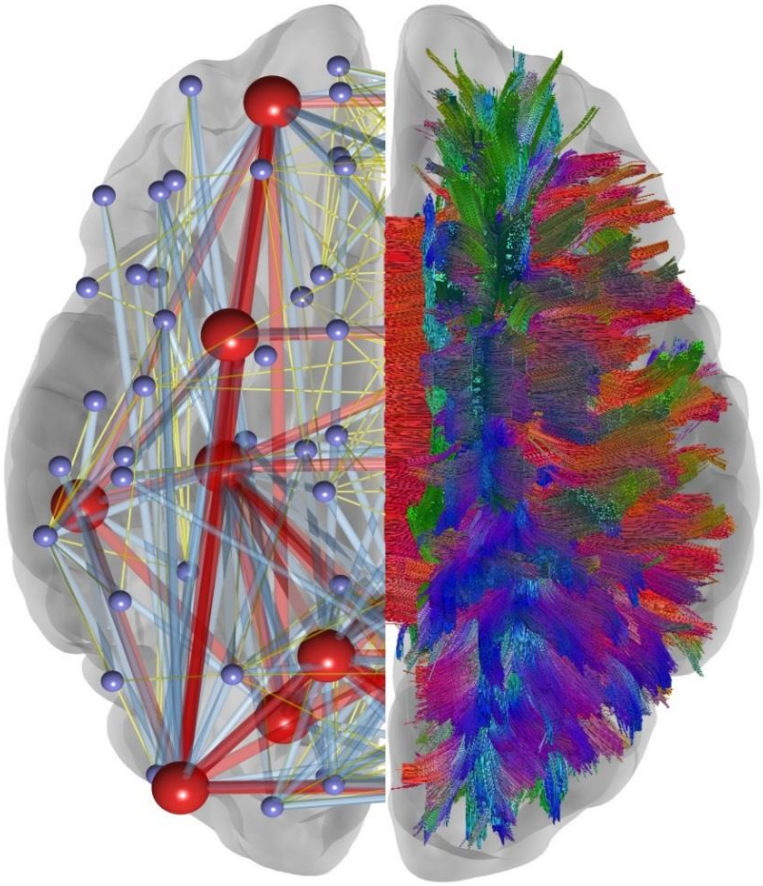
Effects of an integrative group-based cognitive rehabilitation on cognition and brain connectivity in multiple sclerosis

Oihane Rilo Cano

Directors:

Dr. Naroa Ibarretxe Bilbao

Dr. Natalia Ojeda del Pozo



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Neuropsychology of Severe Medical Conditions

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Effects of an integrative group-based cognitive rehabilitation on cognition and brain connectivity in multiple sclerosis

Doctoral thesis presented by Oihane Rilo Cano,

To obtain the degree of Doctor of Psychology by the University of Deusto

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Oihane Rilo Cano

Director 1, **Director 2,**

Dr. Naroa Ibarretxe Bilbao **Dr. Natalia Ojeda del Pozo**

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This thesis has been carried out in the Research Group of Neuropsychology of Severe Medical Conditions, in the Faculty of Psychology and Education, University of Deusto. This group has been qualified with the maximum research label awarded by the Basque Government (Category A-Excellence).

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Dr. Naroa Ibarretxe Bilbao, director of the Master in Clinical Neuropsychology, assistant professor of the Department of Methods and Experimental Psychology, director 1 of the present thesis; and Dr. Natalia Ojeda del Pozo, principal investigator of the Neuropsychology of Severe Medical Conditions research team, head and aggregate professor of the Department of Methods and Experimental Psychology, director 2 of the present thesis, certify that the present thesis entitled "Effects of an integrative group-based cognitive rehabilitation on cognition and brain connectivity in multiple sclerosis", represents an original research work, which is presented by Oihane Rilo Cano to obtain the degree of Doctor of Psychology.

Director 1,

Director 2,

Dr. Naroa Ibarretxe Bilbao

Dr. Natalia Ojeda del Pozo

Bilbao, December 2018

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"In expanding the field of knowledge we but increase the horizon of ignorance" – "Al expandir el campo del conocimiento no hacemos más que ampliar el horizonte de la ignorancia" (Henry Miller).

Contents

Foreword

The present thesis has been presented to obtain the degree of Doctor of Psychology by the University of Deusto and is the result of three studies conducted in the Neuropsychology of Severe Medical Conditions research group, at the Department of Methods and Experimental Psychology, Faculty of Psychology and Education, University of Deusto.

Study I

Rilo, O., Ibarretxe-Bilbao, N., Peña, J., Mendibe-Bilbao, M., Rodríguez-Antigüedad, A., Gómez-Gastiasoro, A., DeLuca, J., Chiaravalloti, N., and Ojeda, N. The role of processing speed in multiple sclerosis cognitive impairment (under review).

Study II

Rilo, O., Peña, J., Ojeda, N., Rodríguez-Antigüedad, A., Mendibe-Bilbao, M., Gómez-Gastiasoro, A., DeLuca, J., Chiaravalloti, N., and Ibarretxe-Bilbao, N. (2018). Integrative group-based cognitive rehabilitation efficacy in multiple sclerosis: A randomized clinical trial. *Disability and Rehabilitation*, *40*(2), 208-216. doi: 10.1080/09638288.2016.1250168

Study III

Rilo, O., Ojeda, N., Peña, J., Cabrera, A., Rodríguez-Antigüedad, A., Mendibe-Bilbao, M., Gómez-Gastiasoro, A., DeLuca, J., Chiaravalloti, N., and Ibarretxe-Bilbao, N. Effects of an integrative group-based cognitive rehabilitation on brain connectivity in multiple sclerosis: A randomized clinical trial (in preparation).

Glossary of abbreviations

aCompCor = anatomical component correction

AD = axial diffusivity

ADEMBI = Multiple Sclerosis Association of Biscay

BD = Backward Digits Subtest

BET = brain extraction tool

BTA = Brief Test of Attention

BVMT-R = Brief Visual Memory Test – Revised

CIFA = Calibrated Ideational Fluency Assessment

CIS = clinically isolated syndrome

CNS = central nervous system

DAN = dorsal attention network

DMN = default mode network

DWI = diffusion weighted imaging

ECN = executive control network

EDSS = Expanded Disability Status Scale

EDSS LAS = Limb Ataxia Scale of the Expanded Disability Status Scale

FA = fractional anisotropy

FDR = false discovery rate

FMRIB = Functional Magnetic Resonance Imaging of the Brain

FSL = FMRIB software library

FSS = Fatigue Severity Scale

FWHM = full-width at half-maximum

GDS = Geriatric Depression Scale

HC = healthy controls

HLA = human leukocyte antigen

HMN = hippocampal memory network

HVLT-R = Hopkins Verbal Learning Test - Revised

IADLs = Lawton Instrumental Activities of Daily Living Scale

LCT = Letters Comparison Test

MANCOVA = multivariate analysis of covariance

MANOVA = multivariate analysis of variance

MD = mean diffusivity

MMSE = Mini Mental State Examination Test

MNI = Montreal Neurological Institute

MRC = British Medical Research Council Scale

MRI = magnetic resonance imaging

MS = multiple sclerosis

PASAT = Paced Auditory Serial Addition Test

PPMS = primary progressive multiple sclerosis

RD = radial diffusivity

ROIs = regions of interest

RRMS = relapsing-remitting multiple sclerosis

RCT = randomized clinical trial

Rs-fMRI = resting-state functional magnetic resonance imaging

SDMT = Symbol Digit Modalities Test

SN = salience network

SPMS = secondary progressive multiple sclerosis

SPSS = Statistical Software Package for Social Sciences

SST = Strange Stories Test

ST = Stroop Color and Word Test

TAP = Word Accentuation Test

TBSS = Tract-Based Spatial Statistics

TFCE = threshold-free cluster enhancement

TMT-A = Trail Making Test - A

TMT-B = Trail Making Test - B

VAS = Visual Analogue Scale

WAIS-III = Wechsler Adult Intelligence Scale III

WCST = Wisconsin Card Sorting Test

I. Abstract

1. Abstract

1.1. Abstract

People with multiple sclerosis (MS) may present deficits across a broad range of cognitive domains. Processing speed decline is one of the most common cognitive deficits in the disorder, and it can adversely affect the functioning of other cognitive processes. However, it is still unclear whether the distinct MS cognitive deficits occur as a result of processing speed decline or constitute independent deficits regardless of processing speed decline. On the other side, cognitive rehabilitation might be a promising therapeutic approach for addressing cognitive deficits in persons with MS. Nevertheless, further methodologically rigorous randomized clinical trials (RCTs) are required to attain a greater level of evidence for its efficacy in the disorder. Moreover, the neurobiological mechanisms underlying cognitive improvements following cognitive interventions are not yet entirely understood.

The present research consists of three studies. The objective of the *first study* was to investigate the role of processing speed decline in other MS cognitive deficits. The *second study* aimed to assess the efficacy of an integrative group-based cognitive rehabilitation programme on improving cognitive functioning and daily functionality in persons with MS. The *third study* was targeted at examining brain functional and structural connectivity changes in response to the cognitive rehabilitation in MS, as well as the relationship between brain connectivity changes and cognitive improvements following the intervention.

The results of the *first study* showed the presence of significant deficits in diverse cognitive domains (attention, processing speed, episodic memory, verbal fluency, and executive functioning) in people with MS; however these deficits became non-significant once the effect of processing speed was controlled. The results of the *second study* revealed significant cognitive improvements involving several domains (processing speed, working memory, episodic memory and executive functioning) in those persons with MS attending the

cognitive rehabilitation. Finally, the *third study* showed that persons with MS also experienced significant brain functional connectivity decreases within the default mode network (DMN) and the hippocampal memory network (HMN) in response to the cognitive rehabilitation. Additionally, these functional connectivity decreases were significantly associated with some of the cognitive improvements detected following the intervention.

In conclusion, present findings support that processing speed decline may to a large extent lie beneath other cognitive deficits in MS, underscoring the need for identifying the precise source of these deficits to better-inform intervention decisions. Furthermore, the findings of this research provide evidence for the efficacy of integrative group-based cognitive rehabilitations in MS, suggesting that this therapeutic approach can not only improve cognitive functioning but also induce adaptive brain functional connectivity changes in persons with the disorder.

Keywords: multiple sclerosis, cognitive impairment, processing speed, daily functionality, cognitive rehabilitation, magnetic resonance, brain plasticity, brain connectivity.

1.2. Resumen

Las personas con esclerosis múltiple (EM) pueden presentar déficits en un amplio abanico de dominios cognitivos. El deterioro de la velocidad de procesamiento es uno de los déficits cognitivos más comunes en esta patología, y puede afectar negativamente al funcionamiento de otros procesos cognitivos. Sin embargo, aún se desconoce si los distintos déficits cognitivos en la EM ocurren como resultado del deterioro de la velocidad de procesamiento, o si constituyen déficits diferenciados e independientes del deterioro de la velocidad de procesamiento. Por otro lado, la rehabilitación cognitiva podría ser una aproximación terapéutica prometedora para el tratamiento de los déficits cognitivos en personas con EM. No obstante, se requieren nuevos ensayos clínicos aleatorizados metodológicamente rigurosos para conseguir un mayor nivel de evidencia a favor de su eficacia en esta patología. Además, los mecanismos neurobiológicos que subyacen a la mejora cognitiva tras la implementación de una intervención cognitiva todavía no se comprenden en su totalidad.

La presente investigación se compone de tres estudios. El objetivo del *primer estudio* consistió en investigar el rol del deterioro de la velocidad de procesamiento en otros déficits cognitivos en la EM. El *segundo estudio* tuvo por objeto evaluar la eficacia de un programa de rehabilitación cognitiva integral aplicado en formato grupal en la mejora del funcionamiento cognitivo y la capacidad funcional de las personas con EM. El *tercer estudio* se centró en examinar cambios cerebrales en conectividad funcional y estructural en respuesta a la rehabilitación cognitiva en personas con EM, así como la relación entre los cambios en conectividad y las mejoras cognitivas observadas tras la intervención.

Los resultados del *primer estudio* mostraron la presencia de déficits significativos en diversos dominios cognitivos (atención, velocidad de procesamiento, memoria episódica, fluidez verbal y funcionamiento ejecutivo) en personas con EM. Sin embargo, estos déficits

dejaron de ser significativos una vez se controló por el efecto de la velocidad de procesamiento. Por otro lado, los resultados del *segundo estudio* revelaron mejoras cognitivas estadísticamente significativas en varios dominios cognitivos (velocidad de procesamiento, memoria de trabajo, memoria episódica y funcionamiento ejecutivo) en aquellas personas con EM que acudieron a rehabilitación cognitiva. En último lugar, el *tercer estudio* mostró que las personas con EM también presentaron reducciones significativas en la conectividad funcional cerebral de la red neuronal por defecto (RND) y la red de memoria hipocampal (RMH) en respuesta a la rehabilitación cognitiva. Además, estas reducciones en la conectividad funcional se asociaron significativamente con algunas de las mejoras cognitivas detectadas tras la intervención.

En conclusión, los hallazgos encontrados sostienen que el deterioro de la velocidad de procesamiento puede subyacer en gran medida a otros déficits cognitivos en la EM, lo que pone de manifiesto la necesidad de identificar el origen exacto de estos déficits con el fin de mejorar la toma de decisiones de carácter terapéutico. Asimismo, los hallazgos de esta investigación proporcionan evidencia a favor de la eficacia de la rehabilitación cognitiva integral aplicada en formato grupal en la EM, sugiriendo que esta aproximación terapéutica no solamente puede mejorar el funcionamiento cognitivo, sino también inducir cambios cerebrales adaptativos en la conectividad funcional de las personas que presentan esta patología.

Palabras clave: esclerosis múltiple, deterioro cognitivo, velocidad de procesamiento, capacidad funcional, rehabilitación cognitiva, resonancia magnética, plasticidad cerebral, conectividad cerebral.

II. Background

2. Background

2.1. Multiple sclerosis: a brief overview

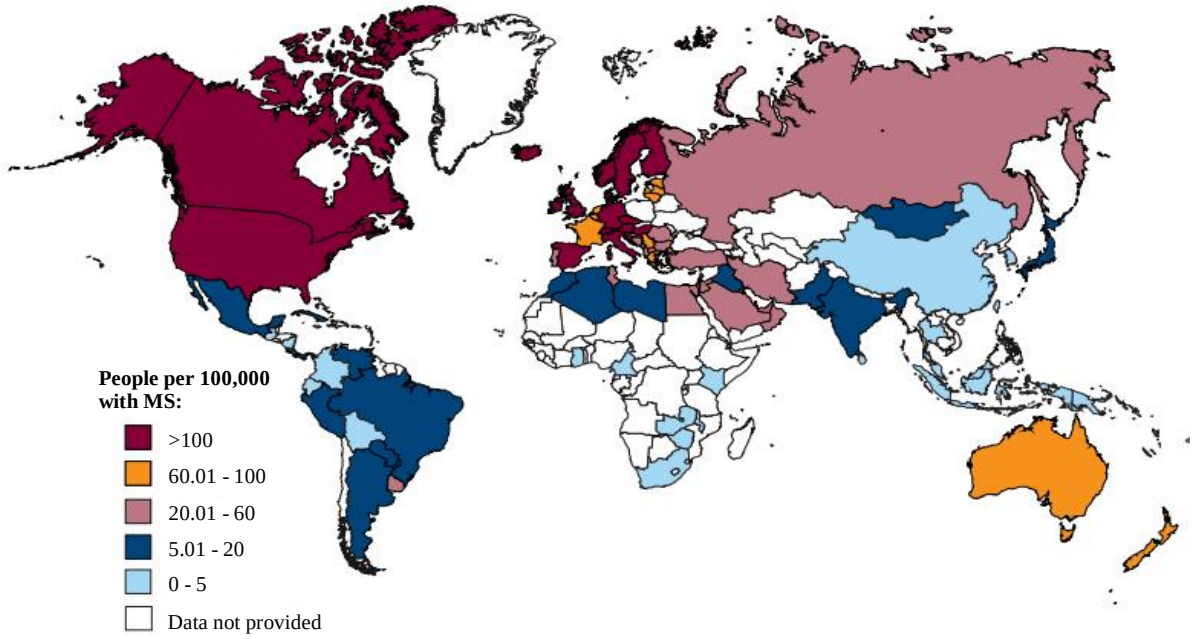
Multiple sclerosis (MS) is a chronic, autoimmune, and neurodegenerative disorder affecting the central nervous system (CNS). This disorder is mainly characterized by recurrent episodes of focal inflammatory demyelination, which lead to a growing burden of axonal damage, and the formation of accumulative sclerotic plaques spatially segregated in the brain and the spinal cord (Compston & Coles, 2008). MS is considered as the most common cause of non-traumatic neurological disability in young adults (Sociedad Española de Neurología, 2017). The onset of the disease frequently occurs around 30 years of age, and it is more prevalent among women than men, with an approximate ratio of 2:1 (Multiple Sclerosis International Federation, 2013).

Over 2.3 million persons suffer from MS worldwide. The prevalence of this disorder is heterogeneous depending on the geographical location (Figure 1) (Multiple Sclerosis International Federation, 2013). In Spain it is estimated that 47.000 persons are affected by MS, and roughly 1.800 new cases are diagnosed each year (Sociedad Española de Neurología, 2017).

MS has been traditionally considered as a motor disorder. Nevertheless, it may result in a broad range of clinical manifestations, including motor, sensory, cognitive and neuropsychiatric alterations (Compston & Coles, 2008; Murphy et al., 2017). Thus, MS motor symptoms and signs involve limb weakness, paresis, spasticity, tremor, depression of tendon reflexes, muscle wasting, peripheral neuropathies, ataxia, dysarthria, eye movement disorders, physical fatigue, etc. (McAlpine & Compston, 2005). Sensory problems include the occurrence of paresthesia, diplopia, visual, auditory, olfactory and taste loss, acute and chronic pain syndromes, as well as the Lhermitte's symptom, among others (McAlpine & Compston, 2005). Cognitive difficulties commonly involve deficits in attention, information

processing, memory, verbal fluency, and/or executive functioning (Chiaravalloti, N. D. & DeLuca, 2008). Finally, several neuropsychiatric alterations such as depressive, anxiety, bipolar or psychotic disorders have also been described in association to MS (Murphy et al., 2017).

Figure 1. Worldwide MS prevalence distribution.



MS = multiple sclerosis. Figure obtained from the Multiple Sclerosis International Federation (2013).

2.2. Phenotypes

Three MS phenotypes have been defined according to the distinct clinical courses observed in the disorder (Lublin et al., 2014). *Relapsing-remitting MS* (RRMS) is the most common phenotype, as it is presented by 85% of persons at the disease onset (Multiple Sclerosis International Federation, 2013). RRMS is characterized by the occurrence of clinical worsening episodes, or relapses, followed by a variable degree of recovery and a stable course between episodes (Lublin, Reingold, & National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis, 1996;

Lublin et al., 2014). These relapses take place because of the inflammation and demyelination of focal areas within the CNS, which are commonly identified as gray or white matter lesions through magnetic resonance imaging (MRI) (Dendrou, Fugger, & Friese, 2015).

