014).

B. Regional White Matter Pathology

As the WM is greatly altered in MS, abnormalities within this brain tissue in relation to fatigue symptom have been extensively studied (Palotai & Guttmann, 2020). Continuing on the relevance of lesion load, one study found that among periventricular, juxta cortical, frontal lobe, deep white matter and basal ganglia lesions, only lesions located in the frontal lobes were more frequently observed in fatigued pwMS compared to non-fatigued patients (Morgante et al., 2011). Similarly, Sepulcre and colleagues (2009) found that fatigue in pwMS was correlated to lesions within the right parietotemporal and the left frontal WM regions. Regarding WM regional volumes, progression of corpus callosum atrophy over time seem to be especially predictive of fatigue symptom (Yaldizli et al., 2011, in a follow-up of about 5 years). Similarly, a large range of data have been provided with the recent study of WM microstructural integrity. This is especially the case of DTI studies, in which fatigue in pwMS has been linked to the integrity (reduced fractional anisotropy and increased axial diffusivity or mean diffusivity) of an extensive number of WM tracts (Figure 11, ARM et al., 2019). According to Palotai and colleagues (2020), discrepancies among studies might be due to the different fatigue measure used (often FSS and MFIS) and the variety of pwMS included (from different disease courses, disease duration and level of disability). Indeed, in most studies, patients were compared according to their fatigue level (high-fatigue vs. low-fatigue patients group), but other factors associated to fatigue that have not been controlled for (such as depression or disability) might lead to the observed inconsistencies.

Figure 11. White Matter Neural Tracts Associated to Fatigue in pwMS



WM tracts that have been associated to fatigue in pwMS in DTI studies. A: Arcuate fasciculus; B: Forceps minor; C: Corpus callosal tracts; D: Cingulum bundle; E: Ulcinate fasciculus; G: Thalamic: Fibres between posterior hypothalamus and mesencephalon; H: Anterior internal capsule; I: the entire fibre tracts. Adapted from ARM et al., 2019.

Overall, in DTI studies, fractional anisotropy was particularly linked to fatigue, especialy in fronto-striatal and parieto-striatal networks (ARM et al., 2019). These results support the hypothesis that a disruption of the striato-thalamo-crotical network (Chaudhuri & Behan, 2000) might be associated to cognitive fatigue in pwMS (see for example Genova et al., 2013).

C. Regional Grey Matter Pathology

Due to the lack of consistencies across studies assessing the link between fatigue and WM integrity, recent studies started to investigate the role of cortical and DGM nuclei (Palotai & Guttmann, 2020). Overall, fatigue in pwMS has been associated to atrophy of frontal, temporal, parietal, occipital and insular cortices, as well as of the caudate, the putamen, the pallidum, the accumbens, thalamus, amygdala, cerebellum and brainstem (see Palotai & Guttmann, 2020 and ARM et al., 2019 for recent reviews). For

instance, Sepulcre and colleagues (2009) found that fatigue score at the MFIS in a wide range of pwMS from different disease courses was correlated to atrophy in the left superior frontal gyrus and the middle frontal gyrus, bilaterally. In a sample of RRMS, Damasceno and colleagues (2016) found that, among numerous MRI measuresn only the volumes of the caudate and the accumbens significantly predicted fatigue when controlling for disability level. Similarly, a multicenter cohort study with a large sample of pwMS from disease onset and on a 4 years follow-up, found that fatigue was associated to decreased volumes of the caudate, the putamen, the pallidum (all bilaterally) and the pons (Fleischer et al., 2022).

Again, few studies assessed cognitive fatigue specifically. Those studies found a link between cognitive fatigue and cortical thinning in the right inferior parietal and the middle cingulate, as well as volume loss in the right rostral, middle frontal, pre and post central gyrus, the PCC, the middle cingulate gyrus and the frontal lobes (ARM et al., 2019). Calabrese and colleagues (2010) found that the cognitive sub-scale of the MFIS was significantly correlated with the volume of the striatum, and with cortical thickness of the posterior parietal cortex and the middle frontal gyrus. In turn, physical fatigue was linked to striatum volume and superior frontal gyrus cortical thickness (2010). Recently, Saberi and colleagues (2021) used thalamic shape analysis to better understand the role of this structure regarding fatigue in MS. They found that cognitive fatigue, but not physical fatigue, was correlated to a smaller volume of the left thalamus, which corresponded to an inward deformity of the left anteromedial thalamic surface. The authors suggest that structural alterations of the anteromedial thalamus could impede its role in reward processing and estimation of effort, thus leading to increased cognitive fatigue (Saberi et al., 2021).

Overall, as is the case for analyses of the WM, GM tissues provide additional evidences for the STC loop hypothesis in MS-fatigue pathophysiology. Indeed, atrophy of the frontal cortex as well as structural alterations within the striatum and the thalami are often observed in fatigued pwMS, and have been linked to the cognitive aspects of fatigue.

IV. Functional Brain Correlates of Cognitive Fatigue in pwMS

Surprisingly, fMRI studies assessing the functional substrates of MS-fatigue are quite rare (see ARM et al., 2019 for a review). Most of them studied the link between fatigue questionnaires and networks functional connectivity during rest, and a handful of fMRI studies assed brain activity related to cognitive fatigue during the administration of a cognitive task. As will be developed in this section, fMRI studies also provided conflicting results, showing hyperactivity in some cases, hypoactivity in some others. However, these results suggest again that the STC network is involved in fatigue

A. Resting-State Activity

Several studies evidenced functional connectivity (FC) modifications correlating with fatigue scales during RS. Notably, increased FC between the caudate and several brain regions have been found, including the motor cortex, sensori-motor corex and dorsolateral prefrontal cortex, while some authors found a decreased functional connectivity between the cingulate and the sensory motor cortex (ARM et al., 2019). The same observation is made for regions belonging to the DMN (for instance increase connectivity in the PCC but decrease in the ACC in Bisecco et al., 2017, yet decreased FC between basal ganglia and prefrontal cortex, precuneus and PCC in Finke et al., 2015). There is also discrepancies for FC related to the thalamus during rest in fatigued patients (see Capone, Collorone, Cortese, Di Lazzaro, & Moccia, 2020 for a review on the role of thalamus in fatigue). For instance, both patterns (hyper/hypo FC) were observed in a study from Hidalgo de la Cruz and colleagues (2018): by comparison to HC and fatigue-free patients, fatigued pwMS showed reduced RS FC between the thalamus and frontal areas (superior, middle), the PCC, anterior insula, the postcentral, middle temporal and occipital cortices, but increased FC between the thalmus and the sensorimotor network as well as the precunueus, posterior insula and the cerebellum. When considering fatigue modality, cognitive fatigue score in all pwMS was positively correlated with FC between the thalamus and the precuneus, while a negative correlation was observed with the FC between the thalamus and the posterior cerebellum. In turn, physical fatigue in pwMS was associated to an increased FC between the thalamus and the sensorimotor network. Hence, different functional alterations (hyper vs hypo) might be observed depending on (i) the modality of fatigue

and (ii) the thalamo-crotical connection studied, which could reflect different componants of MS-fatigue (Hidalgo de la Cruz et al., 2018). Additionally, these inconsistencies might relate to two mechanisms: decreased activity due to structural alterations or increased activity due to compensatory, but costly, mechanisms (Capone et al., 2020).

B. Task-Based fMRI studies

Regarding task-fMRI studies, the same conclusion can be drawn. Studies evidenced both hyper and hypo activity of cerebral regions, either in areas involved in the ongoing task or in regions known to be implicated in fatigue symptom (e.g. the thalamus and basal ganglia). For instance, DeLuca and colleagues (2008) studied the effects of time on task while performing a modified version of the SDMT in the scanner. As ToT increased, compared to HC, brain activity in pwMS increased in the basal ganglia, frontal areas (superior, medial, middle and inferior), parietal regions (precuneus and cuneus) as well as in occipital lobes. Importantly, RTs gradually decreased with ToT, in both pwMS and HC. This suggest that pwMS displayed the same learning effect than HC, thanks to an increased cognitive effort (i.e. increased cerebral recruitment) to counteract the effects of cognitive fatigue, or alternatively, that this increased effort would trigger fatigue (DeLuca et al., 2008). Similar fatigue-related regions were observed in a study from Engstrom and colleagues (2013) during which pwMS and HC performed a working memory task, thought with constracting results regarding pattern of brain activity. In this study, pwMS showed lower brain activity within the thalamus and the BG and more extended brain activity in the parietal posterior cortex compared to control, during the whole task. When correlations with state fatigue scales were assessed, a positive correlation with activity in the posterior parietal cortex and in the right substentia nigra were observed, in all participants (Engström et al., 2013). Unfortunately, these correlations were not tested in pwMS specifically. However, in a study from Genova and colleagues using a switching task (2013), state fatigue in pwMS was positively associated to activity in the bilateral prefrontal cortex, left postcentral gyrus, precuneus, precentral gyrus and the inferior temporal gyrus. Brain activity was in turn negatively associated to state fatigue in the left superior frontal gyrus, right cuneus and bilateral temporal regions. In comparison to HC, pwMS showed increased

activity of the caudate during the task, suggesting that increased activity in this region may induce enhanced fatigue sensation (Genova et al., 2013). In a recent study form Chen and colleagues (2020), the effects of cognitive load on cerebral activity in relation to state fatigue was assessed with an in-scanner modified SDMT task. While HC recruited more anterior regions (superior and middle frontal gyri, insula, superior temporal gyrus) as cognitive load and fatigue increased, pwMS continued to activate posterior regions (precuneus, lingual gyrus, occipital gyrus). Importantly, participants in the HC group benefited from a learning effect during the task (RTs decreased with ToT), but pwMS did not improve their performance. The authors conclude that pwMS may not efficiently allocate cerebral resources while performing the task, which could lead to an increase in fatigue feeling (Chen et al., 2020).

To sum up, most off the time, increased brain activity associated to fatigue during a cognitive task was interpreted as a maladaptive functional reorganization to comply with task demand (ARM et al., 2019). This increased brain activity can manifest itself either by a recruitment of regions that are usually not associated to the task (interpreted as reflecting new connections to compensate from structural damage) or an increased activation within existing networks, mainly the STC, the DMN and the sensori-motor networks. In turn, when a decreased activity was observed during the task, it was usually attributed to structural alterations and network collapse or by a disruption of the BG functions, leading to increased fatigue (ARM et al., 2019).

V. Fatigue in Early MS – What do we know?

The large majority of studies described in this chapter so far were conducted on heterogeneous samples of pwMS with various disability, disease course, disease duration and age. Only a hand-full of studies was specifically interested in understanding the underlying mechanisms of fatigue in early MS. Yet, this is paramount, because patients in the first stages of the disease can already present a persisting and disabling fatigue symptom (Runia, Jafari, Siepman, & Hintzen, 2015). To note, patients in the early stages of the disease are younger and present a lower disease burden and disability level than patients in the later stages of the disease, which are all

factors that have been associated to fatigue prevalence in pwMS (see for instance Weiland et al., 2015). For these reasons, the prevalence of fatigue symptom in the early stage of the disease is particularly puzzling.

Runia and colleagues (2015) investigated the prevalence and severity of fatigue symptom in a sample of CIS patients. Fatigue prevalence in this sample was about 46%, and this symptom was an independent risk factor to develop subsequent clinical manifestations (i.e. dissemination in time). Additionally, fatigue in early MS may already have an impact on cognition. In a study from Simioni and colleagues (2007), fatigue in patients with low disability and short disease duration was predictive of cognitive impairment, though this link was not significant anymore when controlling for disability or QoL. Hence, QoL and fatigue seem already linked in early MS. In a longitudinal study, disability, depression, cognition and fatigue were assessed during the year of clinical onset, and all those variables independently predicted QoL at a 36-months follow up (Nourbakhsh, Julian, & Waubant, 2016). Similarly, Håkansson and colleagues (2019), found that fatigue score correlates significantly with reported anxiety, depression and quality of life at baseline and at 1-year follow-up in patients with recent disease history. However, fatigue was neither associated to cognition (except for one working memory task), disease duration, disability, lesion load, brain volume nor inflammatory markers. The authors concluded that fatigue in early MS is associated with self-report questionnaires but not with objective measures of clinical severity (Håkansson et al., 2019).

This poor association between brain structural alterations and fatigue in early MS was also noticed by others (Bardia Nourbakhsh, Azevedo, et al., 2016; Wilting et al., 2016). In these studies, early fatigue was not significantly associated to lesion volume and location as well as GM, WM, BG and total parenchymal volumes. However, in both studies, abnormalities within the thalamus was linked to fatigue symptom. Nourbakhsh and colleagues (2016) found that baseline thalamic volume predicted subsequent evolution of physical fatigue, but that cognitive fatigue was not significantly associated to brain measures. However, in Wilting et al. (2016), only the cognitively fatigued patients (according to FSMC) exhibited structural abnormalities within the thalamus. Namely, compared to fatigue-free patients, cognitively fatigued patients showed

reduced fractional anisotropy and increased mean diffusivity in the thalamus. In a study from Derache and colleagues (2013), fatigue score of newly diagnosed patients was associated to decreased GM density of the thalami. Additionally, patients showed a reduction of cortical GM located in the frontal (middle, superior and inferior, bilaterally) and the left temporal cortices, and this reduction was significantly greater in fatigued pwMS. Another brain region that has been linked to early fatigue from a structural point of view is the cerebellum. Accordingly, Lazzarotto and colleagues (2020) found that fatigue severity in newly diagnosed RRMS with fatigue and depressive symptoms had smaller Vermis Crus I cerebellar volume compared to depressed patients without fatigue. Additionally, volume of the cerebellar lobule right V significantly predicted fatigue severity, while the Vermis Crus I predicted depression (Lazzarotto et al., 2020). Noteworthy, the Vermis Crus I has been previously associated to affective functions, which is consistent with its early relationship with depression in pwMS (Lazzarotto et al., 2020). In turn, cerebellar lobule V is implicated in motor processing (Guell & Schmahmann, 2020).

Few studies investigated the functional substrates of early MS-fatigue, but those study suggest that functional alterations are alreay present and associated to fatigue. For instance, Derache and colleagues (2013) found that trait fatigue is negatively associated to cerebral metabolic rate of glucose within the BG. In a study from Stefancin and colleagues in young pwMS (mean age of 26 years old) and relatively early disease course (mean disease duration between 5 and 6 years), fatigue score was significantly and negatively correlated to RS FC between the left insula and the PCC as well as between the right thalamus and the left parietal operculum (Stefancin, Govindarajan, Krupp, Charvet, & Duong, 2019). Consistently, a decreased FC was observed in fatigued patients compared to non-fatigued between the left insula and the PCC, the right thalamus and the left parietal operculum, as well as between the thalamus and the right superior frontal gyrus. Finally, fatigued pwMS exhibited a stronger FC between the right thalamus and the right precentral gyrus, and a trend following the same direction was observed between the left hippocampus and the left precentral gyrus. As far as we know, no other functional study has been conducted in early pwMS to specifically explore fatigue substrates.

In a study assessing the effects of cognitive load on pupil size in early pwMS, Rodez Benavent and colleagues (2017) found that patients do not exhibit an increased pupillary response to cognitive load. In this study, HC who exhibited low cognitive scores during neuropsychological testing had an increased task related pupil response (i.e. dilation), likely due to an increased cognitive load. In patients, however, task related pupil response was not enhanced, even in cognitively impaired pwMS. Interestingly, a statistical trend was observed between smaller pupillary response and fatigue in pwMS, sugesting that pupillary response may be an objective measure of fatigue in early MS.

To conclude, little is known about fatigue in early pwMS. However, despite the small number of studies exploring this field, results obtained appear to be less discrepant that what was observed in pwMS with longer disease duration. Hence, the reduction of confounding factors concomitant to the specific exploration of the early stages of the disease (age, disability, comorbidities…) might prevent from several methodological issues and provide more robust results. As a consequence, studying the underlying mechanism of MS-fatigue in samples with short disease duration seems very promising, and more studies are needed. As the reader might have notice, behavioral and fMRI studies using fatigue induction protocols are especially lacking in the field of early MS.

Experimental Part

Objective and Hypotheses

Cognitive fatigue (CF) is a very frequent complaint in patients with Multiple Sclerosis (MS), at any stage of the disease. However, the mechanisms leading to pathological mental fatigue remain poorly understood, especially in the early stages of the disease. This thesis aims at exploring the effects of cognitive fatigue in the early stages of MS compared to a population of matched healthy controls, from a cognitive, physiological (eye metrics) and cerebral perspective.

In order to explore cognitive fatigue in early pwMS, an extensive research protocol was designed. Patients with early MS and matched healthy subjects were invited to participate to the FCSEP study (*Fatigue Cognitve dans la Sclérose en Plaques)*, which comprised five appointments (**Studies 2 to 6**). By doing so, we collected a large amount of measures to investigate how fatigue variables relate to each other in a single sample of pwMS and HC. Namely, our participants performed three different cognitive tasks: two fatigue inducing task: The Time Load Dual Back (TLDB, Borragán et al., 2017) and a computerized Stroop task (Stroop, 1935), and a probe N-Back task (Kirchner, 1958). Besides, measures of subjective states and eye metrics were collected, as well as brain functional and structural MRI data. Finally, each participant performed a full comprehensive neuropsychological assessment. Another set of cognitive data[7] was also obtained from a sample of pwMS with varying disease courses and duration and matched healthy subjects (**Study 1**).

With this large set of variables, several research questions will be addressed. **In studies 1 & 2**, we will attempt to better characterize the link between cognition and fatigue depending on its characteristics (Cognitive *vs.* Physical, Trait *vs.* State). In **Studies 3 & 4,** we will investigate the consequences of two CF induction methods (manipulation of cognitive load and long lasting task) on subjective state and cognitive performances. Additionally, the relevance of eye metrics data as objective measure of

[7] These data were collected in the context of a previous PhD thesis conducted in our lab (Lommers, 2019)

physiological fatigue state will be evaluated (**Study 3**). Finally, the functional and structural brain substrates of cognitive fatigue will be explored by means of Magnetic Resonance Imaging (MRI) acquisitions in **Studies 5 & 6**. The rationale for these 4 research questions is detailed below

1. *Fatigue and Cognition in Multiple Sclerosis:*

Is there a link between trait fatigue and cognition in pwMS? In other words, can daily fatigue symptoms affect cognitive scores during neuropsychological assessment? Alternatively, does cognitive impairment worsen fatigue symptoms? Results from previous studies raised conflicting results. Some authors found a clear association between trait fatigue and cognitive scores (Andreasen et al., 2019; Heesen et al., 2010), while others did not (Morrow et al., 2009), or found that this link was mediated by other factors such as depression (Golan et al., 2018; Jougleux-Vie et al., 2014). Surprisingly, the multimodal aspects of fatigue have rarely been considered in such studies. **Study 1** will explore the link between performance in several cognitive domains (attention, processing speed, verbal and visual learning, working memory and executive functioning) and mental fatigue, physical fatigue, depression, anxiety and disability. Stepwise regression analyses will be performed to determine which variable of interest better predicts cognition, in pwMS and in HC. We hypothesize that fatigue, and especially mental fatigue, will significantly predict cognition beyond disability and mood symptoms in pwMS.

In **Study 2**, we will shortly explore the cognitive status of a sample of early pwMS by comparison with matched HC. Besides, we will determine if a full comprehensive neuropsychological assessment (approximately 2H) is susceptible to increase state subjective fatigue. We will then explore if subjective fatigue changes due to assessment alter neuropsychological performance. We hypothesis that the prolonged cognitive effort required to perform the entire neuropsychological assessment will induce subjective fatigue, in both groups, but will not be related to cognitive scores, as compensatory mechanisms might be sufficient to preserve against performance fatigability in the early stages of the disease.

2. Exploring and Confronting the Effects of Cognitive Load and Long Lasting Protocols

In the FCSEP study, fatigue has been induced by means of two cognitive tasks assessing the effects of Time on Task on performance and subjective state. In **Studies 3 & 4, w**e will assess if the effect of CF in early pwMS occurs as a function of tasks' characteristics, namely: Duration and cognitive load. We hypothesize that if mental fatigue in pwMS relies on the same mechanisms as in controls, we should observe a similar decline in performances between groups during the cognitive tasks. However, if fatigue in pwMS depends on disease-specific mechanisms, even early in the disease, we should observe a faster and/or steeper decline in performances for MS patients. According to the current literature, the second hypothesis should be favored. Indeed, several studies showed that pwMS present a faster and/or steeper decrease in performance when performing a prolonged cognitive task, by comparison with healthy subjects (Agyemang et al., 2021; Sandry et al., 2014). However, little is known about such effects in early MS.

In **Study 3**, we will compare the ToT effects of a relatively short dual task (32 minutes) on CF, as a function of the cognitive load induced. Importantly, cognitive load was individually adjusted to control for eventual cognitive deficits in pwMS. Participants performed the Time Load Dual Back task (TLDB, Borragán et al., 2017) during two sessions, and cognitive load was manipulated across sessions. We hypothesize that performance (accuracy and RTs) will decrease with ToT, especially in the high cognitive load condition. Besides, we expect subjective fatigue to increase in the high cognitive load condition only, since it should require more effort to be performed. As we controlled for cognitive demand, we expect that pwMS will not show a stepper/faster performance decrement with ToT. However, we expect that pwMS will show an increased fatigue sensation following the task compared to controls, in both conditions, suggesting an increased sensitivity to fatigue.

In **Study 4**, we will describe the effects of a long-lasting Stroop task (Stroop, 1935) of 96 minutes on performance and subjective state in both groups. We expect performance to decrease and subjective fatigue to increase as a function of ToT. As we will not control for cognitive demand here, we expect that the task will be more

challenging for pwMS compared to HC, and that the effects of CF will consequently be enhanced in this group (steeper or faster performance decrement and increased worsening of subjective state). Additionally, we expect performance at items requiring the most resources to be especially altered, in both groups. Next, we will investigate which fatigue induction protocol has the most deleterious effect on subjective fatigue (cognitive load *vs.* task's duration). To do so, results from subjective scales administered following the TLDB task and at the Stroop task (at 32 and 96 minutes) will be compared. As subjective fatigue seems particularly dependent of effort, we hypothesize that the HCL condition of the TLDB will induce more subjective fatigue compared to the LCL condition or the Stroop task after 32 minutes, in both groups. However, comparing results from the 32 minutes HCL condition with those obtained at the end of the 96 minutes Stroop may lead to a different conclusion. This last analysis is more exploratory but will interesting to determine which frequently used CF induction protocol is more effective: a task of short duration but inducing a high cognitive demand, or a relatively less demanding and monotonous task of long duration. We tentatively propose that the former will be more effective.

3. Can Eye Metrics Provide an Objective Measure of Cognitive Fatigue in early MS?

As developed in the introduction, eye metric variables are very valuable and promising in the field of CF. In **Study 3**, eye metrics were recorded while participants performed the TLDB in the HCL and LCL conditions. We aim to determine if blinks frequency, pupil size and pupil response speed could be used as objective predictors of CF in early MS. Hence, pupil variables reflect the activity of the ANS, which is often disrupted in pwMS and may relate to fatigue symptom (Adamec, Crnošija, Junaković, Krbot Skorić, & Habek, 2018; Crnošija et al., 2016; de Rodez Benavent et al., 2017). Here, we expect that pupil variables, rather than blink frequency, will be particularly sensitive to CF induction. Measures of pupil response speed, which are less conventional, were added for an exploratory investigation as it would be of great interest to observe that pupil dilation and/or constriction speed is affected by ToT and cognitive load.

4. Exploring the Brain Substrates of Cognitive Fatigue in Early Multiple Sclerosis

Finally, this thesis also aims to clarify the cerebral substrates of CF in early MS. In **Study 5**, pwMS and matched HC performed an in-scanner fMRI N-Back task (Kirchner, 1958) of varying difficulty (1 to 3 Back) following fatigue induction with the TLDB task (see **Study 3**). As already mentioned, we hypothesize that the HCL condition of the TLDB will be more fatiguing than the LCL condition. Consequently, in **Study 5**, we will compare the cerebral activity of pwMS and HC following the fatiguing HCL condition and the control LCL condition. We hypothesize that brain activity following HCL will show more between-group differences than following LCL, as we expect higher fatigue level for pwMS in the former. Additionally, we anticipate that these between-group differences will be modulated and exacerbated with task difficulty. Finally, this study will attempt to find a cerebral signature of MS related fatigue during the early stages of the disease. Namely, cerebral activity correlated to trait fatigue will be assessed and tested for between-group differences. We expect that trait fatigue will be associated to specific brain activity patterns depending on group, reflecting different underlying mechanisms of CF whether it is physiological or pathological.

The last study, **Study 6**, will shortly explore the link between trait cognitive fatigue and brain microstructure integrity in pwMS and HC. Recently, advanced MRI technic provided exciting and promising results in the field of MS research. Hence, the study of brain's microstructure seems to be highly relevant in the case of MS, as it can detect subtle alterations within lesions and normal appearing tissue that is not visible with conventional structural MRI (Lommers et al., 2019). In this thesis, we will apply a newly developed MRI technic, the Multi Parameter Mapping protocol, to investigate if several quantitative MRI parameters (Magnetization Transfer saturation, Proton Density, Transverse R2* and longitudinal RI relaxation rates) reflecting tissue integrity (myelin, iron and free water content) are associated to trait CF in pwMS and HC. Identifying specific microstructural alterations relating to CF in this study would provide insight on fatigue pathophysiology from the early stages of the disease. To do so, we will investigate if a global measure of each parameters within the normal appearing cortical GM, DGM and WM are associated to fatigue score. We expect to find an association between cognitive fatigue and brain microstructure in pwMS, especially

in the normal appearing WM and DG. More precisely, we expect that magnetization transfer ratio within the WM and DGM nuclei will be particularly good predictors of CF, as a reflection of a diffuse decrease in myelin content and alteration of the structural connectome for the former (Lommers et al., 2021, 2019) and of abnormalities within regions that have been associated to fatigue for the latter (Palotai & Guttmann, 2020).

Methods

Study 1: Determinants of cognition in pwMS

A. General Procedure

As above mentioned, the first study was conducted retrospectively on data collected for a previous research project (see Lommers et al., 2021, 2019). The aim of this study was to determine if scores at different cognitive domains were associated to depression, anxiety, cognitive fatigue, physical fatigue and disability, when including all these variables in a same model and when controlling for demographics.

B. Population

For this study, data from 30 pwMS and 28 HC matched on age, sex and education were analyzed. Patients in the MS group presented with diverse clinical courses and disease duration. All participants were free from neurological or psychiatric disease. Inclusion criteria were age between 18 and 65 years old in both groups, and in pwMS, inclusion criteria were an EDSS score below or equal to 6.5 and the absence of relapse within the last 4 weeks.

C. Material and Methods

Depression, anxiety and fatigue (both cognitive and physical) were assessed by means of questionnaires with the Hospital Anxiety and Depression scale (HADS, Zigmond & Snaith, 1983) and the Modified-Fatigue Impact Scale (MFIS, Ritvo et al., 1997), respectively. The EDSS (Kurtzke, 1983) was used a measure of disability in the pwMS group.

Each participant underwent a standardized comprehensive neuropsychological assessment, and included tests of attention, verbal and visual memory, processing speed, working memory and executive functioning. Raw cognitive scores were first transformed in percentiles or Z-scores on the basis of the normative sample available for each task. Next, we summarized these values in six composite scores reflecting cognitive functions that are frequently impaired in MS disease course: processing speed, working memory, verbal learning, visual learning, executive functions and

attention (Bobko, Roth, & Buster, 2007; Chiaravalloti & DeLuca, 2008).

For each composite cognitive score, a stepwise regression analyses were performed to determine if depression, anxiety, fatigue (cognitive and physical) as well as disability were predictive of cognition when entered in a same model. Analyses were performed in each group separately.

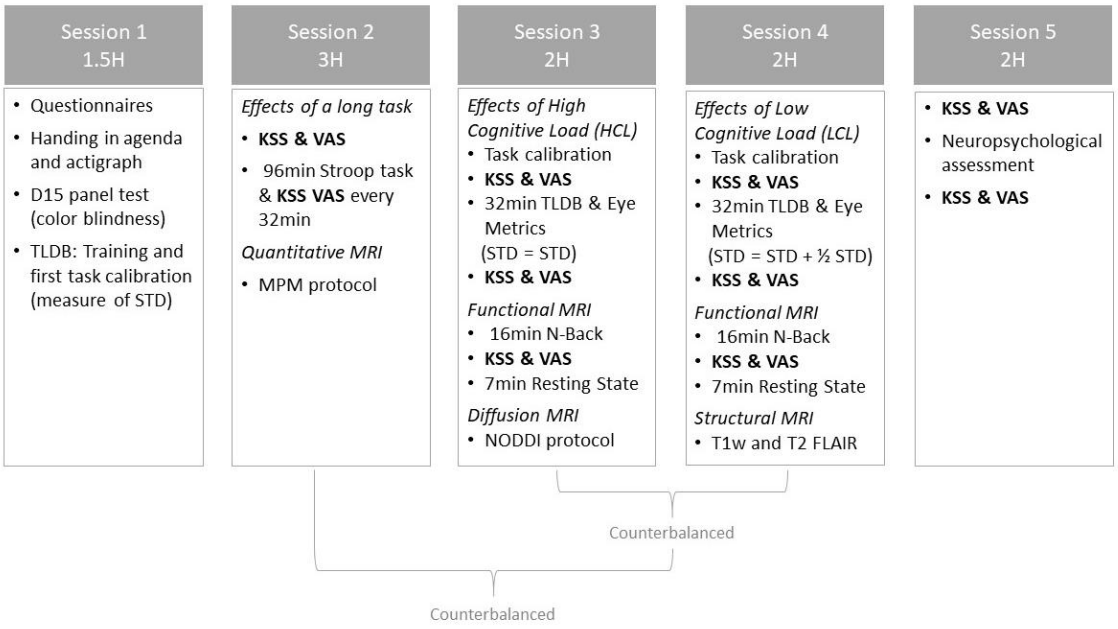
Studies 2 to 6: The FCSEP research project

A. General Procedure

This study was approved by the local ethics committees of the University Hospital of Liège (B707201835630) and of the Psychology, Speech Therapy and Educational Sciences faculty of the University of Liège (ref. 1718-45). Participants received detailed information on the protocol and gave written informed consent prior their participation to this study. Participation to this study implied 5 appointments of 1 to 3 hours (Figure 12) and was completed within 7 weeks, with each appointment from 2 to 14 days apart. The study was presented as investigating the effect of MS on attentional functioning, to avoid expectancies about fatigue occurrence (the real aim was explained at the end of the last appointment). Participants were asked to observe a stable sleep-wake cycle during their participation, with a sleep duration of at least 7 hours per night, to wear an actigraph device and to fill in a fatigue & sleep diary daily until the last appointment. Stimulating beverages (such as coffee, tea and energy drinks) were prohibited during the 24 hours preceding an appointment. To limit circadian confounds, appointments for a single participant were scheduled at the same time of the day, according to her/his preference.

The first session consisted in administering several questionnaires, explaining the fatigue and sleepiness diary, and handing in the actigraph device. The D15 panel test (Farnsworth, 1947) was administered in order to exclude volunteers presenting color blindness. Finally, participants performed a first training on the Time Load Dual-Back (TLDB; Borragán, Slama, Destrebecqz, & Peigneux, 2016). The TLDB was administered in session 3 & 4 to assess the effect of cognitive load on the induction of cognitive fatigue.

Figure 12. General timeline of the FCSEP study



Content of the 5 sessions of the FCSEP study. TLDB: Time Load Dual Back; KSS: Karolinska Sleepiness Scale; VAS: Visual Analog Scale; STD: Stimulus Time Duration (maximal load level assessed during task calibration).

Appointments 2 to 4 were counterbalanced across participants for the next three visits. During session 2, an off-scanner computerized version of the Stroop task (Stroop, 1935) was administered during 96 minutes to assess the effect of a long-lasting cognitive task on cognitive fatigue. Subjective states were recorded at the beginning of the task and every 32 minutes. MRI acquisitions were then performed following the Multi Parameter Mapping protocol (MPM) to obtain quantitative MRI measures. Sessions 3 and 4 started by a short training to the TLDB, followed by a pre-test session for task's calibration. The TLDB task was then administered in either the High Cognitive Load (HCL) or the Low Cognitive Load (LCL) condition to induce CF, while eye metrics were recorded. Several subjective states were assessed at the beginning and the end of the task. Following fatigue induction, fMRI acquisitions were conducted while participants performed an N-Back task with three levels of difficulty. Subjective states were assessed again, and a 7 minutes fMRI acquisition was performed during rest. Finally, structural (T1w & Fluid-attenuated Inversion Recovery: FLAIR) or diffusion (Neurite Orientation

Dispersion and Density Imaging: NODDI) sequences were acquired. Unfortunately, resting-state fMRI and NODDI data will not be presented and discussed in this thesis. For sessions 2 to 4, participants were tested in the same room, with no visual or auditory disturbance. Temperature and light set were kept constant for all participants. Finally, a last appointment was dedicated to a full comprehensive neuropsychological assessment.

B. Participants

Twenty-five pwMS and 25 HC were recruited for this study. Patients were recruited at the specialized outpatient clinic for MS of the university hospital of Liège and presented either a RRMS or CIS course of the disease, according to the 2017 McDonald criteria (Thompson et al., 2018). HC were recruited to match each volunteer in the pwMS group on age, gender and years of education. Inclusion criteria for pwMS were an absence of relapse in the last 6 months, disease duration below or equal to 5 years and a score at the EDSS (Kurtzke, 1983) under 4. Exclusion criteria for both groups comprised the existence of other neurological or psychiatric diseases, a history of mild or severe traumatic brain injury, the use of medication affecting fatigue state and/or alertness[8], substance abuse, color blindness, native language other than French and age above 45 years old. In the pwMS group, six participants dropped out of the study due to the COVDI-19 pandemic (n=4) or personal reasons and disease management (n=2). In the HC group, three participants were excluded from the study for not meeting inclusion criteria or not following study protocol (one participant showed white matter hyper-intensities in T2 FLAIR image, one participant experienced minor head injury with concussion between two sessions and one participant could not observe the recommendation for interruption of stimulants prior to the study due to a high consumption of energy drinks). Additionally, three participants in the HC group dropped out from the study due to personal reasons or high anxiety triggered by the

[8] The following medications were considered as an exclusion criteria if they were not stopped at least 5 half-life prior participation to the study: benzodiazepine, neuroleptic, tricyclic antidepressant, beta blocker, anticholinergic and antiepileptic drugs.

MRI environment. Consequently, 19 pwMS and 19 matched HC participated to the full protocol.

Regarding fMRI data, one participant in the pwMS group felt asleep during the N-Back task and was therefore excluded from fMRI analysis. Data from four participants (2 pwMS, 2 HC) were also removed from task fMRI analysis due to poor quality of images acquired.

C. Material and Design

Questionnaires

Participants were asked to fill in several questionnaires assessing depression (Beck Depression Inventory: BDI-II; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), anxiety (State-Trait anxiety inventory: STAI; Spielberger, Gorsuch, Ushene, Vagg, & Jacobs, 1983), sleep quality (Pittsburgh Sleep Quality Index: PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1998), daytime sleepiness (Epworth Sleepiness Scale: ESS; Johns, 1991), fatigue (Fatigue Scale for Motor and Cognitive Function: FSMC; Penner et al., 2009 - Fatigue Severity Scale: FSS; Krupp, LaRocca, Muir-Nash, & Steinberg, 1989 - Brugmann Fatigue Scale: BFS; Mairesse et al., 2019) as well as personality traits (NEO-Five Factor Inventory: NEO-FFI; Costa & McCrae, 1992).

The Beck Depression Inventory (Beck et al., 1961) is a 23-item Likert scale assessing the intensity of depressive symptoms and attitudes during the two preceding weeks. Items score range from 0 to 3, and total score from 0 to 63. As recommended by the authors, a final score of 10 or above is usually indicative of a mild depression, score above 29 suggest severe depression. Yet, several cutoff values have been proposed over the years, with the optimal score depending on the population studied (Y. P. Wang & Gorenstein, 2013).

The State-Trait anxiety inventory Y1 and Y2 (Spielberger et al., 1983) are two scales measuring anxiety. While the Y1 form assess state anxiety (current feeling, at the moment of assessment), the Y2 form refers to trait anxiety (anxiety in the everyday life, rather stable personality trait). Each scale is comprised of 20 items on a 4-point Likert scales, with a final score ranging from 20 to 80.

The Pittsburgh Sleep Quality Index (Buysse et al., 1998) is a 19-item questionnaire assessing subjective sleep quality over the previous month. Rating is performed across 7 components which are clinically relevant (for example, sleep duration and sleep disorders). The total score varies from 0 to 21, with a score above 5 suggestive of sleep disorder.

The Epworth Sleepiness Scale (Johns, 1991) is an 8-item of 4-point Likert scale (each ranging from 0 to 3) assessing the propensity of falling asleep during daily activities (while watching TV for example). Final score ranges from 0 to 24 and values above 10 are suggestive of excessive daytime sleepiness.

The Fatigue Scale for Motor and Cognitive Function (Penner et al., 2009) is a 20-item scale designed to assess fatigue symptom in MS population with a score ranging from 20 to 100. Each item reflects on daily-life situations associated with fatigue, with a 5-point Likert scale. Based on several fatigue questionnaires as well as on interviews conducted with neurologists, physiotherapists and pwMS, this scale is one of the most recommended tools to assess fatigue in MS (Elbers et al., 2012) and show a great reliability and validity (Penner et al., 2009). Two sub scores can be calculated from this questionnaire, in order to assess physical and cognitive fatigue. Several cutoff values are proposed for the total score as well as for sub-scales to detect normal, mild, moderate and severe fatigue.

The Fatigue Severity Scale (Krupp et al., 1989) is a 9-item fatigue scale assessing fatigue severity during the preceding week. The global score corresponds to the mean score obtained at the 9 questions and varies between 1 and 7, with a high score suggesting severe fatigue. A global score of 4 or above is usually considered as indicative of severe fatigue symptoms.

The Brugmann Fatigue Scale (Mairesse et al., 2019) is a scale measuring the propensity to rest during the day, in the same way as the ESS scale. This scale assesses cognitive and physical fatigue by means of two scales of 4 items each, ranging from 0 to 3. Total score for each sub-scale varies from 0 to 12. For each scale, a cutoff value of 6 is recommended by the authors.

The NEO-Five Factor Inventory (P. T. Costa & McCrae, 1992) quantifies the five domains of personality (known as the "big five" in the field of psychology), namely: neuroticism, extraversion, openness, agreeableness and conscientiousness. This scale is comprised of 60 affirmations prompting an answer on a 5-point Likert scale ranging from "strongly disagree" to "strongly agree".

Assessment of Subjective State

In order to assess the evolution of subjective states during our protocol, a sleepiness scale (Karolinska Sleepiness Scale: KSS; Åkerstedt & Gillberg, 1990) and several Visual Analog Scales (VAS; Lee, Hicks, & Nino-Murcia, 1991) were administered at several time points (see below and Figure 12). The KSS Likert scale ranged from 1 (very alert) to 9 (very sleepy) and the VAS scales comprised assessment of seven states on a scale from 0 to 100 (Motivation, Happiness, Fatigue, Openness, Stress, Anxiety, Effort).

Stroop Task – Effects of Task Duration on CF

In order to assess the effect of a long-lasting cognitive task on CF, we administered a computerized modified version of the Stroop task (Stroop, 1935) during 96 minutes (Session 2). Stimuli were displayed on a computer screen (the words "BLUE", "RED", "YELLOW" or "GREEN", or the symbol "XXXX"), with the color font varying in one of the following: blue, red, yellow or green. In this task, participants were instructed to determine the color of the font of each stimulus by pressing one of the four keyboard keys identified by white stickers. This task comprised three kinds of items: Congruent items (C), in which the color of the font matched the word displayed (for instance, the word "BLUE" written in blue); Incongruent items (I), in which the color and the word differed ("BLUE" written in red), and Neutral items (N) corresponding to the "XXXX" symbol printed in one of the four colors. Every second item, a neutral item was presented. When following an incongruent item, neutral items were considered as "Buffer Neutrals" and were excluded from analysis in order to avoid negative priming effect (i.e. a delay in answer due to the previous incongruent item). Stimuli were presented one by one, every 3000ms. As soon as participants gave an answer, the stimulus was replaced by a fixation cross lasting until the 3000ms trial duration was elapsed, with a maximum presentation duration of 2500ms. In this procedure, the same number of items was presented to each participant. Task duration was determined

according to previous work from Gilsoul & Collette (2018) using the same protocol in healthy adults. In their study, performance decrement (increase in reaction time) due to cognitive fatigue was observed after 80 minutes of performing the task for young adults and 60 minutes for middle-aged participants. Subjective state (KSS and VAS) were assessed at the beginning of the task and every 32 minutes until the end.

Time Load Dual Back – Effects of Cognitive Load on CF

The TLDB (Borragán et al., 2016, Figure 13) is a computerized dual task during which letters and digits are presented alternatively on a computer screen, combining a number parity judgment task and a classical N-Back working memory task. For each digit, participants were instructed to determine if it was either odd or even by pressing the appropriate key from the numeric pad (2 = even; 3 = odd). For each letter, participants had to detect when the letter presented was the same as the previous one (the letter presented before the digit) by pressing the space bar.

By adjusting the time available to process stimuli (i.e. the Stimulus Time Duration, STD), cognitive load induced during the task can be manipulated, while maintaining the same task complexity. Practically, individual STD was recorded during calibration[9], corresponding to the shortest STD at which participant's performance remained above 85%. This STD thus corresponds to the maximal load level for each participant (Borragán et al., 2017, 2016) and was used during the High Cognitive Load condition of the task (HCL). In the Low Cognitive Load condition (LCL), the STD was 50% slower (STD + ½ STD). Consequently, the pace of the task was tailored for each participant, thus inducing the same level of cognitive load for every subject.

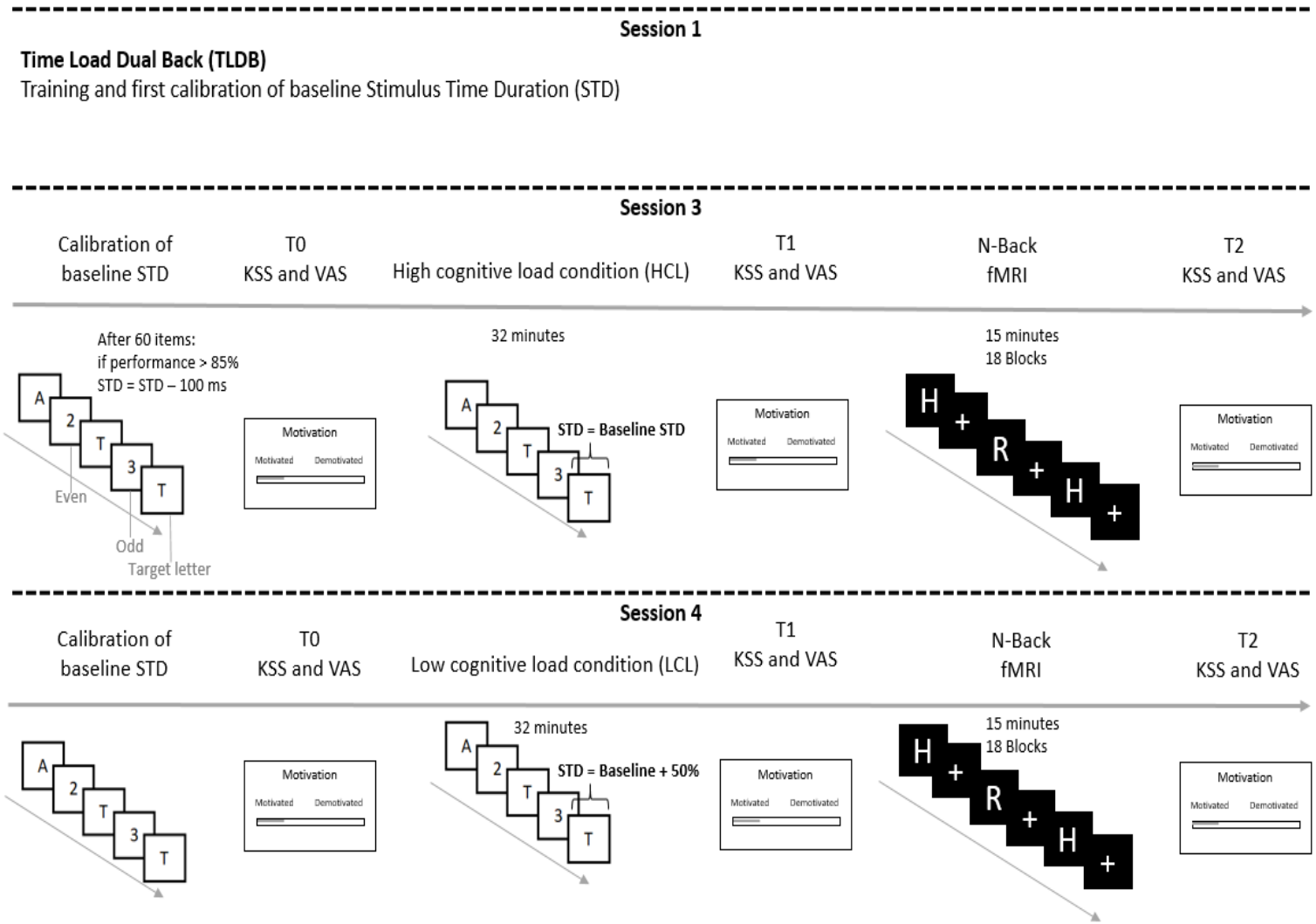
[9] Individual STD were recorded prior to each experimental session (HCL and LCL) to take into account daily variation in vigilance and fatigue state. In its original version, the calibration of the task can last about 15 minutes if final STD is very short (every 60 trials, if performance remained above 85%, STD is reduced by 100ms starting from 1700ms). This is problematic since fatigue might be already induced during a long calibration (even though breaks were provided regularly). To avoid this problem, a calibration of the task was performed on Session 1 to get a first individual measure. 300ms were added to the STD measured on Session 1, and the result obtained was used in further calibration as a reference starting point (instead of the 1700ms starting point).

In this study we used an extended version of the TLDB which lasts 16 minutes in its original version (Borragán et al., 2016). Results from a previous study in a MS suggest that cognitive fatigue starts to arise at the end of the original task (Borragán et al., 2018). In the present study we therefore decided to double task length in order to investigate the effects of a more prolonged cognitive effort. Consequently, participants performed the TLDB task for 32 min.

Eye metrics

During the TLDB task (Sessions 3 & 4), eyelids gap and pupil size of the right eye were recorded by a portable device: the Drowsimeter R100 from Phasya© (Phasya s.a., Belgium https://www.phasya.com/en/drowsimeter-r100). By using images recorded with a camera positioned on glasses, this device provides objective measures of eye metrics (in pixels) at a frequency of 120 Hz. Corrective lenses were available and could be integrated to the device for participants wearing glasses.

Figure 13: Assessing the effects of cognitive load on fatigue: procedure



N-Back Task - fMRI

On sessions 3 & 4, participants underwent an fMRI session following fatigue induction (Figure 13). The task used to assess the effects of cognitive fatigue on cognition and associated functional brain activity was a computerized N-Back task (Kirchner, 1958) with three levels of difficulty (1 to 3-Back). During the N-Back task, participants are presented letters (consonants of high and low frequencies in French language) and had to detect if the current letter matched the one presented N-position(s) before. Namely, if the letter is the same as the last one (1-Back), the second last one (2-Back), or the third last one (3-Back). For each letter, participants had to provide an answer by pressing the appropriate response button (Left = "Yes, it is the same letter"; Right = "No, it is not the same"). The task was composed of 18 successive blocks of 16 stimuli, with 6 blocks per difficulty. The order of the 18 blocks was pseudorandomized. Among the 16 letters presented, 5 trials corresponded to a target trial, during which the "Yes" answer was expected, and the first one-to-three letters were considered as "buffer" trials, during which no answer was expected (1 buffer at the beginning of "1-Back" blocks, 2 for the "2-Back", and 3 buffers for the "3-Back"). Stimuli were displayed in large white font on a black background. Each block started with instructions displayed during 5000ms on the screen regarding the upcoming block difficulty (1-Back, 2-Back or 3-Back) and a reminder of the corresponding response button. In each block, letters were presented with a time presentation interval of 1700ms followed by an inter-stimulus fixation cross of 500ms. At the end of the block, a fixation cross of 12000ms was displayed before the beginning of the next block. The total task duration was of approximately 15 minutes. The task was displayed on a screen visible to participants through a mirror attached to the head coil. After the experimenter explained the task to the participant, a training session outside of the scanner was performed, and repeated until the participant felt comfortable with the task. A last training session was performed inside the scanner to ensure participants were able to use the MRI keypads correctly.

Resting State - fMRI

A resting state acquisition of 7 minutes was performed on session 3 & 4 following the N-Back task. Participants were asked to keep their eyes open and stare at a withe fixation cross displayed on a black background. Live video of the eyes enabled the

experimenter to ensure that the participant was not sleeping. This method was chosen instead to eye-closed resting state acquisition since fatigue induced during the protocol increased the risk of participants falling asleep.

MRI Data Acquisition and Sequences

All MRI data were acquired on a 3T scanner (Magnetom PRISMA, Siemens Medical Solution, Erlangen, Germany) with a 64-channel head coil.

In order to extract structural and quantitative maps of T1, T2*, proton density (PD) and magnetization transfer (MT) at 1 mm resolution, a multi-parameter protocol based on a 3D multi-echo fast low angle shot (FLASH) sequence was performed during Session 2 (N. Weiskopf & Helms, 2008). Three co-localised 3D multi-echo FLASH data sets were acquired with predominantly proton density weighting (PDw: Repetition Time: TR =24.5 ms, Flip Angle: FA = 6°), T1 weighting (T1w: 24.5 ms/21°), and MT weighting (MTw: 24.5 ms/6°; excitation preceded by an off-resonance Gaussian MT pulse of 4 ms duration, 220° nominal FA, 2 kHz frequency offset) in a total acquisition time of approximately 19 min.

During Sessions 3 & 4, T2*-weighted functional images were acquired with the multi-band gradient-echo echo-planar imaging (EPI) sequence (CMRR, University of Minnesota) using axial slice orientation and covering the whole brain/most of the brain (36 slices, multiband factor = 2, Field of View: FoV = 216x216 mm^2, voxel size 3x3x3 mm^3, 25% interslice gap, matrix size 72x72x36, TR = 1170 ms, Echo Time: TE = 30 ms, FA = 90). The three initial volumes were discarded to avoid T1 saturation effects. Additional identical multiband-EPI volumes were performed before the main fMRI time series with identical orientation but opposite phase encoding direction to derive deformation maps to be applied to the whole fMRI series for distortion correction. Respiration and pulse signals were recorded during fMRI time series in order to derive physiological regressors and correct for physiological noise in the BOLD signal. The same settings were used for resting state fMRI.

For anatomical reference, a high-resolution T1-weighted image was acquired for each subject (Session 4, T1-weighted 3D magnetization-prepared rapid gradient echo (MPRAGE) sequence, TR = 1900 ms, TE = 2.19 ms, inversion time (TI) = 900 ms, FoV =

256x240 mm², matrix size = 256x240x224, voxel size = 1x1x1 mm³, acceleration factor in phase-encoding direction R=2). An additional T2 FLAIR sequence was acquired and used for lesion segmentation (Session 4, TR = 5000 ms, TE = 5.16 ms, inversion time (TI) = 1800 ms, FoV = 256x240 mm², matrix size = 256x240x224, voxel size = 1x1x1 mm³, acceleration factor in phase-encoding direction R=2).

Finally, diffusion-weighted (DW) data were acquired (Session 3, following fMRI acquisitions) using a multiband SE-EPI sequence (Center for Magnetic Resonance Research (CMRR), University of Minnesota), with 2mm isotropic spatial resolution. Acquisition parameters include: TR = 4070 ms, TE = 70.20 ms, 70 transverse slices, slice thickness = 2 mm and slice acceleration factor = 2, in-plane resolution 2x2 mm² (FoV = 192x216 mm², matrix = 96x108) and acceleration factor 2, bandwidth per pixel = 2264 Hz/Px. The multi-shell diffusion-weighted imaging (DWI) scheme included 118 volumes. The first volume was discarded to avoid T1 saturation effect. The remaining 117 volumes correspond to a total of 105 DW images interleaved with 12 b=0 images. The set of diffusion directions was created using electrostatic repulsion (Slater et al., 2019) is defined over three shells (b = 650, 1000 & 2000). Susceptibility-induced and eddy current-induced distortions, as well as movements, were estimated and corrected using *topup* (Andersson, Skare, & Ashburner, 2003) and *eddy* (Andersson & Sotiropoulos, 2016) in FSL 5.0.9. The estimation of susceptibility-induced distortions relied on the acquisition of 5 additional b=0 volumes with the same acquisition parameters as above, but inverted phase encoding direction (Andersson et al., 2003).

Images quality was systematically controlled during the scanning session in order to re-run a sequence (if applicable) in case of poor quality. Moreover, FLAIR images of participants in the HC group were examined by a neurologist in order to detect any neurological anomaly incompatible with participation to this study.

MRI Data Management

MRI data were organized according to the Brain Imaging Data Structure format (Gorgolewski et al., 2016, BIDS version 1.2, https://bids.neuroimaging.io/) using the BIDSme tool developed in our lab by Nikita Beliy (version 1.3.5r5): https://gitlab.uliege.be/CyclotronResearchCentre/Public/bidstools/bidsme.

Preprocessing of all images was carried out using SPM12 (Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm).

Neuropsychological Assessment

The last session was dedicated to neuropsychological assessment performed by a trained neuropsychologist (Figure 14). Session started and ended by an assessment of subjective state with the KSS and several VAS. The flexibility test from the Test of Attentional Performance (TAP, version 2.3, Zimmermann & Fimm, 2010) was also administered twice in order to explore the effects of fatigue state induced by neuropsychological assessment on reaction times and number of errors. Composition of the full assessment was carefully designed in order to reflect on cognitive domains that are frequently impaired in MS, namely memory, attention executive functioning, working memory and visual processing (Chiaravalloti & DeLuca, 2008).

Flexibility from the TAP*:* This computerized test evaluates set shifting abilities (Zimmermann & Fimm, 2010). In the version administered in this study, subjects were prompted with letters and digits, presented on the right and the left side of the screen simultaneously. For each trial, participants had to detect as quickly as possible the side where the letter was presented by pressing the right or the left key, accordingly.

California Verbal Learning Test (CVLT): The CVLT (Deweer, Poitrenaud, Kalafat, & Van Der Linden, 2008) is a verbal memory test during which subjects are first prompted with a grocery shopping list of 16 items read aloud by the experimenter (List A). Participants are told to memorize the list and retrieve as many items as possible, in any order. The list is presented 5 successive times in the same order and comprises items belonging to 4 categories (tools, clothing, herbs & spices, fruits). Following the 5 learning trials, an interfering list is presented to the subject (List B) of 16 new items from 4 categories (kitchen utensils, fish, herbs & spices, fruits). After retrieval of the List B, subjects are asked about the List A again, without any recall of the list from experimenter (short delay free recall). A cued recall is then performed, with the experimenter asking the subject to recall the items belonging to each category. Long delay free and cued recalls are achieved after 20 minutes. Finally, a recognition task is performed. Subjects have to detect which items read by the experimenter belong

to List A in a list of 44 items comprising different kinds of distractors among the 16 targets.

D2 Test of Attention: The D2 (Brickenkamp & Zillmer, 1998) is a test of selective attention during which subjects are asked to cross target items as fast as possible. Targets are the letter "d" in lower case and surrounded by 2 dots and are presented among distractors such as the letter "p" or letter "d" with 1 or 3 dots. Participants have to complete each line of the paper sheet from left to right and are asked to go to the next line every 20 seconds, with 14 lines completed in total.

Alertness form the TAP: In this computerized task, subjects had to respond as quickly as possible to a fixation cross appearing at the center of the screen by pressing a key. The cross was always presented at the same location but with varying delay. The task is administered in two conditions: with or without preceding auditory stimulus to warn the upcoming appearance of the cross. Four sessions are administered following an ABBA experimental design and starting with the "without warning stimulation" condition.

Brief Visuospatial Memory Test – Revised (BVMT-R)*:* The BVMT-R (R. H. B. Benedict, Groninger, Schretlen, Dobraski, & Shpritz, 1996) is a visual memory test during which the experimenter shows a stimuli page with 6 geometric figures for 10 seconds. The subject is asked to draw from recall the different figures as accurately as possible and in their right position. Three learning recall are performed, along with a 25-minutes delayed recall.

Digit Span from the Wechsler Adult Intelligence Scale – III (WAIS-III): In the digit span test from the WAIS-III (Wechsler, 2000), subjects have to repeat series of digits read aloud by the experimenter. The series increase in length every two trials and the test is stopped after two consecutive errors at trials of same length. The task is administered in two retrieval conditions forward (subjects have to repeat digits in the order they have been provided) and backward (subjects have to repeat digits starting from the last one and finishing with the first one provided).

Verbal Fluency: In the present version of the verbal fluency test (Université de Liège, 2017), subjects had to provide as many words as possible within 2 minutes

avoiding words from the same family and proper names. This was done in two conditions: words starting with the letter "P" (phonemic fluency) and names of animals (semantic fluency). Number of words provided after 15 second, 1 minute and 2 minutes were recorded.

Random Number Generation (RNG): Subjects were asked to provide a random series of 100 digits between 1 and 9, as if they were rolling a nine-sided dice. Participants had to provide a digit every second and were helped by a metronome set at 60 bpm. Answers were analyzed using the RGcalc software (Towse & Neil, 1998).

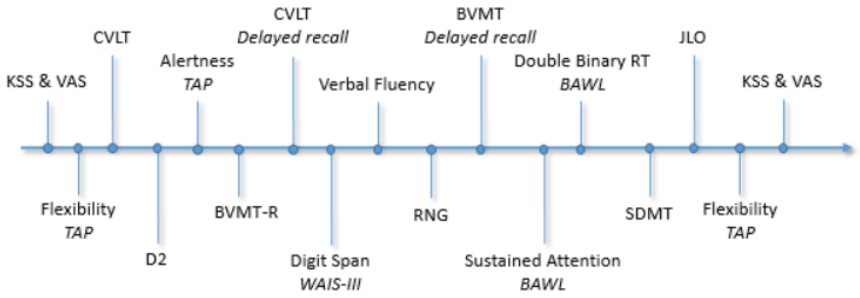
Sustained attention from the Batterie d'Attention William Lennox (BAWL): The sustained attention task from the BAWL (Leclercq, 2007) follows a Go-no-Go protocol. Subjects had to react to letters of variable size presented on the screen by pressing a key, while inhibiting responding to the digit "3" when it appeared. Participants were frequently prompted by letter items, while the appearance of the "3" item was very rare.

Double Binary RT from the BAWL: In the first step of this task, participant had to react to two target items (red cross and blue circle) and inhibit answer to 2 distractor items (blue cross and red circle) in a series of 32 items. Then, the task was repeated while the participant had to repeat series of digits read aloud by the experimenter (dual-task). Finally, the same amount of digit series was administered again for comparison (simple-task).

Symbol Digit Modalities Test (SDMT): The SDMT (Smith, 1982) is a substitution task during which participants have to provide digits corresponding to symbols according to a reference key. Subjects have to provide as many digits as possible within 90 seconds and are required to process each item from left to right. In this study, the written mode was administered, though an oral version also exists.

Judgment of Line Orientation (JLO): The JLO (Benton, 1978) is a visual perception test. Subjects are asked to match two lines of different orientations with a reference panel composed of 11 lines of orientations ranging from 0 to 180 degrees. The version administered was comprised of 5 practice items and 30 trials of 2 lines.

Figure 14. Timeline of the neuropsychological assessment (Session 5)



General Discussion

The purpose of this thesis was the exploration of cognitive fatigue in the early stages of MS. This was achieved using several methods, including the examination of the effects of time on task and/or a probe task on subjective states, cognitive performance, eye-metrics and brain activity (assessed with fMRI). Trait fatigue, which reflects the persistence of fatigue in everyday life, was also studied through cognition and brain measures (at the functional and microstructure levels).

In this Discussion, the results which we have obtained thanks to six studies will be brought together and we will address our initial research questions:

- *Is there a link between fatigue and cognition in MS?*
- *What are the effects of long-lasting procedures and cognitive load on cognitive fatigue? Which procedure triggers fatigue the most?*
- *Can eye metrics provide an objective measure of fatigue state?*
- *What are the cerebral substrates of cognitive fatigue in the early stages of the disease?*

In this section, we will also clarify the current limitations of this thesis and we will make proposals for further investigations, which could complete and expand our findings. We will start by addressing the limit due to sample size and extensive statistical testing of a same population. Indeed, this limit applies to the present work as a whole and have to be kept in mind when interpreting our results.

I. Sample Size and Multiple Testing

Due to our strict inclusion criteria, the sample studied in this thesis is, indeed, quite small. Since the primary aim of this work was to focus on the very early stages of the disease, recruiting newly diagnosed patients was needed, but finding participants with enough resilience to volunteer was challenging. Moreover, the administered protocol was dense and the statistical analyses were performed on the same sample for studies 2 to 6. Choosing between (i) administering an extensive protocol in a single sample of participants and (ii) recruiting a new sample for each study is a methodological question that raised many concerns when developing our research project. Due to the

lack of data in the literature in our research field, the first option was preferred in order to fully characterize fatigue in our volunteers and be able to easily and reliably confront findings from each study. Hence, the objective of this thesis was greatly exploratory and further work would be needed to confirm some of our results.

Given our sample size, our statistical power was small, and several effects might not have been detected if not strong. Whenever possible, Bayesian inference, rather than frequentist analysis, was preferred in our statistical design to mitigate this issue. One of the great advantages of Bayesian statistical inference is that the Bayes Factor (BF) computed provides the grade of evidence not only for an effect, but also for an absence of effect. This is particularly relevant in studies with low statistical power, because it clearly indicates whether an absence of effect is due to the sample studied (i.e. with an inconclusive result) or if the effect is not present at all (Keysers et al., 2020). Consequently, Bayesian statistics are particularly appropriate to small sample sizes (van de Schoot, Winter, Ryan, Zondervan-Zwijnenburg, & Depaoli, 2017). With regard to this thesis, several effects studied yield inconclusive results, especially group effects. This is unfortunate, as it limits our interpretations, but it provides valuable information for further studies that might be interested in similar research questions. Hence, a BF_{10} of 2.5 is much more informative and easily interpretable than $p > .05$ (Jarosz & Wiley, 2014). Of course, information about effect size and its confidence interval in frequentist analyses are also useful to determine the reason behind a negative result (Nakagawa & Cuthill, 2007), but BF factor is more straightforward by providing the grade of evidence supporting a hypothesis according to the data studied (Dienes, 2014).

If a limited sample size can lead to false negative, multiple testing can in turn provide false positive results. Again, Bayesian inference is useful here, as it does not require correction for multiple comparisons when different hypotheses are tested (Ryan, Brock, Gates, & Slade, 2020; Sjölander & Vansteelandt, 2019). Indeed, the concept of Type I error does not make much sense in Bayesian theory, because this statistical method provides an estimation for both hypotheses and it does not depend on a hypothetical Gaussian distribution. Nevertheless, it seems probable that repeated testing may randomly lead to false positive. Concerning that matter, it has been

suggested that Bayesian statistics are more robust than classical frequentist analyses when it comes to false-positive rate (Kelter, 2021).

Yet, the extensive protocol used in our sample comes with an important limitation. The similarity of effects observed across studies could, in fact, be inherent to the unicity of the sample used. For instance, the observation that early pwMS did not display increased sensitivity to fatigue compared to control in several of our studies can be due to idiosyncratic characteristics of our set of volunteers. Consequently, we cannot conclude with enough confidence that patients in the early stages of the disease do not show fatigue susceptibility despite our consistent observations across studies. These findings could simply relate to the fact that our specific small sample of patients was not particularly sensitive to fatigue and the reproducibility of our results should be verified.

Overall, we acknowledge that the results provided by this work should be taken with caution. Nevertheless, they provide a unique broad picture of cognitive fatigue in early MS.

II. Fatigue and Cognition: Two Closely Related Symptoms of Multiple Sclerosis

The first two studies aimed at exploring the link between CF and cognition in two samples of pwMS with different disease duration. In **Study 1**, we found that in pwMS, trait CF is linked to executive function and processing speed, while trait physical fatigue is associated to working memory. In healthy subjects, only an association between executive functioning and depression was observed. In **Study 2**, we found additional support suggesting that cognitive deficits are frequent in the early stages of the disease and that they might also be subtle. We did not find evidence for an association between cognition and fatigue except for visual memory performance, which was negatively correlated to subjective fatigue induced by neuropsychological assessment. However, several tests yield inconclusive results, including tests that are frequently used in neuropsychological assessment in the context of MS.