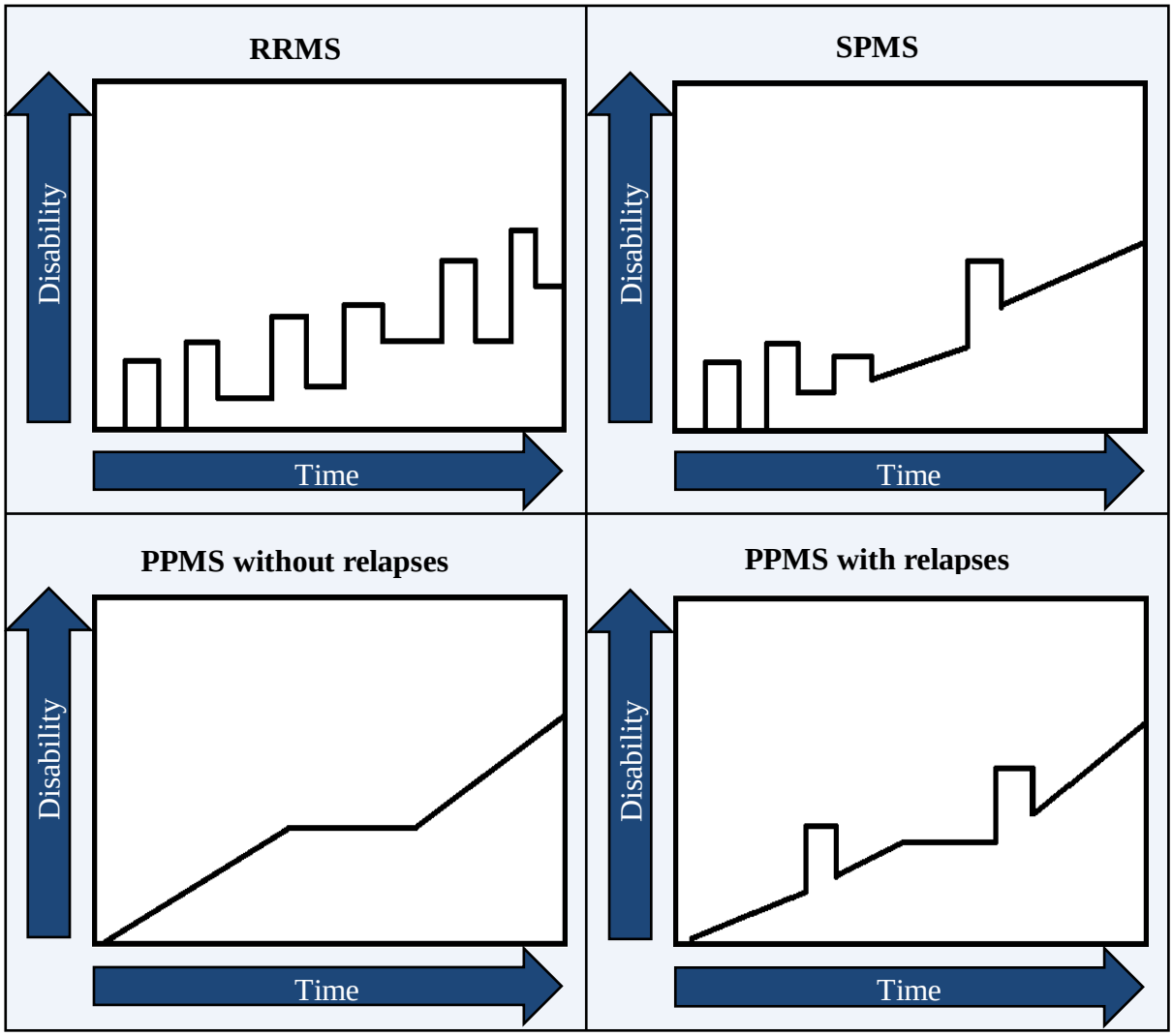
Secondary-progressive MS (SPMS) is determined by the development of a progressive MS form in persons that initially presented RRMS. It is outlined by a nearly continuous clinical worsening, in the presence or absence of relapses (Lublin et al., 1996; Lublin et al., 2014), which is mainly caused by the progressive atrophy of the CNS (Dendrou et al., 2015). Approximately, 80% of persons with RRMS develop into a progressive course at around 40 years of age (Multiple Sclerosis International Federation, 2013).

The disease can also present a progressive course from the onset, as occurs in about 15% of persons with MS (Multiple Sclerosis International Federation, 2013). This MS phenotype is referred to as *primary-progressive MS* (PPMS) and is defined by a gradual clinical worsening course, although periods of stability may also occur (Lublin et al., 1996; Lublin et al., 2014). In 5% of persons with PPMS this progressive worsening is also accompanied with acute relapses, which may present a variable degree of recovery (Lublin et al., 1996). A graphic representation of the clinical course characterizing each MS phenotype is shown in Figure 2.

2.3. Etiology

The cause of MS is considered to be multifactorial. Both genetic and environmental risk factors for the development of the disorder have been identified. The interaction between these factors seems to play a relevant role in the understanding of MS development. Nevertheless, the precise etiology of this condition still remains undefined (Alfredsson & Olsson, 2018; Leray, Moreau, Fromont, & Edan, 2016; Olsson, Barcellos, & Alfredsson, 2017).

Figure 2. Graphic representation of the clinical course characterizing each MS phenotype.



RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; PPMS = primary progressive multiple sclerosis.

Genetic factors have been estimated to account for approximately 30% of the risk of presenting MS. To date, over 100 genes have been associated with the development of the disorder, and most of them are thought to play an immunological role within the organism (Dendrou et al., 2015). A polygenic model, in which MS genetic risk is defined by the combination of the effect of a single allele with moderate influence and several alleles with a small influence has been proposed (Leray et al., 2016). Genes within the human leukocyte antigen (HLA) complex are considered as the most relevant genetic risk factors of MS. Thereby, HLA class I and class II genes encode the products that present antigens to CD4+ T

and CD8+ T lymphocytes, respectively. Specifically, the class I variant HLA-A*02 would protect against the development of the disorder, while the class II variant HLA-DRB1*15:01 has been strongly related to an enhanced risk of MS (Dendrou et al., 2015). In addition, genome wide association studies have also found multiple non-HLA single nucleotide polymorphisms with IL7R and IL2RA genes that are modestly associated with MS (Leray et al., 2016; Olsson et al., 2017).

Life style and environmental factors are critical contributors to MS development. Among the explored risk factors, the infection with Epstein-Barr virus during adolescence or later in life has been reported to present the strongest association to MS (Alfredsson & Olsson, 2018; Leray et al., 2016; Olsson et al., 2017). Nevertheless, the mechanism by which this virus could promote the development of MS is not yet entirely understood (Alfredsson & Olsson, 2018; Olsson et al., 2017). Moreover, MS prevalence appears to increase the further the distance to the equator (Figure 1), which might be explained by a lesser sun exposure in these regions and the consequent reduction of vitamin D levels within the organism (Leray et al., 2016). However, the MS prevalence presented in some locations do not conform to that theory, so the notion of specific areas with low and high MS prevalence, instead of a gradual change in MS prevalence depending on the latitude might be more accurate (Leray et al., 2016).

In addition, migration studies have shown that when migratory movements take place from high to low MS risk regions at young ages (less than 15 years of age) emigrants exhibit a lower risk for developing the disorder than expected according to their origin country, while if the migration occurs at older ages the risk presented by the population of the origin country is retained (Berg-Hansen & Celius, 2015; Compston & Coles, 2008). Heterogeneous results have been obtained regarding migratory movements from low to high MS risk regions. Traditionally, these studies have reported no changes in the risk for developing the disorder;

however, some recent studies have revealed an increased MS risk in these emigrants in the absence of such a specific influence of the age of migration (Berg-Hansen & Celius, 2015; Compston & Coles, 2008). Accordingly, findings derived from migration studies seem to point out the special influence that life style and environmental factors can exert on the development of MS.

Moreover, obesity during adolescence has been found to increase the risk for developing MS, being this increase more pronounced in persons with a body mass index above 27 (Alfredsson & Olsson, 2018). A modest association has also been observed between smoking cigarettes and MS susceptibility (Alfredsson & Olsson, 2018; Leray et al., 2016; Olsson et al., 2017). Specifically, it has been suggested that lung irritation, as a result of smoking, might produce immune responses to biological components and organ-specific inflammatory diseases (Olsson et al., 2017). On the other side, infection with cytomegalovirus has been associated to a reduced risk of MS (Olsson et al., 2017). Some studies have also suggested that oral tobacco, alcohol and coffee consumption could play a protective role against MS, whereas passive smoking, salt intake and organic solvent exposure might constitute potential triggers of the disorder. Nonetheless, further research is particularly needed in this respect (Leray et al., 2016; Olsson et al., 2017).

2.4. Neuropathology

The neuropathology of MS constitutes a very complex issue that has not yet been fully elucidated. Actually, two distinct neuropathological theories have been suggested to underlie MS, referred to as the Outside-In and the Inside-Out model (Bhise & Dhib-Jalbut, 2016; Dendrou et al., 2015).

The *Outside-In model* proposes that MS is initiated by an immunological dysregulation of the peripheral nervous system, which is characterized by the activation of

myelin-reactive auto-T cells. These cells would overcome the blood-brain barrier and invade the CNS, giving rise to an inflammatory reaction. Subsequently, this reaction would promote a primary demyelination process, resulting in a secondary axonal degeneration. Finally, this pathological process would lead to the development of demyelinated white and gray matter lesions (or plaques) within the CNS (Bhise & Dhib-Jalbut, 2016; Dendrou et al., 2015). It must be noted that according to this theory (Outside-In model), lesions would develop from the outside (myelin) to the inside (axons) (Peterson & Fujinami, 2007).

Conversely, the *Inside-Out model* suggests that MS pathology is initiated due to a primary neuronal or axonal degeneration within the CNS. This degeneration would subsequently promote the recruitment of myelin-reactive auto-T cells along the damaged axon, which, in turn, would result in a secondary axonal demyelination. Finally, this pathological process would also lead to the development of demyelinated white and gray matter plaques within the CNS. It must be noted that according to this theory (Inside-Out model), lesions would develop from the inside (axons) to the outside (myelin) (Peterson & Fujinami, 2007; Sato et al., 2015).

Even though evidences in favor of both models have been obtained, the Outside-In model has received the greatest experimental and clinical support to date (Bhise & Dhib-Jalbut, 2016). In this regard, it should be mentioned that the Inside-Out model has been more recently proposed and, thereby, additional evidences in its favor might be obtained in the forthcoming years. In any event, it is still unclear whether only one or both models could initiate MS, as well as if both models might contribute to MS pathology regardless of which one triggers the disorder (Calabrese et al., 2015; Kamm, Uitdehaag, & Polman, 2014; Peterson & Fujinami, 2007).

2.4.1. Brain lesions

White and gray matter demyelinated lesions are recognized as the pathological hallmark of MS (Lassmann, 2018). These lesions are especially prone to arise in periventricular, juxtacortical and infratentorial regions of the brain as well as in the spinal cord (Brownlee, Hardy, Fazekas, & Miller, 2017).

Several types of *white matter lesions* can be distinguished in the MS brain according to their histological characteristics (Filippi, Rocca et al., 2012; Lassmann, 2018). Acute active lesions are strongly infiltrated by macrophages, microglia, T cells, astrocytes and new oligodendrocytes (Filippi, Rocca et al., 2012; Olsen & Akirav, 2015). Macrophages, microglia and T cells segregate proinflammatory cytokines that have an important role in demyelination and oligodendrocytes death (Olsen & Akirav, 2015). Macrophages are distributed across the entire lesion and commonly contain myelin debris in consequence of phagocytosis processes (Olsen & Akirav, 2015). New oligodendrocytes can also be present in lesions with signs of remyelination (Filippi, Rocca et al., 2012; Olsen & Akirav, 2015). Chronic active lesions are more sharply circumscribed than acute active lesions. Within these lesions macrophages are specially accumulated at the expanding edge of the plaque, diminishing their amount toward the lesion inactive center. Acute and chronic active lesions are more frequent in RRMS than in other clinical phenotypes of the disorder, and seem to represent the pathological substrate of abrupt clinical worsening episodes in RRMS (Filippi, Rocca et al., 2012; Lassmann, 2018).

Smouldering lesions are characterized by an inactive demyelinated center and a slowly expanding edge that is infiltrated only by few myelin-landen macrophages (Filippi, Rocca et al., 2012; Lassmann, 2018). These lesions contribute to the progressive deterioration associated with the disorder (Filippi, Rocca et al., 2012). Finally, chronic inactive lesions are clearly outlined and completely demyelinated, showing a significant loss of oligodendrocytes,

a variable degree of axonal loss, and a minor infiltration or an absence of macrophages (Filippi, Rocca et al., 2012; Lassmann, 2018; Popescu, Pirko, & Lucchinetti, 2013). Within these lesions astrocytes produce glial fibers that fill in the space between demyelinated axons resulting in the formation of glial scars (Popescu et al., 2013). Both smouldering and inactive chronic lesions are more frequent in the progressive courses of MS (Filippi, Rocca et al., 2012; Lassmann, 2018).

With regards to *gray matter lesions*, the loss of oligodendrocytes and the consequent demyelination is also their main characteristic. This demyelination process is accompanied by a variable degree of axonal, neuronal, glial and synaptic loss. The main histological difference between gray and white matter lesions is that in the former the degree of T-cell inflammation, macrophages and microglial activation is noticeably lower (Filippi, Rocca et al., 2012; Lassmann, 2018). These lesions can be present in the cerebral and cerebellar cortex, the deep gray matter of the brain, and the spinal cord (Lassmann, 2018). Three main types of cortical lesions have been identified according to their location in the brain. Specifically, type 1 lesions would be located in the cortico-subcortical edges of the brain (affecting both gray and white matter tissue), type 2 lesions in the intracortical perivenous regions and type 3 lesions in the subpial layers of the cerebral cortex (Lassmann, 2018).

2.4.2. Brain remyelination

As previously stated, remyelination processes also take place in the MS brain. Brain remyelinated lesions, named shadow plaques, are highly demarcated from the surrounding brain tissue. Within these plaques, remyelinated axons present thinner and shorter myelin sheaths when compared to healthy axons (Lassmann, 2018). Despite this, the new sheaths are usually able to restore normal impulse conduction (Olsen & Akirav, 2015). Remyelination processes are specifically accomplished by new stem cell-derived oligodendrocytes.

Accordingly, the amount of brain remyelination is limited by the depletion of new oligodendrocytes as a result of previous extensive rounds of remyelination. Other factors that also restrict MS brain remyelination include the formation of glial scars that block the migration of new oligodendrocytes to demyelinated axons or a high degree of axonal damage that impedes axons association with myelin (Lassmann, 2018; Olsen & Akirav, 2015).

2.4.3. Normal-appearing white and gray matter

Even though focal lesions constitute the main feature of MS pathology, diffuse abnormalities within the macroscopically normal appearing white and gray matter have also been detected. Thus, normal-appearing white matter is histopathologically characterized by the presence of diffuse demyelination, axonal loss, macrophages, microglia and astrocytic gliosis (Filippi, Rocca et al., 2012; Lassmann, 2018). On another note, normal appearing gray matter also presents demyelination and neuronal loss (Klaver et al., 2015). These pathological abnormalities within the normal appearing brain tissue are to some extent caused by anterograde and retrograde degeneration mechanisms that are secondary to the neuronal and axonal damage within focal lesions. However, other mechanisms seem to be implicated in diffuse brain damage, since it also progresses with independence of focal lesions (Lassmann, 2018).

2.4.4. Brain atrophy

The progressive loss of brain volume also constitutes a relevant pathological feature of MS (Filippi, Rocca et al., 2012; Rocca, M. A. et al., 2017). It is estimated that persons with MS experience a whole brain volume loss of between 0.5% and 1.5% per year (Vollmer et al., 2016). Brain atrophy has been noticed at every stages of the disorder, which challenges the traditional notion that brain atrophy only occurs in advanced stages of MS (Rocca, M. A.

et al., 2017; Sastre-Garriga, Pareto, & Rovira, 2017). Both white and gray matter volume loss contribute to overall brain atrophy (DeLuca, G. C., Yates, Beale, & Morrow, 2015; Preziosa et al., 2016; Sastre-Garriga et al., 2017). Moreover, gray matter atrophy has been found to affect the cerebral cortex as well as diverse subcortical structures such as the thalamus, the hippocampus and the basal ganglia (DeLuca, G. C. et al., 2015; Preziosa et al., 2016; Sastre-Garriga et al., 2017).

Several pathological substrates of brain atrophy have been described in MS. On one side, a white matter volume decrease is observed within white matter lesions and in the normal-appearing white matter. White matter lesions show a loss of volume due to the myelin, oligodendrocytes and axonal loss as well as by the shrinkage of astrocytes volume when forming the glial scars. In the normal-appearing white matter, the loss of volume appears to be a consequence of diffuse demyelination and axonal loss (Filippi, Rocca et al., 2012; Rocca, M. A. et al., 2017). On the other side, a gray matter volume decrease is also observed within gray matter lesions and in the normal-appearing gray matter. Within both kinds of gray matter tissues the volume decrease seems to be produced by neuronal atrophy/loss, axonal loss and, to a lesser extent, by gray matter demyelination (Klaver et al., 2015; Rocca, M. A. et al., 2017).

2.5. Diagnosis

The most widely used diagnostic criteria for MS were originally defined by McDonald et al. (2001). These diagnostic criteria have been revised and updated in several occasions due to the increasing knowledge about the disorder, the emerging technology, and the evolving consensus among experts (Polman et al., 2005; Polman et al., 2011; Thompson et al., 2017). According to the most recently recommended criteria, the 2017 McDonald diagnostic criteria (Thompson et al., 2017), MS diagnosis relies on the integration of clinical,

neuroimaging and laboratory evidences. The 2017 McDonald diagnostic criteria for patients presenting clinical relapses or a gradual progression from the disease onset are provided in Table 1 and Table 2, respectively.

Table 1. 2017 McDonald diagnostic criteria for patients presenting a clinical relapse at onset.

	Clinical relapses[a]	**CNS lesions**[b] **with objective clinical evidence**	**Additional data required for the diagnosis**
1	≥2	≥2	None
2	≥2	1 (and a stark evidence of a previous relapse, without objective clinical evidence, involving a different anatomical site)	None
3	≥2	1	Dissemination in space[c] evidenced by: • An additional clinical relapse involving a different anatomical site • ≥1 T2-hyperintense lesions in at least two of the following areas of the CNS: o Periventricular brain region (in individuals older than 50 years or with vascular risk factors a higher number of periventricular lesions is recommended) o Cortical or juxtacortical brain region o Infratentorial brain region o Spinal cord
4	1	≥2	Dissemination in time[d] evidenced by: • An additional clinical relapse • The simultaneous presence of gadolinium-enhancing and non-enhancing MRI lesions • A new gadolinium-enhancing or T2-hyperintense lesion on follow-up MRI scan (when compared to a baseline scan) Or detection of CSF-specific oligoclonal bands
5	1	1	Dissemination in space[c] (evidenced as previously described) And fulfillment of at least one of the following evidences: i. Dissemination in time[d] (evidenced as previously described) ii. Detection of CSF-specific oligoclonal bands

CNS = central nervous system; MRI = magnetic resonance imaging; CSF = cerebrospinal fluid. [a] A relapse is defined as a monophasic clinical episode with patient-reported symptoms, which have a duration of at least 24 hours (with or without recovery), occur in the absence of fever or infection and are accompanied by objective findings reflecting focal or multifocal demyelination within the CNS. [b] A lesion is defined as an area of hyperintensity on T2-weighted structural or proton-density-weighted MRI, with at least 3 mm in long axis. [c] Dissemination in space is referred to the development of lesions in different anatomical sites of the CNS. [d] Dissemination in time is referred to the development of new CNS lesions. MS can be diagnosed when a patient meets the criteria presented in any of the five rows of the table and there is no better explanation for its clinical presentation. Table modified from Thompson et al. (2017).

Table 2. 2017 McDonald diagnostic criteria for patients presenting a disability progression from onset.

- ≥ 1 year of disability progression, prospectively or retrospectively established, independent of clinical relapse
- And fulfillment of two or more of the following evidences:
  - ≥ 1 T2-hyperintense lesions in one or more of the following brain areas:
    - Periventricular region
    - Cortical or juxtacortical region
    - Infratentorial region
  - ≥ 2 T2-hyperintense lesions in the spinal cord
  - Detection of CSF-specific oligoclonal bands

CSF = cerebrospinal fluid. Table modified from Thompson et al. (2017).

2.6. Cognitive impairment

Cognitive impairment in MS has been disregarded for many years (Benedict, Ralph HB et al., 2017). Nonetheless, at present there is no doubt that cognitive deficits are a frequent concomitant of the disorder (Grzegorski & Losy, 2017). Cognitive impairment is estimated to affect from 43% to 70% of persons with MS. It concerns all clinical courses and can be detected since the clinical onset of the disorder (Chiaravalloti, N. D. & DeLuca, 2008). Cognitive deficits have been noted to differ among patients. However, a specific cognitive profile arises when groups of patients are taken into consideration (Bagert, Camplair, & Bourdette, 2002). This cognitive profile is mainly characterized by the presence of deficits in attention, processing speed, working memory, verbal and visual memory, language, executive

functioning and social cognition (Chiaravalloti, N. D. & DeLuca, 2008; Grzegorski & Losy, 2017).

Little is known about how the distinct courses of the disorder might differentially affect cognitive performance (Johnen et al., 2017). Specifically, cognitive impairment seems to be more frequent and severe in the progressive forms of MS (SPMS and PPMS) as compared with the relapsing-remitting one (Chiaravalloti, N. D. & DeLuca, 2008; Johnen et al., 2017). Thus, in a recent and large comparative study the prevalence of cognitive impairment was 44% in RRMS, 79% in SPMS and 91% in PPMS (Ruano et al., 2017). In addition, the presence of a more severe cognitive impairment in the progressive courses of the disorder has been shown not only when considering overall cognitive impairment but also specific cognitive domains in isolation, such as processing speed, verbal and visual memory, verbal fluency or executive functioning (Johnen et al., 2017; Ruano et al., 2017). Concerning the presence of differences in the frequency and severity of cognitive impairment between persons with PPMS and SPMS, heterogeneous results have been obtained. In general, while some studies suggest a more frequent and severe cognitive impairment in persons with SPMS (Denney, Sworowski, & Lynch, 2005; Huijbregts et al., 2004; Planche, Gibelin, Cregut, Pereira, & Clavelou, 2016), others report a lack of such between-group differences (Henry, A., Tourbah, Chaunu, Bakchine, & Montreuil, 2017; Potagas et al., 2008; Ruano et al., 2017). In this regard, it must be stressed that the previously mentioned large study did not detect significant cognitive differences between persons with SPMS and PPMS (Ruano et al., 2017).

The existence of specific cognitive profiles in accordance with the distinct subtypes of MS has also been debated in the literature, given that studies have yielded inconsistent results on this matter (Denney et al., 2005; Huijbregts et al., 2004; Johnen et al., 2017; Planche et al., 2016; Potagas et al., 2008; Ruano et al., 2017; Ruet, Deloire, Charre-Morin, Hamel, & Brochet, 2013; Zakzanis, 2000). Nevertheless, the large study previously mentioned (Ruano

et al., 2017) and a recent meta-analysis (Johnen et al., 2017), the latter specifically focused on PPMS and RRMS, have not supported the notion of subtype-specific cognitive deficits. Taking all the above into consideration, the same overall pattern of cognitive impairment might be shared among the distinct courses of MS, albeit the progressive forms of MS would be associated with a more frequent and severe cognitive impairment as compared with the relapsing-remitting course. Nevertheless, further research is still needed in this respect.

On the other side, it is known that the likelihood of suffering from cognitive impairment in MS increases with the progression of the disease (Amato, M. P., Zipoli, & Portaccio, 2006; Strober, Rao, Lee, Fischer, & Rudick, 2014). Different longitudinal studies have also shown that MS cognitive impairment tends to get worse over time (Amato, M. P. et al., 2006; Strober et al., 2014). This cognitive worsening would be characterized not only by a more pronounced impairment in those cognitive domains that were initially affected but also by the emergence of other cognitive deficits (Amato, M. P. et al., 2006; Strober et al., 2014). In this regard, it must be stated that cognitive impairment advances more slowly and less steadily in MS than in other neurodegenerative conditions such as Alzheimer's disease (Amato, M. P. et al., 2006). Actually, the progression of cognitive impairment to dementia states is not commonly discussed in the literature (Westervelt, 2015), and is considered as an infrequent feature of the disorder (Chiaravalloti, N. D. & DeLuca, 2008; Grzegorski & Losy, 2017; Westervelt, 2015). A retrospective study has estimated that dementia might approximately affect 22% of persons with MS (Benedict, R. H. & Bobholz, 2007). However, the prevalence of dementia and its time of occurrence are still uncertain in the disorder, given the lack of prospective studies investigating this issue (Defer & Branger, 2015; Westervelt, 2015).

In any event, cognitive impairment has been regarded as a relevant cause of disability in persons with MS (Bagert et al., 2002). Thus, the presence of cognitive impairment in the

disorder has been associated with difficulties in daily life activities (such as cooking, telephone usage, medication management, bill payment and driving) (Ben Ari, Johansson, Ytterberg, Bergström, & von Koch, 2014; Kalmar, Gaudino, Moore, Halper, & DeLuca, 2008; Rao, Stephen M. et al., 1991; Schultheis, Garay, & DeLuca, 2001), negative work events (Benedict, Ralph HB, Rodgers, Emmert, Kininger, & Weinstock-Guttman, 2014) and unemployment statuses (Benedict, Ralph HB et al., 2005; Rao, Stephen M. et al., 1991; Strober, Chiaravalloti, Moore, & DeLuca, 2014). The relationship between cognitive impairment and a reduced engagement in social as well as leisure activities has also been stated in the disorder (Ben Ari et al., 2014; Hakim et al., 2000; Rao, Stephen M. et al., 1991). Moreover, cognitive deficits have also been related to emotional disturbances (e.g. depression) (Chiaravalloti, N. D. & DeLuca, 2008), personality changes (e.g. lower extraversion and conscientiousness) (Roy, Drake, Fuchs et al., 2018; Roy, Drake, Eizaguirre et al., 2018), a poorer health perception (Ruet, Deloire, Charre-Morin et al., 2013), and a decreased quality of life (Benito-León, Manuel Morales, Rivera-Navarro, & Mitchell, 2003; Fernández, Baumstarck-Barrau, Simeoni, Auquier, & MusiQoL study group, 2011; Ford, Gerry, Johnson, & Tennant, 2001). Accordingly, studying the efficacy of interventions intended to improve cognitive performance takes on special relevance in the disorder.

2.6.1. Attention

Attention refers to a basic, but sophisticated, capacity whereby individuals become receptive to stimuli, whether external or internal, and process the incoming information (Lezak, Howieson, & David, 2004). In MS, about 12-25% of patients suffer from attention deficits (Grzegorski & Losy, 2017). Specifically, complex forms of attention (e.g. sustained, selective or divided attention) have been found to be impaired (Chiaravalloti, N. D. & DeLuca, 2008; Grzegorski & Losy, 2017; Prakash, Snook, Lewis, Motl, & Kramer, 2008),

while basic attention abilities (e.g. repeating digits) are generally unaffected in the disorder (Chiaravalloti, N. D. & DeLuca, 2008; Grzegorski & Losy, 2017).

2.6.2. Information processing

Information processing encompasses processing speed and working memory abilities (Chiaravalloti, N. D. & DeLuca, 2008; Grzegorski & Losy, 2017). Processing speed has been defined as the amount of time it takes to execute a cognitive task or the amount of work performed within a specific period of time (Costa, Genova, DeLuca, & Chiaravalloti, 2016). The decline of information processing speed constitutes one of the most frequent cognitive deficits in MS, since it is presented by 20-50% of the patients (Chiaravalloti, N. D. & DeLuca, 2008; Grzegorski & Losy, 2017). This cognitive deficit seems to be the first one to emerge in MS (Amato, Maria P. et al., 2010; Grzegorski & Losy, 2017) and, importantly, it has been found to predict patients' long-term cognitive decline (Chiaravalloti, N. D. & DeLuca, 2008; Grzegorski & Losy, 2017).

On the other side, working memory is responsible for the storage of information during a short length of time and its simultaneous manipulation, which is necessary for the appropriate execution of more complex cognitive processes (Baddeley, 1992). Working memory deficits are present in 6-32% of persons with MS and have also been observed in early stages of the disease (Chiaravalloti, N. D. & DeLuca, 2008). These deficits appear to be more evident as working memory demands of the task increase (Parmenter, Shucard, & Shucard, 2007).

2.6.3. Memory

Memory performance involves processes of encoding, storage and retrieval of information (Baddeley, Kopelman, & Wilson, 2003). The prevalence of memory deficits in

MS rates from 33% to 65% of patients. Therefore, memory seems to constitute the cognitive domain most commonly disturbed as a result of the disorder (Chiaravalloti, N. D. & DeLuca, 2008; Grzegorski & Losy, 2017). Specific types of memory have been found to be usually impaired in MS. Persons with MS commonly exhibit episodic and prospective memory impairments, whereas semantic and implicit memory are usually preserved (Grzegorski & Losy, 2017; Rouleau et al., 2017). With regards to episodic memory, an impaired performance has been observed for both verbal and visual episodic memory; being the latter slightly more affected (Chiaravalloti, N. D. & DeLuca, 2008; Johnen et al., 2017). Distinct cognitive processes have been suggested to underlie episodic memory impairments in the disorder. Thus, early studies specifically suggested that both verbal and visual episodic memory impairments were due to difficulties in retrieval processes. However, subsequent studies pointed out that these deficits might be caused by deficits in encoding processes (Chiaravalloti, N. D. & DeLuca, 2008; Grzegorski & Losy, 2017).

2.6.4. Language

MS can lead to impairments in several language functions including verbal expression, discourse, fluency, and comprehension. Among these functions, verbal fluency has been found to be the domain most severely affected by the disorder (Prakash et al., 2008). Verbal fluency is defined as the ability to generate words according to specific semantic or phonemic criteria (Chiaravalloti, N. D. & DeLuca, 2008). It is estimated that 19% of persons with the disorder present verbal fluency deficits (Drew, Tippett, Starkey, & Isler, 2008). Both semantic and phonemic fluency deficits have been noticed in persons with MS, with a similar degree of impairment (Chiaravalloti, N. D. & DeLuca, 2008; Henry, J. D. & Beatty, 2006).

2.6.5. Executive functioning

Executive functioning consists of a wide range of cognitive skills that are involved in goal-directed behaviors as well as in the adaptation to the ever-changing environment (Chiaravalloti, N. D. & DeLuca, 2008). Disturbances in these cognitive skills are estimated to occur in 17-19% of persons with MS (Chiaravalloti, N. D. & DeLuca, 2008; Henry, J. D. & Beatty, 2006). Specifically, persons with MS exhibit deficits in distinct skills including abstract and conceptual reasoning, planning, problem solving, decision-making, flexibility and inhibition (Chiaravalloti, N. D. & DeLuca, 2008; Roman & Arnett, 2016; Sepúlveda et al., 2017). Perseverative errors are also common in the disorder (Chiaravalloti, N. D. & DeLuca, 2008).

2.6.6. Social cognition

Social cognition enables the interpretation of other persons' intentions and behaviors (Grzegorski & Losy, 2017). This complex construct involves several cognitive and affective components such as theory of mind, empathy and social perception of emotions (Chalah & Ayache, 2017). Theory of mind has been found to be the component of social cognition most consistently affected in MS literature (Chalah & Ayache, 2017). Particularly, this component refers to the understanding and prediction of mental states of others according to their emotions and feelings (affective aspect) or to their aims, thoughts and beliefs (cognitive aspect). Both affective and cognitive aspects of theory of mind have been noticed to be adversely affected as a result of MS (Chalah & Ayache, 2017).

2.6.7. The influence of processing speed on other cognitive domains

Several studies have pointed out the association between processing speed impairment and worse cognitive performance in other domains including attention (De Sonneville et al.,

2002), working memory (Archibald & Fisk, 2000; Barker-Collo, 2006; Chiaravalloti, Nancy D., Stojanovic-Radic, & DeLuca, 2013; DeLuca, J., Chelune, Tulsky, Lengenfelder, & Chiaravalloti, 2004; Forn, Belenguer, Parcet-Ibars, & Ávila, 2008), verbal and visual memory (Chiaravalloti, N. D., Christodoulou, Demaree, & DeLuca, 2003; Chiaravalloti, Stojanovic-Radic et al., 2013; DeLuca, J., Barbieri-Berger, & Johnson, 1994; DeLuca, John, Gaudino, Diamond, Christodoulou, & Engel, 1998; Gaudino, Chiaravalloti, DeLuca, & Diamond, 2001), verbal fluency (Drew, Starkey, & Isler, 2009), and executive functioning (Drew et al., 2009). Certain studies have additionally shown that when extending or individually adjusting the length of time required by each individual to process the presented information, persons with MS perform as well as healthy subjects on attention (Paul, Beatty, Schneider, Blanco, & Hames, 1998), working memory (Demaree, DeLuca, Gaudino, & Diamond, 1999; Leavitt, Lengenfelder, Moore, Chiaravalloti, & DeLuca, 2011; Lengenfelder et al., 2006) and verbal memory tests (Arnett, 2004). Given this, slowed processing speed might play a key influence in other MS cognitive deficits.

Two distinct theoretical models have been outlined depending on the impact that processing speed could exert on other cognitive domains in MS, which are referred to as the Relative Consequence Model and the Independent Consequence Model (DeLuca, J. et al., 2004). The former model proposes that persons with MS present a central processing speed decline that results in other cognitive deficits. According to this model processing speed might only affect other cognitive processes when its decline reaches some critical level or threshold. Conversely, the latter model proposes that cognitive deficits in MS could either be independent, or not exclusively the result, of slowed processing speed. These models were originally proposed to explain the presence of differences in working memory performance between persons with SPMS and RRMS. Thus, J. DeLuca et al. (2004) found that while persons with SPMS presented working memory deficits, those with RRMS did not show such

impairment. The presence of a greater decline in processing speed in persons with SPMS was specifically proposed as a potential explanation for such working memory differences.

Even though distinct studies have revealed that processing speed deficits entail a negative impact on other cognitive domains, it remains unclear whether persons with MS present a central processing speed decline that results in other cognitive deficits (as posed by the Relative Consequence Model) or independent deficits in diverse cognitive domains (as posed by the Independent Consequence Model). To date, some studies have investigated whether MS cognitive deficits remained significant (or not) when controlling for the negative effect of slowed processing speed. However, these studies have mostly focused on the influence of processing speed in executive functioning (Denney & Lynch, 2009; Genova, DeLuca, Chiaravalloti, & Wylie, 2013; Leavitt, Wylie, Krch et al., 2014; Owens, Denney, & Lynch, 2013), so that only one study has examined its effect on attention (Roth, Denney, & Lynch, 2015), working memory (Forn et al., 2008) or verbal fluency (Panou, Simos, Mastorodemos, Fassaraki, & Plaitakis, 2008). These studies specifically reported that differences between persons with MS and healthy subjects in working memory (Forn et al., 2008), verbal fluency (Panou et al., 2008), and executive functioning (Denney & Lynch, 2009; Genova et al., 2013; Leavitt, Wylie, Krch et al., 2014; Owens et al., 2013) became non-significant once the effect of processing speed was controlled (supporting the Relative Consequence Model), whereas attention deficits were still significant (Roth et al., 2015) (supporting the Independent Consequence Model).

These conclusions have been derived from independent studies, while a more comprehensive study focused on multiple cognitive processes might provide a more extensive support for the Relative or Independent Consequence Model. Moreover, a comprehensive study would warrant the attainment of results through the same methodological and statistical processes, as well as using the same pathological and healthy

control sample. As a result, this comprehensive approach would allow the comparability of the results obtained for each of the cognitive domains. On the other side, no study has examined this hypothesis for verbal or visual memory performance. Given the above, one of the objectives of the present work will focus on studying whether MS cognitive deficits remained significant (or not) when controlling for the negative effect of slowed processing speed.

2.7. Magnetic resonance imaging and neural substrates of cognitive impairment

Over the last decades great progress has been made in understanding the neural substrates of cognitive impairment in MS (Benedict, Ralph HB et al., 2017; Cruz-Gómez, Belenguer-Benavides, González-Rosa, Simón-Gozalbo, & Forn, 2011; Rocca, M. A. et al., 2015). Particularly, MRI has played a major part in this progress, as it allows studying both the neuroanatomical and neurofunctional correlates of cognitive impairment in the disorder. While early MRI studies were focused on studying the neuroanatomical correlates of cognitive impairment, the neurofunctional correlates of this clinical manifestation are gaining increasing attention in the MS field (Benedict, Ralph HB et al., 2017; Rocca, M. A. et al., 2015). Thus, the literature is providing increasing evidence that MS cognitive impairment in is not the direct consequence of brain damage, but a balance among tissue injury, tissue repair, and brain functional compensatory mechanisms (Rocca, M. A., De Meo, & Filippi, 2016).

2.7.1. Neuroanatomical substrates of cognitive impairment

Distinct neuroanatomical substrates of cognitive impairment have been outlined in MS (Rocca, Amato et al., 2015). These substrates have been studied through both conventional and non-conventional structural MRI. Thus, conventional structural MRI

studies have reported significant relationships between cognitive impairment and brain lesion load [white matter (T1 hypointense and T2 hyperintense) and gray matter (cortical and subcortical) lesion volumes] (DeLuca, G. C. et al., 2015; Rocca, Amato et al., 2015; Van Munster, Jonkman, Weinstein, Uitdehaag, & Geurts, 2015) as well as brain atrophy [whole brain, white matter and gray matter (cortical and subcortical) tissue volume loss] (DeLuca, G. C. et al., 2015; Rocca, Amato et al., 2015; Rojas, Patrucco, Miguez, & Cristiano, 2016; Van Munster et al., 2015). In addition, non-conventional structural MRI studies have also noticed significant associations between cognitive impairment and microstructural tissue damage in the MS brain (Rocca, Amato et al., 2015).

2.7.1.1. Brain structural connectivity and cognitive impairment

Among the existing non-conventional structural MRI sequences, diffusion weighted imaging (DWI) specifically enables the measurement of the molecular diffusion of water within the brain, whose direction depends on the presence (or absence) of structural brain barriers (i.e. on brain morphology) (Enzinger et al., 2015). As a result, this MRI technique allows drawing inferences about the microstructural properties of different brain tissues or structures (Enzinger et al., 2015), including the white matter tracts that constitute the structural connections of the brain. Several studies have investigated the relationship between brain white matter microstructural damage and cognitive performance in MS by means of DWI acquisitions (Welton, Kent, Constantinescu, Auer, & Dineen, 2015). Thus, a recent meta-analysis on this topic has revealed that MS cognitive impairment is predominantly associated with reduced white matter integrity in the corpus callosum, the cingulum, the fornix and the thalamus (Welton et al., 2015).

The association between white matter microstructural damage and specific cognitive domains has been studied in the disorder as well. For instance, a poorer cognitive performance in working, verbal and visual memory tasks has been associated with lower

integrity of different, but partially overlapping, white matter tracts predominantly located in the parietal, temporal and occipital lobe (Dineen et al., 2009). In another study a similar pattern of results was observed for verbal and visual memory, but with a greater involvement of frontal white matter tracts (Llufriu et al., 2014). In addition, processing speed has been found to correlate with multiple and widespread brain white matter tracts in MS (Manca, Sharrack, Paling, Wilkinson, & Venneri, 2018). Even though these white matter tracts vary among studies, a recent systematic review has described a more consistent involvement of specific commissural and associative tracts in processing speed performance including the corpus callosum, fornix, cingulum, superior and inferior longitudinal fasciculus and posterior thalamic radiations (Manca et al., 2018). The relationship between executive functioning and brain white matter integrity has also been supported in the literature, albeit depending on the specific executive process under assessment distinct tracts have been found to be involved. Thus, deficits in inhibition have been specifically related to lower integrity of fronto-parietal tracts, while deficits in flexibility have been associated with more spread tracts (Genova et al., 2013). Nevertheless, it should be stated that the former association was restricted to a specific frontal tract (the anterior thalamic radiation) after controlling for the influence of processing speed, and that the latter was no longer significant (Genova et al., 2013). Interestingly, the relationship between white matter integrity damage and cognitive impairment has been observed not only in those tracts affected by focal lesions but also in the normal-appearing white matter (Dineen et al., 2009). All these findings lend support to the notion that brain structural white matter damage (i.e. a disconnection syndrome) might lie beneath cognitive impairment in MS (Dineen et al., 2009; Llufriu et al., 2012; Rocca, Amato et al., 2015).

2.7.2. Neurofunctional substrates of cognitive impairment

The neurofunctional correlates of cognitive impairment in MS have been studied through task-based functional MRI (fMRI) as well as resting-state functional MRI (rs-fMRI) (Chiaravalloti, N. D., Genova, & DeLuca, 2015; Rocca, M. A. et al., 2016). Task-based fMRI studies have commonly detected brain functional activity abnormalities associated to the performance of distinct cognitive tasks in the disorder (Chiaravalloti, N. D. et al., 2015; Rocca, M. A. et al., 2016). Likewise, rs-fMRI studies have repeatedly noticed functional connectivity abnormalities within different cognitive resting-state networks in MS (Chiaravalloti, N. D. et al., 2015; Rocca, M. A. et al., 2016). A main limitation concerning task-based fMRI studies is that the obtained results are notably influenced by intersubject variability in task performance, which complicates the interpretation of the results (Rocca, M. A. et al., 2016). This interpretation is further complicated when working with cognitively impaired populations given their high intersubject variability. Because of this effect, there has been an increasing interest in the conduction of rs-fMRI studies to investigate the neurofunctional correlates of cognitive impairment in persons with MS (Rocca, M. A. et al., 2016).

2.7.2.1. Brain functional connectivity and cognitive impairment

Rs-fMRI sequences specifically allow the examination of low-frequency blood oxygen level-dependent (BOLD) synchronous signal fluctuations between different brain regions at rest. As a result, rs-fMRI technique enables drawing inferences about the brain's intrinsic functional architecture. Several cognitive resting-state networks have been identified by means of rs-fMRI in healthy subjects as well as in persons with MS, including the default mode network (DMN) (Buckner, R. L. et al., 2005; Rocca, Maria A. et al., 2018), the salience network (SN) (Menon, 2015; Rocca, M. A. et al., 2012), the dorsal attention network (DAN) (Rocca, Maria A. et al., 2018; Spreng, Sepulcre, Turner, Stevens, & Schacter, 2013), the

executive control network (ECN) (Sbardella, Tona et al., 2015; Seeley et al., 2007; Spreng et al., 2013) and the hippocampal memory network (HMN) (Roosendaal et al., 2010).

The DMN (Figure 3) is the most widely studied cognitive network in both healthy subjects and persons with MS. It is specifically defined as a set of brain regions that are co-activated at rest (Buckner, Randy L., Andrews-Hanna, & Schacter, 2008). This functional network has been related to different internally directed self-referential processes including remembering autobiographical events, making future plans, imagining hypothetical situations, thinking about other people beliefs or intentions and solving moral dilemmas (Buckner, Randy L. et al., 2008).

Figure 3. Graphical representation of the DMN.

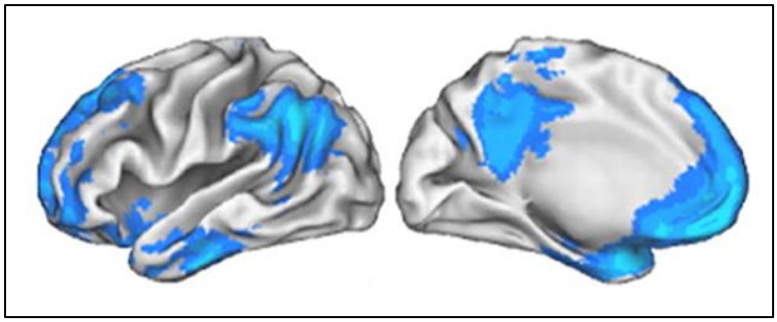


Figure obtained from Buckner et al. (2005).