A. About the Nature of the Link between Fatigue and Cognition

Together, these studies (and more particularly **Study 1**) provide additional support for an association between fatigue and cognition in MS (Andreasen et al., 2019; Heesen et al., 2010). Importantly, our results were obtained after controlling for several confounding factors, namely age, sex, education, depression, anxiety and disability level. But what can be said about the directionality of the link observed? Does fatigue prevent pwMS to perform at their best during cognitive assessment? Do cognitive deficits trigger fatigue symptom, for instance throughout maladaptive compensatory mechanisms? Alternatively, is there another confounding factor that independently contributes to both cognitive impairment and fatigue sensation? Unfortunately, our methodology does not allow to answer those questions. However, these hypotheses are not mutually exclusive and all could very likely be true to some extent. Since state fatigue can have a deleterious impact on cognitive performance (for instance during prolonged cognitive tasks as in Sandry, Genova, Dobryakova, DeLuca, & Wylie, 2014), it is reasonable to speculate that trait fatigue alters cognition as well. In turn, the effects of cognitive deficits on fatigue sensation have also been proposed. Namely, it has been suggested that fatigue arises from cognitive impairments as a consequence of an extra-effort provided to accomplish a cognitive task (DeLuca et al., 2008). Accordingly, Borragán and colleagues (2018) suggested that, when cognitive load is adjusted to cognitive deficits, pwMS may not exhibit an increased fatigue susceptibility compared to healthy subjects. Surprisingly, the rare longitudinal studies assessing cognitive deficits and fatigue in MS suggest that the two symptoms are independent. In a study from Hildebrandt and Eling (2014), cognitive scores at an extensive neuropsychological battery did not predict trait fatigue evolution at one year in pwMS. Similarly, baseline fatigue did not significantly predict cognition in a study from Morrow and colleagues (2009). These are the only two studies, which specifically explored the directionality of the fatigue/cognition association, and both assessed fatigue by means of the FSS which is a scale for global fatigue severity. However, in a study from McNicholas and colleagues (2021), treating pwMS for obstructive sleep apnea was effective in reducing fatigue and improving verbal memory performance, suggesting that alleviating trait fatigue was beneficial to cognitive performance and that the two constructs are, indeed, related. Consequently, more longitudinal studies are needed to better specify the

interaction of these symptoms, especially studies specifically assessing cognitive and not global fatigue, as we found that fatigue relates differently to cognition depending on its modality.

Alternatively, the association observed between cognitive deficits and fatigue in cross-sectional studies could be due to a common underlying mechanism. If we control for several confounding variables in our studies, other factors might partly explain our observations, especially cerebral alterations. Indeed, both cognitive deficits and CF are linked to structural and functional alterations within the CNS (see for instance ARM, Ribbons, Lechner-Scott, & Ramadan, 2019; Bonnet et al., 2010; Calabrese et al., 2012). In **study 5**, we found that fatigue in early MS is linked to specific patterns of brain activity, yet group effects on cognitive performances were mainly inconclusive. However, previous works did evidence fatigue-related brain activity in association with lower performance in pwMS (see for example DeLuca et al., 2008). In **Study 6**, the association between cognition and integrity of normal appearing brain tissues were not investigated, but we found that fatigue is associated to white matter alterations. Numerous studies demonstrated that cognitively impaired patients show microstructural alterations within the global white matter (A. Pokryszko-Dragan et al., 2018; Yu et al., 2012) and in specific tracts (including posterior thalamic radiation and corpus callosum) which were found to relate to fatigue by others (ARM et al., 2019; Bonnier et al., 2014). In a longitudinal study from Fleischer and colleagues (2020), increased effective connectivity between frontal areas and the cerebellum was predictive for lesser fatigue level in patients, suggesting that brain plasticity and functional reserve protects again fatigue. Unfortunately, no cognitive variable was included in the analyses.

In conclusion, all these hypotheses found support to some extent, but further studies are needed to better characterize the association between cognition and fatigue. More precisely, mediation studies could be very useful in this case. Modeling fatigue and cognition determinants in pwMS with its associated factors to determine their specific direct and indirect contributions could be of great interest. The models should include well-known causes for secondary fatigue, such as depression, anxiety, pain, and sleep disorders, as well as confounding demographic variables, and global measures of

brain integrity. For instance, median values of qMRI parameters associated to fatigue in **Study 6** could be easily integrated in such model. Mediating models were already applied to the field of MS symptomatology. This kind of analysis was used to specify the determining factors of quality of life (Young et al., 2021) or to investigate the effects of sleep disorder, depression and disease severity on fatigue symptom (Lauren B. Strober & Arnett, 2005). Using this method to characterize the association between fatigue and cognition by including measures of cerebral integrity would be an exciting innovation.

B. The Effect of Disease Duration

While our results strongly suggest that fatigue relates to cognition in the latter stages of the disease (**Study 1**), we express reservations regarding early MS (**Study2**). As we hypothesized, fatigue in early pwMS was not a high predictor of cognitive performance, and this might be due to their ability to compensate from the deleterious impact of fatigue during cognitive assessment. Similar conclusions were drawn by Berard and colleagues (2018), in a study assessing the diagnosis sensitivity of the PASAT for CF in early pwMS. In this study, between-group differences were observed for fatigue, but only subtle and qualitative differences in cognitive scores were noted. Accordingly, they suggested that pwMS maintained performance throughout compensation and that CF might be a more sensitive measure of cognitive difficulties than performance *per se,* especially in the early stages of the disease (Berard et al., 2018). Yet, such brain compensatory mechanisms triggering fatigue in early MS have not been demonstrated so far.

One of the aims of this work was to investigate if such compensatory mechanism could be observed. In **Study** 5, we have found specific patterns of fatigue-dependent brain activity in patients, while effect of task's difficulty on performance was similar to controls. This provides preliminary evidences for a compensatory mechanism in early pwMS. However, since our control task also induced fatigue state, the effects of fatigue induction could not be explored. Replicating the present study with a more appropriate control task (i.e. session of rest, watching videos…) instead of the Low Cognitive Load condition of the TLDB task would be interesting. By doing so, we could determine if trait fatigue has a differentiated effect on cerebral substrates depending on fatigue state (i.e. following fatigue induction vs rest). Additionally, with such design, it would be

interesting to examine the effects of disease duration. For instance, we could apply this protocol in three different groups of patients: early pwMS with fatigue complaint, early pwMS without fatigue complaint and late pwMS with fatigue complaint. By doing so, we could verify whether early pwMS with fatigue have a similar cognitive performance compared to non-fatigued patients, while exhibiting different patterns of brain activity in relation to state and trait fatigue. This would suggest an effective, but costly, cognitive compensation. In turn, comparing early and late patients with a fatigue complaint would provide a better understanding of the effects of disease duration on the association between fatigue and cognition. In particular, we might observe that late pwMS are not able to compensate from the disease (i.e. cerebral alterations, but maybe also fatigue symptom) and display a decreased performance compared to early pwMS. Confronting cerebral activity in both groups of fatigued patients and non-fatigue early patients would also provide further information about the cerebral substrates of MS-fatigue. This point will be discussed in the section V.

C. Fatigue, Cognition & Neuropsychological Assessment

Several recommendations for cognitive assessment can be derived from our results. Firstly, as fatigue can have an impact on cognitive scores (especially in the later stages of the disease), we recommend to systematically assess this symptom during neuropsychological assessment, preferably with validated trait fatigue scales (rather than VAS). Hence, in **Study 1**, trait fatigue was strongly associated to cognitive scores. As it seems that fatigue has a differentiated impact on cognition depending on its modality (see **Study 1**), it is relevant to assess both cognitive and physical fatigue using appropriate trait scales (e.g. the FSMC) in order to provide a fine-grained evaluation of fatigue complaint. Additionally, in **Study 2**, most correlations between cognitive scores and VAS measures of fatigue evolution have displayed evidence for an absence of effect. Taken together, results from **Studies 1 & 2** suggest that fatigue elicited by cognitive assessment has less impact on cognition compared to trait fatigue. This strengthens our recommendation to favor trait scales. Yet further studies should appreciate if this observation remains accurate in the later stages of the disease, as patients may be more sensitive to fatigue induction.

One test, however, was significantly correlated to fatigue induced by assessment, from the early stages of the disease: The BVMT-R for visual memory. This result suggests that fatigue influences cognition in the very early stages of the disease (yet, probably to a lesser extent than later in the disease). What is more, it suggests that cognitive tests which are widely used for cognitive screening in this population might be sensitive to fatigue. As discussed in **Study 2**, further studies focusing on tests that are frequently employed (such as from the BICAMS) are greatly needed in order to clearly specify the extent to which fatigue alters neuropsychological performance, at different disease stages. Until then, we recommend clinicians to remain particularly cautious in the interpretation of cognitive profile in patients with a fatigue complaint.

In conclusion, fatigue measures may provide valuable information in the interpretation of neuropsychological assessment, especially regarding scores at visual memory tests (**Study 2**), executive functioning, processing speed and working memory (**Study 1**).

III. Duration vs Load: Which one matters the most?

In **Studies 3 & 4**, fatigue was induced by means of different protocols. In the former, we were interested in observing the effect of cognitive load on subjective and objective fatigue. In the latter, we have examined the effects of a prolonged cognitive task. Additionally, the effect of tasks' characteristics (i.e. cognitive load and duration) on subjective state was confronted in **Study 4**. This last analysis was performed in order to determine which frequently used CF induction protocol is more prone to be effective: a task of short duration but inducing a high cognitive demand, or a relatively less demanding and monotonous task of long duration. We hypothesized that the former would induce a higher fatigue sensation, as it requires more cognitive effort.

Results from **Study 3** show that, when cognitive load is individually adjusted for their cognitive abilities, newly diagnosed pwMS and HC behave similarly during fatigue induction. This was the case both in terms of performance decrement and of accrued fatigue sensation. Performance at the task was lower when cognitive load was high, and decreased with ToT, regardless of cognitive load and group. In **Study 4**, early pwMS

showed decreased accuracy at the Stroop task compared to healthy subjects, which was suggestive of an alteration of cognitive control or attentional processes. Performance (accuracy and RTs) also decreased with ToT. The interaction between group and time on RTs showed evidence for an absence of effect (similar increase of RTs with ToT in both groups) but analysis on accuracy yield inconclusive results. As in **Study 3**, patients and HC exhibited a similar increase of subjective fatigue across the task. Concerning the effect of task's characteristics, task of long duration seems to be more effective in inducing subjective fatigue in our sample. However, we suggested that this result might be driven by a confounding effect of motivation.

A. Objective Performance Fatigability

First, it is worth noting that performance decreased with ToT in every procedure. Regarding the TLDB, ToT had an effect on accuracy, but the interaction with cognitive load was inconclusive. Thus, in our study, whether a HCL exacerbates performance fatigability by comparison to a LCL condition is unclear. The effect of cognitive load was often suggested and was observed in some studies (Borragán et al., 2018, 2017; Guastello et al., 2012), but not other (Chatain et al., 2019). In a recent study from Luna and colleagues (2022), cognitive load modulated the effects of ToT on performance fatigability for accuracy but not reaction times. The authors suggested that cognitive load affects the executive (signal detection) but not the arousal (fast RTs without control) component of vigilance tasks. Variability in measures of performance for fatigability may at least partially explain the lack of consistency across studies, with such measures being more or less sensitive to fatigue induction (Walker, Berard, Berrigan, Rees, & Freedman, 2012). Hence, accuracy at the TLDB remained quite high during the task, and it is likely that the interaction effect between ToT and cognitive load did not yield significant results due to a poor sensitivity of our measure. Besides, we suggest that doubling task's duration in **Study 3** compared to its original version (Borragán et al., 2017) led to performance fatigability even if cognitive load was low, due to prolonged ToT. Consequently, we might have found an interaction with cognitive load if the task would have been shorter (as in Borragán et al., 2018, 2017), as using a longer task might have masked the effect of cognitive load on performance decrement.

Regarding group-related performance fatigability, we found evidence suggesting that pwMS *do not* exhibit an increased vulnerability to fatigue compared to controls, for all measures of the TLDB and for RTs during the Stroop. Effects on accuracy at the Stroop were inconclusive, thus we cannot exclude that early pwMS exhibit a subtle vulnerability to fatigue induction on this measure. Interestingly, this is also the only measure of performance that exhibited evidence for an effect of group in **Studies 3 & 4**, with pwMS showing lower accuracy compared to HC. Consequently, we could hypothesize that pwMS display a steeper performance decrement compared to controls only in tasks where a cognitive deficit is observed. In other words, fatigue induction may exacerbate cognitive deficits in early pwMS, thus leading to increased performance fatigability, possibly due to the additional effort provided by patients to perform the task. This hypothesis is close to the one proposed by Borragán and colleagues (2018), according to which pwMS may not exhibit increased fatigability of performance when the task is adjusted to individual abilities. One possible way to test this hypothesis would be to use the TLDB in a different setting: administering the classical HCL condition with adjusted stimulus time presentation, and a modified version of the task with a fixed time constraint for every participant. Alternatively, results from the classical TLDB could be compared to performance obtained at a task that is known to be altered in pwMS, as for example the PASAT administered for the same duration, which was previously shown to be a sensitive tool for cognitive fatigue in MS (Walker et al., 2012).

To conclude on objective fatigability, both cognitive load and prolonged ToT lead to performance decrement. However, it is not clear whether early pwMS are more vulnerable to fatigue induction, and this might depend on the sensitivity of the measures used, the characteristics of the task, and patients' cognitive abilities. More studies with stronger statistical power are needed.

B. Subjective Feeling of Fatigue

Concerning subjective state, pwMS and HC experienced a similar increase in fatigue sensation due to fatigue induction in both studies. This is quite an encouraging result, as it suggests that pwMS in the early stages of the disease do not exhibit a severe vulnerability to fatigue induction, even if the ongoing task is not adjusted for cognitive

deficits (**Study 4**). When exploring the task's characteristics that are more likely to induce a high fatigue sensation, we observed that long-lasting protocols are very effective in inducing subjective fatigue, even if they are not time-constrained.

On this topic, one important limitation must be addressed. In both studies, participants were not aware of task duration. However, as subjective states in **Study 3** were assessed only at the beginning and the end of the task, participants could guess that they fully completed the task at the moment of the last assessment. This was not the case in **Study 4**, as several assessments of subjective state were performed during the task, and participants could not be aware that the task was over when filling the last scales. If we believe that this design did not affect performance, it might have biased results obtained in subjective scales. Hence, it has been shown that reported fatigue is higher if the end of the task is unknown. When we have to keep aside competing goals for an unknown duration, theSir pressure may be reflected in the fatigue sensation (Katzir, Emanuel, & Liberman, 2020). Consequently, interpretation of results on behavioral scales from **Studies 3 & 4** requires particular caution, and the higher fatigue level observed in **Study 4** might relate to participants being not aware of the end point. This limitation could have been alleviated by applying a consistent methodology to assess subjective feelings across studies. Nevertheless, the present design was preferred in order to (i) avoid task interruption during the TLDB task due to subjective assessment, which may lead to fatigue recovery[10] and (ii) obtain a measure of subjective state following 32 minutes of Stroop (for comparison with the TLDB).

This observation regarding reported fatigue at the end of a task relates to another aforementioned limit: The confounding effect of motivation loss. Hence, in our supplemental analyses, we found that motivation was drastically decreased at the end of the Stroop task. Again, this might be due to the unpredictable end of this task. Yet, as a similar decrease in motivation was observed following the 32-min Stroop and the

[10] A recent study from our lab found that 5 minutes breaks provided every 40 minutes during a Stroop task alleviate the effects of ToT in RTs (Gilsoul et al., 2021). In our protocol, brief task interruptions (~1/2 minutes) could be considered as short breaks. Assessing fatigue following each block of the TLDB might have been problematic, as task would have been interrupted every 10 minutes.

TLDB of same duration (but with acknowledged end), there might be more than just an effect of end expectancy. In **Study 4**, we interpreted this motivational drop as relating to the long duration of the task and its repetitive and monotonous nature. The relationships between lack of motivation and fatigue are discussed in the next section.

C. Fatigue and Motivation

Motivation is a core feature of fatigue and this notion is present in every model of cognitive fatigue described in this thesis (see **Chapter III**). Hence, in the *Motivation Control Model* of Hockey (2013), motivation to pursue the ongoing goal is a major determinant of effort regulation. In the *Costs vs Benefits* model of Boksem & Tops (2008), the balance between expected reward and aversive event determines fatigue state and it is clear that dopamine is highly involved in fatigue genesis (Dobryakova et al., 2015). Consequently, one could ask if there is such a thing as fatigue without motivation drop. Form a behavioral point of view, we could easily conceptualize the difference between not wanting to perform (lack of motivation) and not being able to perform (excessive effort, in relation to the energy depletion hypothesis of fatigue). But what does this mean from a subjective perspective? How can we differentiate subjective fatigue from subjective lack of motivation? Is fatigue just a matter of lack of reward? If it does, what can be said about trait fatigue? Is it a symptom of a general loss of motivation? Those questions are still under debate. If we keep on with Hockey's definition of fatigue, all those propositions might be true. Hence, if we consider fatigue as an emotion, as a signal from the body to stop the ongoing task due to competing goals and effort provided, then, fatigue and low motivation might be indissociable.

Several authors attempted to uncover this mystery of fatigue and motivation in healthy subjects. In a study from Hopstaken and colleagues (Hopstaken et al., 2015b), boosting motivation following fatigue induction was effective to completely restore performance and stimulus-evoked pupil dilation. Yet, subjective fatigue decreased but did not reach initial state (Hopstaken et al., 2015b). Similarly, Herlambang and colleagues (Herlambang et al., 2019) found that reward incentives favor performance maintenance, but does not prevent from increased fatigue sensation. Interestingly, performance recovery during fatigue state was proportionate to reward amount, with higher performance recovery when a higher reward could be obtained, but again,

reward was not linked to fatigue sensation (Gergelyfi, Jacob, Olivier, & Zénon, 2015). Moreover, in a study from Gergelyfi and colleagues (2021), adding a control group not subject to fatigue induction demonstrated that the effects of reward on performance did not depend on fatigue induction. Hence, reward will always boost performance, whatever the fatigue state. Additionally, they observed that fatigue state did not affect brain activity in the reward circuit, but in task-related activations and in the DMN (Gergelyfi et al., 2021). Taken together, these results strongly support that fatigue and motivational drop are two distinct but interacting phenomena. As proposed by Müller and Apps (2018); we suggest that when fatigue arises, motivation will decrease as a consequence of increased effort. Yet, restoration of motivation may not fully suppress the deleterious impacts of fatigue. Results of subjective scales are especially in favor of this hypothesis, as manipulation of motivation does not allow to decrease fatigue reports to its baseline measure (Hopstaken, 2015). Interestingly, subjective scales seem to capture something, which escapes from objective measures of performance fatigability, because pserformance seems more sensitive to motivation fluctuations.

Coming back to MS, only a few studies have investigated the effects of motivation on fatigue. In a study from Pardini and colleagues, fatigued RRMS patients displayed lower reward responsiveness (as measured by a scale assessing reward activation) in comparison to non-fatigued pwMS (Pardini et al., 2013). Dobryakova and colleagues (2018) found that subjective fatigue is lower when a reward could be obtained during a fatigue induction protocol, both in pwMS and in HC. However, and in accordance with Pardini et al. (2013), trait fatigue was negatively correlated to motivational tendencies, also in both groups. As pwMS demonstrated significantly higher trait fatigue in comparison to controls, the authors suggest that pwMS might be less sensitive to reward. In healthy subjects, it has been show that dopamine is linked to reward-related effort, as levodopa intake leads to stronger grasping force than placebo when a reward can be obtained, suggesting that dopamine modulates perception of reward value (Zénon, Devesse, & Olivier, 2016). Hence, it would be interesting to investigate if decreased reward responsiveness could partly explain fatigue vulnerability in pwMS (both in terms of performance decrement and subjective state), due to an alteration of the reward network and a dopamine imbalance (Dobryakova et al., 2015). For instance,

we could develop a PET study to explore if dopamine pre-synaptic synthesis (with FDOPA or FMT) or D2 receptors (with D2 binding tracers) are reduced in fatigued patients compared to non-fatigued pwMS and healthy controls, which could suggest a decreased sensitivity to reward (Hatano, Ishiwata, & Elsinga, 2006). Many PET studies assessing the effects of dopamine metabolism on motivation were conducted in the field of Parkinson's disease, substance abuse and eating disorders, but this method has not been applied to Multiple Sclerosis so far (Hommer, Bjork, & Gilman, 2011; Val-Laillet et al., 2015; Volkow, Fowler, & Wang, 1999). Additionally, we could conduct an fMRI study in a similar sample to explore the effects of fatigue induction with manipulation of reward incentives. Rewards with different salience levels (e.g. low, medium and low) during a cognitive task in a block design could be administered in order to observe if pwMS need a larger reward to obtain a similar brain activity and behavioral reward responsiveness to HC.

To conclude this section, we cannot state with confidence that task's length is more relevant than cognitive load in fatigue induction protocols. Both methods led to performance decrement and subjective state of fatigue, and both groups mostly displayed a similar sensitivity to fatigue induction. Motivation is a major cofound of cognitive fatigue and more attention should be allocated to this psychological state.

IV. Seeking a Sensitive and Objective Measure of Cognitive Fatigue in MS

Clearly, subjective scales for state fatigue imply serval limits. Firstly, they are unspecific and can reflect (or be "contaminated" by) other psychological states, such as motivation, sleepiness and depression. Secondly, as they are subjective by nature, we observe a high variability across subjects regarding fatigue reports. This type of measures is essential, because fatigue is a subjective symptom. Yet, to obtain reliable observations in fatigue studies, an objective tool to assess this symptom is required. Unfortunately, performance decrement is not always sensitive to fatigue induction and does not correlate well with subjective state. This is why, in **Study 3**, we have investigated the objectivity and sensitivity of eye-metrics for MS-fatigue measurements.

Several eye-metrics were examined in **Study 3:** Pupil size, pupil response speed and frequency of long blinks (> 300 ms). Pupil diameter was larger in condition of high cognitive load, as previously reported (Joshi & Gold, 2020; Kahneman & Beatty, 1966; Zénon, 2019). However, no effect of ToT was observed. In turn, pupil response speed was faster during dilation compared to constriction, decreased with ToT in patients only, especially in the HCL condition and regardless of response type (constriction vs dilation). We observed that number of long blinks increased during the HCL condition for HC, and in the LCL condition for pwMS, and patients seemed to display more blinks than controls. Taken together, results from **Study 3** suggest that eye metrics data reveal a susceptibility to CF in pwMS, which can be objectively measured, despite similar behavioral measures (performance and subjective state) observed in pwMS and HC.

Concerning eye blinks, we suggested that the increased need for blinking in the patient group could reflect a larger induction of fatigue and sleepiness. As pwMS displayed more numerous long blinks during the LCL, we have tentatively proposed that both conditions produced a high cognitive demand in this group, yet that the slow pace of stimulus presentation during the LCL condition offered the opportunity to produce more numerous long blinks without missing items. In turn, analyses on pupil data produced novel insights on the mechanisms of MS-fatigue. However, noting that ToT did not affect pupil size was a rather surprising observation. Hence, several studies found that pupil diameter tends to decrease with fatigue induction (see Bafna & Hansen, 2021 for a review). If this absence of result might be attributable to our small sample, it may also be due to the duration of the task, which was rather short in comparison to other studies (for instance 2H in Hopstaken et al., 2015 and 50min in McGarrigle, Dawes, Stewart, Kuchinsky, & Munro, 2017). Accordingly, it is possible that the decrease in pupil size observed in previous studies relates to decreased arousal rather than fatigue *per se* (Benoit et al., 2018).

In **Study 3**, we included a measure of pupil response speed because we were interested in distinguishing the effects of the sympathetic nervous system from those of the parasympathetic nervous system. Indeed, pupillary response results from the sympathetic/parasympathetic balance, respectively inducing pupil dilation and constriction (Gibbons, 2019). Interestingly, a link between MS-fatigue and alterations

of the ANS have been proposed (de Rodez Benavent et al., 2017; Niepel et al., 2013). For instance, de Rodez Benavent and colleagues (de Rodez Benavent et al., 2017), have found that fatigued pwMS display a slower and reduced pupillary response to problem solving compared to controls. In the same vein, it was also proposed that the effects of modafinil on fatigue are due to its sympathomimetic effect (Niepel et al., 2013). These observations taken together suggest that alterations of the ANS may relate to fatigue symptom in MS, and that such alterations could be objectively measured with pupillometry.

The exact nature of ANS impairments in MS is still debated, with some authors suggesting that only the parasympathetic system is altered (J. de Seze et al., 2001; Pozzessere et al., 1997) and others observing evidences for altered sympathetic activity (de Rodez Benavent et al., 2017; Niepel et al., 2013) or suggesting that both systems might be affected (Surakka et al., 2008). In **Study 3**, we have found evidences suggesting that the two systems might be impaired in MS, as both constriction and dilation were slowed-down. Consequently, we have proposed that a decreased PRS could indicate increased fatigue susceptibility in patients compared to controls.

Alterations of the sympathetic system may relate to a dysfunction within the Locus Coeruleus (LC) norepinephrine system, which has a crucial role in arousal maintenance (Samuels & Szabadi, 2008). According to de Rodez Benaven and colleagues (2017), alterations of the LC function in MS could lead to a dysregulation of modulatory neurotransmitters prior to any network collapse, and could explain early cognitive impairments and fatigue sensation. Hence, neuronal damage within the LC and reduced level of norepinephrine were observed both in animal models of MS and postmortem histological study of patients (Polak, Kalinin, & Feinstein, 2011). Additionally, disruptions of brainstem monoaminergic fiber tracts were observed in MS, and CF is associated to the integrity of tracts projecting from both the LC and the ventral tegmental area (which is highly implicated in reward throughout dopamine) to the prefrontal cortex (Carandini et al., 2021). In turn, the association between MS-fatigue and alteration of the parasympathetic system is much more intriguing. In cardiovascular studies in healthy subjects, blunted parasympathetic drives was associated to fatigue sensation and interpreted as reflecting cognitive control or

cognitive challenge (Melo, Nascimento, Alves, Walz, & Takase, 2021; Mizuno, Tajima, Watanabe, & Kuratsune, 2014). Interestingly, parasympathetic activation also fosters long term recovery following physical exertion (Ihsan, Watson, & Abbiss, 2016), and a reduction in parasympathetic recovery was recently observed in chronic fatigue syndrome (Van Oosterwijck et al., 2021). In the case of pwMS, we tentatively propose that an alteration of the parasympathetic system could be associated to an overestimation of cognitive challenge, leading to fatigue sensation. Alternatively (or additionally) this could lead to diminished recovery following sustained effort. To note, the concept of increased effort perception as a cause of fatigue in neurological disease has also been suggested in relation to dysfunctions within the central nervous system. In particular, it has been proposed that impaired retroactive loops predicting sensory inputs (in the sensorimotor network) lead to inappropriate over-estimation of the effort that have to be provided to achieve a goal (Kuppuswamy, 2017).

Therefore, it appears that pupil measures are highly promising in unrevealing fatigue mechanisms in MS. The measure obtained in **Study 3**, pupil response speed during cognitive task and with a block design, is quite unusual. Hence, as much as we are aware of, this is the first time that such measure is employed to assess CF. Whether it can provide a robust and reliable measure of fatigue should be further investigated. Traditionally, the distinction between activity of the sympathetic and parasympathetic drives have been studied using analysis of frequency bands leading to the notion of sympathovagal balance (Goldberger, 1999). Indeed, it was shown that the sympathetic nervous system oscillates in lower frequency than the parasympathetic one, although studies yield conflicting results regarding the exact ranges of pupillary signal oscillations (Franco et al., 2014; Ramírez-Moreno et al., 2021). If our measure of PRS happens to be validated, it would be a major step in fatigue investigation. Nowadays, pupillometry devices are very accessible (affordable, portable and non-invasive), and PRS is a raw measure of pupil state variation that can be easily obtained. *In fine*, we hope that this measure will be applied in clinical settings for an objective and sensitive assessment of CF in neurodegenerative diseases.

To further investigate the reliability of this measure, we could imagine a research protocol dedicated to pupillometric data in pwMS. For instance, we could administer a

task that is known to induce CF, preferably of short duration to mitigate the impact of sleepiness and boredom on data acquired. The HCL condition of the TLDB would be a good candidate here. This task could be administered in HC and pwMS in *later stages* of the disease to observe the effects of fatigue on pupil variables. As this domain has not been deeply investigated so far, enrolling participants with a high fatigue complaint and cognitive deficits may favor the detection of fatigue effects, since they might not be as subtle as in the early stages of the disease. Then, several measures could be computed and confronted, including measure of raw pupil diameter, PRS and low vs high frequencies ratio (Duchowski, Krejtz, Gehrer, Bafna, & Bækgaard, 2020), to determine which one displays the best prediction of CF. Additionally, it would be interesting to include measures from eye-tracking, such as amplitude and speed of saccades and distraction form stimuli, as these measures may also be sensitive to fatigue induction (Bafna & Hansen, 2021). Importantly, if such hypothetical study may focus on pupil data, a rigorous account for circadian rhythm and sleep homeostasis should be provided. Hence, if pupil variations may be primarily related to affective and subjective states, steady-state and baseline pupil size is affected by circadian phase and sleep pressure (Daguet, Bouhassira, & Gronfier, 2019; Van Egroo, Gaggioni, Cespedes-Ortiz, Ly, & Vandewalle, 2019). In **Study 3**, we did not control for those variables, though we paid particular attention to this issue. Each participant was tested at the same time of the day, according to her/his preferences, and we emphasized on the fact that she/he should feel fresh and alert when coming to the lab. Besides, post-lunch testing was avoided and we asked participant to keep a stable sleep/wake cycle until the end of their participation and to observe a night of at least 7H of sleep prior to any testing session. Consequently, we consider that circadian and homeostatic factors may have a limited impact on our results, but should be strongly controlled in studies focusing on eye-variables. One possible way would be to test participants based on their chronotype (assessed with a questionnaire) or, preferably, their circadian rhythm (assessed with melatonin or cortisol during a constant routine) and repeating the protocol at different times of the day (for instance, during cortisol peak, 3H after peak, 6H…). In order to control for sleep pressure, participants could be asked to observe fixed sleeping times for the three days preceding the experiment, which could be verified from actimetry recording. By doing so, we could determine which eye-metric

measure is the most sensitive to fatigue and if it provides robust outcomes independently from circadian confounds.

V. The Cerebral Substrates of Fatigue in Early MS

The last objective of this thesis was to explore the functional and structural cerebral substrates of fatigue in the early stages of the disease. Two main findings resulted from our analysis: both the functional integrity of the STC circuity and early microstructural brain alterations are linked to fatigue complaint in the very early stages of the disease.

In **Study 5**, we have found that cerebral activity was associated to trait fatigue, throughout negative correlations in pwMS, and positive correlations in HC. We have also observed group-specific patterns of brain activity when the 2-back and 3-back conditions of the task were compared to the 1-back, with interaction effects in regions belonging to the STC network: the thalami, the cingulate cortex, the basal ganglia (right caudate) and the fronto-parietal cortex. We have concluded that STC networks are involved in fatigue pathophysiology, from the early stages of the disease. The presence of negative associations in pwMS was interpreted as an alteration of automated strategies leading to a reorganized pattern of activation in pwMS, and that this cerebral reorganization could trigger fatigue.

In **Study 6**, microstructural alterations of normal appearing brain tissues were investigated using a MPM protocol. Cognitive fatigue was associated to PD measure in every tissue class and to MT in the NAWM, regardless of group. However, disease-specific (in patients only) negative correlations were found in the NAWM (RI and R2*) and the NACGM (RI). We have concluded that fatigue in the general population may relate to brain reserve and neuronal plasticity, while in pwMS, additional microstructure alterations (e.g. demyelination) may lead to disease-specific CF.

Reaching the end of this thesis, several determinants of cognitive fatigue in MS have been discussed and can be reported: Cognitive impairments, decreased motivation due to underappreciated reward value, increased perception of effort, low arousal due to blunted sympathetic system, and costly network reorganization. But can

we reunite these observations under a same, unifying model of cerebral substrate of MS-fatigue? Can the STC model of CF explain those findings?

A reminder of Chaudhuri & Behan's model of fatigue (2000) might be useful here. According to the authors, fatigue may arise from a dysfunction of the basal ganglia. The BG comprises the caudate nucleus, the putamen, the pallidum, the substantia nigra, the subthalamic nucleus and the amygdala (Chaudhuri & Behan, 2000). All these structures are highly interconnected and receive numerous afferents and send efferent from/to the cortex throughout the thalamus. These complex circuits together are forming feedback loops (or STC loops). Numerous STC loops have been identified. Among them, the most described circuits are the motor loop, with inputs from the sensorimotor cortex, the associative (or cognitive) loop, with main inputs from the dorso-lateral prefrontal cortex, and the limbic (or affective/motivational) loop, involving the anterior cingulate cortex, medial orbitofrontal cortex, the hippocampus and amygdala (DeLong & Wichmann, 2010; Posner et al., 2014). Based on evidences showing that the BG are highly implicated in motivation and in motor, cognitive and emotional processing, as well as on the observation that fatigue is a symptom associated with neurological conditions affecting the BG (for instance, Parkinson's Disease), Chaudhuri & Behan proposed that an alteration of the STC circuity is a primary cause of central fatigue (Chaudhuri & Behan, 2000). Accordingly, they proposed that an interruption of the STC circuity throughout neurodegeneration or changes in neurotransmitter balance will lead to an increased inhibition of thalamic activity. This is consistent with the negative associations found in **Study 5** for the MS group (higher fatigue is associated with decreased activity within the STC). However, in their innovative model, they only suggested that the *associative loop* (cognitive loop) might be involved in fatigue genesis. Herein, we propose that all STC loops might be related to fatigue. Hence, in **Study 5**, we have found evidences suggesting that the *sensorimotor loop* might be affected as well. We also suggest that the *limbic/reward loop* could likely be implicated, though we did not find evidences supporting this hypothesis (see also, Finke et al., 2015)).