In contrast to the DMN, the SN and the DAN are involved in externally directed attention processes. The SN (Figure 4) is involved in the detection of behaviorally salient stimuli, as well as in the subsequent facilitation of access to attention and working memory resources (Menon, 2015). On the other side, the DAN (Figure 5) is responsible for maintaining a stable saliency for those visual stimuli that are relevant for the achievement of goal-directed behaviors (Menon, 2015). Consequently, the latter network is specially activated in those cognitive tasks that require stimuli search and detection, and consists of several brain areas that are implicated in spatial attention, ocular movements and eye-hand coordination (Corbetta & Shulman, 2002).

Figure 4. Graphical representation of the SN.

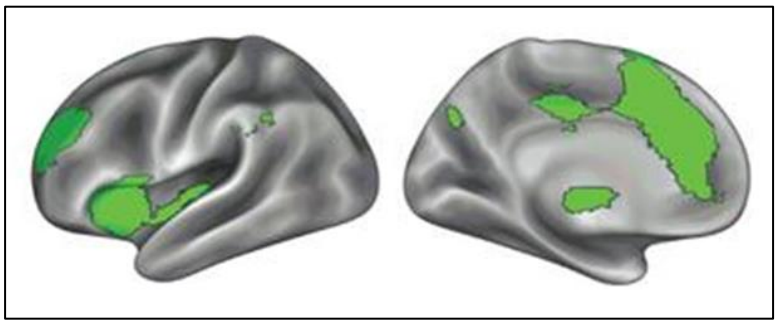


Figure obtained from Weng et al. (2017).

Figure 5. Graphical representation of the DAN.

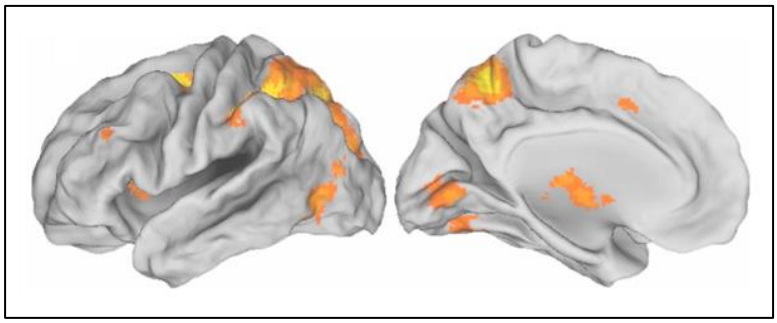


Figure obtained from Spreng, Sepulcre, Turner, Stevens, & Schacter (2013).

The ECN (Figure 6), also called the frontoparietal control network (Spreng et al., 2013), is implicated in goal directed cognition involving sustained attention, working memory, decision-making processes, cognitive flexibility, as well as selection and inhibition of responses (Seeley et al., 2007). Finally, the HMN, understood as the functional connectivity between the hippocampus and other cortical and subcortical brain regions, has been associated with verbal and visual episodic memory performance (Hulst et al., 2015; Leavitt, Wylie, Girgis, DeLuca, & Chiaravalloti, 2014; Rocca, M. A., Pravatà et al., 2015; Roosendaal et al., 2010).

Figure 6. Graphical representation of the ECN.

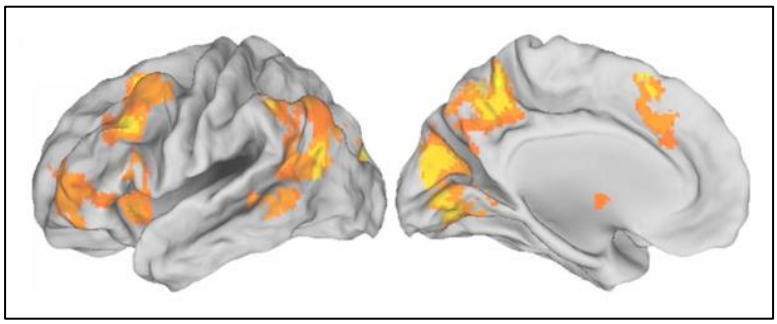


Figure obtained from Spreng et al. (2013).

Widespread functional connectivity abnormalities have been described in the MS brain (Sbardella, Petsas et al., 2015). All the aforementioned networks have been found to be altered in persons with MS, as compared to healthy subjects [DMN (Basile et al., 2014; Bonavita et al., 2016; Bonavita et al., 2011; Meijer et al., 2017; Rocca, M. A. et al., 2010; Rocca, Maria A. et al., 2018; Rocca, M. A. et al., 2012), SN (Bonavita et al., 2016; Cruz-Gómez, Ventura-Campos, Belenguer, Ávila, & Forn, 2014; Rocca, M. A. et al., 2012), DAN (Rocca, Maria A. et al., 2018), ECN (Bonavita et al., 2016; Rocca, M. A. et al., 2012; Sbardella, Tona et al., 2015) and HMN (Cruz-Gómez, Belenguer-Benavides, Martínez-Bronchal, Fittipaldi-Márquez, & Forn, 2016; Rocca, Pravatà et al., 2015; Roosendaal et al., 2010)]. Regardless of the network under consideration, the literature on MS brain functional connectivity abnormalities is heterogeneous and difficult to interpret (Schoonheim, Meijer, & Geurts, 2015). Thus, functional connectivity decreases as well as increases have been described in the disorder within different resting-state networks (Sbardella, Petsas et al., 2015).

Specifically, in persons with clinically isolated syndrome (CIS), which have suffered a first relapse suggestive of MS, brain functional connectivity increases have been reported along with the absence of cognitive deficits (Chiaravalloti, N. D. et al., 2015; Rocca, M. A. et al., 2016). These findings are thought to reflect an adaptive brain plasticity mechanism early

in the disease that preserves cognitive functioning against brain tissue damage (compensatory hypothesis) (Chiaravalloti, N. D. et al., 2015; Rocca, M. A. et al., 2016). Accordingly, functional connectivity decreases in association with cognitive deficits later in the disease have been suggested to indicate that the compensatory mechanism previously described is limited in time (Chiaravalloti, N. D. et al., 2015; Rocca, M. A. et al., 2016; Van Schependom & Nagels, 2017).

This compensatory hypothesis has been challenged by several studies, which have shown that functional connectivity increases can also be associated with worse cognitive performance in the disorder (Chiaravalloti, N. D. et al., 2015; Schoonheim et al., 2015). This negative relationship between functional connectivity increases and cognitive performance might point out that maladaptive brain plasticity changes can also occur in the MS brain (Chiaravalloti, N. D. et al., 2015; Schoonheim et al., 2015). In this regard, it has been proposed that functional connectivity increases might be adaptive in early MS, but maladaptive later in the disease (Chiaravalloti, N. D. et al., 2015). However, the specific periods during which these functional connectivity increases might be adaptive or, conversely, maladaptive have not been accurately established. Additionally, functional connectivity decreases have been found not only in association with worse cognitive performance (as previously stated) but also with better cognitive performance (Sbardella, Tona et al., 2015). Therefore, the latter association could also be indicative of the occurrence of adaptive functional connectivity rearrangements in the MS brain (Sbardella, Tona et al., 2015). In addition, some studies have described complex patterns of functional connectivity changes in MS involving both functional connectivity increases and decreases (Bonavita et al., 2016; Bonavita et al., 2011; Rocca, Maria A. et al., 2018; Rocca, M. A. et al., 2012; Sbardella, Tona et al., 2015). These findings suggest that in the MS brain takes place a global

connectivity redistribution characterized by functional connectivity increases as well as decreases among brain regions, rather than just increases or decreases (Sbardella et al., 2015).

All findings detailed above reflect the complexity of brain functional connectivity changes associated to MS, and suggest that the relationship between brain functional connectivity and cognitive performance is not straightforward in the disorder (Sbardella, Petsas et al., 2015). That is, functional connectivity decreases do not always have a negative impact on cognition and functional connectivity increases do not always have a beneficial effect on cognition. Consequently, the examination of whether the observed brain functional connectivity abnormalities are adaptive or maladaptive takes on particular relevance in MS (Chiaravalloti, N. D. et al., 2015).

2.8. Cognitive rehabilitation

Cognitive rehabilitation can be defined as a behavioral treatment that aims to improve persons' cognitive performance, daily functionality and quality of life (Mitolo, Venneri, Wilkinson, & Sharrack, 2015; Sumowski et al., 2018). Cognitive rehabilitation interventions can rely on the following main principles: restoration, optimization and/or compensation of the impaired function (Muñoz-Céspedes & Tirapu-Ustárroz, 2001). The restoration principle assumes that the impaired cognitive function can be restored by means of its repetitive stimulation. The optimization principle is based on the notion that the cognitive function has not been completely lost but reduced in its efficacy. Therefore, the cognitive function in question can be improved through the utilization of preserved cognitive systems. Finally, the compensation principle emerges from the recognition that the cognitive function and its neural substrates cannot be recovered. Hence, this approach seeks to compensate the lost function by using external aids such as alarms, agendas, etc. (Muñoz-Céspedes & Tirapu-Ustárroz, 2001).

2.8.1. Cognitive changes after cognitive rehabilitation

Over the last two decades, a growing amount of studies have investigated the efficacy of cognitive rehabilitation in improving MS cognitive deficits (Goverover, Y., Chiaravalloti, O'Brien, & DeLuca, 2018; O'Brien, Chiaravalloti, Goverover, & DeLuca, 2008). The main focus of these interventions has changed over time. Traditionally, cognitive rehabilitation interventions were mostly targeted to improve learning and memory deficits. Conversely, more recent interventions have mainly focused on the improvement of other cognitive domains such as attention, processing speed and/or executive functioning (Goverover, Chiaravalloti, O'Brien et al., 2018; Mitolo et al., 2015; O'Brien et al., 2008).

Most cognitive rehabilitation studies have revealed significant cognitive improvements in persons with MS (Mitolo et al., 2015). Nevertheless, the latest extensive Cochrane review on this topic only reported a low level of evidence for the efficacy of cognitive rehabilitation in the disorder (Rosti-Otajärvi & Hämäläinen, 2014). At best, some level of evidence was specifically found for the efficacy of memory rehabilitation in a later Cochrane review (das Nair, Martin, & Lincoln, 2016). These systematic reviews agree in that rigorous RCTs are still needed, owing to the presence of diverse methodological flaws in the literature (das Nair et al., 2016; Rosti-Otajärvi & Hämäläinen, 2014). These flaws include the use of unpowered samples, unsuitable allocation or randomization procedures, incomplete outcome data due to attrition bias or the lack of blinding, among others (das Nair et al., 2016; Goverover, Chiaravalloti, O'Brien et al., 2018; Rosti-Otajärvi & Hämäläinen, 2014). Despite this, some well-designed class I studies on cognitive rehabilitation have revealed promising results, suggesting that cognitive rehabilitation might be an effective intervention tool for addressing cognitive deficits in MS (Charvet et al., 2017; Goverover, Chiaravalloti, O'Brien et al., 2018; Goverover, Y., Chiaravalloti, Genova, & DeLuca, 2018; O'Brien et al., 2008).

Cognitive interventions in MS have been commonly intended at improving just one or a few specific cognitive domains (Goverover, Chiaravalloti, O'Brien et al., 2018; Mitolo et al., 2015). However, interventions targeting multiple domains (i.e. integrative cognitive interventions) might be especially beneficial for persons with this disorder, as they may present a wide range of cognitive deficits (Chiaravalloti, N. D. & DeLuca, 2008; Goverover, Chiaravalloti, O'Brien et al., 2018). Additionally, integrative cognitive interventions might be more efficient and cost-effective compared to those targeting only a few specific cognitive domains (Goverover, Chiaravalloti, O'Brien et al., 2018). On the other side, the large majority of cognitive interventions in MS have been administered in an individual format, whereas group settings would also be more cost-effective in the clinical practice. Therefore, methodologically rigorous RCTs, which implement integrative group-based cognitive interventions, might be of particular interest in MS.

The REHACOP is an integrative cognitive rehabilitation programme designed according to the principles of restoration, optimization and compensation (Ojeda & Peña, 2012). Even though this cognitive programme was originally intended for persons with psychotic disorders (Ojeda & Peña, 2012), its efficacy has been proved in psychotic disorders (schizophrenia) as well as in neurodegenerative conditions (Parkinson's disease) (Peña, J. et al., 2014; Peña, Javier et al., 2016; Sánchez et al., 2014). Schizophrenia, Parkinson's disease, and MS constitute very different disorders characterized by dissimilar cognitive features, including their prevalence, progression and severity of cognitive impairment (Chiaravalloti, N. D. & DeLuca, 2008; Nuechterlein et al., 2004; Palavra, Naismith, & Lewis, 2013). However, persons suffering from any of these disorders may present deficits across a wide range of cognitive domains (including attention, processing speed, working memory, episodic memory, verbal fluency, executive functioning and/or social cognition), which are actually targeted by the REHACOP programme (Chiaravalloti, N. D. & DeLuca, 2008; Nuechterlein

et al., 2004; Palavra et al., 2013). Accordingly, the REHACOP integrative cognitive rehabilitation programme might be effective not only in improving cognitive functioning in schizophrenia and Parkinson's disease but also in MS.

2.8.2. Brain changes after cognitive rehabilitation

MRI has been suggested to play a significant role in the identification of effective cognitive interventions, as it enables the study of brain plasticity (Chiaravalloti, N. D. et al., 2015). Specifically, the study of functional and structural connectivity brain changes following cognitive interventions might be especially relevant in MS, a condition in which the disconnection syndrome has been suggested to lie beneath cognitive impairment (Rocca, Amato et al., 2015). In addition, the combination of both imaging sequences might provide different but complementary information for the understanding of the neurobiological mechanisms underlying cognitive rehabilitation effects.

Several studies have investigated the effects of cognitive rehabilitation on brain functional connectivity in MS (Bonavita et al., 2015; De Giglio, Tona et al., 2016; Ernst et al., 2016a; Ernst et al., 2016b; Filippi, Riccitelli et al., 2012; Leavitt, Wylie, Girgis et al., 2014; Parisi et al., 2014). Most of this literature has focused on the DMN (Bonavita et al., 2015; Ernst et al., 2016a; Ernst et al., 2016b; Filippi, Riccitelli et al., 2012; Leavitt, Wylie, Girgis et al.,2014). Consequently, only a few studies have examined other cognitive networks such as the SN (Filippi, Riccitelli et al., 2012), DAN (Filippi, Riccitelli et al., 2012), ECN (Filippi, Riccitelli et al., 2012), HMN (Leavitt, Wylie, Girgis et al.,2014), thalamic network (De Giglio, Tona et al., 2016) or the anterior cingulate network (Parisi et al., 2014).

Most of the aforementioned functional connectivity studies have noted an increased functional connectivity within the explored networks following the cognitive intervention (Bonavita et al., 2015; De Giglio, Tona et al., 2016; Ernst et al., 2016a; Ernst et al., 2016b;

Filippi, Riccitelli et al., 2012; Leavitt, Wylie, Girgis et al., 2014; Parisi et al., 2014). Additionally, in some of these studies, FC increases were associated with improvements in cognitive performance (De Giglio, Tona et al., 2016; Filippi, Riccitelli et al., 2012; Parisi et al., 2014). Nevertheless, recent studies have reported functional connectivity decreases, along with FC increases or not, within the DMN and the thalamic network, following the implementation of different cognitive interventions (De Giglio, Tona et al., 2016; Ernst et al., 2016a; Ernst et al., 2016b). Interestingly, in one of these studies in which both functional connectivity increases and decreases were found, both kinds of findings were associated with cognitive improvements (De Giglio, Tona et al., 2016).

A summary of MS studies examining the effects of cognitive interventions on brain functional connectivity is provided in Table 3. Only those studies meeting the following criteria were considered: i) RCTs or matched controlled trials; ii) carried out on adult persons with MS; iii) examining both cognitive and resting-state functional connectivity MRI changes following cognitive rehabilitation; and iv) not combining the cognitive rehabilitation with other interventions (e.g. physical training, brain direct stimulation, etc.). Of note, only cognitive and functional connectivity longitudinal results, baseline vs. immediate follow-up, were reported in the table. Moreover, repeated measures analysis of variance (ANOVA) Time x Group interactions were preferentially described when possible.

On the other side, only a few studies have examined the effects of cognitive rehabilitation on brain structure. Thus, only three previous studies have specifically looked at cognitive rehabilitation effects on brain structural connectivity (Campbell, Langdon, Cercignani, & Rashid, 2016; De Giglio, Upadhyay et al., 2016; Filippi, Riccitelli et al., 2012). Two of these studies did not detect white matter microstructural changes after cognitive rehabilitation (Campbell et al., 2016; Filippi, Riccitelli et al., 2012). However, a preliminary study reported an AD decrease in the corpus callosum, which was associated

with a better cognitive performance (De Giglio, Upadhyay et al., 2016). With regards to other structural measures, nor did other studies found structural changes in lesion load, gray o white matter brain volume following the implementation of cognitive interventions (Bonavita et al., 2015; Filippi, Riccitelli et al., 2012).

A summary of MS studies examining the effects of cognitive interventions on brain structure is provided in Table 4. Only those studies meeting the following criteria were included in the table: i) RCTs or matched controlled trials; ii) carried out on adult persons with MS; and iii) examining both cognitive and structural MRI changes following a cognitive intervention. Of note, only cognitive and structural longitudinal results, baseline vs. immediate follow-up, were reported in the table. Moreover, repeated measures ANOVA Time x Group interactions were preferentially described when possible.

Despite the fact that distinct studies have investigated the neurobiological mechanisms underlying cognitive improvements in response to cognitive interventions in MS, these mechanisms are not yet entirely understood. Thus, traditionally only brain functional connectivity increases had been described following cognitive rehabilitation, whereas latest studies have revealed that adaptive functional connectivity decreases can also occur in the MS brain. In addition, very little is known about the structural basis of cognitive improvements following cognitive interventions in the disorder (De Giglio, Upadhyay et al., 2016). Accordingly, further research is needed in order to increase our understanding about the neurobiological processes that lie beneath cognitive rehabilitation improvements in MS.

Table 3. Summary of studies examining the effects of cognitive interventions on brain functional connectivity in MS.

Author (year)	Study design	Sample size	Cognitive intervention	Assessment and statistical analyses	Main significant results after the intervention
De Giglio, Tona et al. (2016)	Randomized single-blinded controlled trial (personnel responsible for MRI acquisition and cognitive assessment was blinded to participants' group assignment)	TG n = 11 (RR) CG n = 11 (RR)	***Dr. Kawashima's Brain Training:*** • Format: video game • Setting: at home and individual • Targets: At, VSP, memory and calculation • Duration: 8 weeks (5 sessions/week of 30 min)	***Rs-fMRI:*** • Assessment: FC within the thalamic network • Statistical analysis: two sample t-test [a paired t-test (baseline vs. follow-up) was first carried out for each group and the obtained results were compared through the two sample t-test] ***Cognition:*** • Assessment: SDMT, PASAT and ST • Statistical analysis: repeated measures ANOVA (Time x Group interaction)	***Brain FC changes:*** • Within the thalamic network: ○ The TG showed an increased FC of the thalamus with the bilateral posterior cingulate cortex, precuneus and lateral parietal cortex compared to the CG ○ The TG also showed a decreased FC of the thalamus with the vermis, the cerebellar hemispheres and the left dorsolateral prefrontal cortex compared to the CG ***Cognitive changes:*** • The TG presented cognitive improvements on the PASAT and ST compared to the CG ***Association between brain FC and cognition:*** • The FC increase of the thalamus with the lateral parietal cortices was associated with cognitive improvements on the SDMT (that showed a significant improvement on a paired t-test) • The FC increase of the thalamus with the right parietal cortex was associated with cognitive improvements on the ST • The FC decrease of the thalamus with the vermis and the cerebellar hemispheres was associated with cognitive improvements on the PASAT
Ernst et al. (2016a)	Randomized double-blinded placebo-controlled trial (personnel responsible for verifying cognitive	TG n = 10 (RR) CG n = 10 (RR)	***Mental visual imagery facilitation programme:*** • Format: non reported • Setting: individual • Target: mental	***Rs-fMRI:*** • Assessment: FC within the DMN • Statistical analysis: paired t-test (baseline vs. follow-up) for each group	***Brain FC changes:*** • Within the DMN: ○ The TG showed a decreased FC in the bilateral cingulate cortex and right precuneus

Author (year)	Study design	Sample size	Cognitive intervention	Assessment and statistical analyses	Main significant results after the intervention
	scoring accuracy for 20% of the cognitive assessments and participants were blinded to groups assignment)		visualization of scenes • Duration: 6 sessions of 120 min (one or two sessions/week)	***Cognition:*** • Assessment: adapted version of the Autobiographical Interview (internal and external details scores) • Statistical analysis: repeated measures ANOVA (Time x Group x detail interaction)	○ The CG showed an increased FC in the superior, middle and inferior frontal gryus ***Cognitive changes:*** • The TG presented cognitive improvements on the Autobiographical Interview compared to the CG
Ernst et al. (2016b)	Randomized double-blinded placebo-controlled trial (personnel responsible for verifying cognitive scoring accuracy for 20% of the cognitive assessments and participants were blinded to groups assignment)	TG n = 10 (RR) CG n = 7 (RR)	***Mental visual imagery facilitation programme:*** • Format: non reported • Setting: individual • Target: mental visualization of scenes • Duration: 6 sessions of 120 min (one or two sessions/week)	***Rs-fMRI:*** • Assessment: FC within the DMN • Statistical analysis: paired t-test (baseline vs. follow-up) for each group ***Cognition:*** • Assessment: adapted version of the Autobiographical Interview • Statistical analysis: repeated measures ANOVA (Time x Group interaction)	***Brain FC changes:*** • Within the DMN: ○ The TG showed an increased FC in the left lingual gyrus, left precuneus (BA19), left middle temporal gyrus and right posterior cingulate cortex (BA30), as well as a decreased FC in the right precuneus, left precuneus (BA7), right posterior cingulate cortex (BA23) and left angular gyrus. ○ The CG showed a decreased FC in the bilateral medial frontal gyrus and the right anterior cingulate cortex. ***Cognitive changes:*** • The TG presented cognitive improvements on the Autobiographical Interview compared to the CG
Bonavita et al. (2015)	Matched placebo-controlled trial (participants were subdivided in two age, gender and education matched groups)	TG n = 14 (RR) CG n = 18 (RR)	***RehaCom:*** • Format: computer-based • Setting: individual • Targets: At, IP and EF • Duration: 8 weeks (2 sessions/week of 50 min)	***Rs-fMRI:*** • Assessment: FC within the DMN • Statistical analysis: paired t-test (baseline vs. follow-up) for each group ***Cognition:*** • Assessment: BRB (SDMT, PASAT, SRT, SPART, WLG) and ST • Statistical analysis: paired t-test	***Brain FC changes:*** • Within the DMN: the TG showed an increased FC in the posterior cingulate and bilateral parietal cortex ***Cognitive changes:*** • The TG presented cognitive improvements on the SDMT, PASAT, SRT-D and SPART-D. ***Association between brain FC and cognition:*** • After the intervention, the FC of the posterior

Author (year)	Study design	Sample size	Cognitive intervention	Assessment and statistical analyses	Main significant results after the intervention
				(baseline vs. follow-up) for each group	cingulate cortex was negatively associated with the ST. According to the authors, this association was not clinically significant, since the TG did not improve its performance on the ST after the intervention.
Leavitt, Wylie, Girgis et al. (2014)	Randomized single-blinded placebo-controlled trial (personnel responsible for MRI acquisition and cognitive assessment was blinded to participants' group assignment)	TG n = 7 (6RR & 1PR) CG n = 7 (3RR, 2PP & 2SP)	***Modified Story Memory Technique (mSMT):*** • Format: computer-based • Setting: individual • Target: memory • Duration: 5 weeks (2 sessions/week of 45-60 min)	***Rs-fMRI:*** • Assessment: FC within the DMN and HMN • Statistical analysis: repeated measures ANOVA (Time x Group interaction) ***Cognition:*** • Assessment: CVLT • Statistical analysis: chi-square test (to explore group differences in the percentage of participants showing an improvement greater than a 10% on the CVLT)	***Brain FC changes:*** • Within the DMN: the TG showed an increased FC between the posterior cingulate cortex and the thalamus bilaterally compared to the CG • Within the HMN: the TG also showed an increased FC between the left hippocampus and bilateral insula, as well as between the right hippocampus and the left postcentral, precentral, middle frontal and cingulate gyrus compared to the CG ***Cognitive changes:*** • Significant results were not found. According to the authors, these results were probably due to the small sample size, since previous studies using larger samples reported memory improvements in the TG after the implementation of the mSMT
Parisi et al. (2014)	Randomized single-blinded controlled trial (personnel responsible for MRI acquisition and analysis was blinded to participants' group assignment)	TG n = 10 (RR) CG n = 10 (RR)	***RehaCom:*** • Format: computer-based • Setting: individual • Targets: At, IP and EF • Duration: 12 weeks (3 sessions/week of 1 hour)	***Rs-fMRI:*** • Assessment: FC of the anterior cingulate cortex • Statistical analysis: repeated measures ANOVA (Time x Group interaction) ***Cognition:*** • Assessment: some tests of the BRB (SDMT, PASAT, SRT and SPART), WCST, COWA and TEA	***Brain FC changes:*** • Of the anterior cingulate cortex: ○ The TG showed an increased FC between the anterior cingulate cortex and the right inferior parietal lobe compared to the CG ○ The CG showed a decreased FC between the anterior cingulate cortex and the right inferior temporal lobe compared to the TG ***Cognitive changes:*** • The TG presented cognitive improvements on the PASAT, COWA (phonemic cue test) and

Author (year)	Study design	Sample size	Cognitive intervention	Assessment and statistical analyses	Main significant results after the intervention
				• Statistical analysis: hierarchical linear mixed model (Time x Group interaction)	WCST compared to the CG ***Association between brain FC and cognition:*** • The FC increase of the anterior cingulate cortex with the right middle frontal gyrus (observed in a paired t-test of the TG) and inferior parietal lobe was associated with improvements on the PASAT
Filippi, Riccitelli et al. (2012)	Randomized single-blinded controlled trial (personnel responsible for MRI acquisition and analysis was blinded to participants' group assignment)	TG n = 10 (RR) CG n = 10 (RR)	***RehaCom:*** • Format: computer-based • Setting: individual • Targets: At, IP and EF • Duration: 12 weeks (3 sessions/week of 1 hour)	***Rs-fMRI:*** • Assessment: FC within the primary and secondary visual network, sensorimotor network, auditory network, DMN, ECN, SN, and WMN • Statistical analysis: hierarchical linear mixed model (Time x Group interaction) ***Cognition:*** • Assessment: some tests of the BRB (SDMT, PASAT, SRT and SPART), WCST, COWA and TEA • Statistical analysis: hierarchical linear mixed model (Time x Group interaction)	***Brain FC changes:*** • Within the DMN: the TG showed an increased FC of the right posterior cingulate cortex, precuneus and the inferior parietal lobule compared to the CG that presented a decreased FC on these brain regions • Within the SN: the CG showed a decreased FC of the anterior cingulate cortex compared to the TG. • Within the ECN: the CG showed a decreased FC of the left dorsolateral prefrontal cortex compared to the TG ***Cognitive improvements:*** • The TG presented cognitive improvements on the PASAT, COWA (phonemic cue test) and WCST compared to the CG ***Association between brain FC and cognition:*** • Changes in resting-state FC were associated with improvements on the PASAT and WCST

MRI = magnetic resonance imaging; TG = treatment group; RR = relapsing-remitting; CG = control group; At = attention; VSP = visuospatial processing; Rs-fMRI = resting-state functional magnetic resonance imaging; FC = functional connectivity; SDMT = Symbol Digit Modalities Test; PASAT = Paced Auditory Serial Addition Test; ST = Stroop Color-Word Test; ANOVA = analysis of variance; DMN = default mode network; BA = Brodmann area; IP = information processing; EF = executive functioning; BRB = Rao's Brief Repeatable Battery; SRT = Selective Reminding Test; SPART = 10/36 Spatial Recall Test; WLG = Word List Generation; SRT-D = Selective Reminding Test-Delayed; SPART-D = 10/36 Spatial Recall Test-Delayed; PR = progressive-relapsing; PP = primary-progressive; SP = secondary-progressive; HMN = hippocampal memory network; CVLT = California Verbal Learning Test; WCST = Wisconsin Card Sorting Test; COWA = Controlled Oral Word Association; TEA = Test of Everyday Attention; ECN = executive control network; SN = salience network; WMN = working memory network.

Table 4. Summary of studies examining the effects of cognitive interventions on brain structure in MS.

Author (year)	Study design	Sample size	Cognitive intervention	Assessment and statistical analyses	Main significant results after the intervention
Campbell et al. (2016)	Randomized single-blinded active-controlled trial (personnel responsible for MRI analysis was blinded to participants' group assignment)	TG n = 19 (14RR & 5SP) CG n = 19 (13RR & 6SP)	***RehaCom:*** • Format: computer-based • Setting: at home and individual • Targets: divided At, WM and visuospatial memory • Duration: 6 weeks (3 sessions/week of 45 min)	***MRI:*** • *QMT:* ○ Assessment: white and gray matter QMT parameters ○ Statistical analysis: repeated measures ANOVA (Time x Group interaction) ***Cognition:*** • Assessment: BICAMS (SDMT, CVLT and BVMT) • Statistical analysis: independent sample t-test comparing cognitive gain scores of each group	***Structural brain changes:*** • White and gray matter QMT parameters**:** no significant results ***Cognitive changes:*** • The TG presented cognitive improvements on the SDMT compared to the CG
De Giglio, Upadhyay et al. (2016)	Randomized single-blinded controlled trial (personnel responsible for MRI acquisition and cognitive assessment was blinded to participants' group assignment)	TG n = 9 (RR) CG n = 9 (RR)	***Dr. Kawashima's Brain Training:*** • Format: video game • Setting: at home and individual • Targets: At, VSP, memory and calculation • Duration: 8 weeks (5 sessions/week of 30 min)	***MRI:*** • *DWI:* ○ Assessment: FA, MD, RD and AD of the entire corpus callosum as well as of the genu, body and splenium ○ Statistical analysis: one-way ANCOVA comparing between groups follow-up data when controlling for baseline scores ***Cognition:*** • Assessment: SDMT, PASAT and ST • Statistical analysis: one-way ANCOVA comparing between groups follow-up data when controlling for baseline scores	***Structural brain changes:*** • FA, MD, RD and AD: the TG showed a decreased AD in the whole corpus callosum as well as in the genu and splenium compared to the CG ***Cognitive changes:*** • The TG presented cognitive improvements on the SDMT, PASAT and ST compared to the CG ***Association between brain structure and cognition:*** • The AD reduction of the whole corpus callosum, as well as of the genu and the splenium, was associated with cognitive improvements on the PASAT

Author (year)	Study design	Sample size	Cognitive intervention	Assessment and statistical analyses	Main significant results after the intervention
Bonavita et al. (2015)	Matched placebo-controlled trial (participants were subdivided in two age, gender and education matched groups)	TG n = 14 (RR) CG n = 18 (RR)	***RehaCom:*** • Format: computer-based • Setting: individual • Targets: At, IP and EF • Duration: 8 weeks (2 sessions/week of 50 min)	***MRI:*** • *T2-weighted structural MRI:* ○ Assessment: lesion load ○ Statistical analysis: student's t test (baseline vs. follow up) for each group • *T1-weighted structural MRI:* ○ Assessment: parenchymal brain volume ○ Statistical analysis: calculation of the percentage of brain volume change in the TG ***Cognition:*** • Assessment: BRB (SDMT, PASAT, SRT, SPART, WLG) and ST • Statistical analysis: paired t-test (baseline vs. follow-up) for each group	***Structural brain changes:*** • Lesion load: no significant results • Parenchymal brain volume: a 0.06% brain volume decrease was found, which was in line with the annual range expected for persons with MS ***Cognitive changes:*** • The TG presented cognitive improvements on the SDMT, PASAT, SRT-D and SPART-D
Filippi, Riccitelli et al. (2012)	Randomized single-blinded controlled trial (personnel responsible for MRI acquisition and analysis was blinded to participants' group assignment)	TG n = 10 (RR) CG n = 10 (RR)	***RehaCom:*** • Format: computer-based • Setting: individual • Targets: At, IP and EF • Duration: 12 weeks (3 sessions/week of 1 hour)	***MRI:*** • *T1-weighted structural MRI:* ○ Assessment: gray and white matter volumes ○ Statistical analysis: ANCOVA comparing gray and white matter volume changes of each group and controlling for age • *DWI:* ○ Assessment: FA and MD of the NAWM ○ Statistical analysis: paired t-test (baseline vs. follow-up) for each group	***Structural brain changes:*** • Gray and white matter volumes: no significant results • FA and MD of the NAWM: no significant results ***Cognitive changes:*** • The TG presented cognitive improvements on the PASAT, COWA (phonemic cue test) and WCST

Author (year)	Study design	Sample size	Cognitive intervention	Assessment and statistical analyses	Main significant results after the intervention
				Cognition: • Assessment: some tests of the BRB (SDMT, PASAT, SRT and SPART), WCST, COWA and TEA • Statistical analysis: hierarchical linear mixed model (Time x Group interaction)	

MRI = magnetic resonance imaging; TG = treatment group; RR = relapsing-remitting; SP = secondary-progressive; CG = control group; At = attention; WM = working memory; QMT = quantitative magnetization transfer; ANOVA = analysis of variance; BICAMS = Brief International Cognitive Assessment for MS; SDMT = Symbol Digit Modalities Test; CVLT = California Verbal Learning Test; BVMT = Brief Visual Memory Test; DWI = diffusion weighted imaging; VSP = visuospatial processing; FA = fractional anisotropy; MD = mean diffusivity; RD = radial diffusivity; AD = axial diffusivity; ANCOVA = analysis of covariance; PASAT = Paced Auditory Serial Addition Test; ST = Stroop Color-Word Test; IP = information processing; EF = executive functioning; BRB = Rao's Brief Repeatable Battery; SRT = Selective Reminding Test; SPART = 10/36 Spatial Recall Test; WLG = Word List Generation; SRT-D = Selective Reminding Test-Delayed; SPART-D = 10/36 Spatial Recall Test-Delayed; NAWM = normal-appearing white matter; WCST = Wisconsin Card Sorting Test; COWA = Controlled Oral Word Association; TEA = Test of Everyday Attention.

III. Approach to the present research, objectives and hypotheses

3. Approach to the present research, objectives and hypotheses

The present thesis consists of three studies which mainly aim to examine the role of slowed processing speed in other cognitive deficits and the effects of an integrative group-based cognitive rehabilitation programme on cognition, daily functionality and brain connectivity in persons with MS. A brief summary of the background as well as the objectives and hypotheses of each study are detailed below.

3.1. Study I

"The role of processing speed in MS cognitive impairment"

Background

Cognitive impairment is a common consequence of MS. Diverse studies assert that processing speed decline negatively affects other cognitive domains in the disorder. Nevertheless, it is still uncertain whether persons with MS present a core processing speed decline that gives rise to other cognitive deficits or from deficits in several cognitive domains which are independent of processing speed decline.

Objectives

i. The first objective of this study was to examine the cognitive deficits presented by persons with MS, when compared to healthy subjects, in a wide range of cognitive domains (attention, processing speed, working memory, verbal memory, visual memory, verbal fluency, inhibition and flexibility).

ii. The second and main objective of this study was to re-examine the cognitive deficits presented by persons with MS when controlling for the effect of processing speed and visual memory (as a control covariate) in independent analyses.

Hypotheses

i. With regards to the first objective, it was hypothesized that persons with MS would exhibit cognitive deficits in all the cognitive domains that were assessed.

ii. In relation to the second objective, it was hypothesized that those cognitive deficits initially presented by persons with MS would become non-significant when controlling for the effect of processing speed, but would remain significant when controlling for the effect of visual memory.

3.2. Study II

"Integrative group-based cognitive rehabilitation efficacy in multiple sclerosis: a randomized clinical trial"

Background

Cognitive rehabilitation might be a promising therapeutic approach for addressing cognitive deficits in persons with MS. However, recent reviews have only reported a low or some level of evidence for the efficacy of cognitive rehabilitation in the disorder due to the presence of methodological flaws in the literature. Accordingly, these reviews agree in that methodologically rigorous RCTs are still needed.

Objectives

i. The objective of the present study was to assess the efficacy of an integrative group-based cognitive rehabilitation programme, the REHACOP, on improving cognitive functioning (attention, processing speed, working memory, episodic memory, verbal fluency, executive functioning and social cognition) and daily functionality in persons with MS.

Hypotheses

i. With regards to the objective of the present study, it was hypothesized that persons with MS attending the cognitive rehabilitation would improve their cognitive functioning and daily functionality when compared to those who did not receive the cognitive intervention.

3.3. Study III

"Effects of integrative group-based cognitive rehabilitation on brain connectivity in multiple sclerosis: a randomized clinical trial"

Background

The neurobiological mechanisms underlying cognitive improvements following cognitive rehabilitation are not yet entirely understood in MS. Specifically, the study of brain functional and structural connectivity changes following cognitive interventions might be especially relevant in MS, given that the disconnection syndrome has been suggested to lie beneath cognitive impairment in the disorder.

Objectives

i. The main objective of this study was to examine brain functional and structural connectivity changes following the implementation of the REHACOP cognitive rehabilitation programme in persons with MS:
    a. Brain functional connectivity changes were examined within specific cognitive networks (DMN, SN, DAN, HMN and ECN).
    b. Brain structural connectivity changes were examined in the whole brain.

ii. The second objective of this study was to investigate the relationship between brain functional/structural connectivity changes and cognitive improvements following the cognitive intervention.

Hypotheses

i. With regards to the first objective, it was hypothesized that:

    a. Persons with MS attending the cognitive rehabilitation would exhibit brain functional connectivity changes when compared to those who did not receive the cognitive intervention.

    b. Persons with MS attending the cognitive rehabilitation would not exhibit brain structural connectivity changes when compared to those who did not receive the cognitive intervention.

ii. In relation to the second objective, it was hypothesized that significant relationships would be detected between brain functional connectivity changes and cognitive improvements following the cognitive intervention.

IV. Methods

4. Methods

4.1. Study sample

The sample of the present study consisted of 44 persons with MS and 44 healthy controls (HC) matched for sex, age and education. MS participants were included in the study according to the following inclusion criteria: i) being diagnosed with MS according to McDonald et al. (2001) diagnostic criteria; ii) suffering from RRMS, SPMS or PPMS; iii) being aged between 20-60 years; and iv) being cognitively impaired or preserved. Each MS participant included in the study was assigned a matched HC (1:1 ratio). Inclusion criteria for HC were as follows: i) being of the same sex as a particular MS participant; and ii) having a maximum of ± 3 years of age and education when compared to such participant.

With regards to MS participants and HC exclusion criteria, these included: i) a Mini Mental State Examination Test (MMSE) (Folstein, Folstein, & McHugh, 1975) total score lower than 24; ii) the presence of severe psychiatric disorders (e.g. schizophrenia, bipolar disorder, etc.); iii) the diagnosis of neurological disorders (different from MS for the patients' group, such as stroke, epilepsy, etc.); and iv) history of traumatic brain injury with a loss of consciousness for over 30 minutes. MS participants were also excluded from the study if they i) had suffered a relapse during the month prior to the cognitive/MRI assessment; or ii) were being treated with corticosteroids, given the negative impact that this pharmacological treatment can entail on cognitive performance (Rogers & Panegyres, 2007). Likewise, those participants that refused the MRI assessment or presented neuroimaging artifacts in the rs-fMRI or DWI acquisitions were excluded from the corresponding MRI analyses.

The recruitment process of the participants with MS is detailed in Figure 7. MS participants were randomly allocated to the intervention (n = 22) or the waiting list control condition (n = 22). Two MS participants, one from each condition, did not complete the study. Hence, forty-two participants with the disorder, 21 from each condition, completed

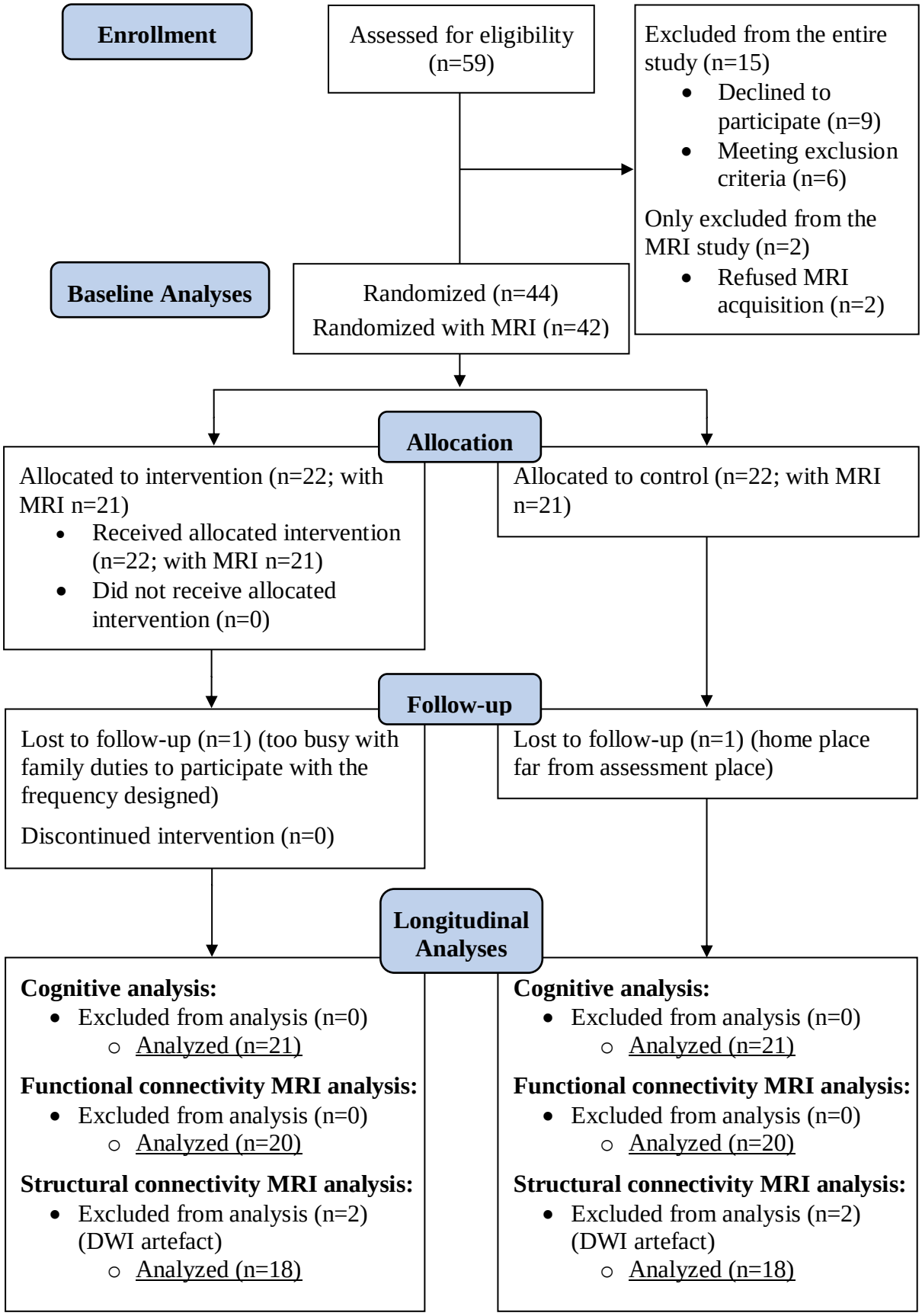
their participation in the study. From these 42 MS participants two refused the MRI acquisition (one from each condition), and other four (two from each condition) presented MRI acquisition artifacts in the DWI sequence. Accordingly, brain functional connectivity analyses were conducted with 40 participants (20 in each condition) and structural connectivity analyses with 36 participants (18 in each condition).