Consequently, we could consider that MS-fatigue is linked to different STC loop functional alterations, which may depend on the localization of structural alterations,

and could lead to several causes of increased fatigue sensitivity. Hence, alteration within the *associative loop* could explain the link between fatigue and cognition, as it modulates the activity of the prefrontal cortex (Boberg et al., 2021; Borragán et al., 2018; DeLong & Wichmann, 2010). Alterations of the *sensorimotor loop* could induce an increased effort and exhaustion perception mediated by outputs on the precuneus and the precentral gyrus (Finke et al., 2015; Fontes et al., 2015). Finally, alterations within the *limbic loop* could explain decreased reward sensitivity and may be associated to fatigue as well (Finke et al., 2015; Zénon et al., 2016). Overall, alterations within the thalamus could lead to every scenario, depending on the nucleus affected (Capone et al., 2020).

In turn, we could suggest that structural alterations leading to functional reorganization might also trigger cognitive fatigue, independently from STC loops integrity, and as a consequence of compensatory mechanisms to preserve network efficiency (ARM et al., 2019). Finally, decreased arousal might be a consequence of a decreased dopaminergic activity and alterations within the LC, as discussed in the previous section (Niepel et al., 2013).

The effects of the different STC loops and the thalamus are particularly puzzling, as conflicting results have been observed regarding how its activity and connectivity relates to fatigue in MS (ARM et al., 2019; Capone et al., 2020). Further functional studies focusing on the deep grey matter should provide insights regarding their implication. As the circuity of STC loops is made of inhibitory and excitatory connections, it might be possible that some regions show hyper and hypo activity in relation to fatigue, depending on the nature of the disruption within the loop. However, alterations of functional connectivity might be more informative. High field MRI could detect with more precision the nature of such functional alterations of the DGM in early MS (Puckett et al., 2018). More specifically, it would be interesting to pay attention to functional connectivity of the different BG structures and thalamic nuclei during a cognitive task. Ideally, a protocol similar to ours could be employed, with an fMRI task encompassing several levels of difficulty (thus requiring several amounts of cognitive effort). Two groups of early pwMS could be recruited, with or without fatigue complaint, and additional variables of reward responsiveness, cognitive deficits and

effort perception during the task could be added as covariate of interest to see if they relate to abnormalities within specific STC loops in fatigued compared to fatigue free patients.

From a structural point of view, **Study 6** has shown that microstructural alterations within the NAWM and the NACGM relates to MS-fatigue, from the early stages of the disease. Concerning NACGM alterations, Voxel Based Quantitative analyses would be relevant in order to better specify the nature of such alterations. Those analyses are currently ongoing in our lab, but according to what was already discussed in this thesis, we can hypothesize that demyelination within the prefrontal and the sensorimotor cortices might particularly be linked to fatigue symptoms in early MS. However, following the discussion on the implication of the STC circuity, we were quite surprised to find that NADGM integrity was not associated to fatigue. As discussed in **Study 6**, we suggested that DGM alterations occurs gradually with disease duration and are preferably linked to fatigue in the later stages of MS. Hence, the probability to observe atrophy within the BG and the thalamus increases with disease duration, as those regions are highly vulnerable to Wallerian neurodegeneration and local damages (Eshaghi, Prados, et al., 2018; M.M. Schoonheim & Geurts, 2019). Tentatively, we could propose that in the early stages of the disease, structural alterations within the NADGM are not sufficiently massive to be related to fatigue. Alternatively, a demyelination within white matter tracks connecting the different stakeholders of the STC circuity (BG, thalamus and cortical regions) may already disrupt these loops and be involved in fatigue genesis. Later on, this demyelination may lead to neuronal losses, leading to BG and thalamus shrinkage. Accordingly, tractography studies evidenced that, among other tracts, cortico-striatal and thalamic radiation WM fibers alterations are linked to fatigue symptom in MS (see Palotai & Guttmann, 2020 for a review).

To investigate this hypothesis, DTI studies, as for instance NODDI protocol, would be of great interest. Hence, NODDI is a technique that provides voxelwise information about neurite density (a proxy for neuroaxonal damage) and neurite orientation dispersion (reflecting structural integrity), two measures that are altered in pwMS (Collorone et al., 2021). Associating results provided by MPM and NODDI technics would be an innovative way to detect specific WM tracks alterations in early pwMS in

relation to fatigue. Additionally, this kind of analysis could bridge the gap that we observe between fMRI results from **Study 5** and quantitative results raised by **Study 6**. Accordingly, we could expect to observe that CF is linked to a concomitant decrease in neurite density and myelin content (as mostly reflected by MT and RI) within white matter tracts connecting different hubs of STC loops.

VI. Fatigue in Early MS: Paving the Way for Further Investigations

Hopefully, the physiopathological mechanisms of CF in the early stages of MS should be clearer when reaching the end of this thesis. Despite our small sample size, some answers could be provided. Yet, several question remained unresolved, and many new were raised.

For a neuropsychologist, how CF relates to cognitive deficits is an essential question. Clearly, CF and cognitive abilities (especially executive functioning and processing speed) are related beyond the confounding effects of depression, anxiety and disability. The extent and the nature of such relationship in each stage of the disease remain to be elucidated. Particularly, the effects of CF during cognitive assessment deserve better attention. Hence, our results suggest that neuropsychological outcomes could be affected by fatigue. Additionally, the deleterious impact of fatigue on QoL, occupations and employment, stresses the need to systematically and meticulously assess this symptom in clinical settings. Many secondary causes of CF in MS can be treated, such as depression and sleep disorders, and doing so could clearly improve well-being in pwMS. Moreover, we suggest that fatigue should also be assessed in research settings. In fact, if depression is assessed in almost every MS study, fatigue remains somewhat underappreciated and is not systematically included in research protocols. Yet, as it is the case for depression, it is a major symptom of the disease leading to a plethora of deleterious events. A systematic inclusion of fatigue scales in research protocols would be beneficial.

Which of cognitive load or task duration is primarily relevant in inducing fatigue in early pwMS is a question not clearly answered in this thesis. However, we have demonstrated that both methods effectively induce performance fatigability and

increase subjective state of fatigue. Importantly, our results raised concerns about the confounding effect of motivation in our research protocol, and we hypothesized that pwMS may show a decreased sensitivity to reward, which could, in turn, favor fatigue sensation.

Seeking for an objective and reliable measure of CF is a topic that raised many discussions and concerns in the fatigue literature. In this thesis, it was proposed that pupil response speed can be a relevant measure of fatigue state, while offering the benefits sought of being easily computed and discriminating between sympathetic and parasympathetic effects. Further studies are needed to validate this measure and to determine its robustness.

Finally, this thesis aimed to explore the cerebral substrates of CF in early pwMS. We have demonstrated that alterations of the STC circuity, as often proposed in the literature, is implicated in fatigue genesis from the early stages of the disease. This thesis has proposed that early alterations (demyelination and axonal loss) of white matter tracts connecting the BG, thalamus and cortical regions might be responsible for the primary causes of CF in early MS.

Overall, five specific, but not mutually exclusive, causes of CF in early MS were proposed in this work: decrease in motivation, increased perception of effort, decreased arousal, extra effort due to cognitive deficits and costly functional brain reorganization due to structural alterations. Our results are in line with what has been observed regarding fatigue in the later stages of the disease, and suggest that many mechanisms are already at play following the first clinical episode, including brain microstructure and STC functional alterations. The impact of fatigue during the first stages of the disease might be subtle at first, but should be considered carefully as it is a major determinant of quality of life. For instance, fatigue predicts future employment and is associated to a deterioration of professional duties from the early stages of the disease (Jaworski et al., 2020; Sainz de la Maza et al., 2022). Some secondary causes of fatigue in MS have been identified (see **Chapter III)** and should be screened and treated in clinical routine. Further studies are needed to better understand the primary causes of MS-fatigue in order to developp effective therapies and adjustment of environment, thus improving quality of life throught, for instance, social and occupational

engagments. For example, if CF is due to an extra effort produced to compensate from cognitive defictis, environmental changes could be implemented in the work place, when applicable. If both long lasting procedures and high cognitive load are detrimential, proposing breaks more freqently and spliting the different work-objectives into smaller tasks might be beneficial to improve both fatigue sensation and work productivity. The motivational and arousal aspects of fatigue can also be considered as targets for psychological intervations, for instance in insisiting on the importance of rewarding activities to reduce fatigue and to learn the specific times of the day when alertness is at its best to complete challenging and low-rewarding tasks. We have recently developped a study in our laboratory testing the effects of a psychological intervention focusing on psychoeducation and cognitivie rehabilitation in post-COVID patients presenting a persisting cognitive complaint. As one of the target objective is cognitive fatigue, we have developped a serie of tips and recommandations to improve fatigue management in everyday life (psychoeducation on the causes of fatigue, how to explain this symptom to relatives, how to recognize fatigue to protect against after-effects, the importance of pleasant activity to boost motivation, how to improve sleep quality...). Data acquisition is ongoing, but if this protocol proves to be effective in reducing fatigue complaint in the studied population, it could be implemented in pwMS as well.

References

Adamec, I., Crnošija, L., Junaković, A., Krbot Skorić, M., & Habek, M. (2018). Progressive multiple sclerosis patients have a higher burden of autonomic dysfunction compared to relapsing remitting phenotype. *Clinical Neurophysiology*, *129*(8), 1588–1594. https://doi.org/10.1016/j.clinph.2018.05.009

André, N., Audiffren, M., & Baumeister, R. F. (2019). An Integrative Model of Effortful Control. *Frontiers in Systems Neuroscience*, *13*. https://doi.org/10.3389/fnsys.2019.00079

Agyemang, C., Berard, J. A., & Walker, L. A. S. (2021). Cognitive fatigability in multiple sclerosis: How does performance decline over time on the Paced Auditory Serial Addition Test? *Multiple Sclerosis and Related Disorders*, *54*(November 2020), 103130. https://doi.org/10.1016/j.msard.2021.103130

Åkerstedt, T., & Gillberg, M. (1990). Subjective and Objective Sleepiness in the Active Individual. *International Journal of Neuroscience*, *52*(1–2), 29–37. https://doi.org/10.3109/00207459008994241

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel Organization of Functionally Segregated Circuits Linking Basal Ganglia and Cortex. *Annual Review of Neuroscience*, *9*(1), 357–381. https://doi.org/10.1146/annurev.ne.09.030186.002041

Amato, Maria P., Portaccio, E., Goretti, B., Zipoli, V., Iudice, A., Pina, D. Della, … De Stefano, N. (2010). Relevance of cognitive deterioration in early relapsing-remitting MS: A 3-year follow-up study. *Multiple Sclerosis*, *16*(12), 1474–1482. https://doi.org/10.1177/1352458510380089

Amato, Maria Pia, Ponziani, G., Siracusa, G., & Sorbi, S. (2001). Cognitive dysfunction in early-onset multiple sclerosis: A reappraisal after 10 years. *Archives of Neurology*, *58*(10), 1602–1606. https://doi.org/10.1001/archneur.58.10.1602

Amato, Maria Pia, Zipoli, V., & Portaccio, E. (2006). Multiple sclerosis-related cognitive changes: A review of cross-sectional and longitudinal studies. *Journal of the*

Neurological Sciences, *245*(1–2), 41–46. https://doi.org/10.1016/j.jns.2005.08.019

Amtmann, D., Askew, R. L., Kim, J., Chung, H., Ehde, D. M., Bombardier, C. H., … Johnson, K. L. (2015). Pain affects depression through anxiety, fatigue, and sleep in multiple sclerosis. *Rehabilitation Psychology*, *60*(1), 81–90. https://doi.org/10.1037/rep0000027

Anderson, A. J., Ren, P., Baran, T. M., Zhang, Z., & Lin, F. (2019). Insula and putamen centered functional connectivity networks reflect healthy agers' subjective experience of cognitive fatigue in multiple tasks. *Cortex*, *119*, 428–440. https://doi.org/10.1016/J.CORTEX.2019.07.019

Andersson, J. L. R., Skare, S., & Ashburner, J. (2003). How to correct susceptibility distortions in spin-echo echo-planar images: application to diffusion tensor imaging. *NeuroImage*, *20*(2), 870–888. https://doi.org/10.1016/S1053-8119(03)00336-7

Andersson, J. L. R., & Sotiropoulos, S. N. (2016). An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. *NeuroImage*, *125*, 1063–1078. https://doi.org/10.1016/j.neuroimage.2015.10.019

Andica, C., Hagiwara, A., Kamagata, K., Yokoyama, K., Shimoji, K., Saito, A., … Aoki, S. (2019). Gray Matter Alterations in Early and Late Relapsing-Remitting Multiple Sclerosis Evaluated with Synthetic Quantitative Magnetic Resonance Imaging. *Scientific Reports*, *9*(1), 1–10. https://doi.org/10.1038/s41598-019-44615-3

André, N., Audiffren, M., & Baumeister, R. F. (2019). An Integrative Model of Effortful Control. *Frontiers in Systems Neuroscience*, *13*. https://doi.org/10.3389/fnsys.2019.00079

Andreasen, A. K., Iversen, P., Marstrand, L., Siersma, V., Siebner, H. R., & Sellebjerg, F. (2019). Structural and cognitive correlates of fatigue in progressive multiple sclerosis. *Neurological Research*, *41*(2), 168–176. https://doi.org/10.1080/01616412.2018.1547813

ARM, J., Ribbons, K., Lechner-Scott, J., & Ramadan, S. (2019). Evaluation of MS related

central fatigue using MR neuroimaging methods: Scoping review. *Journal of the Neurological Sciences*, *400*(August 2018), 52–71. https://doi.org/10.1016/j.jns.2019.03.007

Arnett, P. A., Barwick, F. H., & Beeney, J. E. (2008). Depression in multiple sclerosis: Review and theoretical proposal. *Journal of the International Neuropsychological Society*. Cambridge University Press. https://doi.org/10.1017/S1355617708081174

Arnett, P. A., Rao, S. M., Bernardin, L., Grafman, J., Yetkin, F. Z., & Lobeck, L. (1994). Relationship between frontal lobe lesions and Wisconsin card sorting test performance in patients with multiple sclerosis. *Neurology*, *44*(3), 420–425. https://doi.org/10.1212/wnl.44.3_part_1.420

Ashburner, J., & Ridgway, G. R. (2013). Symmetric diffeomorphic modeling of longitudinal structural MRI. *Frontiers in Neuroscience*, *6*(FEB), 1–19. https://doi.org/10.3389/fnins.2012.00197

Asplund, C. L., Todd, J. J., Snyder, A. P., & Marois, R. (2010). A central role for the lateral prefrontal cortex in goal-directed and stimulus-driven attention. *Nature Neuroscience*, *13*(4), 507–512. https://doi.org/10.1038/nn.2509

Atlas of MS. (n.d.). Retrieved January 4, 2022, from https://www.atlasofms.org/

Attarian, H. P., Brown, K. M., Duntley, S. P., Carter, J. D., & Cross, A. H. (2004a). The relationship of sleep disturbances and fatigue in multiple sclerosis. *Archives of Neurology*, *61*(4), 525–528. https://doi.org/10.1001/archneur.61.4.525

Baecher-Allan, C., Kaskow, B. J., & Weiner, H. L. (2018). Multiple Sclerosis: Mechanisms and Immunotherapy. *Neuron*, *97*(4), 742–768. https://doi.org/10.1016/j.neuron.2018.01.021

Bafna, T., & Hansen, J. P. (2021). Mental fatigue measurement using eye metrics: A systematic literature review. *Psychophysiology*, *58*(6), 1–23. https://doi.org/10.1111/psyp.13828

Bagnato, F., Hametner, S., Boyd, E., Endmayr, V., Shi, Y., Ikonomidou, V., … Brian Welch, E. (2018). Untangling the R2* contrast in multiple sclerosis: A combined

MRI-histology study at 7.0 Tesla. *PLoS ONE*, *13*(3). https://doi.org/10.1371/journal.pone.0193839

Bailey, A., Channon, S., & Beaumont, J. G. (2007). The relationship between subjective fatigue and cognitive fatigue in advanced multiple sclerosis. *Multiple Sclerosis*, *13*(1), 73–80. https://doi.org/10.1177/1352458506071162

Bakshi, R, Shaikh, Z. A., Miletich, R. S., Czarnecki, D., Dmochowski, J., Henschel, K., & Janardhan, V. (2000). Fatigue in multiple sclerosis and its relationship to depression and neurologic disability. *Multiple Sclerosis*, *6*(February), 181–185.

Bakshi, Rohit. (2003). Fatigue associated with multiple sclerosis : diagnosis , impact and management. *Multiple Sclerosis*, *9*, 219–227.

Barun, B. (2013). Pathophysiological background and clinical characteristics of sleep disorders in multiple sclerosis. *Clinical Neurology and Neurosurgery*, *115*(SUPPL.1). https://doi.org/10.1016/j.clineuro.2013.09.028

Beatty, W. W., Goodkin, D. E., & Monson, N. (1990). Clinical and Demographic Predictors of Cognitive Performance in Multiple Sclerosis: Do Diagnostic Type, Disease Duration, and Disability Matter? *Archives of Neurology*, *47*(3), 305–308. https://doi.org/10.1001/archneur.1990.00530030081019

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An Inventory for Measuring Depression. *Archives of General Psychiatry*, *4*(6), 561. Retrieved from http://archpsyc.jamanetwork.com/article.aspx?doi=10.1001/archpsyc.1961.01710120031004

Benedict, R., & Bobholz, J. (2007). Multiple Sclerosis. *Seminars in Neurology*, *27*(1), 078–085. https://doi.org/10.1055/s-2006-956758

Benedict, R. H. B., Amato, M. P., DeLuca, J., & Geurts, J. J. G. (2020). Cognitive impairment in multiple sclerosis: clinical management, MRI, and therapeutic avenues. *The Lancet Neurology*, *19*(10), 860–871. https://doi.org/10.1016/S1474-4422(20)30277-5

Benedict, R. H. B., Bruce, J. M., Dwyer, M. G., Abdelrahman, N., Hussein, S., Weinstock-Guttman, B., … Zivadinov, R. (2006). Neocortical atrophy, third ventricular width, and cognitive dysfunction in multiple sclerosis. *Archives of Neurology*, *63*(9), 1301–1306. https://doi.org/10.1001/archneur.63.9.1301

Benedict, R. H. B., Groninger, L., Schretlen, D., Dobraski, M., & Shpritz, B. (1996). Revision of the brief visuospatial memory test: Studies of normal performance, reliability, and, validity. *Psychological Assessment*, *8*(2), 145–153. https://doi.org/10.1037/1040-3590.8.2.145

Benedict, R. H. B., Wahlig, E., Bakshi, R., Fishman, I., Munschauer, F., Zivadinov, R., & Weinstock-Guttman, B. (2005). Predicting quality of life in multiple sclerosis: Accounting for physical disability, fatigue, cognition, mood disorder, personality, and behavior change. *Journal of the Neurological Sciences*, *231*, 29–34. https://doi.org/10.1016/j.jns.2004.12.009

Benedict, R. H. B., Weinstock-Guttman, B., Fishman, I., Sharma, J., Tjoa, C. W., & Bakshi, R. (2004). Prediction of Neuropsychological Impairment in Multiple Sclerosis: Comparison of Conventional Magnetic Resonance Imaging Measures of Atrophy and Lesion Burden. *Archives of Neurology*, *61*(2), 226–230. https://doi.org/10.1001/archneur.61.2.226

Benoit, C. E., Solopchuk, O., Borragán, G., Carbonnelle, A., Van Durme, S., & Zénon, A. (2018). Cognitive task avoidance correlates with fatigue-induced performance decrement but not with subjective fatigue. *Neuropsychologia*. https://doi.org/10.1016/j.neuropsychologia.2018.06.017

Benton, A. L. (1978). Visuospatial Judgment. *Archives of Neurology*, *35*(6), 364. https://doi.org/10.1001/archneur.1978.00500300038006

Berard, J. A., Smith, A. M., & Walker, L. A. S. (2018). A longitudinal evaluation of cognitive fatigue on a task of sustained attention in early relapsing-remitting multiple sclerosis. *International Journal of MS Care*, *20*(2), 55–61. https://doi.org/10.7224/1537-2073.2016-106

Berard, J. A., Smith, A. M., & Walker, L. A. S. (2019). Predictive Models of Cognitive

Fatigue in Multiple Sclerosis. *Archives of Clinical Neuropsychology : The Official Journal of the National Academy of Neuropsychologists*, *34*(1), 31–38. https://doi.org/10.1093/arclin/acy014

Bergendal, G., Fredrikson, S., & Almkvist, O. (2007). Selective decline in information processing in subgroups of multiple sclerosis: An 8-year longitudinal study. *European Neurology*, *57*(4), 193–202. https://doi.org/10.1159/000099158

Bisecco, A., Nardo, F. Di, Docimo, R., Caiazzo, G., D'Ambrosio, A., Bonavita, S., … Gallo, A. (2017). Fatigue in multiple sclerosis: The contribution of resting-state functional connectivity reorganization. *Multiple Sclerosis Journal*, pp. 1–10. https://doi.org/10.1177/1352458517730932

Blanchard-Dauphin, A., & Allart, E. (2017). Prise en charge de la spasticité, des mouvements anormaux et du syndrome cérébelleux. In *La Sclérose en Plaques - Clinique et Thérapeutique*. Issy-les-Moulineaux: Elsevier Masson.

Boberg, E., Iacobaeus, E., Greenfield, M. S., Wang, Y., Msghina, M., & Le Blanc, K. (2021). Reduced prefrontal cortex and sympathetic nervous system activity correlate with fatigue after aHSCT. *Bone Marrow Transplantation*, (April), 1–10. https://doi.org/10.1038/s41409-021-01539-9

Bobholz, J. A., & Rao, S. M. (2003). Cognitive dysfunction in multiple sclerosis: a review of recent developments. *Current Opinion in Neurology*, *16*(3), 283–288. https://doi.org/10.1097/01.wco.0000073928.19076.84

Bobko, P., Roth, P. L., & Buster, M. A. (2007). The Usefulness of Unit Weights in Creating Composite Scores. *Organizational Research Methods*, *10*(4), 689–709. https://doi.org/10.1177/1094428106294734

Bodini, B., Veronese, M., García-Lorenzo, D., Battaglini, M., Poirion, E., Chardain, A., … Stankoff, B. (2016). Dynamic Imaging of Individual Remyelination Profiles in Multiple Sclerosis. *Annals of Neurology*, *79*(5), 726–738. https://doi.org/10.1002/ana.24620

Boeschoten, R. E., Braamse, A. M. J., Beekman, A. T. F., Cuijpers, P., van Oppen, P.,

Dekker, J., & Uitdehaag, B. M. J. (2017). Prevalence of depression and anxiety in Multiple Sclerosis: A systematic review and meta-analysis. *Journal of the Neurological Sciences*, *372*, 331–341. https://doi.org/10.1016/j.jns.2016.11.067

Boksem, M. A. S., Meijman, T. F., & Lorist, M. M. (2005). Effects of mental fatigue on attention: An ERP study. *Cognitive Brain Research*, *25*(1), 107–116. https://doi.org/10.1016/j.cogbrainres.2005.04.011

Boksem, M. A. S., Meijman, T. F., & Lorist, M. M. (2006). Mental fatigue, motivation and action monitoring. *Biological Psychology*, *72*(2), 123–132. https://doi.org/10.1016/j.biopsycho.2005.08.007

Boksem, M. A. S., & Tops, M. (2008). Mental fatigue: Costs and benefits. *Brain Research Reviews*, *59*(1), 125–139. https://doi.org/10.1016/j.brainresrev.2008.07.001

Bonavita, S., Gallo, A., Sacco, R., Della Corte, M., Bisecco, A., Docimo, R., … Tedeschi, G. (2011). Distributed changes in default-mode resting-state connectivity in multiple sclerosis. *Multiple Sclerosis Journal*, *17*(4), 411–422. https://doi.org/10.1177/1352458510394609

Bonnet, M. C., Allard, M., Dilharreguy, B., Deloire, M., Petry, K. G., & Brochet, B. (2010). Cognitive compensation failure in multiple sclerosis. *Neurology*, *75*(14), 1241–1248. https://doi.org/10.1212/WNL.0b013e3181f612e3

Bonnet, Melissa C., Deloire, M. S. A., Salort, E., Dousset, V., Petry, K. G., & Brochet, B. (2006). Evidence of cognitive compensation associated with educational level in early relapsing-remitting multiple sclerosis. *Journal of the Neurological Sciences*, *251*(1–2), 23–28. https://doi.org/10.1016/j.jns.2006.08.002

Bonnier, G., Roche, A., Romascano, D., Simioni, S., Meskaldji, D., Rotzinger, D., … Granziera, C. (2014). Advanced MRI unravels the nature of tissue alterations in early multiple sclerosis. *Annals of Clinical and Translational Neurology*, *1*(6), 423–432. https://doi.org/10.1002/acn3.68

Bora, E., Özakbaş, S., Velakoulis, D., & Walterfang, M. (2016). Social Cognition in Multiple Sclerosis: a Meta-Analysis. *Neuropsychology Review*, *26*(2), 160–172.

https://doi.org/10.1007/s11065-016-9320-6

Borragan, G. (2016). PhD Thesis: *Behavioural Bases and Functional Dynamics of Cognitive Fatigue*.

Borragán, G., Benoit, C.-E., Schul, N., Strauss, M., De Schepper, M., Roekens, V., & Peigneux, P. (2022). Impaired sequential but preserved motor memory consolidation in multiple sclerosis disease. *Neuroscience*, *487*, 99–106. https://doi.org/10.1016/j.neuroscience.2021.12.029

Borragán, G., Gilson, M., Atas, A., Slama, H., Lysandropoulos, A., De Schepper, M., & Peigneux, P. (2018a). Cognitive fatigue, sleep and cortical activity in multiple sclerosis disease. A Behavioral, Polysomnographic and Functional Near-Infrared Spectroscopy Investigation. *Frontiers in Human Neuroscience*, *12*(September), 1–12. https://doi.org/10.3389/fnhum.2018.00378

Borragán, G., Slama, H., Bartolomei, M., & Peigneux, P. (2017). Cognitive fatigue: A Time-based Resource-sharing account. *Cortex*, *89*, 71–84. https://doi.org/10.1016/j.cortex.2017.01.023

Borragán, G., Slama, H., Destrebecqz, A., & Peigneux, P. (2016). Cognitive Fatigue Facilitates Procedural Sequence Learning. *Frontiers in Human Neuroscience*, *10*(March), 1–8. https://doi.org/10.3389/fnhum.2016.00086

Braley, T. J., & Chervin, R. D. (2010). Fatigue in Multiple Sclerosis : Mechanisms, Evaluation, and Treatment. *SLEEP*, *33*(8), 1061–1067.

Brass, S. D., Benedict, R. H., Weinstock-Guttman, B., Munschauer, F., & Bakshi, R. (2006). Cognitive impairment is associated with subcortical magnetic resonance imaging grey matter T2 hypointensity in multiple sclerosis. *Multiple Sclerosis Journal*, *12*(4), 437–444. https://doi.org/10.1191/135248506ms1301oa

Brass, S. D., Chen, N., Mulkern, R. V., & Bakshi, R. (2006). Magnetic Resonance Imaging of Iron Deposition in Neurological Disorders. *Topics in Magnetic Resonance Imaging*, *17*(1), 31–40. https://doi.org/10.1097/01.rmr.0000245459.82782.e4

Brickenkamp, R., & Zillmer, E. (1998). *d2 Test of Attention 1st edition* (Hogrefe Pu).

Göttingen.

Brissart, H., Leininger, M., Le Perf, M., Taillemite, L., Morele, E., & Debouverie, M. (2012). La mémoire de travail dans la sclérose en plaques : Revue de la littérature. *Revue Neurologique*, *168*(1), 15–27. https://doi.org/10.1016/j.neurol.2011.05.005

Brissart, Helene, Morele, E., Baumann, C., Le Perf, M., Leininger, M., Taillemite, L., … Debouverie, M. (2013). Cognitive impairment among different clinical courses of multiple sclerosis. *Neurological Research*, *35*(8), 867–872. https://doi.org/10.1179/1743132813Y.0000000232

Broch, L., Simonsen, C. S., Flemmen, H. Ø., Berg-Hansen, P., Skardhamar, Å., Ormstad, H., & Celius, E. G. (2021). High prevalence of fatigue in contemporary patients with multiple sclerosis. *Multiple Sclerosis Journal - Experimental, Translational and Clinical*, *7*(1), 205521732199982. https://doi.org/10.1177/2055217321999826

Brochet, B. (2017). Diagnostic positif de la sclérose en plaques. In *La Sclérose en Plaques - Clinique et Thérapeutique* (pp. 79–111). Issy-les-Moulineaux: Elsevier Masson. https://doi.org/10.1016/B978-2-294-75020-5/00002-8

Brochet, Bruno. (2018). Neuroprotection and cognition in multiple sclerosis: Effects of cognitive and brain reserve. *Cognition and Behavior in Multiple Sclerosis.*, 321–343. https://doi.org/10.1037/0000097-016

Brochet, Bruno, Clavelou, P., Defer, G., De Seze, J., Louapre, C., Magnin, E., … Vermersch, P. (2022, February 1). Cognitive Impairment in Secondary Progressive Multiple Sclerosis: Effect of Disease Duration, Age, and Progressive Phenotype. *Brain Sciences*. MDPI. https://doi.org/10.3390/brainsci12020183

Brochet, Bruno, & Ruet, A. (2019). Cognitive Impairment in Multiple Sclerosis With Regards to Disease Duration and Clinical Phenotypes. *Frontiers in Neurology*, *10*(March), 1–7. https://doi.org/10.3389/fneur.2019.00261

Browne, P., Chandraratna, D., Angood, C., Tremlett, H., Baker, C., Taylor, B. V., & Thompson, A. J. (2014, September 1). Atlas of multiple sclerosis 2013: A growing global problem with widespread inequity. *Neurology*. Lippincott Williams and

Wilkins. https://doi.org/10.1212/WNL.0000000000000768

Burke, S. E., Babu Henry Samuel, I., Zhao, Q., Cagle, J., Cohen, R. A., Kluger, B., & Ding, M. (2018). Task-Based Cognitive Fatigability for Older Adults and Validation of Mental Fatigability Subscore of Pittsburgh Fatigability Scale. *Frontiers in Aging Neuroscience*, *10*(OCT), 1–7. https://doi.org/10.3389/fnagi.2018.00327

Buyanova, I. S., & Arsalidou, M. (2021). Cerebral White Matter Myelination and Relations to Age, Gender, and Cognition: A Selective Review. *Frontiers in Human Neuroscience*, *15*(July), 1–22. https://doi.org/10.3389/fnhum.2021.662031

Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1998). The Pittsburg Sleep Quality Index: A New Instrument for Psychiatric Practice and Research. *Psychiatry Research*.

Calabrese, M., Filippi, M., & Gallo, P. (2010, August 13). Cortical lesions in multiple sclerosis. *Nature Reviews Neurology*. Nature Publishing Group. https://doi.org/10.1038/nrneurol.2010.93

Calabrese, M., Magliozzi, R., Ciccarelli, O., Geurts, J. J. G., Reynolds, R., & Martin, R. (2015). Exploring the origins of grey matter damage in multiple sclerosis. *Nature Reviews Neuroscience*, *16*(3), 147–158. https://doi.org/10.1038/nrn3900

Calabrese, M., Poretto, V., Favaretto, A., Alessio, S., Bernardi, V., Romualdi, C., … Gallo, P. (2012). Cortical lesion load associates with progression of disability in multiple sclerosis. *Brain*, *135*(10), 2952–2961. https://doi.org/10.1093/brain/aws246

Calabrese, M., Rinaldi, F., Grossi, P., Mattisi, I., Bernardi, V., Favaretto, A., … Gallo, P. (2010). Basal ganglia and frontal/parietal cortical atrophy is associated with fatigue in relapsing-remitting multiple sclerosis. *Multiple Sclerosis*, *16*(10), 1220–1228. https://doi.org/10.1177/1352458510376405

Calamia, M., Markon, K., & Tranel, D. (2012). Scoring higher the second time around: Meta-analyses of practice effects in neuropsychological assessment. *Clinical Neuropsychologist*, *26*(4), 543–570. https://doi.org/10.1080/13854046.2012.680913

Capone, F., Collorone, S., Cortese, R., Di Lazzaro, V., & Moccia, M. (2020). Fatigue in multiple sclerosis: The role of thalamus. *Multiple Sclerosis Journal*, *26*(1), 6–16. https://doi.org/10.1177/1352458519851247

Carandini, T., Mancini, M., Bogdan, I., L Rae, C., W Barritt, A., Sethi, A., … Cercignani, M. (2021). Disruption of brainstem monoaminergic fibre tracts in multiple sclerosis as a putative mechanism for cognitive fatigue: a fixel-based analysis. *NeuroImage: Clinical*, *30*, 102587. https://doi.org/10.1016/j.nicl.2021.102587

Cavanna, A. E. (2007). The precuneus and consciousness. *CNS Spectrums*. MBL Communications. https://doi.org/10.1017/S1092852900021295

Cellini, N., Conte, F., De Rosa, O., Giganti, F., Malloggi, S., Reyt, M., … Ficca, G. (2021). Changes in sleep timing and subjective sleep quality during the COVID-19 lockdown in Italy and Belgium: age, gender and working status as modulating factors. *Sleep Medicine*, *77*, 112–119. https://doi.org/10.1016/j.sleep.2020.11.027

Chard, D., & Miller, D. (2009, July 15). Grey matter pathology in clinically early multiple sclerosis: Evidence from magnetic resonance imaging. *Journal of the Neurological Sciences*. Elsevier. https://doi.org/10.1016/j.jns.2009.01.012

Charvet, L, Kluzer, B., & Krupp, L. (2014). Invisible Symptoms of MS: Fatigue, Depression, and Cognition. In Lawrence Samkoff & A. Goodman (Eds.), *Multiple Sclerosis and CNS Inflammatory Disordes*. Oxford: Wiley.