4.2. Procedure

The current study was approved by the Ethics Committee of the University of Deusto and of the Basque Health System. Specifically, a prospective longitudinal clinical trial, with a non-blinded parallel-group randomized design, was conducted. Therefore, this study was registered with clinicaltrials.gov, number NCT02287454. Moreover, an a priori power analysis was performed to determine the required sample size for carrying out the trial.

The recruitment of the participants with MS was conducted in the University Hospitals of Cruces and Basurto (Biscay, Spain), from January 2013 to September 2015. These participants were informed about the opportunity to collaborate in this trial by their respective neurologists. The recruitment of HC was done through the collaboration of the researchers and MS participants involved in this study, as healthy participants belonged to their family or social settings. This recruitment was carried out from October 2013 to December 2015. All participants filled in a written informed consent prior to their involvement in the study, and individual numerical codes were assigned to each of them to assure confidentiality.

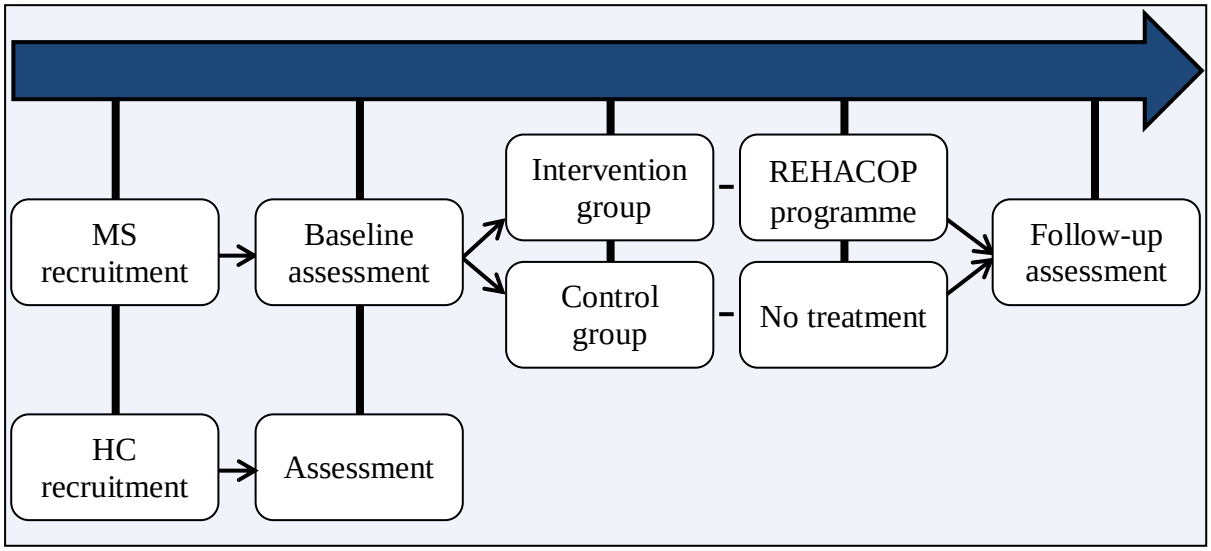
Figure 7. Flow diagram of the study.



MRI = magnetic resonance imaging; DWI = diffusion weighted imaging.

MS participants completed a neurological, cognitive, clinical, functional and MRI assessment at baseline and 3 months follow-up (i.e. after the intervention period). All of them were assessed at the Multiple Sclerosis Association of Biscay (ADEMBI) or at the University of Deusto. Following the baseline assessment, MS participants were randomly allocated to the intervention or control group at a proportion of 1:1 by means of an online random number generator. Those participants allocated to the intervention group attended the cognitive rehabilitation with the REHACOP programme at ADEMBI during three consecutive months (13 weeks). Specifically, three one-hour cognitive sessions were conducted per week, that is, 39 sessions in total. Of note, five MS participants from the intervention group were receiving private cognitive rehabilitation during their participation in this clinical trial. These participants attended a mean of 10 cognitive rehabilitation sessions of 45 min each, which were predominantly targeted to improve short-term memory. The control group did not participate in any intervention during these three months, since it was assigned to a waiting list. Follow-up assessments were accomplished within the first and the second week following the cognitive intervention period. The participants of the control group received the opportunity to participate in the cognitive rehabilitation programme once their collaboration in the study was finished. On the other side, the HC group also underwent a cognitive, clinical, functional and MRI assessment, but only at one time point. HC were assessed at the University of Deusto. The assessment administered to the MS group at baseline and to the HC was exactly the same. The design of this study is summarized in Figure 8.

Figure 8. Summary of study design.



MS = multiple sclerosis; HC = healthy controls; REHACOP programme = REHACOP cognitive rehabilitation programme; control group = waiting list control group.

4.3. Neurological, neuropsychological and clinical/functional assessment

4.3.1. Neurological assessment

The neurological assessment was exclusively administered to the MS sample. Three specific neurological scales were administered with the aim of evaluating MS participants' disability and motor impairment of the dominant upper limb. The neurological exams were administered by two experienced neurologists.

Disability status. MS participants' disability status was measured by means of the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). This scale evaluates the affectation of the pyramidal, cerebellar, brain stem, sensory, sphincter, visual and mental functional systems. The overall scoring of this scale ranges from 0 to 10, with higher scores indicating a greater degree of disability.

Dominant upper limb motor impairment. The motor impairment of the dominant upper limb was evaluated with the Limb Ataxia Scale of the EDSS (EDSS LAS) (Kurtzke, 1983) and the British Medical Research Council Scale (MRC) (Medical Research Council,

1976). The EDSS LAS was used to measure the coordination of the dominant upper limb. Its score ranges from 0 to 4, and higher scores indicate a greater degree of impairment. The MRC was utilized to assess the motor balance of the dominant upper limb. Its score ranges from 0 to 5, with lower scores indicating a greater degree of impairment.

4.3.2. Neuropsychological assessment

All participants underwent an extensive neuropsychological battery. This battery included tests of attention, processing speed, working memory, episodic memory, verbal fluency, executive functioning and social cognition. The neuropsychological assessment was administered by a trained neuropsychologist.

Premorbid IQ. Premorbid IQ was evaluated through the Word Accentuation Test (TAP) (Gomar et al., 2011). In this test the examinee is instructed to read a total of 30 words aloud taking into account their accentuation. Each word is scored as correct or incorrect according to the utilization of an adequate or inadequate accentuation.

Attention. This cognitive domain was assessed by means of the Brief Test of Attention (BTA) (Schretlen, 1997). The BTA comprises two forms, the numbers and the letters form. In the numbers form 10 strings, each containing numbers and letters in an arbitrary order, are auditory presented at a pace of one letter/number per second. The examinee is asked to count the number of numbers heard in each sequence. Subsequently, in the letters form, the same 10 strings are auditory presented again and the examinee is asked to count the number of letters heard in each sequence.

Processing speed. Different neuropsychological test were utilized to measure processing speed, being these the written version of the Symbol Digit Modalities Test (SDMT) (Smith, A., 2002), the Salthouse Letters Comparison Test (LCT) (Salthouse & Babcock, 1991) and the Trail Making Test - A (TMT-A) (Reitan & Wolfson, 1985). In the

SDMT a reference key, in which several symbols are matched with specific numbers, and series of symbols with an empty space beneath are shown on a sheet. The examinee is requested to write in the empty space beneath each symbol the fitting number according to the reference key. The time limit for performing this task is a minute and a half. In the LCT the examinee is required to compare diverse couples of letter strings that are presented on two sheets of paper. In the first sheet these strings are conformed of three letters, while in the second one consist of six letters. The examinee is instructed to compare the pairs of letter strings and to write an "I" if they were equal or a "D" if they were dissimilar. The time limit for completing each sheet is 30 seconds. In the TMT-A 25 encircled numbers, from 1 to 25, are shown dispersed in a piece of paper in a random fixed order. The examinee is asked to connect the numbers in ascending order as quickly as possible. The time it takes the examinee to finish the task is recorded.

Working memory. This cognitive domain was measured with the Backward Digits Subtest (BD) of the Wechsler Adult Intelligence Scale III (WAIS-III) (Weschler, 2002). In this test the examiner reads sequences of numbers aloud at a pace of one number per second, and the examinee is asked to repeat each sequence in inverse order.

Episodic memory. The Hopkins Verbal Learning Test - Revised (HVLT-R) was administered to evaluate participants' verbal learning and long-term recall capacity (Brandt & Benedict, 2001). In this test the examiner reads aloud a list of 12 words three times at a pace of one item per second. Immediately after each reading, the examinee is asked to repeat as many words as he/she can recall (learning task). After a period of 20 minutes the examinee is asked to freely recall the list of words (delayed free recall task). Equivalent forms of the HVLT-R were administered at baseline (form 2) and follow-up (form 4) assessments to avoid a learning effect. In addition, the Brief Visual Memory Test - Revised (BVMT-R) was used to measure participants' visual learning and long-term recall capacity. In this test a sheet of

paper with six geometric figures is visually presented to the person being evaluated three times, during ten seconds at a time. Immediately after each presentation, the examinee is instructed to draw the six figures as accurately as possible and in their adequate location on a white piece of paper (learning task). After a period of 20 minutes, the examinee is instructed to freely recall and draw the six figures, as accurately as possible and in their correct location, on a white piece of paper (delayed free recall task). Equivalent forms of the BVMT-R were administered at baseline (form 1) and follow-up (form 3) assessments to avoid a learning effect.

Verbal fluency. The evaluation of semantic and phonemic verbal fluency was performed through the Calibrated Ideational Fluency Assessment (CIFA) (Schretlen & Vannorsdall, 2010). In the semantic fluency task the examinee is asked to say as many animals as possible for one minute, as well as supermarket items for another minute. In the phonemic fluency task the examinee is instructed to say as many words beginning with the letter "P" as possible for a period of three minutes.

Executive functioning. The Stroop Color and Word Test (ST) (Golden, 2001) and the Trial Making Test – B (TMT-B) (Reitan & Wolfson, 1985) were administered to evaluate inhibition and flexibility, respectively. The ST consists of three parts, the color, the word and the color-word trial. In the word trial, a sheet with color words (red, blue and green) is presented to the examinee, which is required to read aloud the color words. In the color trial, a sheet with series of four X "XXXX" printed in red, blue or green is presented to the examinee, which is instructed to say aloud the color ink in which each series of X was print. In the color-word response inhibition trial, a sheet with color words printed in incongruent colors is presented to the examinee, which is asked to name the color ink in which each word was presented. The time frame for the execution of each trial is 45 seconds. In the TMT-B 25 encircled numbers (from 1 to 13) and letters (from A to L) are shown dispersed in a piece of

paper and in a random fixed order. The examinee is asked to connect the circles as quickly as possible and alternating between numbers and letters in ascending and alphabetical order, respectively (i.e. 1-A-2-B-3-C, etc.). The time it takes the examinee to finish the task is recorded. A time limit of 5 minutes was established for the accomplishment of the task.

Social cognition. The Happé's Strange Stories Test (SST) (Fletcher et al., 1995; Pousa, 1999) was utilized in order to assess theory of mind. This test consists of eight brief stories, which can be classified according to the described situation: double bluff (two stories), white lies (two stories), persuasion (two stories) or mistakes (two stories). In this test the examinee is asked to read the stories, and to answer a question after each reading. Questions require making inferences about the intentions of the main character of the story. Responses are scored from 0 to 2 (0 = non-related responses; 1 = implicit responses; 2 = explicit responses). To avoid a test-retest learning effect four different stories were administered at baseline (stories 2, 3, 5 and 8) and follow-up (stories 1, 4, 6 and 7). One story of each type (double bluff, white lies, persuasion and mistakes) was administered at each time point.

Of note, in all these tests a higher score indicates a greater cognitive performance, except for the TMT-A and TMT-B.

4.3.3. Clinical/functional assessment

Additionally, some clinical and functional scales were administered with the aim of evaluating participants' depressive and fatigue symptoms, as well as daily functionality. The clinical and functional assessment was administered by a trained neuropsychologist.

Depressive symptoms. The Geriatric Depression Scale (GDS) (Martínez et al., 2002) was applied to evaluate participants' depressive symptoms. Specifically, the short form of the

GDS consisting of 15 items with two answer options (yes or no) was utilized. In this scale higher scores indicate a greater level of depression.

Fatigue symptoms. Physical and mental fatigue symptoms were evaluated by means of the Fatigue Severity Scale (FSS) (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989) and the Visual Analogue Scale (VAS), respectively. The FSS is conformed of nine items, focused on physical fatigue and its impact in daily life functioning, with seven answer options each (1 = totally disagree / 7 = totally agree). On the other side, the VAS consists of a single item in which the person being evaluated is requested to indicate their degree of mental fatigue, from 0% to 100%, in a horizontal line. In both scales higher scores indicate a greater level of fatigue.

Instrumental activities. Participants also completed the Lawton Instrumental Activities of Daily Living Scale (IADLs) (Lawton & Brody, 1969) that is targeted to measure the capacity to perform eight different instrumental activities (using a telephone, doing shopping, cooking, performing household tasks, doing laundry, using public transport, taking the medicine as prescribed and handling finances). In this scale higher scores indicate a greater level of autonomy in the performance of instrumental activities.

A summary of the neurological, neuropsychological and clinical/functional assessment is provided in Table 5.

Table 5. Neurological, neuropsychological and clinical/functional assessment.

Neurological assessment			
Area		**Neurological test**	
Disability status		Expanded Disability Status Scale (EDSS)	
Motor impairment of the dominant upper limb		Limb Ataxia Scale of the Expanded Disability Status Scale (EDSS LAS)	
		British Medical Research Council Scale (MRC)	
Neuropsychological assessment			
Cognitive domain		**Neuropsychological test**	
Premorbid intelligence		Word Accentuation Test (TAP)	
Global cognition		Mini-Mental State Examination Test (MMSE)	
Attention		Brief Test of Attention (BTA)	
Processing speed		Symbol Digit Modalities Test (SDMT)	
		Salthouse Letters Comparison Test (LCT)	
		Trail Making Test - A (TMT-A)	
Working memory		Backward Digits (BD) Subtest of the Wechsler Adult Intelligence Scale (WAIS-III)	
Episodic memory	***Verbal memory***	Hopkins Verbal Learning Test - Revised (HVLT-R)	Learning
			Delayed recall
	Visual memory	Brief Visual Memory Test - Revised (BVMT-R)	Learning
			Delayed recall
Verbal fluency		Calibrated Ideational Fluency Assessment (CIFA)	Animals
			Supermarket items
			P words
Executive functions	***Inhibition***	Stroop Color and Word Test (ST)	
	Flexibility	Trail Making Test - B (TMT-B)	
Theory of mind		Happé's Strange Stories Test (SST)	
Clinical/functional assessment			
Domain		**Clinical/functional test**	
Depression		Geriatric Depression Scale (GDS)	
Fatigue		Fatigue Severity Scale (FSS)	
		Mental Fatigue Visual Analogue Scale (VAS)	
Instrumental activities		Lawton Instrumental Activities of Daily Living Scale (IADLs)	

4.4. MRI assessment

MRI data was acquired on a Philips Achieva 3-Tesla scanner at OSATEK, the MRI Unit of the Hospital of Galdakao (Spain). All MRI sessions were acquired by an experienced neuroradiologist. In each MRI session structural T1-weighted imaging, DWI and rs-fMRI sequences were obtained. The same imaging protocol was utilized at baseline and follow-up assessment.

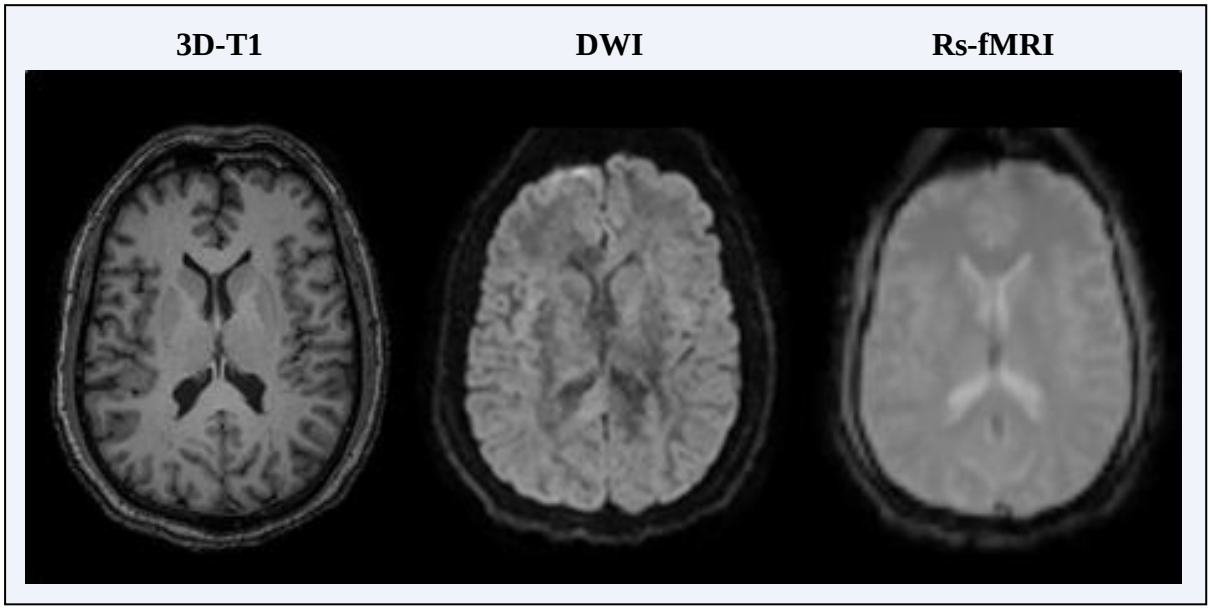
Structural high-resolution T1-weighted Turbo Field Echo 3D images were obtained in a sagittal orientation (anterior-posterior phase encoding direction) and using a multi-shot sequence (TR = 7.4 ms, TE = 3.4 ms, flip angle = 9º, matrix size = 228 x 218 mm, FOV = 250 x 250 mm, slices = 300, slice thickness = 1.1 mm, voxel size = 0.98 x 0.98 x 0.60 mm, and AT = 4'55'').

DWI was obtained in an axial orientation (anterior-posterior phase encoding direction) using a single-shot EPI sequence (TR = 7540 ms, TE = 76 ms, flip angle = 90º, matrix size = 120 x 117 mm; FOV = 240 x 240 mm, contiguous slices = 66, slice thickness = 2 mm, and voxel size = 1.67 x 1.67 x 2.0 mm) with diffusion weighting along 32 uniformly distributed directions (b = 1,000 s/mm^2) and a non-diffusion weighted image (b = 0 s/mm^2). Two identical repetitions were acquired (total acquisition time = 9'31'').

Finally, rs-fMRI was obtained in an axial orientation (anterior-posterior phase encoding direction) and using a multi-slice gradient echo planar imaging sequence (TR = 2100 ms, TE = 16 ms, flip angle = 80º, matrix size = 80 x 78 mm, FOV = 240 x 240 mm, volumes/run = 214, slices = 40, slice thickness = 3 mm, slice gap = 0.25 mm, voxel size = 3 x 3 x 3 mm, and AT = 7'40''). Participants were instructed to rest, not focus their thoughts on anything in particular, keep their eyes closed and not fall asleep.