Charvet, Leigh, Shaw, M., Dobbs, B., Frontario, A., Sherman, K., Bikson, M., … Kasschau, M. (2018). Remotely Supervised Transcranial Direct Current Stimulation Increases the Benefit of At-Home Cognitive Training in Multiple Sclerosis. *Neuromodulation*, *21*(4), 383–389. https://doi.org/10.1111/ner.12583

Chatain, C., Radel, R., Vercruyssen, F., Rabahi, T., Vallier, J.-M., Bernard, T., & Gruet, M. (2019). Influence of cognitive load on the dynamics of neurophysiological adjustments during fatiguing exercise. *Psychophysiology*, (September 2018), e13343. https://doi.org/10.1111/psyp.13343

Chaudhuri, A., & Behan, P. O. (2000). Fatigue and basal ganglia. *Journal of the*

Neurological Sciences, *179*, 34–42. Retrieved from http://www.sciencedirect.com/science/article/pii/S0022510X00004111%0Apapers2://publication/uuid/4E2A9FEC-EEDA-4392-AE1B-98B06EE34D7F

Chaudhuri, A., & Behan, P. O. (2004a). Fatigue in neurological disorders. *Lancet*, *363*, 978–988. https://doi.org/10.1016/S0140-6736(04)15794-2

Chaudhuri, A., & Behan, P. O. (2004b, October 1). Multiple sclerosis is not an autoimmune disease. *Archives of Neurology*. American Medical Association. https://doi.org/10.1001/archneur.61.10.1610

Chen, J. T., Collins, D. L., Atkins, H. L., Freedman, M. S., Arnold, D. L., Antel, J. P., … Halpenny, M. (2008). Magnetization transfer ratio evolution with demyelination and remyelination in multiple sclerosis lesions. *Annals of Neurology*, *63*(2), 254–262. https://doi.org/10.1002/ana.21302

Chen, J., Taylor, B., Palmer, A. J., Kirk-Brown, A., van Dijk, P., Simpson, S., … van der Mei, I. (2018). Estimating MS-related work productivity loss and factors associated with work productivity loss in a representative Australian sample of people with multiple sclerosis. *Multiple Sclerosis Journal*, 1–11. https://doi.org/10.1177/1352458518781971

Chen, M. H., Wylie, G. R., Sandroff, B. M., Dacosta-Aguayo, R., DeLuca, J., & Genova, H. M. (2020). Neural mechanisms underlying state mental fatigue in multiple sclerosis: a pilot study. *Journal of Neurology*, 1–11. https://doi.org/10.1007/s00415-020-09853-w

Chiaravalloti, N. D., & DeLuca, J. (2008). Cognitive impairment in multiple sclerosis. *The Lancet Neurology*, *7*(12), 1139–1151. https://doi.org/10.1016/S1474-4422(08)70259-X

Chiaravalloti, N. D., Moore, N. B., Nikelshpur, O. M., & DeLuca, J. (2013). An RCT to treat learning impairment in multiple sclerosis: The MEMREHAB trial. *Neurology*, *81*(24), 2066–2072. https://doi.org/10.1212/01.wnl.0000437295.97946.a8

Chica, A. B., Bartolomeo, P., & Valero-Cabré, A. (2011). Dorsal and ventral parietal

contributions to spatial orienting in the human brain. *Journal of Neuroscience*, *31*(22), 8143–8149. https://doi.org/10.1523/JNEUROSCI.5463-10.2010

Christodoulou, C. (2005). The Assessment and Measurement of Fatigue. In J. DeLuca (Ed.), *Fatigue as a Windov to the Brain* (pp. 19–35). Cambridge, MA: MIT Press.

Christodoulou, C., Melville, P., Scherl, W. F., Macallister, W. S., Abensur, R. L., Troxell, R. M., & Krupp, L. B. (2009). Negative affect predicts subsequent cognitive change in multiple sclerosis. *Journal of the International Neuropsychological Society*, *15*(1), 53–61. https://doi.org/10.1017/S135561770809005X

Claros-Salinas, D., Dittmer, N., Neumann, M., Sehle, A., Spiteri, S., Willmes, K., … Dettmers, C. (2013). Induction of cognitive fatigue in MS patients through cognitive and physical load. *Neuropsychological Rehabilitation*, *23*(2), 182–201. https://doi.org/10.1080/09602011.2012.726925

Claros-salinas, D., Dittmer, N., Sehle, A., Spiteri, S., & Schoenfeld, M. A. (2013). Neuropsychological Rehabilitation : An International Induction of cognitive fatigue in MS patients through cognitive and physical load. *Neuropsychological Rehabilitation*, *23*(2), 182–201. https://doi.org/10.1080/09602011.2012.726925

Cohen-Adad, J. (2014). What can we learn from T2* maps of the cortex? *NeuroImage*, *93*, 189–200. https://doi.org/10.1016/j.neuroimage.2013.01.023

Collorone, S., Prados, F., Kanber, B., Cawley, N. M., Tur, C., Grussu, F., … Toosy, A. T. (2021). Brain microstructural and metabolic alterations detected in vivo at onset of the first demyelinating event. *Brain*, *144*(5), 1409–1421. https://doi.org/10.1093/brain/awab043

Compston, A., Confavreux, C., Lassmann, H., McDonald, I., Miller, D., Noseworthy, J., … Wekerle, H. (2006). *McAlpine's Multiple Sclerosis*. Elsevier. https://doi.org/10.1016/B978-0-443-07271-0.X5001-0

Cook, D. B., O'Connor, P. J., Lange, G., & Steffener, J. (2007). Functional neuroimaging correlates of mental fatigue induced by cognition among chronic fatigue syndrome patients and controls. *NeuroImage*, *36*(1), 108–122.

https://doi.org/10.1016/j.neuroimage.2007.02.033

Corfield, E. C., Martin, N. G., & Nyholt, D. R. (2016). Co-occurrence and symptomatology of fatigue and depression. *Comprehensive Psychiatry*, *71*, 1–10. https://doi.org/10.1016/j.comppsych.2016.08.004

Cori, J. M., Anderson, C., Shekari Soleimanloo, S., Jackson, M. L., & Howard, M. E. (2019). Narrative review: Do spontaneous eye blink parameters provide a useful assessment of state drowsiness? *Sleep Medicine Reviews*, *45*, 95–104. https://doi.org/10.1016/j.smrv.2019.03.004

Costa, P. T., & McCrae, R. R. (1992). The Five-Factor Model of Personality and Its Relevance to Personality Disorders. *Journal of Personality Disorders*, *6*(4), 343–359. https://doi.org/10.1521/pedi.1992.6.4.343

Costa, S. L., Deluca, J., Sandroff, B. M., Goverover, Y., & Chiaravalloti, N. D. (2018). Role of Demographic and Clinical Factors in Cognitive Functioning of Persons with Relapsing-Remitting and Progressive Multiple Sclerosis. *Journal of the International Neuropsychological Society*, *24*(2), 139–146. https://doi.org/10.1017/S1355617717000777

Costa, S. L., Genova, H. M., Deluca, J., & Chiaravalloti, N. D. (2017, May 1). Information processing speed in multiple sclerosis: Past, present, and future. *Multiple Sclerosis*. SAGE Publications Ltd. https://doi.org/10.1177/1352458516645869

Craig, A. D. (2002). How do you feel? Interoception: The sense of the physiological condition of the body. *Nature Reviews Neuroscience*, *3*(8), 655–666. https://doi.org/10.1038/nrn894

Cramer, H., Lauche, R., Azizi, H., Dobos, G., & Langhorst, J. (2014). Yoga for Multiple Sclerosis: A Systematic Review and Meta-Analysis. *PLoS ONE*, *9*(11), e112414. https://doi.org/10.1371/journal.pone.0112414

Crnošija, L., Adamec, I., Lovrić, M., Junaković, A., Krbot Skorić, M., Lušić, I., & Habek, M. (2016). Autonomic dysfunction in clinically isolated syndrome suggestive of multiple sclerosis. *Clinical Neurophysiology*, *127*(1), 864–869.

https://doi.org/10.1016/j.clinph.2015.06.010

Cryan, J. F., O'Riordan, K. J., Sandhu, K., Peterson, V., & Dinan, T. G. (2020, February 1). The gut microbiome in neurological disorders. *The Lancet Neurology*. Lancet Publishing Group. https://doi.org/10.1016/S1474-4422(19)30356-4

Daguet, I., Bouhassira, D., & Gronfier, C. (2019). Baseline pupil diameter is not a reliable biomarker of subjective sleepiness. *Frontiers in Neurology*, *10*(FEB). https://doi.org/10.3389/fneur.2019.00108

Damasceno, A., Damasceno, B. P., & Cendes, F. (2016). Atrophy of reward-related striatal structures in fatigued MS patients is independent of physical disability. *Multiple Sclerosis*, *22*(6), 822–829. https://doi.org/10.1177/1352458515599451

Davies, G. R., Ramió-Torrentà, L., Hadjiprocopis, A., Chard, D. T., Griffin, C. M. B., Rashid, W., … Miller, D. H. (2004). Evidence for grey matter MTR abnormality in minimally disabled patients with early relapsing-remitting multiple sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry*, *75*(7), 998–1002. https://doi.org/10.1136/jnnp.2003.021915

de Rodez Benavent, S. A., Nygaard, G. O., Harbo, H. F., Tønnesen, S., Sowa, P., Landrø, N. I., … Laeng, B. (2017). Fatigue and cognition: Pupillary responses to problem-solving in early multiple sclerosis patients. *Brain and Behavior*, *7*(7), e00717. https://doi.org/10.1002/brb3.717

de Seze, J., Arndt, C., Stojkovic, T., Ayachi, M., Gauvrit, J. Y., Bughin, M., … Vermersch, P. (2001). Pupillary disturbances in multiple sclerosis: Correlation with MRI findings. *Journal of the Neurological Sciences*, *188*(1–2), 37–41. https://doi.org/10.1016/S0022-510X(01)00540-8

de Seze, Jérôme, & Bigaut, K. (2021). Multiple sclerosis diagnostic criteria: From poser to the 2017 revised McDonald criteria. *Presse Medicale*, *50*(2). https://doi.org/10.1016/j.lpm.2021.104089

Debouverie, M., Pittion-Vouyovitch, S., Louis, S., & Guillemin, F. (2007). Validity of a French version of the fatigue impact scale in multiple sclerosis. *Multiple Sclerosis*,

13(8), 1026–1032. https://doi.org/10.1177/1352458507077942

Deloire, M., Ruet, A., Hamel, D., Bonnet, M., & Brochet, B. (2010). Early cognitive impairment in multiple sclerosis predicts disability outcome several years later. *Multiple Sclerosis*, *16*(5), 581–587. https://doi.org/10.1177/1352458510362819

Deloire, M. S. A., Bonnet, M. C., Salort, E., Arimone, Y., Boudineau, M., Petry, K. G., & Brochet, B. (2006). How to detect cognitive dysfunction at early stages of multiple sclerosis? *Multiple Sclerosis*, *12*(4), 445–452. https://doi.org/10.1191/1352458506ms1289oa

DeLong, M., & Wichmann, T. (2010). Changing views of basal ganglia circuits and circuit disorders. *Clinical EEG and Neuroscience*, *41*(2), 61–67. https://doi.org/10.1177/155005941004100204

DeLuca, J. (2005). Fatigue: Its Definition, Its Study, and Its Future. In J. DeLuca (Ed.), *Fatigue as a Windov to the Brain* (pp. 265–280). Cambridge, MA: MIT Press.

DeLuca, J., Barbieri-Berger, S., & Johnson, S. K. (1994). The Nature of Memory Impairments in Multiple Sclerosis: Acquisition versus Retrieval. *Journal of Clinical and Experimental Neuropsychology*, *16*(2), 183–189. https://doi.org/10.1080/01688639408402629

DeLuca, J., Gaudino, E. A., Diamond, B. J., Christodoulou, C., & Engel, R. A. (1998). Acquisition and storage deficits in multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*, *20*(3), 376–390. https://doi.org/10.1076/jcen.20.3.376.819

DeLuca, J., Genova, H. M., Hillary, F. G., & Wylie, G. (2008). Neural correlates of cognitive fatigue in multiple sclerosis using functional MRI. *Journal of the Neurological Sciences*, *270*(1–2), 28–39. https://doi.org/10.1016/j.jns.2008.01.018

Demaree, H. A., DeLuca, J., Gaudino, E. A., & Diamond, B. J. (1999). Speed of information processing as a key deficit in multiple sclerosis: Implications for rehabilitation. *Journal of Neurology Neurosurgery and Psychiatry*, *67*(5), 661–663. https://doi.org/10.1136/jnnp.67.5.661

Dendrou, C. A., Fugger, L., & Friese, M. A. (2015). Immunopathology of multiple sclerosis. *Nature Reviews Immunology*, *15*(9), 545–558. https://doi.org/10.1038/nri3871

Derache, N., Grassiot, B., Mézenge, F., Emmanuelle Dugué, A., Desgranges, B., Constans, J. M., & Defer, G. L. (2013). Fatigue is associated with metabolic and density alterations of cortical and deep gray matter in Relapsing-Remitting-Multiple Sclerosis patients at the earlier stage of the disease: A PET/MR study. *Multiple Sclerosis and Related Disorders*, *2*(4), 362–369. https://doi.org/10.1016/j.msard.2013.03.005

Deweer, B., Poitrenaud, J., Kalafat, M., & Van Der Linden, M. (2008). *California Verbal Learning Test*. Editions du Centre de Psychologie Appliquée (ECPA).

Diamond, B. J., Johnson, S. K., Kaufman, M., & Graves, L. (2008). Relationships between information processing, depression, fatigue and cognition in multiple sclerosis. *Archives of Clinical Neuropsychology*, *23*(2), 189–199. https://doi.org/10.1016/j.acn.2007.10.002

Dienes, Z. (2014). Using Bayes to get the most out of non-significant results. *Frontiers in Psychology*, *5*, 781. https://doi.org/10.3389/fpsyg.2014.00781

DiGiuseppe, G., Blair, M., & Morrow, S. A. (2018). Prevalence of cognitive impairment in newly diagnosed relapsing-remitting multiple sclerosis. *International Journal of MS Care*, *20*(4), 153–157. https://doi.org/10.7224/1537-2073.2017-029

Dobryakova, E., Genova, H. M., DeLuca, J., & Wylie, G. R. (2015). The dopamine imbalance hypothesis of fatigue in multiple sclerosis and other neurological disorders. *Frontiers in Neurology*. https://doi.org/10.3389/fneur.2015.00052

Dobryakova, E., Hulst, H. E., Spirou, A., Chiaravalloti, N. D., Genova, H. M., Wylie, G. R., & DeLuca, J. (2018). Fronto-striatal network activation leads to less fatigue in multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *24*(9), 1174–1182. https://doi.org/10.1177/1352458517717087

Doshi, A., & Chataway, J. (2016, December 1). Multiple sclerosis, a treatable disease.

Clinical Medicine (London, England). Clin Med (Lond). https://doi.org/10.7861/clinmedicine.16-6-s53

Dotan, R., Woods, S., & Contessa, P. (2021, May 8). On the reliability and validity of central fatigue determination. *European Journal of Applied Physiology*. Springer Science and Business Media Deutschland GmbH. https://doi.org/10.1007/s00421-021-04700-w

Drew, M., Tippett, L. J., Starkey, N. J., & Isler, R. B. (2008). Executive dysfunction and cognitive impairment in a large community-based sample with Multiple Sclerosis from New Zealand: A descriptive study. *Archives of Clinical Neuropsychology*, *23*(1), 1–19. https://doi.org/10.1016/j.acn.2007.09.005

Dubois, B., Kobelt, G., Berg, J., Capsa, D., & Gannedahl, M. (2017). New insights into the burden and costs of multiple sclerosis in Europe: Results for Belgium. *Multiple Sclerosis Journal*, *23*(2_suppl), 29–40. https://doi.org/10.1177/1352458517708100

Duchowski, A. T., Krejtz, K., Gehrer, N. A., Bafna, T., & Bækgaard, P. (2020). The Low/High Index of Pupillary Activity. In *Conference on Human Factors in Computing Systems - Proceedings* (pp. 1–12). New York, NY, USA: Association for Computing Machinery. https://doi.org/10.1145/3313831.3376394

Dujardin, K., Sockeel, P., Cabaret, M., De Sèze, J., & Vermersch, P. (2004). BCcogSEP: A French test battery evaluating cognitive functions in multiple sclerosis. *Revue Neurologique*, *160*(1), 51–62. https://doi.org/10.1016/s0035-3787(04)70847-4

Dulau, C., Deloire, M., Diaz, H., Saubusse, A., Charre-Morin, J., Prouteau, A., & Brochet, B. (2017). Social cognition according to cognitive impairment in different clinical phenotypes of multiple sclerosis. *Journal of Neurology*, *264*(4), 740–748. https://doi.org/10.1007/s00415-017-8417-z

Duntley, S. P. (2005). Fatigue and Sleep. In J. DeLuca (Ed.), *Fatigue as a Windov to the Brain* (pp. 209–227). Cambridge, MA: MIT Press.

Elbers, R. G., Rietberg, M. B., van Wegen, E. E. H., Verhoef, J., Kramer, S. F., Terwee, C. B., & Kwakkel, G. (2012). Self-report fatigue questionnaires in multiple sclerosis,

Parkinson's disease and stroke: a systematic review of measurement properties. *Quality of Life Research*, *21*(6), 925–944. https://doi.org/10.1007/s11136-011-0009-2

Elkady, A. M., Cobzas, D., Sun, H., Seres, P., Blevins, G., & Wilman, A. H. (2019). Five year iron changes in relapsing-remitting multiple sclerosis deep gray matter compared to healthy controls. *Multiple Sclerosis and Related Disorders*, *33*(November 2018), 107–115. https://doi.org/10.1016/j.msard.2019.05.028

Engström, M., Flensner, G., Landtblom, A. M., Ek, A. C., & Karlsson, T. (2013). Thalamo-striato-cortical determinants to fatigue in multiple sclerosis. *Brain and Behavior*, *3*(6), 715–728. https://doi.org/10.1002/brb3.181

Ernst, A. (2020). Autobiographical memory and future thinking impairments in multiple sclerosis: Cognitive and neural mechanisms, functional impact and rehabilitation. *Annals of Physical and Rehabilitation Medicine*, *63*(2), 159–166. https://doi.org/10.1016/j.rehab.2019.06.006

Eshaghi, A., Marinescu, R. V., Young, A. L., Firth, N. C., Prados, F., Jorge Cardoso, M., … Ciccarelli, O. (2018). Progression of regional grey matter atrophy in multiple sclerosis. *Brain*, *141*(6), 1665–1677. https://doi.org/10.1093/brain/awy088

Eshaghi, A., Prados, F., Brownlee, W. J., Altmann, D. R., Tur, C., Cardoso, M. J., … Ciccarelli, O. (2018). Deep gray matter volume loss drives disability worsening in multiple sclerosis. *Annals of Neurology*, *83*(2), 210–222. https://doi.org/10.1002/ana.25145

Esposito, F., Otto, T., Zijlstra, F. R. H., & Goebel, R. (2014). Spatially distributed effects of mental exhaustion on resting-state FMRI networks. *PLoS ONE*, *9*(4), 1–14. https://doi.org/10.1371/journal.pone.0094222

Farnsworth, D. (1947). *The Farnsworth dichotomous test for color blindness, Panel D-15: Manual.* The Psychological Corp.

Faul, F., Erdfelder, E., Buchner, A., & Lang, A. G. (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behavior Research*

Methods, *41*(4), 1149–1160. https://doi.org/10.3758/BRM.41.4.1149

Feinstein, A., Lapshin, H., O'Connor, P., & Lanctôt, K. L. (2013). Sub-threshold cognitive impairment in multiple sclerosis: The association with cognitive reserve. *Journal of Neurology*, *260*(9), 2256–2261. https://doi.org/10.1007/s00415-013-6952-9

Feinstein, A., Magalhaes, S., Richard, J. F., Audet, B., & Moore, C. (2014). The link between multiple sclerosis and depression. *Nature Reviews Neurology*, *10*(9), 507–517. https://doi.org/10.1038/nrneurol.2014.139

Feinstein, A., & Pavisian, B. (2017, June 1). Multiple sclerosis and suicide. *Multiple Sclerosis*. SAGE Publications Ltd. https://doi.org/10.1177/1352458517702553

Fields, R. D. (2008). White matter in learning, cognition and psychiatric disorders. *Trends in Neurosciences*, *31*(7), 361–370. https://doi.org/10.1016/j.tins.2008.04.001

Fietsam, A. C., Darling, W. G., Sosnoff, J. J., Workman, C. D., Kamholz, J., & Rudroff, T. (2021). Cerebellar Contributions to Motor Impairments in People with Multiple Sclerosis. *Cerebellum*, (0123456789). https://doi.org/10.1007/s12311-021-01336-6

Filippi, M., & Agosta, F. (2007). Magnetization transfer MRI in multiple sclerosis. *Journal of Neuroimaging*, *17*(SUPPL. 1), 22–26. https://doi.org/10.1111/j.1552-6569.2007.00132.x

Filippi, M., Rocca, M. A., Colombo, B., Falini, A., Codella, M., Scotti, G., & Comi, G. (2002). Functional Magnetic Resonance Imaging Correlates of Fatigue in Multiple Sclerosis. *NeuroImage*, *15*(3), 559–567. https://doi.org/10.1006/nimg.2001.1011

Finke, C., Schlichting, J., Papazoglou, S., Scheel, M., Freing, A., Soemmer, C., … Brandt, A. U. (2015). Altered basal ganglia functional connectivity in multiple sclerosis patients with fatigue. *Multiple Sclerosis*, *21*(7), 925–934. https://doi.org/10.1177/1352458514555784

Fisk, J. D., Pontefract, A., Ritvo, P. G., Archibald, C. J., & Murray, T. J. (1994). The Impact of Fatigue on Patients with Multiple Sclerosis. *Canadian Journal of Neurological Sciences / Journal Canadien Des Sciences Neurologiques*, *21*(1), 9–14.

https://doi.org/10.1017/S0317167100048691

Flachenecker, P., Reiners, K., Krauser, M., Wolf, A., & Toyka, K. V. (2001). Autonomic dysfunction in multiple sclerosis is related to disease activity and progression of disability. *Multiple Sclerosis*, *7*(5), 327–334. https://doi.org/10.1191/135245801681138031

Fleischer, V., Ciolac, D., Gonzalez-Escamilla, G., Grothe, M., Strauss, S., Molina Galindo, L. S., … Muthuraman, M. (2022). Subcortical Volumes as Early Predictors of Fatigue in Multiple Sclerosis. *Annals of Neurology*, *91*(2), 192–202. https://doi.org/10.1002/ana.26290

Fleischer, V., Muthuraman, M., Anwar, A. R., Gonzalez-Escamilla, G., Radetz, A., Gracien, R. M., … Groppa, S. (2020). Continuous reorganization of cortical information flow in multiple sclerosis: A longitudinal fMRI effective connectivity study. *Scientific Reports*, *10*(1). https://doi.org/10.1038/s41598-020-57895-x

Flensner, G., Ek, A. C., Söderhamn, O., & Landtblom, A. M. (2011). Sensitivity to heat in MS patients: A factor strongly influencing symptomology - an explorative survey. *BMC Neurology*, *11*. https://doi.org/10.1186/1471-2377-11-27

Fontaine, B., & Lyon-caen, O. (1996). La sclérose en plaques. *Annales de l'institut Pasteur*, *7*(2), 125–131.

Fontes, E. B., Okano, A. H., De Guio, F., Schabort, E. J., Min, L. L., Basset, F. A., … Noakes, T. D. (2015). Brain activity and perceived exertion during cycling exercise: An fMRI study. *British Journal of Sports Medicine*, *49*(8), 556–560. https://doi.org/10.1136/bjsports-2012-091924

Franco, A., Neves, C. M., Quintão, C., Vigário, R., & Vieira, P. (2014). Singular Spectrum Analysis of Pupillometry Data. Identification of the Sympathetic and Parasympathetic Activity. *Procedia Technology*, *17*, 273–280. https://doi.org/10.1016/j.protcy.2014.10.237

Gale, C. R., & Martyn, C. N. (1995, November 1). Migrant studies in multiple sclerosis. *Progress in Neurobiology*. Pergamon. https://doi.org/10.1016/0301-

0082(95)80008-V

Galland-Decker, C., Marques-Vidal, P., & Vollenweider, P. (2019). Prevalence and factors associated with fatigue in the Lausanne middle-aged population: A population-based, cross-sectional survey. *BMJ Open*, *9*(8), 1–10. https://doi.org/10.1136/bmjopen-2018-027070

Genova, H. M., Lancaster, K., Lengenfelder, J., Bober, C. P., DeLuca, J., & Chiaravalloti, N. D. (2020). Relationship between social cognition and fatigue, depressive symptoms, and anxiety in multiple sclerosis. *Journal of Neuropsychology*, *14*(2), 213–225. https://doi.org/10.1111/jnp.12185

Genova, H. M., Rajagopalan, V., DeLuca, J., Das, A., Binder, A., Arjunan, A., … Wylie, G. (2013a). Examination of cognitive fatigue in multiple sclerosis using functional magnetic resonance imaging and diffusion tensor imaging. *PLoS ONE*, *8*(11), 1–10. https://doi.org/10.1371/journal.pone.0078811

Genova, H. M., Sumowski, J. F., Chiaravalloti, N., Voelbel, G. T., & Deluca, J. (2009). Cognition in multiple sclerosis: A review of neuropsychological and fMRI research. *Frontiers in Bioscience*, *14*(5), 1730–1744. https://doi.org/10.2741/3336

Gergelyfi, Mónika, Jacob, B., Olivier, E., & Zénon, A. (2015). Dissociation between mental fatigue and motivational state during prolonged mental activity. *Frontiers in Behavioral Neuroscience*, *9*, 176. https://doi.org/10.3389/fnbeh.2015.00176

Gergelyfi, Mónika, Sanz-Arigita, E. J., Solopchuk, O., Dricot, L., Jacob, B., & Zénon, A. (2021). Mental fatigue correlates with depression of task-related network and augmented DMN activity but spares the reward circuit. *NeuroImage*, *243*(March), 118532. https://doi.org/10.1016/j.neuroimage.2021.118532

Gibbons, C. H. (2019). *Basics of autonomic nervous system function*. *Handbook of Clinical Neurology* (1st ed., Vol. 160). Elsevier B.V. https://doi.org/10.1016/B978-0-444-64032-1.00027-8

Gilsoul, J., Bahri, M.A., Phillips, M., Depierreux, F., Salmon, E., Maquet, P. & Collette, F. *in prep,* Age-Related Changes in Cerebral Activity during a Working Memory Task Following Cognitive Fatigue: An fMRI Investigation

Gilsoul, J., & Collette, F. (2018). How does cognitive fatigue affect Young, Middle-aged, and Older people? A distribution analysis of Time-on-Task effect by fitting the ex-Gaussian parameters to the response time distributions. *Frontiers in Neuroscience*, *12*. https://doi.org/10.3389/conf.fnins.2018.95.00051

Gilsoul, J., Libertiaux, V., & Collette, F. (2021). Cognitive fatigue in young, middle-aged, and older: Breaks as a way to recover. *Applied Psychology*. John Wiley and Sons Inc. https://doi.org/10.1111/apps.12358

Glanz, B. I., Healy, B. C., Hviid, L. E., Chitnis, T., & Weiner, H. L. (2012). Cognitive deterioration in patients with early multiple sclerosis: A 5-year study. *Journal of Neurology, Neurosurgery and Psychiatry*, *83*(1), 38–43. https://doi.org/10.1136/jnnp.2010.237834

Godefroy, O. (2007). *Fonctions exécutives et pathologies neurologiques et psychiatriques.* (O. Godefroy & G. de réflexion sur les fonctions Executives, Eds.). Marseille: Editions Solal.

Golan, D., Doniger, G. M., Wissemann, K., Zarif, M., Bumstead, B., Buhse, M., … Gudesblatt, M. (2018). The impact of subjective cognitive fatigue and depression on cognitive function in patients with multiple sclerosis. *Multiple Sclerosis Journal*, *24*(2), 196–204. https://doi.org/10.1177/1352458517695470

Goldberger, J. J. (1999). Sympathovagal balance: How should we measure it? *American Journal of Physiology - Heart and Circulatory Physiology*, *276*(4 45-4). https://doi.org/10.1152/ajpheart.1999.276.4.h1273

González Torre, J. A., Cruz-Gómez, Á. J., Belenguer, A., Sanchis-Segura, C., Ávila, C., & Forn, C. (2017). Hippocampal dysfunction is associated with memory impairment in multiple sclerosis: A volumetric and functional connectivity study. *Multiple Sclerosis*, *23*(14), 1854–1863. https://doi.org/10.1177/1352458516688349

Gorgolewski, K. J., Auer, T., Calhoun, V. D., Craddock, R. C., Das, S., Duff, E. P., … Poldrack, R. A. (2016). The brain imaging data structure, a format for organizing and describing outputs of neuroimaging experiments. *Scientific Data*, *3*. https://doi.org/10.1038/sdata.2016.44

Gracien, R. M., Reitz, S. C., Hof, S. M., Fleischer, V., Zimmermann, H., Droby, A., … Klein, J. C. (2016). Assessment of cortical damage in early multiple sclerosis with quantitative T2 relaxometry. *NMR in Biomedicine*, *29*(4), 444–450. https://doi.org/10.1002/nbm.3486

Grahek, I., Shenhav, A., Musslick, S., Krebs, R. M., & Koster, E. H. W. (2018). Motivation and cognitive control in depression. *BioRxiv*, *32*(0), 371–381. https://doi.org/10.1101/500561

Granberg, T., Fan, Q., Treaba, C. A., Ouellette, R., Herranz, E., Mangeat, G., … Mainero, C. (2017). In vivo characterization of cortical and white matter neuroaxonal pathology in early multiple sclerosis. *Brain*, *140*(11), 2912–2926. https://doi.org/10.1093/brain/awx247

Greeke, E. E., Chua, A. S., Healy, B. C., Rintell, D. J., Chitnis, T., & Glanz, B. I. (2017). Depression and fatigue in patients with multiple sclerosis. *Journal of the Neurological Sciences*, *380*, 236–241. https://doi.org/10.1016/j.jns.2017.07.047

Griffin, C. M., Chard, D. T., Parker, G. J. M., Barker, G. J., Thompson, A. J., & Miller, D. H. (2002). The relationship between lesion and normal appearing brain tissue abnormalities in early relapsing remitting multiple sclerosis. *Journal of Neurology*, *249*(2), 193–199. https://doi.org/10.1007/PL00007864

Gronwall, D. M. A. (1977). Paced auditory serial addition task: A measure of recovery from concussion. *Perceptual and Motor Skills*, *44*(2), 367–373. https://doi.org/10.2466/pms.1977.44.2.367

Gruchot, J., Weyers, V., Göttle, P., Förster, M., Kremer, D., Hartung, H. P., & Küry, P. (2019, August 1). The molecular basis for remyelination failure in multiple sclerosis. *Cells*. MDPI. https://doi.org/10.3390/cells8080825

Grzegorski, T., & Losy, J. (2019). What do we currently know about the clinically isolated syndrome suggestive of multiple sclerosis? An update. *Reviews in the Neurosciences*, *0*(0). https://doi.org/10.1515/revneuro-2019-0084

Guastello, S. J., Boeh, H., Schimmels, M., Gorin, H., Huschen, S., Davis, E., … Poston, K. (2012). Cusp catastrophe models for cognitive workload and fatigue in a verbally cued pictorial memory task. *Human Factors*, *54*(5), 811–825. https://doi.org/10.1177/0018720812442537

Guell, X., & Schmahmann, J. (2020). Cerebellar Functional Anatomy: a Didactic Summary Based on Human fMRI Evidence. *Cerebellum*, *19*(1), 1–5. https://doi.org/10.1007/s12311-019-01083-9

Guillemin, C., Lommers, E., Delrue, G., Gester, E., Maquet, P., & Collette, F. (2022). The Complex Interplay Between Trait Fatigue and Cognition in Multiple Sclerosis. *Psychologica Belgica*, *62*(1), 108. https://doi.org/10.5334/pb.1125

Gunal, D. I., Afsar, N., Tanridag, T., & Aktan, S. (2002). Autonomic dysfunction in multiple sclerosis: Correlation with disease-related parameters. *European Neurology*, *48*(1), 1–5. https://doi.org/10.1159/000064949

Guo, Z., Chen, R., Liu, X., Zhao, G., Zheng, Y., Gong, M., & Zhang, J. (2018). The impairing effects of mental fatigue on response inhibition : An ERP study. *PLoS ONE*, 1–18. https://doi.org/10.1371/journal.pone.0198206

Guthrie, T. C., & Nelson, D. A. (1995). Influence of temperature changes on multiple sclerosis: critical review of mechanisms and research potential. *Journal of the Neurological Sciences*, *129*(1), 1–8. https://doi.org/10.1016/0022-510X(94)00248-M

Håkansson, I., Johansson, L., Dahle, C., Vrethem, M., & Ernerudh, J. (2019). Fatigue scores correlate with other self-assessment data, but not with clinical and biomarker parameters, in CIS and RRMS. *Multiple Sclerosis and Related Disorders*, *36*, 101424. https://doi.org/10.1016/J.MSARD.2019.101424

Hametner, S., Endmayr, V., Deistung, A., Palmrich, P., Prihoda, M., Haimburger, E., …

Grabner, G. (2018). The influence of brain iron and myelin on magnetic susceptibility and effective transverse relaxation - A biochemical and histological validation study. *NeuroImage*, *179*, 117–133. https://doi.org/10.1016/j.neuroimage.2018.06.007

Hancock, P. A., & Desmond, P. A. (2001). *Stress, Workload, and Fatigue*. *Stress, Workload, and Fatigue*. Mahwah, NJ: Lawrence Erlbaum Associates Publishers. https://doi.org/10.1201/b12791

Hanken, K., Sander, C., Schlake, H.-P., Kastrup, A., Eling, P., & Hildebrandt, H. (2019). Fatigue in Multiple Sclerosis is related to relapses, autonomic dysfunctions and introversion: A quasi-experimental study. *Multiple Sclerosis and Related Disorders*, *36*, 101401. https://doi.org/10.1016/J.MSARD.2019.101401

Hankomäki, E., Multanen, J., Kinnunen, E., & Hämäläinen, P. (2014). The progress of cognitive decline in newly diagnosed MS patients. *Acta Neurologica Scandinavica*, *129*(3), 184–191. https://doi.org/10.1111/ane.12161

Hatano, K., Ishiwata, K., & Elsinga, P. (2006). PET Tracers for Imaging of the Dopaminergic System. *Current Medicinal Chemistry*, *13*(18), 2139–2153. https://doi.org/10.2174/092986706777935258

Hayes, C. E., & Donald Acheson, E. (2008). A unifying multiple sclerosis etiology linking virus infection, sunlight, and vitamin D, through viral interleukin-10. *Medical Hypotheses*, *71*(1), 85–90. https://doi.org/10.1016/j.mehy.2008.01.031

Heaton, K. J., Williamson, J. R., Lammert, A. C., Finkelstein, K. R., Haven, C. C., Sturim, D., … Quatieri, T. F. (2020). Predicting changes in performance due to cognitive fatigue: A multimodal approach based on speech motor coordination and electrodermal activity. *Clinical Neuropsychologist*, *34*(6), 1190–1214. https://doi.org/10.1080/13854046.2020.1787522

Heesen, C., Schulz, K. H., Fiehler, J., Von der Mark, U., Otte, C., Jung, R., … Gold, S. M. (2010). Correlates of cognitive dysfunction in multiple sclerosis. *Brain, Behavior, and Immunity*, *24*(7), 1148–1155. https://doi.org/10.1016/j.bbi.2010.05.006

Henry, J. D., & Beatty, W. W. (2006). Verbal fluency deficits in multiple sclerosis. *Neuropsychologia*, *44*(7), 1166–1174. https://doi.org/10.1016/j.neuropsychologia.2005.10.006

Herlambang, M. B., Taatgen, N. A., & Cnossen, F. (2019). The Role of Motivation as a Factor in Mental Fatigue. *Human Factors: The Journal of the Human Factors and Ergonomics Society*, *3*, 001872081982856. https://doi.org/10.1177/0018720819828569

Hernández-Torres, E., Wiggermann, V., Machan, L., Sadovnick, A. D., Li, D. K. B., Traboulsee, A., … Rauscher, A. (2019). Increased mean R2* in the deep gray matter of multiple sclerosis patients: Have we been measuring atrophy? *Journal of Magnetic Resonance Imaging*, *50*(1), 201–208. https://doi.org/10.1002/jmri.26561

Hidalgo de la Cruz, M., D'Ambrosio, A., Valsasina, P., Pagani, E., Colombo, B., Rodegher, M., … Rocca, M. A. (2018). Abnormal functional connectivity of thalamic sub-regions contributes to fatigue in multiple sclerosis. *Multiple Sclerosis Journal*, *24*(9), 1183–1195. https://doi.org/10.1177/1352458517717807

Hildebrandt, H., & Eling, P. (2014). A longitudinal study on fatigue, depression, and their relation to neurocognition in multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*, *36*(4), 410–417. https://doi.org/10.1080/13803395.2014.903900

Hindle, J. V., Martyr, A., & Clare, L. (2014, January). Cognitive reserve in Parkinson's disease: A systematic review and meta-analysis. *Parkinsonism and Related Disorders*. Parkinsonism Relat Disord. https://doi.org/10.1016/j.parkreldis.2013.08.010

Hockey, R. (2013). *The Psychology of Fatigue*. *The Psychology of Fatigue: Work, Effort and Control*. Cambridge: Cambridge University Press. https://doi.org/10.1017/CBO9781139015394

Hoffmann, S., Tittgemeyer, M., & von Cramon, D. Y. (2007). Cognitive impairment in multiple sclerosis. *Current Opinion in Neurology*, *20*(3), 275–280. https://doi.org/10.1097/WCO.0b013e32810c8e87

Hommer, D. W., Bjork, J. M., & Gilman, J. M. (2011). Imaging brain response to reward in addictive disorders. *Annals of the New York Academy of Sciences*, *1216*(1), 50–61. https://doi.org/10.1111/j.1749-6632.2010.05898.x

Hopstaken, J. F., van der Linden, D., Bakker, A. B., & Kompier, M. A. J. (2015a). A multifaceted investigation of the link between mental fatigue and task disengagement. *Psychophysiology*, *52*(3), 305–315. https://doi.org/10.1111/psyp.12339

Hopstaken, J. F., van der Linden, D., Bakker, A. B., & Kompier, M. A. J. (2015b). The window of my eyes: Task disengagement and mental fatigue covary with pupil dynamics. *Biological Psychology*, *110*, 100–106. https://doi.org/10.1016/j.biopsycho.2015.06.013

Houtchens, M. K., Benedict, R. H. B., Killiany, R., Sharma, J., Jaisani, Z., Singh, B., … Bakshi, R. (2007). Thalamic atrophy and cognition in multiple sclerosis. *Neurology*, *69*(12), 1213–1223. https://doi.org/10.1212/01.wnl.0000276992.17011.b5

Hu, M., Muhlert, N., Robertson, N., & Winter, M. (2019). Perceived fatigue and cognitive performance change in multiple sclerosis: Uncovering predictors beyond baseline fatigue. *Multiple Sclerosis and Related Disorders*, *32*, 46–53. https://doi.org/10.1016/j.msard.2019.04.011

Ifantopoulou, P., Artemiadis, A. K., Bakirtzis, C., Zekiou, K., Papadopoulos, T.-S., Diakogiannis, I., … Orologas, A. (2019). Cognitive and brain reserve in multiple sclerosis––A cross-sectional study. *Multiple Sclerosis and Related Disorders*, *35*, 128–134. https://doi.org/10.1016/J.MSARD.2019.07.027

Ihsan, M., Watson, G., & Abbiss, C. R. (2016, August 1). What are the Physiological Mechanisms for Post-Exercise Cold Water Immersion in the Recovery from Prolonged Endurance and Intermittent Exercise? *Sports Medicine*. Springer International Publishing. https://doi.org/10.1007/s40279-016-0483-3$ Inzlicht, M., Shenhav, A., & Olivola, C. Y. (2018, April 1). The Effort Paradox: Effort Is Both Costly and Valued. *Trends in Cognitive Sciences*. Elsevier Ltd.

https://doi.org/10.1016/j.tics.2018.01.007

Ishii, A., Tanaka, M., Shigihara, Y., Kanai, E., Funakura, M., & Watanabe, Y. (2013). Neural effects of prolonged mental fatigue: A magnetoencephalography study. *Brain Research*, *1529*, 105–112. https://doi.org/10.1016/j.brainres.2013.07.022

Ishii, A., Tanaka, M., & Watanabe, Y. (2014). Neural mechanisms of mental fatigue. *Reviews in the Neurosciences*, *25*(4), 469–479. https://doi.org/10.1515/revneuro-2014-0028

Islas, M. Á. M., & Ciampi, E. (2019). Assessment and impact of cognitive impairment in multiple sclerosis: An overview. *Biomedicines*, *7*(1), 1–19. https://doi.org/10.3390/biomedicines7010022

Jaeger, B. C., Edwards, L. J., Das, K., & Sen, P. K. (2017). An R^2 statistic for fixed effects in the generalized linear mixed model. *Journal of Applied Statistics*, *44*(6), 1086–1105. https://doi.org/10.1080/02664763.2016.1193725

Jamil, T., Ly, A., Morey, R. D., Love, J., Marsman, M., & Wagenmakers, E. J. (2017). Default "Gunel and Dickey" Bayes factors for contingency tables. *Behavior Research Methods*, *49*(2), 638–652. https://doi.org/10.3758/s13428-016-0739-8

Jarosz, A. F., & Wiley, J. (2014). What Are the Odds? A Practical Guide to Computing and Reporting Bayes Factors. *The Journal of Problem Solving*, *7*(1), 1037–1040. https://doi.org/10.7771/1932-6246.1167

Jaworski, M. G., Fuchs, T. A., Dwyer, M. G., Wojcik, C., Zivadinov, R., Weinstock-Guttman, B., & Benedict, R. H. (2020). Conscientiousness and deterioration in employment status in multiple sclerosis over 3 years. *Multiple Sclerosis Journal*, 1352458520946019. https://doi.org/10.1177/1352458520946019

Jeffreys, H. (1961). *Theory of Probability. 3rd Edition*. Oxford: Clarendon Press.

Jennekens-Schinkel, A., Sanders, E. A. C. M., Lanser, J. B. K., & Van der Velde, E. A. (1988). Reaction time in ambulant multiple sclerosis patients. Part I. Influence of prolonged cognitive effort. *Journal of the Neurological Sciences*, *85*(2), 173–186. https://doi.org/10.1016/0022-510X(88)90154-2

Johnen, A., Landmeyer, N. C., Bürkner, P.-C., Wiendl, H., Meuth, S. G., & Holling, H. (2017). Distinct cognitive impairments in different disease courses of multiple sclerosis—A systematic review and meta-analysis. *Neuroscience & Biobehavioral Reviews*, *83*, 568–578. https://doi.org/10.1016/J.NEUBIOREV.2017.09.005

Johns, M. W. (1991). A New Method for Measuring Daytime Sleepiness: The Epworth Sleepiness Scale. *Sleep*, *14*(6), 540–545. https://doi.org/10.1093/sleep/14.6.540

Johnson, S. C., Baxter, L. C., Wilder, L. S., Pipe, J. G., Heiserman, J. E., & Prigatano, G. P. (2002). Neural correlates of self-reflection. *Brain*, *125*(8), 1808–1814. https://doi.org/10.1093/brain/awf181

Joshi, S., & Gold, J. I. (2020). Pupil Size as a Window on Neural Substrates of Cognition. *Trends in Cognitive Sciences*, *24*(6), 466–480. https://doi.org/10.1016/j.tics.2020.03.005

Jougleux-Vie, C., Duhin, E., Deken, V., Outteryck, O., Vermersch, P., & Zéphir, H. (2014). Does Fatigue Complaint Reflect Memory Impairment in Multiple Sclerosis? *Multiple Sclerosis International*, *2014*, 1–6. https://doi.org/10.1155/2014/692468

Kahneman, D., & Beatty, J. (1966). Pupil diameter and load on memory. *Science*, *154*(3756), 1583–1585. https://doi.org/10.1126/science.154.3756.1583

Kalron, A., Aloni, R., & Allali, G. (2018). The relationship between depression, anxiety and cognition and its paradoxical impact on falls in multiple sclerosis patients. *Multiple Sclerosis and Related Disorders*, *25*, 167–172. https://doi.org/10.1016/j.msard.2018.07.029

Kato, Y., Endo, H., & Kizuka, T. (2009). Mental fatigue and impaired response processes: Event-related brain potentials in a Go/NoGo task. *International Journal of Psychophysiology*, *72*(2), 204–211. https://doi.org/10.1016/j.ijpsycho.2008.12.008

Katzir, M., Emanuel, A., & Liberman, N. (2020). Cognitive performance is enhanced if one knows when the task will end. *Cognition*.

https://doi.org/10.1016/j.cognition.2020.104189

Kelter, R. (2021). Analysis of type I and II error rates of Bayesian and frequentist parametric and nonparametric two-sample hypothesis tests under preliminary assessment of normality. *Computational Statistics*, *36*(2), 1263–1288. https://doi.org/10.1007/s00180-020-01034-7

Kenward, M. G., & Roger, J. H. (2009). An improved approximation to the precision of fixed effects from restricted maximum likelihood. *Computational Statistics and Data Analysis*, *53*(7), 2583–2595. https://doi.org/10.1016/j.csda.2008.12.013

Keysers, C., Gazzola, V., & Wagenmakers, E.-J. (2020). Using Bayes factor hypothesis testing in neuroscience to establish evidence of absence. *Nature Neuroscience*, *23*(7), 788–799. https://doi.org/10.1038/s41593-020-0660-4

Khalil, M., Enzinger, C., Langkammer, C., Petrovic, K., Loitfelder, M., Tscherner, M., … Fazekas, F. (2011). Cognitive impairment in relation to MRI metrics in patients with clinically isolated syndrome. *Multiple Sclerosis Journal*, *17*(2), 173–180. https://doi.org/10.1177/1352458510384009

Khalil, M., Langkammer, C., Ropele, S., Petrovic, K., Wallner-Blazek, M., Loitfelder, M., … Fazekas, F. (2011). Determinants of brain iron in multiple sclerosis: A quantitative 3T MRI study. *Neurology*, *77*(18), 1691–1697. https://doi.org/10.1212/WNL.0b013e318236ef0e

Kingwell, E., Marriott, J. J., Jetté, N., Pringsheim, T., Makhani, N., Morrow, S. A., … Marrie, R. A. (2013). Incidence and prevalence of multiple sclerosis in Europe: A systematic review. *BMC Neurology*, *13*, 128. https://doi.org/10.1186/1471-2377-13-128

Kiraç, L. B., Ekmekçi, Ö., Yüceyar, N., & Kocaman, A. S. (2014). Assessment of early cognitive impairment in patients with clinically isolated syndromes and multiple sclerosis. *Behavioural Neurology*, *2014*. https://doi.org/10.1155/2014/637694

Kirchner, W. K. (1958). Age differences in short-term retention of rapidly changing information. *Journal of Experimental Psychology*, *55*(4), 352–358.

https://doi.org/10.1037/h0043688

Klaassen, E. B., Evers, E. A. T., de Groot, R. H. M., Backes, W. H., Veltman, D. J., & Jolles, J. (2014). Working memory in middle-aged males: Age-related brain activation changes and cognitive fatigue effects. *Biological Psychology*, *96*(1), 134–143. https://doi.org/10.1016/j.biopsycho.2013.11.008

Klimas, N., Fletcher, M. A., Maher, K., & Lawrence, R. (2005). Psychoneuroimmunology and fatigue. In J. DeLuca (Ed.), *Fatigue as a Windov to the Brain*. Cambridge, MA: MIT Press.

Kluger, B. M., Krupp, L. B., & Enoka, R. M. (2013). Fatigue and fatigability in neurologic illnesses: Proposal for a unified taxonomy. *Neurology*, *80*(4), 409–416. https://doi.org/10.1212/WNL.0b013e31827f07be

Kohl, A. D., Wylie, G. R., Genova, H. M., Hillary, F. G., & DeLuca, J. (2009). The neural correlates of cognitive fatigue in traumatic brain injury using functional MRI. *Brain Injury*, *23*(5), 420–432. https://doi.org/10.1080/02699050902788519

Kos, D., Kerckhofs, E., Nagels, G., D'hooghe, M. B., & Ilsbroukx, S. (2008). Review article: Origin of fatigue in multiple sclerosis: Review of the literature. *Neurorehabilitation and Neural Repair*, *22*(1), 91–100. https://doi.org/10.1177/1545968306298934

Kos, Daphne, Kerckhofs, E., Carrea, I., Verza, R., Ramos, M., & Jansa, J. (2005). Evaluation of the Modified Fatigue Impact Scale in four different European countries. *Multiple Sclerosis*, *11*(1), 76–80. https://doi.org/10.1191/1352458505ms1117oa

Koubiyr, I., Besson, P., Deloire, M., Charre-Morin, J., Saubusse, A., Tourdias, T., … Ruet, A. (2019). Dynamic modular-level alterations of structural-functional coupling in clinically isolated syndrome. *Brain*, *142*(11), 3428–3439. https://doi.org/10.1093/brain/awz270

Koubiyr, I., Deloire, M., Brochet, B., Besson, P., Charré-Morin, J., Saubusse, A., … Ruet, A. (2021). Structural constraints of functional connectivity drive cognitive

impairment in the early stages of multiple sclerosis. *Multiple Sclerosis Journal*, *27*(4), 559–567. https://doi.org/10.1177/1352458520971807

Koubiyr, I., Deloire, M., Coupé, P., Dulau, C., Besson, P., Moroso, A., … Ruet, A. (2018). Differential gray matter vulnerability in the 1 year following a clinically isolated syndrome. *Frontiers in Neurology*, *9*(OCT), 1–8. https://doi.org/10.3389/fneur.2018.00824

Krupp, L. B., Alvarez, L. A., LaRocca, N. G., & Scheinberg, L. C. (1988). Fatigue in Multiple Sclerosis. *Arch. Neurol.*, *45*, 435–437. Retrieved from http://archneur.jamanetwork.com/

Krupp, L. B., & Elkins, L. E. (2000). Fatigue and declines in cognitive functioning in multiple sclerosis. *Neurology*, *55*(7), 934–939. https://doi.org/10.1212/WNL.55.7.934

Krupp, L. B., LaRocca, N. G., Muir-Nash, J., & Steinberg, A. D. (1989). The Fatigue Severity Scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Archives of Neurology*, *46*(10), 1121. https://doi.org/10.1001/archneur.1989.00520460115022

Krupp, L. B., Serafin, D. J., & Christodoulou, C. (2010). Multiple sclerosis-associated fatigue. *Expert Rev. Neurother.*, *10*(9), 1437–1447. https://doi.org/10.1586/ern.10.99.

Krupp, L., Christodoulou, C., & Schombert, H. (2005). Multiple Sclerosis and Faituge. In J. DeLuca (Ed.), *Fatigue as a Windov to the Brain*. Cambridge, MA: MIT Press.

Kuppuswamy, A. (2017). The fatigue conundrum. *Brain*, *140*, 2240–2245. https://doi.org/10.1093/brain/awx153

Kurth, S., Majerus, S., Bastin, C., Collette, F., Jaspar, M., Bahri, M. A., & Salmon, E. (2016). Effects of aging on task- and stimulus-related cerebral attention networks. *Neurobiology of Aging*, *44*, 85–95. https://doi.org/10.1016/j.neurobiolaging.2016.04.015

Kurtzke, J. F. (1983). Rating neurologic impairment in multiple sclerosis: An expanded

disability status scale (EDSS). *Neurology*, *33*(11), 1444–1452. https://doi.org/10.1212/wnl.33.11.1444

Kutzelnigg, A., Lucchinetti, C. F., Stadelmann, C., Brück, W., Rauschka, H., Bergmann, M., … Lassmann, H. (2005). Cortical demyelination and diffuse white matter injury in multiple sclerosis. *Brain*, *128*(11), 2705–2712. https://doi.org/10.1093/brain/awh641

Lampit, A., Heine, J., Finke, C., Barnett, M. H., Valenzuela, M., Wolf, A., … Hill, N. T. M. (2019, September 1). Computerized Cognitive Training in Multiple Sclerosis: A Systematic Review and Meta-analysis. *Neurorehabilitation and Neural Repair*. SAGE Publications Inc. https://doi.org/10.1177/1545968319860490

Langdon, D. W., Amato, M. P., Boringa, J., Brochet, B., Foley, F., Fredrikson, S., … Benedict, R. H. B. (2012). Recommendations for a brief international cognitive assessment for multiple sclerosis (BICAMS). *Multiple Sclerosis Journal*. Mult Scler. https://doi.org/10.1177/1352458511431076

Lazzarotto, A., Margoni, M., Franciotta, S., Zywicki, S., Riccardi, A., Poggiali, D., … Gallo, P. (2020). Selective Cerebellar Atrophy Associates with Depression and Fatigue in the Early Phases of Relapse-Onset Multiple Sclerosis. *Cerebellum*. https://doi.org/10.1007/s12311-019-01096-4

Le Page, E., Edan, G., & Veillard, D. (2017). Traitement de la poussée. In *La Sclérose en Plaques - Clinique et Thérapeutique*. Issy-les-Moulineaux: Elsevier Masson.

Leal, G., Neves, C., & Vieira, P. M. (2012). Pupillometry: Development of equipment for studies of autonomic nervous system. *IFIP Advances in Information and Communication Technology*, *372 AICT*, 553–562. https://doi.org/10.1007/978-3-642-28255-3_61

Leavitt, V. M., & DeLuca, J. (2010). Central Fatigue: Issues Related to Cognition, Mood and Behavior, and Psychiatric Diagnoses. *PM and R*, *2*(5), 332–337. https://doi.org/10.1016/j.pmrj.2010.03.027

Leavitt, V. M., Lengenfelder, J., Moore, N. B., Chiaravalloti, N. D., & DeLuca, J. (2011).

The relative contributions of processing speed and cognitive load to working memory accuracy in multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*, *33*(5), 580–586. https://doi.org/10.1080/13803395.2010.541427

Lebrun-Frénay, C. (2017). Introduction : les différentes formes évolutives de SEP. In *La Sclérose en Plaques - Clinique et Thérapeutique*. Issy-les-Moulineaux: Elsevier Masson.

Leclercq, M. (2007). Batterie d'attention William Lennox (BAWL) version 4.0. Louvain-la-Neuve, Belgium.

Lee, K. A., Hicks, G., & Nino-Murcia, G. (1991). Validity and reliability of a scale to assess fatigue. *Psychiatry Research*, *36*(3), 291–298. https://doi.org/10.1016/0165-1781(91)90027-M

Léotard, A. (2021). Introduction à l'identification et l'évaluation de la fatigue cognitive et physicque: focus sur les pathologies neurologiques. In *Sommeil, fatigue et troubles cognitifs* (pp. 47–67). Paris: De Boeck Supérieur.

Lerdal, A., Gulowsen Celius, E., Krupp, L., & Dahl, A. A. (2007). A prospective study of patterns of fatigue in multiple sclerosis. *European Journal of Neurology*, *14*(12), 1338–1343. https://doi.org/10.1111/j.1468-1331.2007.01974.x

Lim, J., Teng, J., Wong, K. F., & Chee, M. W. L. (2016). Modulating rest-break length induces differential recruitment of automatic and controlled attentional processes upon task reengagement. *NeuroImage*, *134*, 64–73. https://doi.org/10.1016/j.neuroimage.2016.03.077

Lim, J., Wu, W. chau, Wang, J., Detre, J. A., Dinges, D. F., & Rao, H. (2010). Imaging brain fatigue from sustained mental workload: An ASL perfusion study of the time-on-task effect. *NeuroImage*, *49*(4), 3426–3435. https://doi.org/10.1016/j.neuroimage.2009.11.020

Lin, X. G., Zhang, X. L., Liu, Q. Q., Zhao, P. W., Zhong, J. G., Pan, P. L., … Yi, Z. Q. (2021). Social cognition in multiple sclerosis and its subtypes: A meta-analysis. *Multiple Sclerosis and Related Disorders*, *52*(April), 102973.

https://doi.org/10.1016/j.msard.2021.102973

Linnhoff, S., Fiene, M., Heinze, H. J., & Zaehle, T. (2019). Cognitive fatigue in multiple sclerosis: An objective approach to diagnosis and treatment by transcranial electrical stimulation. *Brain Sciences*, *9*(5), 1–23. https://doi.org/10.3390/brainsci9050100

Lommers, E. (2019). *MULTIPARAMETER MRI QUANTIFICATION OF MICROSTRUCTURAL BRAIN ALTERATIONS IN MULTIPLE SCLEROSIS*. ULiège - Université de Liège [Applied Sciences] PhD Thesis.

Lommers, E., Guillemin, C., Reuter, G., Fouarge, E., Delrue, G., Collette, F., … Phillips, C. (2021). Voxel-Based quantitative MRI reveals spatial patterns of grey matter alteration in multiple sclerosis. *Human Brain Mapping*, *42*(4), 1003–1012. https://doi.org/10.1002/hbm.25274

Lommers, E., Simon, J., Reuter, G., Delrue, G., Dive, D., Degueldre, C., … Maquet, P. (2019). Multiparameter MRI quantification of microstructural tissue alterations in multiple sclerosis. *NeuroImage: Clinical*, *23*, 101879. https://doi.org/10.1016/j.nicl.2019.101879

Lorist, M. M. (2008). Impact of top-down control during mental fatigue. *Brain Research*, *1232*, 113–123. https://doi.org/10.1016/j.brainres.2008.07.053

Lorist, M. M., Boksem, M. A. S., & Ridderinkhof, K. R. (2005). Impaired cognitive control and reduced cingulate activity during mental fatigue. *Cognitive Brain Research*, *24*(2), 199–205. https://doi.org/10.1016/j.cogbrainres.2005.01.018

Loy, B. D., Taylor, R. L., Fling, B. W., & Horak, F. B. (2017). Relationship between perceived fatigue and performance fatigability in people with multiple sclerosis: A systematic review and meta-analysis. *Journal of Psychosomatic Research*, *100*, 1–7. https://doi.org/10.1016/J.JPSYCHORES.2017.06.017

Lubetzki, C., Zalc, B., Williams, A., Stadelmann, C., & Stankoff, B. (2020). Remyelination in multiple sclerosis: from basic science to clinical translation. *The Lancet Neurology*, *19*(8), 678–688. https://doi.org/10.1016/S1474-4422(20)30140-

Lublin, F. D., & Reingold, S. C. (1996, April 1). Defining the clinical course of multiple sclerosis: Results of an international survey. *Neurology*. Lippincott Williams and Wilkins. https://doi.org/10.1212/WNL.46.4.907

Lublin, F. D., Reingold, S. C., Cohen, J. A., Cutter, G. R., Sørensen, P. S., Thompson, A. J., … Polman, C. H. (2014, July 15). Defining the clinical course of multiple sclerosis: The 2013 revisions. *Neurology*. Lippincott Williams and Wilkins. https://doi.org/10.1212/WNL.0000000000000560

Luna, F. G., Barttfeld, P., Martín-Arévalo, E., & Lupiáñez, J. (2022). Cognitive load mitigates the executive but not the arousal vigilance decrement. *Consciousness and Cognition*, *98*(April 2021), 103263. https://doi.org/10.1016/j.concog.2021.103263

Lynch, S. G., Parmenter, B. A., & Denney, D. R. (2005). The association between cognitive impairment and physical disability in multiple sclerosis. *Multiple Sclerosis*, *11*(4), 469–476. https://doi.org/10.1191/1352458505ms1182oa

Macaron, G., Baldassari, L. E., Nakamura, K., Rao, S. M., McGinley, M. P., Moss, B. P., … Conway, D. S. (2020). Cognitive processing speed in multiple sclerosis clinical practice: association with patient-reported outcomes, employment and magnetic resonance imaging metrics. *European Journal of Neurology*, *27*(7), 1238–1249. https://doi.org/10.1111/ene.14239

Mairesse, O., Damen, V., Newell, J., Kornreich, C., Verbanck, P., & Neu, D. (2019). The Brugmann Fatigue Scale: An Analogue to the Epworth Sleepiness Scale to Measure Behavioral Rest Propensity. *Behavioral Sleep Medicine*, *17*(4), 437–458. https://doi.org/10.1080/15402002.2017.1395336

Manconi, M., Ferini-Strambi, L., Filippi, M., Bonanni, E., Ludice, A., Murri, L., … Londrillo, F. (2008). Multicenter case-control study on restless legs syndrome in multiple sclerosis: The REMS Study. *Sleep*, *31*(7), 944–952. https://doi.org/10.5665/sleep/31.7.944

Manjaly, Z.-M., Harrison, N. A., Critchley, H. D., Do, C. T., Stefanics, G., Wenderoth, N., … Stephan, K. E. (2019). Pathophysiological and cognitive mechanisms of fatigue in multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry*, jnnp-2018-320050. https://doi.org/10.1136/jnnp-2018-320050

Marasescu, R., Cerezo Garcia, M., & Aladro Benito, Y. (2016). Afectación visuoespacial/visuoconstrucción en pacientes con esclerosis múltiple. Relación con el volumen lesional regional y la atrofia subcortical. *Neurologia*, *31*(3), 169–175. https://doi.org/10.1016/j.nrl.2015.06.003

Marchesi, O., Vizzino, C., Meani, A., Conti, L., Riccitelli, G. C., Preziosa, P., … Rocca, M. A. (2020). Fatigue in multiple sclerosis patients with different clinical phenotypes: a clinical and magnetic resonance imaging study. *European Journal of Neurology*, *27*(12), 2549–2560. https://doi.org/10.1111/ene.14471

Marino, F. E. (2009). Heat reactions in multiple sclerosis: An overlooked paradigm in the study of comparative fatigue. *International Journal of Hyperthermia*. Int J Hyperthermia. https://doi.org/10.1080/02656730802294020

Mascord, D. J., & Heath, R. A. (1992). Behavioral and physiological indices of fatigue in a visual tracking task. *Journal of Safety Research*, *23*(1), 19–25. https://doi.org/10.1016/0022-4375(92)90036-9

Mathôt, S. (2013). A simple way to reconstruct pupil size during eye blinks. *Figshare*, *17*(April 2013), 491–496. https://doi.org/https://figshare.com/articles/journal_contribution/A_simple_way_to_reconstruct_pupil_size_during_eye_blinks/688001

Mathôt, S. (2018). Pupillometry: Psychology, Physiology, and Function, *1*(1), 1–23.