An example of the images acquired with each MRI sequence is shown in Figure 9.

Figure 9. MRI and fMRI acquisitions.



3D-T1 = structural T1-weighted imaging; DWI = diffusion weighted imaging; Rs-fmri = resting-state functional magnetic resonance imaging.

4.5. Cognitive rehabilitation programme

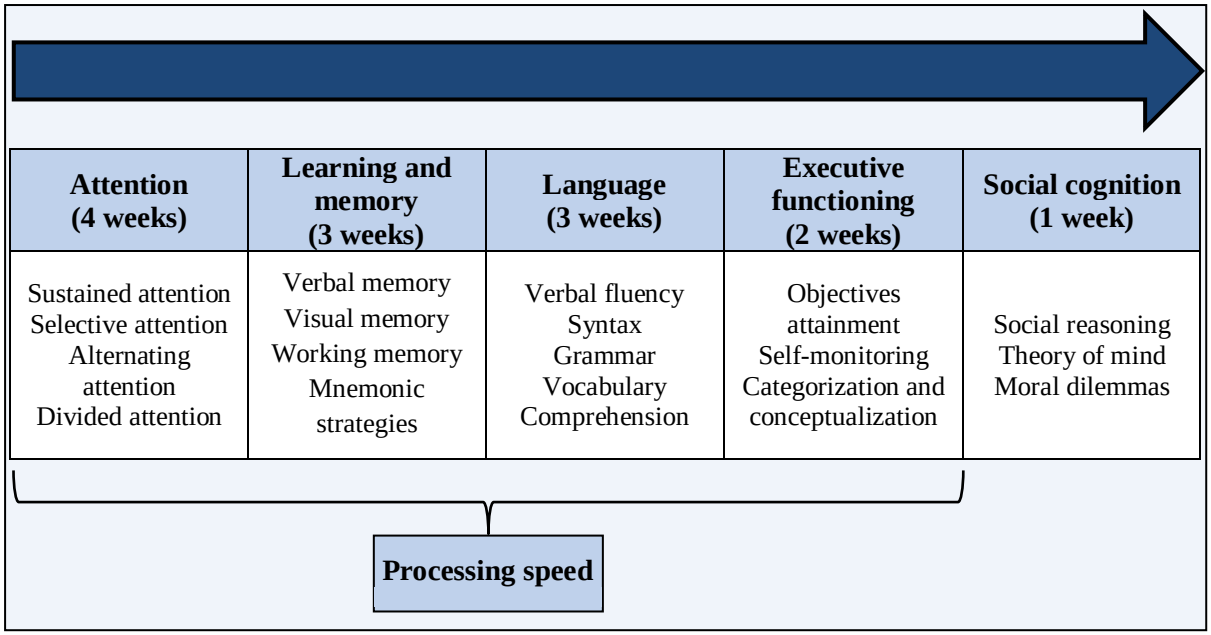
The REHACOP (www.rehacop.deusto.es) is an integrative paper-pencil cognitive rehabilitation programme that has been designed according to the principles of restoration, optimization and compensation (Ojeda & Peña, 2012). This programme provides materials for 20 weeks of rehabilitation, with a frequency of three sessions per week of 90 minutes each. It comprises a total of 300 tasks and is arranged into eight different modules. Each module of the REHACOP is targeted to the rehabilitation of specific domains including attention, learning and memory, language, executive functioning, social cognition, social skills, activities of daily living and psycho-education. Processing speed is also trained during the first four modules, given that subjects are instructed to complete diverse paper-pencil tasks as quickly as possible or within specific periods of time.

The REHACOP programme is highly structured and hierarchically organized. It uses a bottom-up approach with a final integration of top-down tasks in the module of activities of daily living. In other words, the target of the rehabilitation gradually advances from basic to

increasingly more complex and sophisticated cognitive processes, and the intervention concludes with daily living complex tasks that require the appropriate performance of more basic cognitive processes. Tasks within each module are additionally organized by subtypes of abilities and three levels of difficulty, which also ensures an increasing level of cognitive effort and demand within the different modules. Moreover, this cognitive rehabilitation programme enables individual and group administrations.

For the purpose of the present study, only the first five modules of the REHACOP cognitive rehabilitation programme were implemented. Specifically, the intervention group received the cognitive intervention during 13 consecutive weeks, with a frequency of three sessions per week (39 sessions) of one hour each. All cognitive sessions were administered in group format. The timetable of the cognitive intervention included: i) four weeks focused on attention capacities (sustained, selective, alternating and divided attention); ii) three weeks training learning and memory [memory stimulation (verbal and visual learning and delayed recall as well as working memory) was combined with mnemonic training]; iii) three weeks exercising language abilities (verbal fluency, syntax, grammar, vocabulary and comprehension); iv) two weeks training executive functioning [objectives planning and attainment, self-monitoring (problem-solving as well as verbal and social reasoning), categorization and conceptualization]; and v) one week focused on social cognition (social reasoning, theory of mind and moral dilemmas). In order to generalize the utilization of learning strategies to daily life functioning, participants were asked to perform tasks at home during the learning and memory module three days per week. A few examples of such tasks are: writing a diary detailing what they had done some days before, doing shopping without a checklist or reading a piece of news and explaining it in the next cognitive rehabilitation session. The cognitive rehabilitation timetable is summarized in Figure 10.

Figure 10. Cognitive rehabilitation timetable.



Four rehabilitation groups, of between five and eight participants each, were conducted. These groups were supervised by two neuropsychologists trained in the administration of the REHACOP programme. All groups performed exactly the same tasks during the cognitive intervention. The same procedure was followed for the performance of each cognitive task: i) the neuropsychologist explained the corresponding task to the entire group; ii) every participant performed the task individually; iii) the task was corrected with the participation of the entire group; iv) participants had the opportunity to discuss with the group the difficulties experienced and the strategies used during the completion of the task.

4.6. Statistical and MRI analyses

4.6.1. Study I

The Shapiro-Wilk test was applied to explore the distribution of the data. Socio-demographic and clinical differences between the MS and the HC group were explored through Mann-Whitney U and Chi-square tests for quantitative and qualitative variables, respectively.

Objective I

Raw cognitive scores were converted into standardized values by considering the means and standard deviations of the HC group. Those variables in which higher scores indicated lower cognitive performance (i.e. the TMT-A and TMT-B) were recoded. Subsequently, a composite score was created for each cognitive domain assessed with several measures by calculating their respective average value. Composites scores were as follows: i) processing speed (SDMT, LCT and TMT-A); ii) verbal episodic memory (HVLT-R learning and delayed free recall); iii) visual episodic memory (BVMT-R learning and delayed free recall); iv) verbal fluency [CIFA phonemic (words beginning with P) and semantic (animals and supermarket categories) cued conditions]; and v) inhibition (ST color-word trial and interference score). The internal consistency of each composite score was assessed with Cronbach's alpha. All composite scores showed a satisfactory internal consistency (processing speed $\alpha = 0.85$, verbal memory $\alpha = 0.87$, visual memory $\alpha = 0.89$, verbal fluency $\alpha = 0.85$, and inhibition $\alpha = 0.80$). Additionally, given that the manual dexterity of the dominant upper limb was a potential confounding factor in processing speed (SDMT LCT and TMT-A) and flexibility tasks (TMT-B) in MS participants, these two measures were regressed on the EDSS Limb Ataxia Scale and the MRC. The standardized residuals were saved and used as the definitive processing speed and flexibility scores, free of the influence of motor impairment.

Cognitive differences [in processing speed, attention, working memory, verbal and visual episodic memory, verbal fluency and executive functioning (inhibition and flexibility)] between MS participants and HC were examined through a multivariate analysis of covariance (MANCOVA). This MANCOVA, and the following ones, included premorbid IQ, depression and physical fatigue as covariates, since significant differences were detected between the MS and the HC group in such features.

Objective II

A second MANCOVA was additionally performed in order to explore whether the initial between-group cognitive differences were attenuated when controlling for the effect of processing speed. Of note, in this MANCOVA processing speed was not included as dependent variable. Finally, a third MANCOVA was carried out to verify the specific role of processing speed on MS cognitive impairment. As noticed in prior studies, and in the present one, visual memory is one of the cognitive domains most frequently impaired in persons with MS (Table 8). Because of this reason, visual memory was specifically chosen as a control covariate. Nevertheless, as visual memory might include an inherent component of processing speed, the composite score of visual memory was regressed on processing speed and the standardized residual was saved. Then, the third MANCOVA was conducted to explore between-group cognitive differences when controlling for visual memory (free of its processing speed component). In this MANCOVA visual memory was not included as dependent variable.

The Holm-Bonferroni stepwise correction for multiple comparisons was applied in order to reduce the type I error rate in each MANCOVA. Effect sizes were estimated with partial eta-squared. The magnitude of the effect size was interpreted according to Cohen (1988): small = 0.01 – 0.06, moderate = 0.061 – 0.14 and large > 0.14. All statistical analyses were carried out by means of the Statistical Software Package for Social Sciences (SPSS), version 23.0.

4.6.2. Study II

An a priori power analysis was performed to determine the sample size required to explore the efficacy of a cognitive intervention in persons with MS. This analysis was based on a former clinical trial in the disorder (Cerasa et al., 2013). It was found that a sample size

of 42 subjects, 21 in each condition, was enough to detect between-group cognitive differences with a Cohen's d of 0.88, a power of 80% and an alpha level of 5%. This analysis was accomplished using the G*Power 3 software (Faul, Erdfelder, Lang, & Buchner, 2007).

The Shapiro-Wilk test was applied to explore the distribution of the data. The comparison of the sociodemographic and clinical characteristics between the intervention and the control group, at baseline, was performed by means of a multivariate analysis of variance (MANOVA) (or Mann-Whitney U test) and the Chi-square test, as appropriate.

Given that distinct measures were used to evaluate some cognitive domains, several composite scores were created. To this end, all raw cognitive measures were converted into standardized values according to the entire MS sample. Subsequently, TMT-A and TMT-B scores were recoded, so that higher scores indicated a greater cognitive performance. Composite scores were created for processing speed (SDMT, LCT and TMT-A), episodic memory [verbal (HVLT-R learning and delayed free recall) and visual (BVMT-R learning and delayed free recall)], verbal fluency [CIFA phonemic (words beginning with P) and semantic (animals and supermarket categories) cued conditions] and executive functioning [ST (color-word trial and interference scores) and TMT-B]. The internal consistency of each composite score was assessed through Cronbach´s alpha. All composite scores showed a satisfactory internal consistency (processing speed $\alpha = 0.88$, episodic memory $\alpha = 0.77$, verbal fluency $\alpha = 0.85$, and executive functioning $\alpha = 0.70$).

Cognitive and functional differences between the intervention and the control group at baseline were examined with a MANCOVA. In that analysis the impact of physical and mental fatigue was controlled. A repeated measures MANCOVA was also carried out in order to assess the efficacy of the REHACOP cognitive rehabilitation programme on improving cognitive functioning and daily life functionality. In the latter analysis the impact of physical and mental fatigue was also controlled along with the influence of having

included MS participants with different cognitive profiles (with and without cognitive impairment), which might profit in a different way from the cognitive rehabilitation. MS participants' cognitive profile was defined taking into consideration their cognitive performance on the SDMT. Thus, SDMT raw scores were converted into standardized scores based on the mean and standard deviation of the HC group. Cognitive impairment was defined as a raw score below 1.5 SD according to the mean of the HC group. A dichotomous variable determining the cognitive profile of each MS participant (impaired or preserved) was created, and included as a covariate in the MANCOVA. Effect sizes were estimated with partial eta-squared. The statistical significance was thresholded at 5% ($p \leq 0.05$) for every analysis.

4.6.3. Study III

The Shapiro-Wilk test was used to examine the distribution of the socio-demographic and clinical data. Socio-demographic and clinical differences between the intervention and the control group at baseline were explored using MANOVA (or Mann-Whitney U test) and Chi-square test, as appropriate.

Objective I

Objective I.a

Resting-state fMRI data was analyzed by means of the Conn Functional Connectivity Toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012), version 15.h. The default preprocessing and denoising pipeline was applied to the time series of functional images acquired at baseline and follow-up. This pipeline included: i) fMRI data realignment to the first scan and unwarping; ii) coregistration to structural T1-weighted images; iii) slice-timing correction for interleaved bottom-up acquisitions; iv) structural T1-weighted images segmentation and spatial normalization into the standard Montreal Neurological Institute

(MNI) space; v) motion outliers detection in the fMRI data with ART-based scrubbing (z-threshold = 9 and movement threshold = 2 mm); vi) smoothing using a 8 mm full-width at half-maximum (FWHM) Gaussian kernel; vii) detection of movement and physiological confounds through the anatomical component correction (aCompCor) strategy; viii) removal of confounding effects by linearly regressing out of the fMRI signal the realignment, scrubbing and aCompCor parameters; and ix) fMRI signal band-pass filters restriction from 0.008 to 0.09 Hz (Weissenbacher et al., 2009).

Brain functional connectivity within the DMN, SN, DAN, ECN and HMN was examined by using a region of interest (ROI-to-ROI) approach. Selected regions of interest (ROIs) for the DMN (Buckner, Randy L. et al., 2008; Fox et al., 2005), SN (Seeley et al., 2007), DAN (Spreng et al., 2013) and ECN (Desikan et al., 2006; Spreng et al., 2013) had been previously identified as nodes conforming such networks (Table 6). Independent analyses were performed for each network, in which the corresponding ROIs were considered as seeds and targets. ROIs were selected from the FSL Harvard-Oxford Cortical Structural (Desikan et al., 2006), DMN (Fox et al., 2005) and Talairach atlases (Lancaster et al., 2000; Talairach & Tournoux, 1988). Because the nodes involved in the HMN have not been as well-defined as those conforming the remaining networks, the right and left hippocampi were selected as seeds and all brain regions included in the Harvard-Oxford as targets.

Longitudinal ROI to ROI functional connectivity analyses were independently conducted for each resting state network with the Conn Toolbox. The efficacy of the REHACOP programme on inducing brain functional connectivity changes was examined through repeated measures MANOVA (Time x Group interactions). These analyses were corrected for multiple comparisons across space by applying the false discovery rate (FDR).

Table 6. Anatomical regions used as network nodes (seeds and targets) for ROI-to-ROI functional connectivity analyses.

DMN (Buckner, Randy L. et al., 2008; Fox et al., 2005)	SN (Seeley et al., 2007)
• Medial prefrontal cortex • Anterior cingulate cortex • Posterior cingulate cortex • Precuneous • Lateral parietal cortex • Anterior middle temporal gyrus • Posterior middle temporal gyrus • Hippocampus	• Anterior insula (BA13) • Dorsal anterior cingulate cortex (BA32) • Dorsolateral prefrontal cortex (BA9 and BA46) • Supplementary motor cortex • Superior temporal pole • Frontal, central and parietal opercular cortex • Dorsomedial thalamus • Hypothalamus • Amygdala • Putamen • Substantia nigra
DAN (Spreng et al., 2013)	**ECN (Desikan et al., 2006; Spreng et al., 2013)**
• Frontal eye fields (BA8) • Middle temporal motion complex (BA37) • Superior parietal lobule • Superior occipital gyrus	• Dorsolateral prefrontal cortex (BA9 and BA46) • Superior medial prefrontal cortex • Rostrolateral prefrontal cortex (BA10) • Middle frontal gurus (BA6 and BA9) • Anterior insula (BA13) • Dorsal anterior cingulate cortex • Anterior inferior parietal lobule (BA40)

DMN = default mode network; SN = salience network; DAN = dorsal attention network; ECN = executive control network; BA = Brodmann area.

Objective I.b

DWI data was analyzed through the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL) (Smith, S. M. et al., 2004), version 5.0.8. DWI preprocessing included: i) correction of head movements and eddy current distortions(Andersson & Sotiropoulos, 2016)(Andersson & Sotiropoulos, 2016); ii) removal of non-brain voxels with the Brain Extraction Tool (BET) (S. M. Smith, 2002); and iii) calculation of fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) maps by fitting a tensor model to the raw diffusion data using FMRIB's Diffusion Toolbox (DTIFIT).

Afterwards, the Tract-Based Spatial Statistics (TBSS) approach, designed for the analysis of voxel-wise multi-subject diffusion data, was implemented (S. M. Smith et al., 2006). Firstly, the most representative subject of the sample was selected. Secondly, the most representative FA map was affine aligned into 1x1x1 mm MNI152 standard space. The remaining FA maps were also transformed into this standard space by combining a non-affine transformation to the most representative FA map with an affine transformation from the most representative FA map to the standard space. Thirdly, the mean FA skeleton image that represented the tracts that all MS participants had in common was created and thresholded at 0.2 to avoid the inclusion of non-skeleton voxels. Fourthly, the all FA image that enclosed the standard-space version of each subject's FA image was skeletonized by projecting it onto the mean FA skeleton mask image. MD, RD and AD maps were also obtained by running the TBSS approach for non FA data. This process applied the previously described non-affine and affine registration to each type of diffusion data, merged all subjects' warped MD, RD and AD data in three independent files, and projected these files onto the mean FA skeleton mask.

Longitudinal voxel-wise structural connectivity analysis was conducted by means of the FSL using the randomize permutation algorithm (Winkler, Ridgway, Webster, Smith, & Nichols, 2014). The efficacy of the REHACOP programme on inducing brain structural connectivity changes was examined through repeated measures MANOVA (Time x Group interactions). This analysis was corrected for multiple comparisons across space by applying the threshold-free cluster enhancement (TFCE) correction.

Objective II

The association between brain connectivity and cognitive changes following the intervention period was investigated in the entire MS sample. However, prior to perform the

correlational analyses, the efficacy of the REHACOP programme on improving cognitive performance in the sample of this study was verified. To this end, a composite score was created for each cognitive domain assessed with multiple measures, following the procedure previously explained in "Study II". All cognitive composite scores showed satisfactory evidence of internal consistence through Cronbach's alpha [processing speed (SDMT, LCT and TMT-A) $\alpha = 0.89$, episodic memory (HVLT-R and BVMT-R learning and delayed free recall) $\alpha = 0.78$, and executive functioning (ST color-word trial and interference scores as well as TMT-B) $\alpha = 0.70$]. A repeated measures MANCOVA was performed for processing speed, working memory, episodic memory and executive functioning performance. MS participants' cognitive status (cognitively preserved or impaired), as well as physical and mental fatigue scores, were introduced as covariates in this analysis.

Afterwards, baseline and follow-up connectivity values between those brain areas showing significant changes were introduced in the SPSS. Brain connectivity and cognitive change scores were obtained by subtracting baseline from follow-up values (i.e. follow-up minus baseline). Finally, the relationship between brain connectivity and cognitive changes was explored through Pearson's r correlation analysis for parametric data. The statistical significance was thresholded at 5% ($p \leq 0.05$) for every analysis. These analyses were conducted with the SPSS, version 23.0.

V. Results

5. Results

5.1. Study I

The socio-demographic and clinical characteristics of the MS and the HC group are shown in Table 7. Significant differences were observed between both groups in premorbid IQ, depression and physical fatigue. The MS group presented lower premorbid IQ, as well as higher depressive and physical fatigue symptoms when compared to the HC.

Table 7. Socio-demographic and clinical characteristics of the MS and the HC group.

		MS (n = 44)	HC (n = 44)		
		Mean (SD)	Mean (SD)	U/X^2	*p*
Age (years)		43.55 (8.17)	43.70 (8.71)	922.50	0.704
Education (years)		13.39 (3.05)	14.11 (2.87)	846.00	0.305
Gender, n (%)	Males	16 (36.36)	16 (36.36)	0.00	1.000
	Females	28 (63.64)	28 (63.64)		
Disease duration (years)		10.25 (6.67)			
MS subtype, n (%)	RR	34 (77.27)			
	PP	1 (2.27)			
	SP	9 (20.45)			
EDSS, median (range)		3.00 (0.00-6.50)			
MRC, median (range)		5.00 (1.00-5.00)			
EDSS LAS, median (range)		0 (0.00-4.00)			
TAP		23.48 (3.81)	26.02 (2.35)	588.00	<0.001
GDS		5.55 (3.32)	1.20 (2.21)	170.00	<0.001
FSS		41.50 (18.13)	23.39 (12.39)	421.00	<0.001
VAS		26.33 (26.14)	26.21 (23.12)	905.50	0.872

MS = multiple sclerosis; HC = healthy controls; SD = standard deviation; U = Mann-Whitney U test; X^2 = Chi-square test; RR = relapsing-remitting; PP = primary progressive; SP = secondary progressive; EDSS = Expanded Disability Status Scale; MRC = British Medical Research Council Scale; EDSS LAS = Limb Ataxia Scale of the Expanded Disability Status Scale; TAP = Word Accentuation Test; GDS = Geriatric Depression Scale; FSS = Fatigue Severity Scale; VAS = Mental Fatigue Visual Analogue Scale.

With regards to cognition, between-group significant differences were found in processing speed, attention, verbal memory, visual memory, verbal fluency and executive functioning (inhibition and flexibility) (Table 8). Specifically, the MS group presented a poorer cognitive performance in all the aforementioned domains. The observed effect sizes were large for processing speed and visual memory, and moderate for the remaining

cognitive domains. All significant results survived the Holm–Bonferroni correction for multiple comparisons.