Mathôt, S., Fabius, J., Van Heusden, E., & Van der Stigchel, S. (2018). Safe and sensible preprocessing and baseline correction of pupil-size data. *Behavior Research Methods*, *50*(1), 94–106. https://doi.org/10.3758/s13428-017-1007-2

Matías-Guiu, J. A., Cortés-Martínez, A., Montero, P., Pytel, V., Moreno-Ramos, T., Jorquera, M., … Matías-Guiu, J. (2018). Identification of Cortical and Subcortical

Correlates of Cognitive Performance in Multiple Sclerosis Using Voxel-Based Morphometry. *Frontiers in Neurology*, *9*. https://doi.org/10.3389/fneur.2018.00920

McDonald, W. I., Compston, A., Edan, G., Goodkin, D., Hartung, H. P., Lublin, F. D., … Wolinsky, J. S. (2001). Recommended diagnostic criteria for multiple sclerosis: Guidelines from the International Panel on the Diagnosis of Multiple Sclerosis. *Annals of Neurology*, *50*(1), 121–127. https://doi.org/10.1002/ana.1032

McDougall, A. J., & McLeod, J. G. (2003). Autonomic nervous system function in multiple sclerosis. *Journal of the Neurological Sciences*, *215*(1–2), 79–85. https://doi.org/10.1016/S0022-510X(03)00205-3

McGarrigle, R., Dawes, P., Stewart, A. J., Kuchinsky, S. E., & Munro, K. J. (2017). Pupillometry reveals changes in physiological arousal during a sustained listening task. *Psychophysiology*, *54*(2), 193–203. https://doi.org/10.1111/psyp.12772

McMorris, T. (2020). Cognitive Fatigue Effects on Physical Performance: The Role of Interoception. *Sports Medicine*, *50*(10), 1703–1708. https://doi.org/10.1007/s40279-020-01320-w

McMorris, T., Barwood, M., Hale, B. J., Dicks, M., & Corbett, J. (2018, May 1). Cognitive fatigue effects on physical performance: A systematic review and meta-analysis. *Physiology and Behavior*. Elsevier Inc. https://doi.org/10.1016/j.physbeh.2018.01.029

McNicholas, N., Russell, A., Nolan, G., Tubridy, N., Hutchinson, M., Garvey, J. F., & McGuigan, C. (2021). Impact of obstructive sleep apnoea on cognitive function in multiple sclerosis: A longitudinal study. *Journal of Sleep Research*, *30*(3). https://doi.org/10.1111/jsr.13159

Melamud, L., Golan, D., Luboshitzky, R., Lavi, I., & Miller, A. (2012). Melatonin dysregulation, sleep disturbances and fatigue in multiple sclerosis. *Journal of the Neurological Sciences*, *314*(1–2), 37–40. https://doi.org/10.1016/j.jns.2011.11.003

Melo, H. M., Nascimento, L. M., Alves, A. C. de B., Walz, R., & Takase, E. (2021). N2

event-related potential component is associated with cardiac autonomic tone regulation during mental fatigue. *Physiology and Behavior*, *241*(August), 113591. https://doi.org/10.1016/j.physbeh.2021.113591

Merkelbach, S., Haensch, C. A., Hemmer, B., Koehler, J., König, N. H., & Ziemssen, T. (2006). Multiple sclerosis and the autonomic nervous system. *Journal of Neurology*, *253*(1 SUPPL.), 21–25. https://doi.org/10.1007/s00415-006-1105-z

Michel, L. (2017). SEP et Genre. In *La Sclérose en Plaques - Clinique et Thérapeutique* (pp. 62–63). Issy-les-Moulineaux: Elsevier Masson.

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience*. Annu Rev Neurosci. https://doi.org/10.1146/annurev.neuro.24.1.167

Mills, R. J., & Young, C. A. (2011). The relationship between fatigue and other clinical features of multiple sclerosis. *Multiple Sclerosis Journal*, *17*(5), 604–612. https://doi.org/10.1177/1352458510392262

Minagar, A., Barnett, M. H., Benedict, R. H. B., Pelletier, D., Pirko, I., Sahraian, M. A., … Zivadinov, R. (2013, January 8). The thalamus and multiple sclerosis: Modern views on pathologic, imaging, and clinical aspects. *Neurology*. Neurology. https://doi.org/10.1212/WNL.0b013e31827b910b

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The Unity and Diversity of Executive Functions and Their Contributions to Complex "Frontal Lobe" Tasks: A Latent Variable Analysis. *Cognitive Psychology*, *41*(1), 49–100. https://doi.org/10.1006/cogp.1999.0734

Mizuno, K., Tajima, K., Watanabe, Y., & Kuratsune, H. (2014). Fatigue correlates with the decrease in parasympathetic sinus modulation induced by a cognitive challenge. *Behavioral and Brain Functions*, *10*(1). https://doi.org/10.1186/1744-9081-10-25

Modica, C. M., Bergsland, N., Dwyer, M. G., Ramasamy, D. P., Carl, E., Zivadinov, R., & Benedict, R. H. B. (2016). Cognitive reserve moderates the impact of subcortical

gray matter atrophy on neuropsychological status in multiple sclerosis. *Multiple Sclerosis Journal*, *22*(1), 36–42. https://doi.org/10.1177/1352458515579443

Montalban, X., Gold, R., Thompson, A. J., Otero-Romero, S., Amato, M. P., Chandraratna, D., … Zipp, F. (2018). ECTRIMS/EAN Guideline on the pharmacological treatment of people with multiple sclerosis. *Multiple Sclerosis*, *24*(2), 96–120. https://doi.org/10.1177/1352458517751049

Montembeault, M., Brando, E., Charest, K., Tremblay, A., Roger, É., Duquette, P., & Rouleau, I. (2022). Multimodal emotion perception in young and elderly patients with multiple sclerosis. *Multiple Sclerosis and Related Disorders*, *58*(July 2021), 103478. https://doi.org/10.1016/j.msard.2021.103478

Morgante, F., Dattola, V., Crupi, D., Russo, M., Rizzo, V., Ghilardi, M. F., … Quartarone, A. (2011). Is central fatigue in multiple sclerosis a disorder of movement preparation? *Journal of Neurology*, *258*(2), 263–272. https://doi.org/10.1007/s00415-010-5742-x

Moroso, A., Ruet, A., Lamargue-Hamel, D., Munsch, F., Deloire, M., Coupé, P., … Brochet, B. (2017). Microstructural analyses of the posterior cerebellar lobules in relapsing-onset multiple sclerosis and their implication in cognitive impairment. *PLoS ONE*, *12*(8), 1–15. https://doi.org/10.1371/journal.pone.0182479

Morrow, S. A., Weinstock-Guttman, B., Munschauer, F. E., Hojnacki, D., & Benedict, R. H. B. (2009). Subjective fatigue is not associated with cognitive impairment in multiple sclerosis: Cross-sectional and longitudinal analysis. *Multiple Sclerosis*, *15*(8), 998–1005. https://doi.org/10.1177/1352458509106213

Morrow, Sarah A., Rosehart, H., & Pantazopoulos, K. (2016). Anxiety and depressive symptoms are associated with worse performance on objective cognitive tests in MS. *Journal of Neuropsychiatry and Clinical Neurosciences*, *28*(2), 118–123. https://doi.org/10.1176/appi.neuropsych.15070167

Müller, T., & Apps, M. A. J. (2018). Motivational fatigue: A neurocognitive framework for the impact of effortful exertion on subsequent motivation. *Neuropsychologia*. https://doi.org/10.1016/j.neuropsychologia.2018.04.030

Murray, T. J. (1985). Amantadine Therapy for Fatigue in Multiple Sclerosis. *Canadian Journal of Neurological Sciences / Journal Canadien Des Sciences Neurologiques*, *12*(3), 251–254. https://doi.org/10.1017/S0317167100047107

Nakagawa, S., & Cuthill, I. C. (2007, November). Effect size, confidence interval and statistical significance: A practical guide for biologists. *Biological Reviews*. Biol Rev Camb Philos Soc. https://doi.org/10.1111/j.1469-185X.2007.00027.x

Neema, M., Stankiewicz, J., Arora, A., Dandamudi, V. S. R., Batt, C. E., Guss, Z. D., … Bakshi, R. (2007). T1- and T2-based MRI measures of diffuse gray matter and white matter damage in patients with multiple sclerosis. *Journal of Neuroimaging*, *17*(SUPPL. 1), 16–21. https://doi.org/10.1111/j.1552-6569.2007.00131.x

Nelson, M. E., Jester, D. J., Petkus, A. J., & Andel, R. (2021, June 1). Cognitive Reserve, Alzheimer's Neuropathology, and Risk of Dementia: A Systematic Review and Meta-Analysis. *Neuropsychology Review*. Springer. https://doi.org/10.1007/s11065-021-09478-4

Newland, P., Starkweather, A., & Sorenson, M. (2016). Central fatigue in multiple sclerosis: a review of the literature. *Journal of Spinal Cord Medicine*. Taylor & Francis. https://doi.org/10.1080/10790268.2016.1168587

Newton, G., Griffith, A., & Soundy, A. (2020). The experience of fatigue in neurological patients with Multiple Sclerosis: a thematic synthesis. *Physiotherapy (United Kingdom)*, *107*, 306–316. https://doi.org/10.1016/j.physio.2016.11.004

Niepel, G., Bibani, R. H., Vilisaar, J., Langley, R. W., Bradshaw, C. M., Szabadi, E., & Constantinescu, C. S. (2013). Association of a deficit of arousal with fatigue in multiple sclerosis: Effect of modafinil. *Neuropharmacology*, *64*, 380–388. https://doi.org/10.1016/j.neuropharm.2012.06.036

Niino, M., Fukumoto, S., Okuno, T., Sanjo, N., Fukaura, H., Mori, M., … Mifune, N. (2022). Correlation of the symbol digit modalities test with the quality of life and depression in Japanese patients with multiple sclerosis. *Multiple Sclerosis and Related Disorders*, *57*(September 2021), 103427. https://doi.org/10.1016/j.msard.2021.103427

Niino, M., Mifune, N., Kohriyama, T., Mori, M., Ohashi, T., & Kawachi, I. (2014). Apathy / depression, but not subjective fatigue, is related with cognitive dysfunction in patients with multiple sclerosis. *BMC Neurology*, *14*(3).

Noorimotlagh, Z., Azizi, M., Pan, H. F., Mami, S., & Mirzaee, S. A. (2021, May 1). Association between air pollution and Multiple Sclerosis: A systematic review. *Environmental Research*. Academic Press Inc. https://doi.org/10.1016/j.envres.2020.110386

Nourbakhsh, B., Julian, L., & Waubant, E. (2016). Fatigue and depression predict quality of life in patients with early multiple sclerosis: a longitudinal study. *European Journal of Neurology*, *23*(9), 1482–1486. https://doi.org/10.1111/ene.13102

Nourbakhsh, Bardia, Azevedo, C., Nunan-Saah, J., Maghzi, A. H., Spain, R., Pelletier, D., & Waubant, E. (2016). Longitudinal associations between brain structural changes and fatigue in early MS. *Multiple Sclerosis and Related Disorders*, *5*, 29–33. https://doi.org/10.1016/j.msard.2015.10.006

Nourbakhsh, Bardia, Nunan-Saah, J., Maghzi, A. H., Julian, L. J., Spain, R., Jin, C., … Waubant, E. (2016). Longitudinal associations between MRI and cognitive changes in very early MS. *Multiple Sclerosis and Related Disorders*, *5*, 47–52. https://doi.org/10.1016/j.msard.2015.10.010

Nunnari, D., De Cola, M. C., D'Aleo, G., Rifici, C., Russo, M., Sessa, E., … Marino, S. (2015). Impact of depression, fatigue, and global measure of cortical volume on cognitive impairment in multiple sclerosis. *BioMed Research International*, *2015*, 11–13. https://doi.org/10.1155/2015/519785

Nuño, L., Gómez-Benito, J., Carmona, V. R., & Pino, O. (2021). A systematic review of executive function and information processing speed in major depression disorder. *Brain Sciences*, *11*(2), 1–18. https://doi.org/10.3390/brainsci11020147

Nygaard, G. O., Celius, E. G., De Rodez Benavent, S. A., Sowa, P., Gustavsen, M. W., Fjell, A. M., … Aktas, O. (2015). A longitudinal study of disability, cognition and gray matter atrophy in early multiple sclerosis patients according to evidence of disease activity. *PLoS ONE*, *10*(8), 1–15.

https://doi.org/10.1371/journal.pone.0135974

Otto, T., Zijlstra, F. R. H., & Goebel, R. (2014). Neural correlates of mental effort evaluation-involvement of structures related to self-awareness. *Social Cognitive and Affective Neuroscience*, *9*(3), 307–315. https://doi.org/10.1093/scan/nss136

Pakarinen, T., Pietila, J., & Nieminen, H. (2019). Prediction of Self-Perceived Stress and Arousal Based on Electrodermal Activity∗. In *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS* (Vol. 2019, pp. 2191–2195). Institute of Electrical and Electronics Engineers Inc. https://doi.org/10.1109/EMBC.2019.8857621

Palotai, M., & Guttmann, C. R. G. (2020, June 1). Brain anatomical correlates of fatigue in multiple sclerosis. *Multiple Sclerosis Journal*. SAGE Publications Ltd. https://doi.org/10.1177/1352458519876032

Pardini, M., Capello, E., Krueger, F., Mancardi, G., & Uccelli, A. (2013). Reward responsiveness and fatigue in multiple sclerosis. *Multiple Sclerosis Journal*, *19*(2), 233–240. https://doi.org/10.1177/1352458512451509

Parker, L.-S., Topcu, G., De Boos, D., & das Nair, R. (2021). The notion of "invisibility" in people's experiences of the symptoms of multiple sclerosis: a systematic meta-synthesis. *Disability and Rehabilitation*, *43*(23), 3276–3290. https://doi.org/10.1080/09638288.2020.1741698

Parmenter, B. A., Denney, D. R., & Lynch, S. G. (2003). The cognitive performance of patients with multiple sclerosis during periods of high and low fatigue. *Multiple Sclerosis*, *9*(2), 111–118. https://doi.org/10.1191/1352458503ms859oa

Patti, F., Amato, M. P., Trojano, M., Bastianello, S., Tola, M. R., Goretti, B., … COGIMUS Study Group. (2009). Cognitive impairment and its relation with disease measures in mildly disabled patients with relapsing-remitting multiple sclerosis: baseline results from the Cognitive Impairment in Multiple Sclerosis (COGIMUS) study. *Multiple Sclerosis*, *15*(7), 779–788. https://doi.org/10.1177/1352458509105544

Pattyn, N., Neyt, X., Henderickx, D., & Soetens, E. (2008). Psychophysiological investigation of vigilance decrement: Boredom or cognitive fatigue? *Physiology and Behavior*, *93*(1–2), 369–378. https://doi.org/10.1016/j.physbeh.2007.09.016

Pattyn, N., Van Cutsem, J., Dessy, E., & Mairesse, O. (2018). Bridging Exercise Science, Cognitive Psychology, and Medical Practice: Is "Cognitive Fatigue" a Remake of "The Emperor's New Clothes"? *Frontiers in Psychology*, *9*(SEP), 1–13. https://doi.org/10.3389/fpsyg.2018.01246

Paucke, M., Kern, S., & Ziemssen, T. (2018). Fatigue and sleep in multiple sclerosis patients: A comparison of self-report and performance-based measures. *Frontiers in Neurology*, *8*(JAN), 1–7. https://doi.org/10.3389/fneur.2017.00703

Paul, R. H., Beatty, W. W., Schneider, R., Blanco, C., & Hames, K. (1998). Impairments of attention in individuals with Multiple Sclerosis. *Multiple Sclerosis Journal*, *4*(5), 433–439. https://doi.org/10.1177/135245859800400506

Paus, T., Zatorre, R. J., Hofle, N., Caramanos, Z., Gotman, J., Petrides, M., & Evans, A. C. (1997). Time-related changes in neural systems underlying attention and arousal during the performance of an auditory vigilance task. *Journal of Cognitive Neuroscience*, *9*(3), 392–408. https://doi.org/10.1162/jocn.1997.9.3.392

Pazderka-Robinson, H., Morrison, J. W., & Flor-Henry, P. (2004). Electrodermal dissociation of chronic fatigue and depression: Evidence for distinct physiological mechanisms. *International Journal of Psychophysiology*, *53*(3), 171–182. https://doi.org/10.1016/j.ijpsycho.2004.03.004

Penner, I. K., Raselli, C., Stöcklin, M., Opwis, K., Kappos, L., & Calabrese, P. (2009). The Fatigue Scale for Motor and Cognitive Functions (FSMC): Validation of a new instrument to assess multiple sclerosis-related fatigue. *Multiple Sclerosis*, *15*(12), 1509–1517. https://doi.org/10.1177/1352458509348519

Penner, Iris Katharina, McDougall, F., Brown, T. M., Slota, C., Doward, L., Julian, L., … Miller, D. (2020). Exploring the Impact of Fatigue in Progressive Multiple Sclerosis: A Mixed-Methods Analysis. *Multiple Sclerosis and Related Disorders*, *43*(May), 102207. https://doi.org/10.1016/j.msard.2020.102207

Penner, Iris Katharina, & Paul, F. (2017). Fatigue as a symptom or comorbidity of neurological diseases. *Nature Reviews Neurology*, *13*(11), 662–675. https://doi.org/10.1038/nrneurol.2017.117

Penner, Iris Katharina, Rausch, M., Kappos, L., Opwis, K., & Radü, E. W. (2003). Analysis of impairment related functional architecture in MS patients during performance of different attention tasks. *Journal of Neurology*, *250*(4), 461–472. https://doi.org/10.1007/s00415-003-1025-0

Persson, J., Larsson, A., & Reuter-Lorenz, P. A. (2013). Imaging fatigue of interference control reveals the neural basis of executive resource depletion. *Journal of Cognitive Neuroscience*, *25*(3), 338–351. https://doi.org/10.1162/jocn_a_00321

Peters, S. K., Dunlop, K., & Downar, J. (2016, December 27). Cortico-striatal-thalamic loop circuits of the salience network: A central pathway in psychiatric disease and treatment. *Frontiers in Systems Neuroscience*. Frontiers Media S.A. https://doi.org/10.3389/fnsys.2016.00104

Phillips, C. U. de L.-Ul. > G.-C. I. vivo I., & Pernet, C. U. of E. (2018). *Unifying lesion masking and tissue probability maps for improved segmentation and normalization*. *23rd Annual Meeting of the Organization for Human Brain Mapping*. Retrieved from https://github.com/CyclotronResearchCentre/USwithLesion.

Pinter, D., Sumowski, J., DeLuca, J., Fazekas, F., Pichler, A., Khalil, M., … Enzinger, C. (2014). Higher Education Moderates the Effect of T2 Lesion Load and Third Ventricle Width on Cognition in Multiple Sclerosis. *PLoS ONE*, *9*(1), e87567. https://doi.org/10.1371/journal.pone.0087567

Pivot, D., Debouverie, M., Grzebyk, M., Brassat, D., Clanet, M., Clavelou, P., … Guillemin, F. (2016). Geographical heterogeneity of multiple sclerosis prevalence in France. *PLoS ONE*, *11*(12). https://doi.org/10.1371/journal.pone.0167556

Pokryszko-Dragan, A., Banaszek, A., Nowakowska-Kotas, M., Jeżowska-Jurczyk, K., Dziadkowiak, E., Gruszka, E., … Bladowska, J. (2018). Diffusion tensor imaging findings in the multiple sclerosis patients and their relationships to various

aspects of disability. *Journal of the Neurological Sciences*, *391*, 127–133. https://doi.org/10.1016/j.jns.2018.06.007

Pokryszko-Dragan, Anna, Dziadkowiak, E., Zagrajek, M., Slotwinski, K., Gruszka, E., Bilinska, M., & Podemski, R. (2016). Cognitive performance, fatigue and event-related potentials in patients with clinically isolated syndrome. *Clinical Neurology and Neurosurgery*, *149*, 68–74. https://doi.org/10.1016/j.clineuro.2016.07.022

Pokryszko-Dragan, Anna, Zagrajek, M., Slotwinski, K., Bilinska, M., Gruszka, E., & Podemski, R. (2016). Event-related potentials and cognitive performance in multiple sclerosis patients with fatigue. *Neurological Sciences*, *37*(9), 1545–1556. https://doi.org/10.1007/s10072-016-2622-x

Polak, P. E., Kalinin, S., & Feinstein, D. L. (2011). Locus coeruleus damage and noradrenaline reductions in multiple sclerosis and experimental autoimmune encephalomyelitis. *Brain*, *134*(3), 665–677. https://doi.org/10.1093/brain/awq362

Polman, C. H., Reingold, S. C., Banwell, B., Clanet, M., Cohen, J. A., Filippi, M., … Wolinsky, J. S. (2011). Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria. *Annals of Neurology*, *69*(2), 292–302. https://doi.org/10.1002/ana.22366

Poser, C. M., Paty, D. W., Scheinberg, L., McDonald, W. I., Davis, F. A., Ebers, G. C., … Tourtellotte, W. W. (1983). New diagnostic criteria for multiple sclerosis: Guidelines for research protocols. *Annals of Neurology*, *13*(3), 227–231. https://doi.org/10.1002/ana.410130302

Posner, J., Marsh, R., Maia, T. V., Peterson, B. S., Gruber, A., & Simpson, H. B. (2014). Reduced functional connectivity within the limbic cortico-striato-thalamo-cortical loop in unmedicated adults with obsessive-compulsive disorder. *Human Brain Mapping*, *35*(6), 2852–2860. https://doi.org/10.1002/hbm.22371

Povolo, C. A., Blair, M., Mehta, S., Rosehart, H., & Morrow, S. A. (2019). Predictors of vocational status among persons with multiple sclerosis. *Multiple Sclerosis and Related Disorders*, *36*, 101411. https://doi.org/10.1016/J.MSARD.2019.101411

Pozzessere, G., Rossi, P., Valle, E., Froio, C. P., Petrucci, A. F. G., & Morocutti Md, C. (1997). Autonomic involvement in multiple sclerosis: A pupillometric study. *Clinical Autonomic Research*, *7*(6), 315–319. https://doi.org/10.1007/BF02267724

Practice, M. S. C. for C. (1998). Fatigue and Multiple Sclerosis: Evidence-based Management Strategies for Fatigue in Multiple Sclerosis: Clinical Practice Guidelines.

Preibisch, C., & Deichmann, R. (2009). Influence of RF spoiling on the stability and accuracy of T1 mapping based on spoiled FLASH with varying flip angles. *Magnetic Resonance in Medicine*, *61*(1), 125–135. https://doi.org/10.1002/mrm.21776

Przybek, J., Gniatkowska, I., Mirowska-Guzel, D., & Członkowska, A. (2015, September 1). Evolution of diagnostic criteria for multiple sclerosis. *Neurologia i Neurochirurgia Polska*. Urban and Partner. https://doi.org/10.1016/j.pjnns.2015.07.006

Puckett, A. M., Bollmann, S., Poser, B. A., Palmer, J., Barth, M., & Cunnington, R. (2018). Using multi-echo simultaneous multi-slice (SMS) EPI to improve functional MRI of the subcortical nuclei of the basal ganglia at ultra-high field (7T). *NeuroImage*, *172*, 886–895. https://doi.org/10.1016/j.neuroimage.2017.12.005

Rădulescu, A., Herron, J., Kennedy, C., & Scimemi, A. (2017). Global and local excitation and inhibition shape the dynamics of the cortico-striatal-thalamo-cortical pathway. *Scientific Reports*, *7*(1), 1–21. https://doi.org/10.1038/s41598-017-07527-8

Ramírez-Moreno, M. A., Carrillo-Tijerina, P., Candela-Leal, M. O., Alanis-Espinosa, M., Tudón-Martínez, J. C., Roman-Flores, A., … Lozoya-Santos, J. de J. (2021). Evaluation of a fast test based on biometric signals to assess mental fatigue at the workplace—A pilot study. *International Journal of Environmental Research and Public Health*, *18*(22). https://doi.org/10.3390/ijerph182211891

Rao, S. M., Leo, G. J., Haughton, V. M., St. Aubin-Faubert, P., & Bernardin, L. (1989). Correlation of magnetic resonance imaging with neuropsychological testing in

multiple sclerosis. *Neurology*, *39*(2), 161–166. https://doi.org/10.1212/wnl.39.2.161

Rasmussen, A. S., & Habermas, T. (2011). Factor structure of overall autobiographical memory usage: The directive, self and social functions revisited. *Memory*, *19*(6), 597–605. https://doi.org/10.1080/09658211.2011.592499

Reich, D. S., Lucchinetti, C. F., & Calabresi, P. A. (2018). Multiple Sclerosis. *New England Journal of Medicine*, *378*(2), 169–180. https://doi.org/10.1056/NEJMra1401483

Requier, F., Charonitis, M., Guillemin, C., Reyt, M., Bastin, C., Folville, A., Geurten, M., Willems, S., Muto, V., Schmidt, C., Collette, F. *in prep*, The impact of the lockdown situation due to COVID-19 on fatigue

Requier, F., Demnitz-King, H., Whitfield, T., Klimecki, O., Marchant, N., & Collette, F. *in prep,*. The effect of meditation-based interventions on patients with fatigue symptoms: a systematic review and meta-analysis.

Reuter, F., Zaaraoui, W., Crespy, L., Faivre, A., Rico, A., Malikova, I., … Audoin, B. (2011). Cognitive impairment at the onset of multiple sclerosis: Relationship to lesion location. *Multiple Sclerosis Journal*, *17*(6), 755–758. https://doi.org/10.1177/1352458511398265

Reuter, F., Zaaraoui, W., Crespy, L., Faivre, A., Rico, A., Malikova, I., … Audoin, B. (2011). Frequency of cognitive impairment dramatically increases during the first 5 years of multiple sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry*, *82*(10), 1157–1159. https://doi.org/10.1136/jnnp.2010.213744

Riccitelli, G. C., Disanto, G., Sacco, R., Sparasci, D., Sacco, L., Castelnovo, A., … Zecca, C. (2021). Contribution of sleep disturbances to fatigue in multiple sclerosis: a prospective study using clinical and polysomnographic parameters. *European Journal of Neurology*, *28*(9), 3139–3146. https://doi.org/10.1111/ene.14984

Ricigliano, V. A. G., Tonietto, M., Hamzaoui, M., Poirion, É., Lazzarotto, A., Bottlaender, M., … Bodini, B. (2022). Spontaneous remyelination in lesions protects the integrity of surrounding tissues over time in multiple sclerosis. *European Journal of Neurology*. https://doi.org/10.1111/ene.15285

Ritvo, P., Fischer, J., Miller, D., Andrews, H., Paty, D., & LaRocca, N. (1997). *Multiple*

Sclerosis Quality of Life Inventory: A User's Manual. New York, NY: National Multiple Sclerosis Society.

Roach, E. S. (2004, October 1). Is multiple sclerosis an autoimmune disorder? *Archives of Neurology*. American Medical Association. https://doi.org/10.1001/archneur.61.10.1615

Robb, J., Samkoff, L., & Goodman, A. (2014). Symptomatic Management of MS. In L Samkoff & A. Goodman (Eds.), *Multiple Sclerosis and CNS Inflammatory Disordes*. Oxford: Wiley.

Rocca, M. A., Gatti, R., Agosta, F., Broglia, P., Rossi, P., Riboldi, E., … Filippi, M. (2009). Influence of task complexity during coordinated hand and foot movements in MS patients with and without fatigue : AA kinematic and functional MRI study. *Journal of Neurology*, *256*(3), 470–482. https://doi.org/10.1007/s00415-009-0116-y

Rocca, M A, De Meo, E., & Filippi, M. (2016). Functional MRI in investigating cognitive impairment in multiple sclerosis. *Acta Neurologica Scandinavica*. https://doi.org/10.1111/ane.12654

Rocca, Maria A., Meani, A., Riccitelli, G. C., Colombo, B., Rodegher, M., Falini, A., … Filippi, M. (2016). Abnormal adaptation over time of motor network recruitment in multiple sclerosis patients with fatigue. *Multiple Sclerosis*, *22*(9), 1144–1153. https://doi.org/10.1177/1352458515614407

Rocca, Maria A., Parisi, L., Pagani, E., Copetti, M., Rodegher, M., Colombo, B., … Filippi, M. (2014). Regional but not global brain damage contributes to fatigue in multiple sclerosis. *Radiology*, *273*(2), 511–520. https://doi.org/10.1148/radiol.14140417

Rocca, Maria A., Preziosa, P., & Filippi, M. (2018). Application of advanced MRI techniques to monitor pharmacologic and rehabilitative treatment in multiple sclerosis: current status and future perspectives. *Expert Review of Neurotherapeutics*, *0*(0), 1–32. https://doi.org/10.1080/14737175.2019.1555038

Rocca, Maria A, Amato, M. P., De Stefano, N., Enzinger, C., Geurts, J. J., Penner, I. K., …

Filippi, M. (2015). Clinical and imaging assessment of cognitive dysfunction in multiple sclerosis. *The Lancet Neurology*. Elsevier Ltd. https://doi.org/10.1016/S1474-4422(14)70250-9

Rocca, Maria Assunta, Riccitelli, G. C., Meani, A., Pagani, E., Del Sette, P., Martinelli, V., … Filippi, M. (2018). Cognitive reserve, cognition, and regional brain damage in MS: A 2 -year longitudinal study. *Multiple Sclerosis Journal*, 372–381. https://doi.org/10.1177/1352458517750767

Rodgers, S., Manjaly, Z. M., Calabrese, P., Steinemann, N., Kaufmann, M., Salmen, A., … Ajdacic-Gross, V. (2021). The effect of depression on health-related quality of life is mediated by fatigue in persons with multiple sclerosis. *Brain Sciences*, *11*(6). https://doi.org/10.3390/brainsci11060751

Rodriguez, J. D., Lane, K. J., Ousler, G. W., Angjeli, E., Smith, L. M., & Abelson, M. B. (2018). Blink: Characteristics, Controls, and Relation to Dry Eyes. *Current Eye Research*, *43*(1), 52–66. https://doi.org/10.1080/02713683.2017.1381270

Roelcke, U., Kappos, L., Lechner-Scott, J., Brunnschweiler, H., Huber, S., Ammann, W., … Leenders, K. L. (1997). Reduced glucose metabolism in the frontal cortex and basal ganglia of multiple sclerosis patients with fatigue: A 18F-fluorodeoxyglucose positron emission tomography study. *Neurology*, *48*(6), 1566–1571. https://doi.org/10.1212/WNL.48.6.1566

Rommer, P. S., Ellenberger, D., Hellwig, K., Haas, J., Pöhlau, D., Stahmann, A., & Zettl, U. K. (2020). Relapsing and progressive MS: the sex-specific perspective. *Therapeutic Advances in Neurological Disorders*, *13*, 175628642095649. https://doi.org/10.1177/1756286420956495

Rooney, S., Wood, L., Moffat, F., & Paul, L. (2019). Prevalence of fatigue and its association with clinical features in progressive and non-progressive forms of Multiple Sclerosis. *Multiple Sclerosis and Related Disorders*, *28*, 276–282. https://doi.org/10.1016/j.msard.2019.01.011

Roosendaal, S. D., Moraal, B., Vrenken, H., Castelijns, J. A., Pouwels, P. J. W., Barkhof, F., & Geurts, J. J. G. (2008). In vivo MR imaging of hippocampal lesions in multiple

sclerosis. *Journal of Magnetic Resonance Imaging*, *27*(4), 726–731. https://doi.org/10.1002/jmri.21294

Ropele, S., Kilsdonk, I. D., Wattjes, M. P., Langkammer, C., De Graaf, W. L., Frederiksen, J. L., … Fazekas, F. (2014). Determinants of iron accumulation in deep grey matter of multiple sclerosis patients. *Multiple Sclerosis Journal*, *20*(13), 1692–1698. https://doi.org/10.1177/1352458514531085

Rossi, S., Studer, V., Motta, C., De Chiara, V., Barbieri, F., Bernardi, G., & Centonze, D. (2012). Inflammation inhibits GABA transmission in multiple sclerosis. *Multiple Sclerosis Journal*, *18*(11), 1633–1635. https://doi.org/10.1177/1352458512440207

Rotstein, D., & O'Connor, P. (2014). Diagnostic Process. In Lawrence Samkoff & A. Goodman (Eds.), *Multiple Sclerosis and CNS Inflammatory Disordes*. Oxford: Wiley.

Rózanowski, K., Bernat, M., & Kamińska, A. (2015). Estimation of operators' fatigue using optical methods for determination of pupil activity. *International Journal of Occupational Medicine and Environmental Health*, *28*(2), 263–281. https://doi.org/10.13075/ijomeh.1896.00274

Ruet, A. (2015). Cognitive Impairment in Multiple Sclerosis. In B Brochet (Ed.), *Neuropsychiatric symptoms of inflammatory demyelinating diseases.*

Ruet, A., Deloire, M., Charré-Morin, J., Hamel, D., & Brochet, B. (2013). Cognitive impairment differs between primary progressive and relapsing-remitting MS. *Neurology*, *80*(16), 1501–1508. https://doi.org/10.1212/WNL.0b013e31828cf82f

Runia, T. F., Jafari, N., Siepman, D. A. M., & Hintzen, R. Q. (2015). Fatigue at time of CIS is an independent predictor of a subsequent diagnosis of multiple sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry*, *86*(5), 543–546. https://doi.org/10.1136/jnnp-2014-308374

Rutsch, A., Kantsjö, J. B., & Ronchi, F. (2020, December 10). The Gut-Brain Axis: How Microbiota and Host Inflammasome Influence Brain Physiology and Pathology. *Frontiers in Immunology*. Frontiers Media S.A.

https://doi.org/10.3389/fimmu.2020.604179

Ryan, E. G., Brock, K., Gates, S., & Slade, D. (2020). Do we need to adjust for interim analyses in a Bayesian adaptive trial design? *BMC Medical Research Methodology*, *20*(1), 150. https://doi.org/10.1186/s12874-020-01042-7

Saberi, A., Abdolalizadeh, A., Mohammadi, E., Nahayati, M. A., Bagheri, H., Shekarchi, B., & Kargar, J. (2021). Thalamic shape abnormalities in patients with multiple sclerosis-related fatigue. *NeuroReport*, 438–442. https://doi.org/10.1097/WNR.0000000000001616

Sainz de la Maza, S., Maurino, J., Borges, M., Martín-Martínez, J., Sotoca, J., Alonso, A., … Castillo-Triviño, T. (2022). Measuring productivity loss in early relapsing-remitting multiple sclerosis. *Multiple Sclerosis and Related Disorders*, *58*(November 2021). https://doi.org/10.1016/j.msard.2021.103398

Sakkas, G. K., Giannaki, C. D., Karatzaferi, C., & Manconi, M. (2019). Sleep Abnormalities in Multiple Sclerosis. *Current Treatment Options in Neurology*, *21*(1), 4. https://doi.org/10.1007/s11940-019-0544-7

Samuels, E., & Szabadi, E. (2008). Functional Neuroanatomy of the Noradrenergic Locus Coeruleus: Its Roles in the Regulation of Arousal and Autonomic Function Part II: Physiological and Pharmacological Manipulations and Pathological Alterations of Locus Coeruleus Activity in Humans. *Current Neuropharmacology*, *6*(3), 254–285. https://doi.org/10.2174/157015908785777193

Sander, C., Eling, P., Hanken, K., Klein, J., Kastrup, A., & Hilderbrandt, H. (2016). The impact of Ms-related cognitive Fatigue on Future Brain Parenchymal loss and relapse : a 17-Month Follow-up study. *Frontiers in Neurology*, *7*(September). https://doi.org/10.3389/fneur.2016.00155

Sandry, J., Genova, H. M., Dobryakova, E., DeLuca, J., & Wylie, G. (2014). Subjective cognitive fatigue in multiple sclerosis depends on task length. *Frontiers in Neurology*, *5*(OCT), 1–7. https://doi.org/10.3389/fneur.2014.00214

Sanfilipo, M. P., Benedict, R. H. B., Weinstock-Guttman, B., & Bakshi, R. (2006). Gray

and white matter brain atrophy and neuropsychological impairment in multiple sclerosis. *Neurology*, *66*(5), 685–692. https://doi.org/10.1212/01.wnl.0000201238.93586.d9

Santangelo, G., Altieri, M., Gallo, A., & Trojano, L. (2019). Does cognitive reserve play any role in multiple sclerosis? A meta-analytic study. *Multiple Sclerosis and Related Disorders*, *30*(February), 265–276. https://doi.org/10.1016/j.msard.2019.02.017

Scammell, T. E., Arrigoni, E., & Lipton, J. O. (2017, February 22). Neural Circuitry of Wakefulness and Sleep. *Neuron*. Cell Press. https://doi.org/10.1016/j.neuron.2017.01.014

Scheibel, R. S. (2017, August 4). Functional magnetic resonance imaging of cognitive control following traumatic brain injury. *Frontiers in Neurology*. Frontiers Media S.A. https://doi.org/10.3389/fneur.2017.00352

Schmahmann, J. D. (2019). The cerebellum and cognition. *Neuroscience Letters*, *688*(July 2018), 62–75. https://doi.org/10.1016/j.neulet.2018.07.005

Schmidt, P., Gaser, C., Arsic, M., Buck, D., Förschler, A., Berthele, A., … Mühlau, M. (2012). An automated tool for detection of FLAIR-hyperintense white-matter lesions in Multiple Sclerosis. *NeuroImage*, *59*(4), 3774–3783. https://doi.org/10.1016/j.neuroimage.2011.11.032

Schoonheim, M.M., & Geurts, J. J. G. (2019). What Causes Deep Gray Matter Atrophy in Multiple Sclerosis? *American Journal of Neuroradiology*, *40*(1), 107–108. https://doi.org/10.3174/ajnr.A5942

Schoonheim, Menno M., Meijer, K. A., & Geurts, J. J. G. (2015). Network Collapse and Cognitive Impairment in Multiple Sclerosis. *Frontiers in Neurology*, *6*, 82. https://doi.org/10.3389/fneur.2015.00082

Sepulcre, J., Masdeu, J. C., Goñi, J., Arrondo, G., Vélez de Mendizábal, N., Bejarano, B., & Villoslada, P. (2009). Fatigue in multiple sclerosis is associated with the disruption of frontal and parietal pathways. *Multiple Sclerosis*, *15*(3), 337–344.

https://doi.org/10.1177/1352458508098373

Simioni, S., Ruffieux, C., Bruggimann, L., Annoni, J. M., & Schluep, M. (2007). Cognition, mood and fatigue in patients in the early stage of multiple sclerosis. *Swiss Medical Weekly*, *137*(35–36), 496–501. https://doi.org/2007/35/smw-11874

Simmons, R. D. (2010, November). Life issues in multiple sclerosis. *Nature Reviews Neurology*. Nat Rev Neurol. https://doi.org/10.1038/nrneurol.2010.143

Simpson, R., Booth, J., Lawrence, M., Byrne, S., Mair, F., & Mercer, S. (2014). Mindfulness based interventions in multiple sclerosis - a systematic review. *BMC Neurology*, *14*(1), 15. https://doi.org/10.1186/1471-2377-14-15

Simpson, S., Blizzard, L., Otahal, P., Van Der Mei, I., & Taylor, B. (2011). Latitude is significantly associated with the prevalence of multiple sclerosis: A meta-analysis. *Journal of Neurology, Neurosurgery and Psychiatry*, *82*(10), 1132–1141. https://doi.org/10.1136/jnnp.2011.240432

Sisco, S. M., Slonena, E., Okun, M. S., Bowers, D., & Price, C. C. (2016). Parkinson's disease and the Stroop color word test: processing speed and interference algorithms. *Clinical Neuropsychologist*, *30*(7), 1104–1117. https://doi.org/10.1080/13854046.2016.1188989

Sjøgård, M., Wens, V., Van Schependom, J., Costers, L., D'hooghe, M., D'haeseleer, M., … De Tiège, X. (2020). Brain dysconnectivity relates to disability and cognitive impairment in multiple sclerosis. *Human Brain Mapping*, (December 2019), 1–18. https://doi.org/10.1002/hbm.25247

Sjölander, A., & Vansteelandt, S. (2019). Frequentist versus Bayesian approaches to multiple testing. *European Journal of Epidemiology*, *34*(9), 809–821. https://doi.org/10.1007/s10654-019-00517-2

Skarlis, C., & Anagnostouli, M. (2020, April 1). The role of melatonin in Multiple Sclerosis. *Neurological Sciences*. Springer. https://doi.org/10.1007/s10072-019-04137-2

Slater, D. A., Melie-Garcia, L., Preisig, M., Kherif, F., Lutti, A., & Draganski, B. (2019).

Evolution of white matter tract microstructure across the life span. *Human Brain Mapping*, *40*(7), 2252–2268. https://doi.org/10.1002/hbm.24522

Slimani, M., Znazen, H., Bragazzi, N., Zguira, M., & Tod, D. (2018). The Effect of Mental Fatigue on Cognitive and Aerobic Performance in Adolescent Active Endurance Athletes: Insights from a Randomized Counterbalanced, Cross-Over Trial. *Journal of Clinical Medicine*, *7*(12), 510. https://doi.org/10.3390/jcm7120510

Smith, A. (1982). *Symbol Digit Modalities Test (SDMT). Manual (Revised).* Los Angeles: Western Psychological Services.

Sokolov, A. A., Grivaz, P., & Bove, R. (2018, December 1). Cognitive Deficits in Multiple Sclerosis: Recent Advances in Treatment and Neurorehabilitation. *Current Treatment Options in Neurology*. Current Science Inc. https://doi.org/10.1007/s11940-018-0538-x

Sparasci, D., Gobbi, C., Castelnovo, A., Riccitelli, G. C., Disanto, G., Zecca, C., & Manconi, M. (2022). Fatigue, sleepiness and depression in multiple sclerosis: defining the overlaps for a better phenotyping. *Journal of Neurology*, 1–11. https://doi.org/10.1007/s00415-022-11143-

Spielberger, C. D., Gorsuch, R. L., Ushene, R., Vagg, P. R., & Jacobs, G. A. (1983). *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press.

Spiteri, S., Hassa, T., Claros-Salinas, D., Dettmers, C., & Schoenfeld, M. A. (2017). Neural correlates of effort-dependent and effort-independent cognitive fatigue components in patients with multiple sclerosis. *Multiple Sclerosis Journal*, 1–11. https://doi.org/10.1177/1352458517743090

Stampanoni Bassi, M., Mori, F., Buttari, F., Marfia, G. A., Sancesario, A., Centonze, D., & Iezzi, E. (2017). Neurophysiology of synaptic functioning in multiple sclerosis. *Clinical Neurophysiology*, *128*(7), 1148–1157. https://doi.org/10.1016/j.clinph.2017.04.006

Stankiewicz, J. M., Neema, M., & Ceccarelli, A. (2014). Iron and multiple sclerosis.

Neurobiology of Aging. Elsevier Inc. https://doi.org/10.1016/j.neurobiolaging.2014.03.039

Stankoff, B., Freeman, L., Aigrot, M. S., Chardain, A., Dollé, F., Williams, A., … Bottlaender, M. (2011). Imaging central nervous system myelin by positron emission tomography in multiple sclerosis using [methyl-11C]-2-(4-methylaminophenyl)- 6-hydroxybenzothiazole. *Annals of Neurology*, *69*(4), 673–680. https://doi.org/10.1002/ana.22320

Štecková, T., Hluštík, P., Sládková, V., Odstrčil, F., Mareš, J., & Kaňovský, P. (2014). Thalamic atrophy and cognitive impairment in clinically isolated syndrome and multiple sclerosis. *Journal of the Neurological Sciences*, *342*(1–2), 62–68. https://doi.org/10.1016/j.jns.2014.04.026

Steele, S., & Mowry, E. (2014). Etiology. In Lawrence Samkoff & A. Goodman (Eds.), *Multiple Sclerosis and CNS Inflammatory Disordes* (pp. 1–9). Oxford: Wiley.

Stefancin, P., Govindarajan, S. T., Krupp, L., Charvet, L., & Duong, T. Q. (2019). Resting-state functional connectivity networks associated with fatigue in multiple sclerosis with early age onset. *Multiple Sclerosis and Related Disorders*, *31*, 101–105. https://doi.org/10.1016/j.msard.2019.03.020

Stellmann, J. P., Wanke, N., Maarouf, A., Gellißen, S., Heesen, C., Audoin, B., … Poettgen, J. (2021). Cognitive performance shows domain specific associations with regional cortical thickness in multiple sclerosis. *NeuroImage: Clinical*, *30*(January). https://doi.org/10.1016/j.nicl.2021.102606

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society*, *8*(3), 448–460.

Stern, Y. (2009, August). Cognitive reserve. *Neuropsychologia*. NIH Public Access. https://doi.org/10.1016/j.neuropsychologia.2009.03.004

Stern, Y., Arenaza-Urquijo, E. M., Bartrés-Faz, D., Belleville, S., Cantilon, M., Chetelat, G., … Vuoksimaa, E. (2020). Whitepaper: Defining and investigating cognitive

reserve, brain reserve, and brain maintenance. *Alzheimer's & Dementia*, *16*(9), 1305–1311. https://doi.org/10.1016/j.jalz.2018.07.219

Strober, L. B., Bruce, J. M., Arnett, P. A., Alschuler, K. N., DeLuca, J., Chiaravalloti, N., … Román, C. A. F. (2020). Tired of not knowing what that fatigue score means? Normative data of the Modified Fatigue Impact Scale (MFIS). *Multiple Sclerosis and Related Disorders*, *46*, 102576. https://doi.org/10.1016/j.msard.2020.102576

Strober, Lauren B., & Arnett, P. A. (2005). An examination of four models predicting fatigue in multiple sclerosis. *Archives of Clinical Neuropsychology*, *20*(5), 631–646. https://doi.org/10.1016/j.acn.2005.04.002

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology*, *18*(6), 643–662. https://doi.org/10.1037/h0054651

Stüber, C., Morawski, M., Schäfer, A., Labadie, C., Wähnert, M., Leuze, C., … Turner, R. (2014). Myelin and iron concentration in the human brain: A quantitative study of MRI contrast. *NeuroImage*, *93*(P1), 95–106. https://doi.org/10.1016/j.neuroimage.2014.02.026

Stulemeijer, M., Fasotti, L., & Bleijenberg, G. (2005). Fatigue and Stroke. In J. DeLuca (Ed.), *Fatigue as a Windov to the Brain*. Cambridge, MA: MIT Press.

Sumowski, J. F., & Leavitt, V. M. (2013). Cognitive reserve in multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *19*(9), 1122–1127. https://doi.org/10.1177/1352458513498834

Sumowski, J. F., Rocca, M. A., Leavitt, V. M., Dackovic, J., Mesaros, S., Drulovic, J., … Filippi, M. (2014). Brain reserve and cognitive reserve protect against cognitive decline over 4.5 years in MS. *Neurology*, *82*(20), 1776–1783. https://doi.org/10.1212/WNL.0000000000000433

Sumowski, J. F., Rocca, M. A., Leavitt, V. M., Riccitelli, G., Deluca, J., & Filippi, M. (2013). Brain reserve and cognitive reserve in multiple sclerosis: What you've got and how you use it. *Neurology*, *81*(6), 604–604. https://doi.org/10.1212/WNL.0b013e3182a0ef3d

Sumowski, J. F., Rocca, M. A., Leavitt, V. M., Riccitelli, G., Meani, A., Comi, G., & Filippi, M. (2016). Reading, writing, and reserve: Literacy activities are linked to hippocampal volume and memory in multiple sclerosis. *Multiple Sclerosis Journal*, *22*(12), 1621–1625. https://doi.org/10.1177/1352458516630822

Surakka, J., Ruutiainen, J., Romberg, A., Puukka, P., Kronholm, E., & Karanko, H. (2008). Pupillary function in early multiple sclerosis. *Clinical Autonomic Research*, *18*(3), 150–154. https://doi.org/10.1007/s10286-008-0471-2

Tabelow, K., Balteau, E., Ashburner, J., Callaghan, M. F., Draganski, B., Helms, G., … Mohammadi, S. (2019). hMRI – A toolbox for quantitative MRI in neuroscience and clinical research. *NeuroImage*, *194*(December 2018), 191–210. https://doi.org/10.1016/j.neuroimage.2019.01.029

Tajima, S., Yamamoto, S., Tanaka, M., Kataoka, Y., Iwase, M., Yoshikawa, E., … Watanabe, Y. (2010). Medial orbitofrontal cortex is associated with fatigue sensation. *Neurology Research International*, *2010*, 1–6. https://doi.org/10.1155/2010/671421

Tanaka, M. (2015). Effects of Mental Fatigue on Brain Activity and Cognitive Performance: A Magnetoencephalography Study. *Anatomy & Physiology*, *s4*, 0–4. https://doi.org/10.4172/2161-0940.s4-002

Tanaka, M., Ishii, A., & Watanabe, Y. (2014). Neural effects of mental fatigue caused by continuous attention load: A magnetoencephalography study. *Brain Research*, *1561*, 60–66. https://doi.org/10.1016/j.brainres.2014.03.009

Tanaka, M., Shigihara, Y., Funakura, M., Kanai, E., & Watanabe, Y. (2012). Fatigue-associated alterations of cognitive function and electroencephalographic power densities. *PLoS ONE*, *7*(4). https://doi.org/10.1371/journal.pone.0034774

Tanaka, M., & Watanabe, Y. (2012). Supraspinal regulation of physical fatigue. *Neuroscience and Biobehavioral Reviews*, *36*(1), 727–734. https://doi.org/10.1016/j.neubiorev.2011.10.004

Tang, W. K., Chen, Y. K., Mok, V., Chu, W. C. W., Ungvari, G. S., Ahuja, A. T., & Wong,

K. S. (2010). Acute basal ganglia infarcts in poststroke fatigue: An MRI study. *Journal of Neurology*, *257*(2), 178–182. https://doi.org/10.1007/s00415-009-5284-2

Tartaglia, M. C., Narayanan, S., & Arnold, D. L. (2008). Mental fatigue alters the pattern and increases the volume of cerebral activation required for a motor task in multiple sclerosis patients with fatigue. *European Journal of Neurology*, *15*(4), 413–419. https://doi.org/10.1111/j.1468-1331.2008.02090.x

Tedeschi, G., Dinacci, D., Lavorgna, L., Prinster, A., Savettieri, G., Quattrone, A., … Alfano, B. (2007). Correlation between fatigue and brain atrophy and lesion load in multiple sclerosis patients independent of disability. *Journal of the Neurological Sciences*, *263*(1–2), 15–19. https://doi.org/10.1016/j.jns.2007.07.004

Tekok-Kilic, A., Benedict, R. H. B., Weinstock-Guttman, B., Dwyer, M. G., Carone, D., Srinivasaraghavan, B., … Zivadinov, R. (2007). Independent contributions of cortical gray matter atrophy and ventricle enlargement for predicting neuropsychological impairment in multiple sclerosis. *NeuroImage*, *36*(4), 1294–1300. https://doi.org/10.1016/j.neuroimage.2007.04.017

Théaudin, M., & Feinstein, A. (2015). Depression and Multiple Sclerosis: Clinical Aspects, Epidemiology, and Management. In B. Brochet (Ed.), *Neuropsychiatric symptoms of inflammatory demyelinating diseases*. Springer.

Thompson, A. J., Banwell, B. L., Barkhof, F., Carroll, W. M., Coetzee, T., Comi, G., … Cohen, J. A. (2018). Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *The Lancet Neurology*, *17*(2), 162–173. https://doi.org/10.1016/S1474-4422(17)30470-2

Thornton, A. E., Raz, N., & Tucker, K. A. (2002). Memory in multiple sclerosis: Contextual encoding deficits. *Journal of the International Neuropsychological Society*, *8*(3), 395–409. https://doi.org/10.1017/S1355617702813200

Timkova, V., Mikula, P., Fedicova, M., Szilasiova, J., & Nagyova, I. (2021). Psychological well-being in people with multiple sclerosis and its association with illness perception and self-esteem. *Multiple Sclerosis and Related Disorders*, *54*(May),

103114. https://doi.org/10.1016/j.msard.2021.103114

Tomassini, V., Johansen-Berg, H., Leonardi, L., Paixão, L., Jbabdi, S., Palace, J., … Matthews, P. M. (2011). Preservation of motor skill learning in patients with multiple sclerosis. *Multiple Sclerosis Journal*, *17*(1), 103–115. https://doi.org/10.1177/1352458510381257

Tona, F., Petsas, N., Sbardella, E., Prosperini, L., Carmellini, M., Pozzilli, C., & Pantano, P. (2014). Multiple Sclerosis: Altered Thalamic Resting-State Functional Connectivity and Its Effect on Cognitive Function. *Radiology*, *271*(3), 814–821. https://doi.org/10.1148/radiol.14131688

Torrente, F., Yoris, A., Low, D., Lopez, P., Bekinschtein, P., Vázquez, G. H., … Cetkovich, M. (2022). Psychological symptoms, mental fatigue and behavioural adherence after 72 continuous days of strict lockdown during the COVID-19 pandemic in Argentina. *BJPsych Open*, *8*(1). https://doi.org/10.1192/bjo.2021.1065

Torres-Harding, S., & Jason, L. A. (2005). What Is Fatigue? History and Epidemiology. In J. DeLuca (Ed.), *Fatigue as a Windov to the Brain* (pp. 3–17). Cambridge: MIT Press.

Towse, J. N., & Neil, D. (1998). Analyzing human random generation behavior: a review of methods used and a computer program for describing performance. *Behavior Research Methods, Instruments, & Computers*, *30*, 583–591.

Tremblay, A., Charest, K., Brando, E., Roger, E., Duquette, P., & Rouleau, I. (2020). The effects of aging and disease duration on cognition in multiple sclerosis. *Brain and Cognition*, *146*(November), 105650. https://doi.org/10.1016/j.bandc.2020.105650

Trufanov, A., Bisaga, G., Skulyabin, D., Temniy, A., Poplyak, M., Chakchir, O., … Litvinenko, I. (2021). Thalamic nuclei degeneration in multiple sclerosis. *Journal of Clinical Neuroscience*, *89*, 375–380. https://doi.org/10.1016/j.jocn.2021.05.043

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., … Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain.

NeuroImage, *15*(1), 273–289. https://doi.org/10.1006/nimg.2001.0978

Université de Liège. (2017). Normalisation de la version française du test des fluences. *Unpublished Work*.

Val-Laillet, D., Aarts, E., Weber, B., Ferrari, M., Quaresima, V., Stoeckel, L. E., … Stice, E. (2015). Neuroimaging and neuromodulation approaches to study eating behavior and prevent and treat eating disorders and obesity. *NeuroImage: Clinical*. Elsevier Inc. https://doi.org/10.1016/j.nicl.2015.03.016

van As, S., Beckers, D. G. J., Geurts, S. A. E., Kompier, M. A. J., Husain, M., & Veling, H. (2021). The Impact of Cognitive and Physical Effort Exertion on Physical Effort Decisions: A Pilot Experiment. *Frontiers in Psychology*, *12*(November), 1–11. https://doi.org/10.3389/fpsyg.2021.645037

Van Cutsem, J., Marcora, S., De Pauw, K., Bailey, S., Meeusen, R., & Roelands, B. (2017). The Effects of Mental Fatigue on Physical Performance: A Systematic Review. *Sports Medicine*. Springer International Publishing. https://doi.org/10.1007/s40279-016-0672-0

van de Schoot, R., Winter, S. D., Ryan, O., Zondervan-Zwijnenburg, M., & Depaoli, S. (2017). A systematic review of Bayesian articles in psychology: The last 25 years. *Psychological Methods*, *22*(2), 217–239. https://doi.org/10.1037/met0000100

van der Feen, F. E., de Haan, G. A., van der Lijn, I., Huizinga, F., Meilof, J. F., Heersema, D. J., & Heutink, J. (2022). Recognizing visual complaints in people with multiple sclerosis: Prevalence, nature and associations with key characteristics of MS. *Multiple Sclerosis and Related Disorders*, *57*(May 2021), 103429. https://doi.org/10.1016/j.msard.2021.103429

van der Linden, D., Frese, M., & Meijman, T. F. (2003). Mental fatigue and the control of cognitive processes: Effects on perseveration and planning. *Acta Psychologica*. https://doi.org/10.1016/S0001-6918(02)00150-6

Van Egroo, M., Gaggioni, G., Cespedes-Ortiz, C., Ly, J. Q. M., & Vandewalle, G. (2019). Steady-State Pupil Size Varies with Circadian Phase and Sleep Homeostasis in

Healthy Young Men. *Clocks & Sleep*, *1*(2), 240–258. https://doi.org/10.3390/clockssleep1020021

Van Oosterwijck, J., Marusic, U., De Wandele, I., Meeus, M., Paul, L., Lambrecht, L., … Nijs, J. (2021). Reduced parasympathetic reactivation during recovery from exercise in myalgic encephalomyelitis/chronic fatigue syndrome. *Journal of Clinical Medicine*, *10*(19). https://doi.org/10.3390/jcm10194527

Van Ooteghem, P., D'Hooghe, M. B., Vlietinck, R., & Carton, H. (1994). Prevalence of multiple sclerosis in Flanders, Belgium. *Neuroepidemiology*, *13*(5), 220–225. https://doi.org/10.1159/000110383

Veauthier, C. (2015, May 1). Sleep Disorders in Multiple Sclerosis. Review. *Current Neurology and Neuroscience Reports*. Current Medicine Group LLC 1. https://doi.org/10.1007/s11910-015-0546-0

Vissicchio, N. A., Altaras, C., Parker, A., Schneider, S., Portnoy, J. G., Archetti, R., … Foley, F. W. (2019). Relationship between anxiety and cognition in multiple sclerosis: Implications for treatment. *International Journal of MS Care*, *21*(4), 151–156. https://doi.org/10.7224/1537-2073.2018-027

Vleugels, L., Lafosse, C., van Nunen, A. n, Nachtergaele, S., Ketelaer, P., Charlier, M., & Vandenbussche, E. (2000). Visuoperceptual impairment in multiple sclerosis patients diagnosed with neuropsychological tasks. *Multiple Sclerosis Journal*, *6*(4), 241–254. https://doi.org/10.1177/135245850000600406

Vogt, B. A., & Laureys, S. (2005). The Boundaries of Consciousness: Neurobiology and Neuropathology. *Progress in Brain Research*, *150*(05), 205–217. https://doi.org/10.1016/S0079-6123(05)50015-3.Posterior

Volkow, N. D., Fowler, J. S., & Wang, G. J. (1999). Imaging studies on the role of dopamine in cocaine reinforcement and addiction in humans. In *Journal of Psychopharmacology* (Vol. 13, pp. 337–345). SAGE Publications Ltd. https://doi.org/10.1177/026988119901300406

Vukusic, S., Hutchinson, M., Hours, M., Moreau, T., Cortinovis-Tourniaire, P.,

Adeleine, P., & Confavreux, C. (2004). Pregnancy and multiple sclerosis (the PRIMS study): Clinical predictors of post-partum relapse. *Brain*, *127*(6), 1353–1360. https://doi.org/10.1093/brain/awh152

Walker, L. A. S., Berard, J. A., Berrigan, L. I., Rees, L. M., & Freedman, M. S. (2012). Detecting cognitive fatigue in multiple sclerosis: Method matters. *Journal of the Neurological Sciences*, *316*(1–2), 86–92. https://doi.org/10.1016/j.jns.2012.01.021

Wang, C., Ding, M., & Kluger, B. M. (2014). Change in intraindividual variability over time as a key metric for defining performance-based cognitive fatigability. *Brain and Cognition*, *85*(1), 251–258. https://doi.org/10.1016/j.bandc.2014.01.004

Wang, C., Trongnetrpunya, A., Samuel, I. B. H., Ding, M., & Kluger, B. M. (2016). Compensatory Neural Activity in Response to Cognitive Fatigue. *Journal of Neuroscience*, *36*(14), 3919–3924. https://doi.org/10.1523/JNEUROSCI.3652-15.2016

Wang, Y. P., & Gorenstein, C. (2013). Psychometric properties of the Beck Depression Inventory-II: A comprehensive review. *Revista Brasileira de Psiquiatria*, *35*(4), 416–431. https://doi.org/10.1590/1516-4446-2012-1048

Watson, C., Kirkcaldie, M., & Paxinos, G. (2010). *The Brain*. *The Brain*. Elsevier Inc. https://doi.org/10.1016/C2009-0-01579-7

Watson, T. M., Ford, E., Worthington, E., & Lincoln, N. B. (2014). Validation of mood measures for people with multiple sclerosis. *International Journal of MS Care*, *16*(2), 105–109. https://doi.org/10.7224/1537-2073.2013-013

Wechsler, D. (2000). *Wechsler Adults Intelligence Scale WAIS-III*. Paris: Editions du Centre de Psychologie Appliquée.

Weiland, T. J., Jelinek, G. A., Marck, C. H., Hadgkiss, E. J., van der Meer, D. M., Pereira, N. G., & Taylor, K. L. (2015). Clinically Significant Fatigue: Prevalence and Associated Factors in an International Sample of Adults with Multiple Sclerosis Recruited via the Internet. *PLoS ONE*, *10*(2). https://doi.org/10.1371/journal.pone.0115541

Weiskopf, N., & Helms, G. (2008). Multi-parameter mapping of the human brain at 1 mm resolution in less than 20 minutes. In *Proc. Intl. Soc.Magn. Res. Med. 16, 2241*. Toronto.

Weiskopf, Nikolaus, Callaghan, M. F., Josephs, O., Lutti, A., & Mohammadi, S. (2014). Estimating the apparent transverse relaxation time (R2*) from images with different contrasts (ESTATICS) reduces motion artifacts. *Frontiers in Neuroscience*, *8*(SEP), 1–10. https://doi.org/10.3389/fnins.2014.00278

Westfall, P., Johnson, W., & Utts, J. (1997). A Bayesian Perspective on the Bonferroni Adjustment. *Biometrika*, *84*(2).

Whitehouse, C. E., Fisk, J. D., Bernstein, C. N., Berrigan, L. I., Bolton, J. M., Graff, L. A., … Marrie, R. A. (2019). Comorbid anxiety, depression, and cognition in MS and other immune-mediated disorders. *Neurology*, *92*(5). https://doi.org/10.1212/WNL.0000000000006854

Wilting, J., Rolfsnes, H. O., Zimmermann, H., Behrens, M., Fleischer, V., Zipp, F., & Gröger, A. (2016). Structural correlates for fatigue in early relapsing remitting multiple sclerosis. *European Radiology*, *26*(2), 515–523. https://doi.org/10.1007/s00330-015-3857-2

Wingerchuk, D. M. (2012). Smoking: effects on multiple sclerosis susceptibility and disease progression. *Therapeutic Advances in Neurological Disorders*, *5*(1), 13–22. https://doi.org/10.1177/1756285611425694

Yaldizli, Ö., Glassl, S., Sturm, D., Papadopoulou, A., Gass, A., Tettenborn, B., & Putzki, N. (2011). Fatigue and progression of corpus callosum atrophy in multiple sclerosis. *Journal of Neurology*, *258*(12), 2199–2205. https://doi.org/10.1007/s00415-011-6091-0

Yang, T. ting, Wang, L., Deng, X. yang, & Yu, G. (2017). Pharmacological treatments for fatigue in patients with multiple sclerosis: A systematic review and meta-analysis. *Journal of the Neurological Sciences*, *380*, 256–261. https://doi.org/10.1016/j.jns.2017.07.042

Young, C. A., Mills, R., Rog, D., Sharrack, B., Majeed, T., Constantinescu, C. S., … Tennant, A. (2021). Quality of life in multiple sclerosis is dominated by fatigue, disability and self-efficacy. *Journal of the Neurological Sciences*, *426*(April), 117437. https://doi.org/10.1016/j.jns.2021.117437

Yu, H. J., Christodoulou, C., Bhise, V., Greenblatt, D., Patel, Y., Serafin, D., … Wagshul, M. E. (2012). Multiple white matter tract abnormalities underlie cognitive impairment in RRMS. *NeuroImage*, *59*(4), 3713–3722. https://doi.org/10.1016/j.neuroimage.2011.10.053

Zellini, F., Niepel, G., Tench, C. R., & Constantinescu, C. S. (2009). Hypothalamic involvement assessed by T1 relaxation time in patients with relapsing - Remitting multiple sclerosis. *Multiple Sclerosis*, *15*(12), 1442–1449. https://doi.org/10.1177/1352458509350306

Zénon, A. (2019). Eye pupil signals information gain. *Proceedings of the Royal Society B: Biological Sciences*, *286*(1911), 0–1. https://doi.org/10.1098/rspb.2019.1593

Zénon, A., Devesse, S., & Olivier, E. (2016). Dopamine manipulation affects response vigor independently of opportunity cost. *Journal of Neuroscience*, *36*(37), 9516–9525. https://doi.org/10.1523/JNEUROSCI.4467-15.2016

Zigmond, A. S., & Snaith, R. P. (1983). The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica*, *67*(6), 361–370. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x

Zimmermann, P., & Fimm, B. (2010). *Test of Attentional Performance, Version 2.3.1*. Herzogenrath, Germany: Psytest.

Zivadinov, R. (2007). Can imaging techniques measure neuroprotection and remyelination in multiple sclerosis? In *Neurology* (Vol. 68). Neurology. https://doi.org/10.1212/01.wnl.0000275236.51129.d2

Fatigue is one of the most frequent and disabling symptom of Multiple Sclerosis (MS). Despite its incidence, the underlying mechanisms of MS-related fatigue are not completely elucidated. This is particularly the case of cognitive fatigue (i.e. interfering with mental work) occurring in the early stages of the disease, even in patients showing mild lesion load and disability. The theoretical part of the thesis start with a description of MS disease, with a particular emphasis on cognitive symptoms. The concept of fatigue is introduced and defined. Several models of cognitive fatigue in healthy subjects and in neurological populations are developed, as well as the different methods used to study cognitive fatigue. Finally, the introduction of this work ends with a focus on cognitive fatigue in the context of MS.

In the experimental section, the objectives and hypotheses of this thesis are described, before moving forward with the six studies carried out in this framework, which explores cognitive fatigue in the early stages of MS and in healthy controls from a cognitive, physiological (eye metrics) and cerebral perspectives. Namely, four research questions are considered across the studies:

(i) Is there a link between fatigue and cognition in MS? (Studies 1 & 2)
(ii) What are the effects of long-lasting procedures and cognitive load on cognitive fatigue and which procedure triggers fatigue the most? (Studies 3 & 4)
(iii) Can eye metrics provide an objective measure of fatigue state? (Study 3)
(iv) What are the functional and structural cerebral substrates of cognitive fatigue in the early stages of the disease? (Studies 5 & 6)

Results obtained are further discussed addressing these main questions, the limitations of this work, and future directions that could be taken to expand our findings. Overall, five specific, but not mutually exclusive, causes of cognitive fatigue in early MS were proposed and discussed in the light of our results: decrease in motivation, increased perception of effort, decreased arousal, extra effort due to cognitive deficits and costly brain functional reorganization due to structural alterations.