Table 8. Cognitive differences between the MS and the HC group.

	MS	HC	No controlling for cognition			Controlling for PS			Controlling for VSM		
	Mean (SD)	Mean (SD)	F	p	η_p^2	F	p	η_p^2	F	p	η_p^2
PS	-0.62 (1.47)	0.62 (0.71)	15.75	<0.001	0.16	-	-	-	17.72	<0.001	0.18
At	-1.40 (1.50)	<0.01 (0.99)	8.15	0.005	0.09	1.09	ns	0.01	7.35	0.008	0.08
WM	-0.50 (0.84)	<0.01 (1.00)	2.10	ns	0.03	0.09	ns	<0.01	2.20	ns	0.03
VM	-1.40 (1.19)	<0.01 (0.90)	7.04	0.010	0.08	1.23	ns	0.02	6.57	0.012	0.07
VSM	-1.46 (1.32)	<0.01 (0.91)	14.45	<0.001	0.15	3.95	ns	0.05	-	-	-
VF	-1.04 (1.02)	<0.01 (0.82)	9.52	0.003	0.10	2.91	ns	0.03	8.75	0.004	0.10
I	-0.66 (0.96)	<0.01 (0.92)	8.86	0.004	0.10	1.74	ns	0.02	7.99	0.006	0.09
F	-0.95 (3.09)	0.95 (1.00)	11.82	0.001	0.13	0.47	ns	<0.01	11.05	0.001	0.12

MS = multiple sclerosis; HC = healthy controls; SD = standard deviation; F = MANCOVA; η_p^2 = partial eta-squared; PS = processing speed; At = attention; WM = working memory; VM = verbal memory; VSM = visual memory; VF = verbal fluency; I = inhibition; F = flexibility; ns = non-significant.

When controlling for the effect of processing speed, those cognitive differences originally observed between the MS and the HC group were no longer significant and the obtained effect sizes were small for all cognitive domains (Table 8). Conversely, after controlling for the effect of visual memory (free of its inherent processing speed component), significant differences between both groups were still noticed in attention, processing speed, verbal memory, verbal fluency, inhibition and flexibility (Table 8). Thus, processing speed differences showed a large effect size, whereas moderate effect sizes were obtained for the remaining cognitive differences. All significant results survived the Holm–Bonferroni correction.

5.2. Study II

Forty-two out of the 44 MS participants that were randomized to the intervention or control condition completed their participation in the study at follow-up (see Figure 7 in methods section). Specifically, one MS participant from each condition dropped out of the study, giving rise to a withdrawal rate of 3.85%.

The sociodemographic and clinical characteristics of the intervention and control group at baseline are shown in Table 9. Significant differences between both groups were not found in age, years of education, gender, disease duration, MS subtype, EDSS, premorbid IQ, depression or fatigue symptoms.

Table 9. Socio-demographic and clinical characteristics of the intervention and control group at baseline.

		Intervention group (n = 21)	Control group (n = 21)		
		Mean (SD)	Mean (SD)	*F/U/X²*	*p*
Age (years)		43.90 (9.51)	43.67 (6.89)	<0.01	0.926
Education (years)		13.00 (3.03)	13.95 (3.12)	179.50	0.296
Gender, n (%)	Males	8 (38.10)	7 (33.33)	0.10	0.747
	Females	13 (61.90)	14 (66.67)		
Disease duration (years)		9.95 (7.84)	10.67 (5.79)	0.11	0.739
MS subtype, n (%)	RR	15 (71.43)	17 (80.95)	1.24	0.539
	PP	1 (4.76)	0 (0.00)		
	SP	5 (23.81)	4 (19.05)		
EDSS, median (range)		3.5 (1.00-6.00)	2.0 (0.00-6.50)	3.69	0.062
TAP		22.95 (3.94)	24.33 (3.64)	1.39	0.245
GDS		6.38 (3.31)	4.95 (3.31)	163.50	0.148
FSS		45.33 (17.33)	38.95 (18.15)	172.50	0.227
VAS		31.49 (27.76)	20.10 (24.21)	155.00	0.097

SD = standard deviation; F = MANOVA; U = Mann-Whitney U test; X^2 = Chi-square test; MS = multiple sclerosis; RR = relapsing-remitting; PP = primary progressive; SP = secondary progressive; EDSS = Expanded Disability Status Scale; TAP = Word Accentuation Test; GDS = Geriatric Depression Scale; FSS = Fatigue Severity Scale; VAS = Mental Fatigue Visual Analogue Scale.

The raw scores (means and standard deviations) obtained by both groups in each cognitive/functional measure at baseline and follow-up are provided in Table 10.

Table 10. Raw cognitive/functional scores obtained by each group at baseline and follow-up.

		Intervention group	Control group
		Mean (SD)	Mean (SD)
BTA	Baseline	12.43 (3.53)	15.14 (4.05)
	Follow-up	12.81 (4.20)	15.10 (3.71)
SDMT	Baseline	36.67 (9.23)	46.43 (13.46)
	Follow-up	42.62 (12.46)	47.52 (13.00)
LCT	Baseline	20.52 (5.37)	26.19 (8.91)
	Follow-up	25.38 (7.21)	27.38 (9.29)
TMT-A	Baseline	50.90 (23.12)	37.38 (14.59)
	Follow-up	45.24 (16.63)	40.43 (18.23)
BD	Baseline	5.14 (1.77)	6.10 (1.58)
	Follow-up	6.43 (1.75)	6.24 (1.73)
HVLT-R learning	Baseline	20.95 (3.89)	24.86 (3.58)
	Follow-up	24.48 (4.63)	24.81 (4.42)
HVLT-R delayed recall	Baseline	7.19 (2.73)	8.76 (2.10)
	Follow-up	8.71 (2.67)	9.48 (1.81)
BVMT-R learning	Baseline	19.29 (6.40)	21.38 (4.83)
	Follow-up	20.57 (6.49)	21.33 (5.42)
BVMT-R delayed recall	Baseline	8.29 (2.24)	8.62 (2.09)
	Follow-up	8.62 (2.38)	8.24 (2.28)
CIFA animals	Baseline	18.81 (4.39)	21.81 (6.88)
	Follow-up	21.57 (6.28)	22.24 (6.79)
CIFA supermarket	Baseline	16.00 (5.38)	19.00 (4.86)
	Follow-up	18.81 (7.80)	21.10 (5.82)
CIFA P words	Baseline	24.52 (7.88)	28.67 (12.24)
	Follow-up	27.62 (5.59)	30.57 (11.91)
ST word-color	Baseline	34.86 (7.72)	41.48 (11.53)
	Follow-up	42.57 (11.60)	43.62 (11.36)
ST interference	Baseline	-0.26 (7.63)	1.90 (6.12)
	Follow-up	5.34 (8.52)	2.79 (5.47)
TMT-B	Baseline	109.95 (39.54)	86.43 (57.22)
	Follow-up	96.10 (40.48)	82.14 (55.48)
SST	Baseline	6.20 (1.72)	6.67 (1.46)
	Follow-up	6.24 (1.45)	5.76 (1.61)
Lawton's IADLs	Baseline	7.43 (0.87)	7.95 (0.22)
	Follow-up	7.62 (0.87)	7.81 (0.51)

SD = standard deviation; BTA = Brief Test of Attention; SDMT = Symbol Digit Modalities Test; LCT = Letters Comparison Test; TMT-A = Trail Making Test - A; BD = Backward Digits Subtest of the Wechsler Adult Intelligence Scale III; HVLT-R = Hopkins Verbal Learning Test – Revised; BVMT-R = Brief Visual Memory Test – Revised; CIFA = Calibrated Ideational Fluency Assessment; ST = Stroop Color and Word Test; TMT-B = Trail Making Test - B; SST = Strange Stories Test; Lawton's IADLs = Lawton Instrumental Activities of Daily Living Scale.

The MANCOVA detected significant differences in attention, processing speed, working memory, episodic memory, executive functioning and instrumental activities between the intervention and the control group at baseline (Table 11). A lower performance was specifically observed in the intervention group, when compared to the control group, in all the aforementioned cognitive domains as well as in daily life instrumental activities.

Table 11. Cognitive and functional differences between the intervention and control group at baseline.

	Intervention group	Control group		
	Mean (SD)	Mean (SD)	*F*	*p*
At	-0.34 (0.88)	0.34 (1.01)	5.74	0.022
PS	-0.36 (0.74)	0.36 (0.91)	7.29	0.010
WM	-0.28 (1.03)	0.28 (0.92)	4.53	0.040
EM	-0.26 (0.79)	0.26 (0.67)	5.01	0.031
VF	-0.25 (0.67)	0.25 (1.00)	3.31	0.077
EF	-0.24 (0.65)	0.24 (0.85)	5.49	0.025
ToM	-0.16 (1.08)	0.16 (9.11)	1.36	0.250
IADLs	-0.38 (1.28)	0.38 (0.32)	4.60	0.038

SD = standard deviation; F = MANCOVA; At = attention; PS = processing speed; WM = working memory; EM = episodic memory; VF = verbal fluency; EF = executive functioning; ToM = theory of mind; IADLs = instrumental activities of daily living.

With regards to repeated measures MANCOVA, significant Group x Time interactions were detected involving processing speed, working memory, episodic memory and executive functioning (Table 12). Thus, the intervention group exhibited a significant improvement on all these cognitive domains over time when compared to the control group (Table 10, Table 12, and Figure 11). Large effect sizes were observed for processing speed, working memory and episodic memory, while a moderate effect size was found for executive functioning. A trend toward a significant improvement was additionally observed in the intervention group, compared to the control group, for theory of mind and daily life instrumental activities with a moderate effect size. Neither statistically significant nor

tendencies toward statistically significant results were detected for attention or verbal fluency, and small effect sizes were detected for both cognitive domains.

Table 12. Repeated measures MANCOVA Group x Time interactions for cognition and functionality

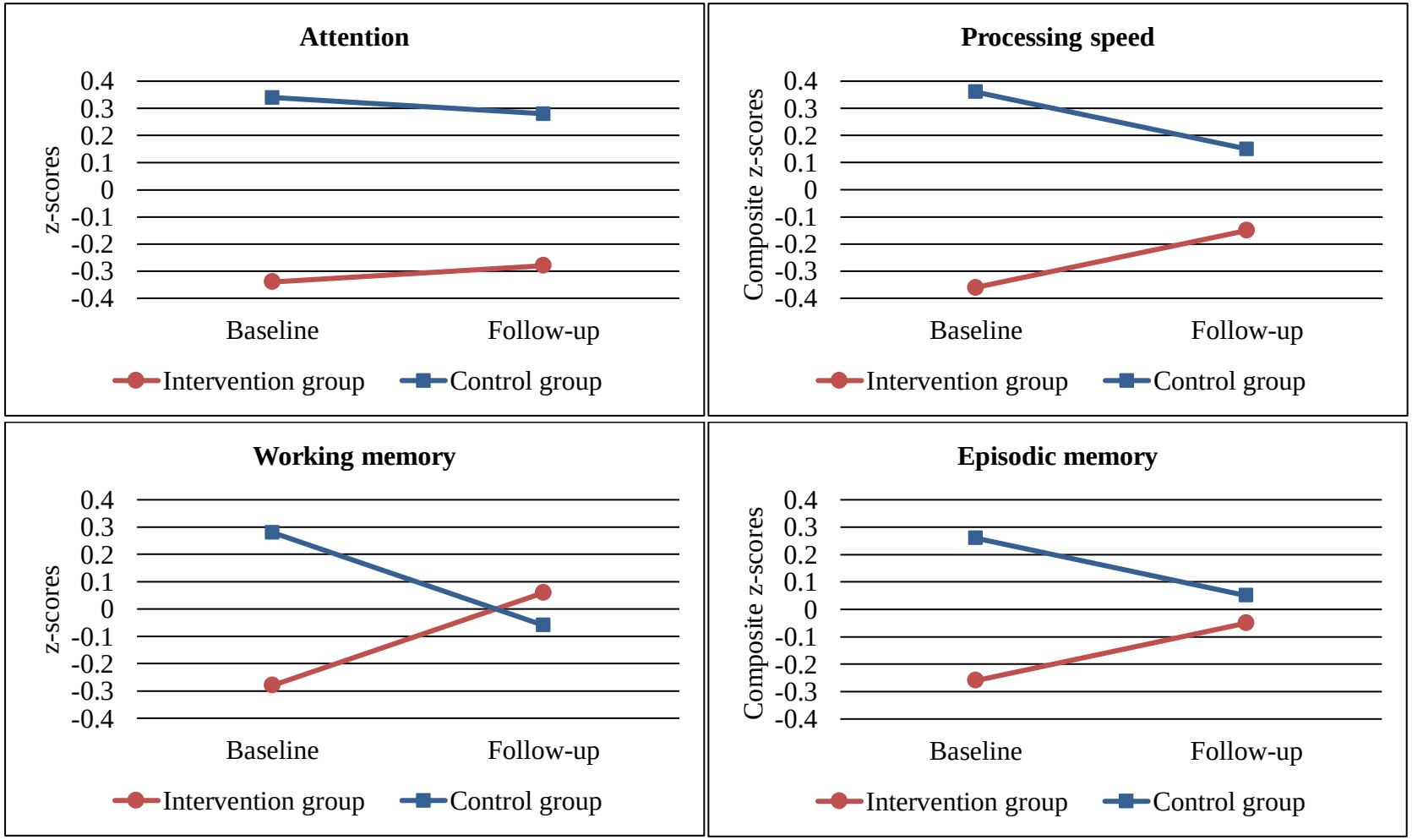
		Intervention group	Control group			
		Mean (SD)	Mean (SD)	*F*	*p*	η_p^2
At	Baseline	-0.34 (0.88)	0.34 (1.01)	0.13	0.722	<0.01
	Follow-up	-0.28 (1.03)	0.28 (0.91)			
PS	Baseline	-0.36 (0.74)	0.36 (0.91)	7.26	0.011	0.16
	Follow-up	-0.15 (0.82)	0.15 (0.97)			
WM	Baseline	-0.28 (1.03)	0.28 (0.92)	6.61	0.014	0.15
	Follow-up	0.06 (1.02)	-0.06 (1.01)			
EM	Baseline	-0.26 (0.79)	0.26 (0.67)	9.38	0.004	0.20
	Follow-up	-0.05 (0.85)	0.05 (0.74)			
VF	Baseline	-0.25 (0.67)	0.25 (1.00)	2.08	0.158	0.05
	Follow-up	-0.13 (0.78)	0.13 (0.91)			
EF	Baseline	-0.24 (0.65)	0.24 (0.85)	5.47	0.025	0.13
	Follow-up	-0.01 (0.85)	0.01 (0.81)			
ToM	Baseline	-0.16 (1.08)	0.16 (9.11)	3.32	0.055	0.10
	Follow-up	0.16 (0.94)	-0.16 (1.05)			
IADLs	Baseline	-0.38 (1.28)	0.38 (0.32)	3.42	0.072	0.09
	Follow-up	-0.13 (1.22)	0.13 (0.72)			

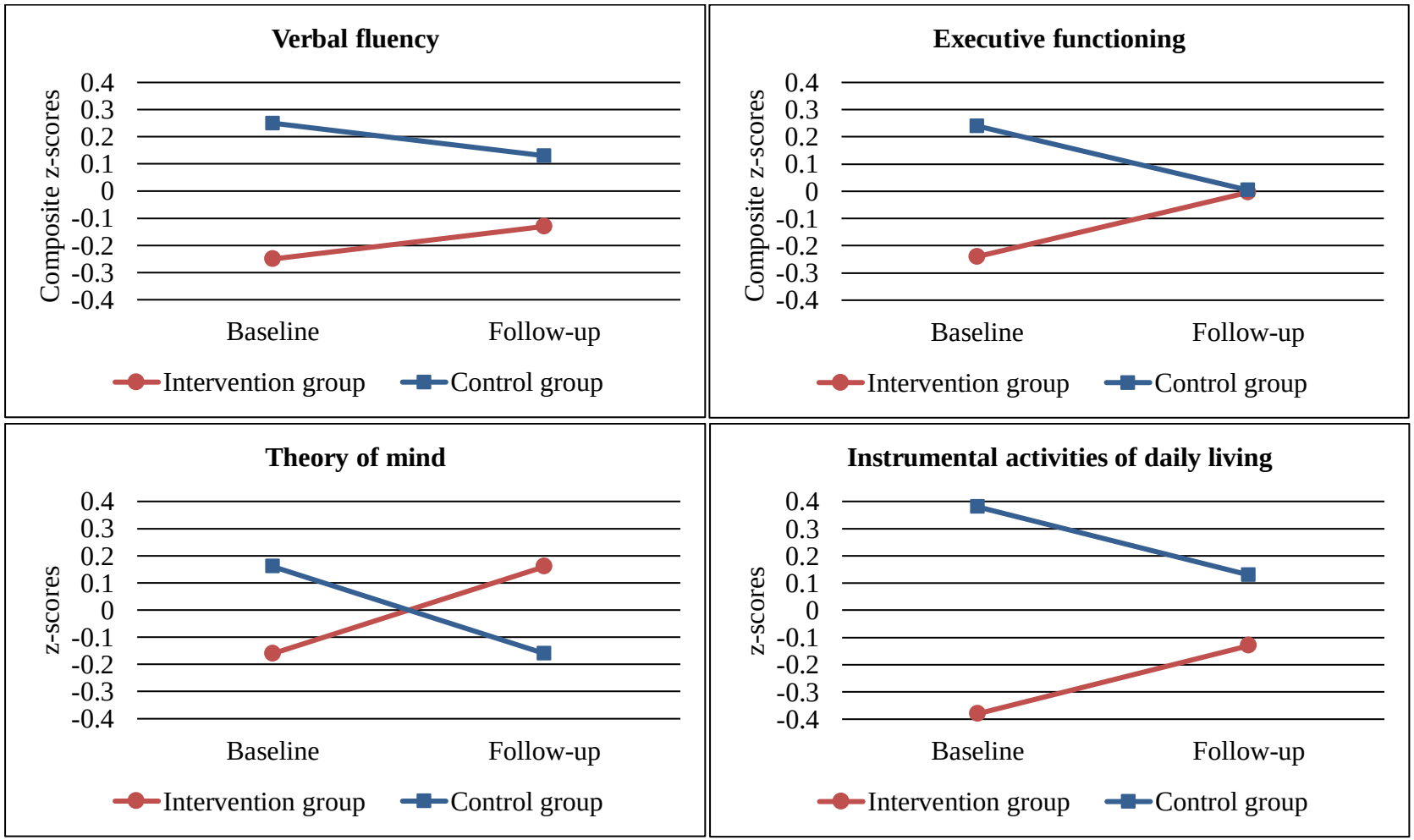
SD = standard deviation; F = repeated measures MANCOVA; η_p^2 = partial eta-squared; At = attention; PS = processing speed; WM = working memory; EM = episodic memory; VF = verbal fluency; EF = executive functioning; ToM = theory of mind; IADLs = instrumental activities of daily living.

Finally, the potential bias toward a favorable outcome for the intervention group, due to the inclusion of five MS participants that were receiving private cognitive rehabilitation in addition to the REHACOP programme, was examined. To this end, an additional repeated measures MANCOVA was conducted specifically excluding these five MS participants from the analysis (i.e. intervention group n = 16 and control group n = 21). Group x Time interactions remained the same, revealing that MS participants only receiving the REHACOP cognitive rehabilitation programme also presented significant enhancements in processing speed (F = 6.80, p = 0.014, η_p^2 = 0.18), working memory (F = 6.11, p = 0.019, η_p^2 = 0.16),

episodic memory (F = 11.38, p = 0.002; η_p^2 = 0.27) and executive functioning (F = 5.16, p = 0.030, η_p^2 = 0.14) when compared to the control group. A trend toward a significant improvement was also found in the intervention group, compared to the control group, for theory of mind (F = 3.00, p = 0.093, η_p^2 = 0.09) and daily life instrumental activities (F = 3.90, p = 0.057, η_p^2 = 0.11).

Figure 11. Standardized cognitive/functional scores obtained by each group at baseline and follow-up.




Verbal fluency
Composite z-scores
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
Baseline
Follow-up
Intervention group
Control group
Executive functioning
Composite z-scores
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
Baseline
Follow-up
Intervention group
Control group
Theory of mind
z-scores
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
Baseline
Follow-up
Intervention group
Control group
Instrumental activities of daily living
z-scores
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
Baseline
Follow-up
Intervention group
Control group

5.3. Study III

From the 42 MS participants that completed their participation in the study, two refused the MRI acquisition (one from each condition), and other four (two from each condition) presented MRI acquisition artifacts in the DWI sequence (see Figure 7 in methods section). Accordingly, brain functional connectivity analyses were conducted with 40 participants (20 in each condition) and structural connectivity analyses with 36 participants (18 in each condition).

The sociodemographic and clinical characteristics of the MS sample included in brain functional connectivity analyses are shown in Table 13. Significant differences between both groups were not found in any of the explored characteristics. The same results were obtained when considering the sample included in brain structural connectivity analyses (data not shown).

Table 13. Socio-demographic and clinical characteristics of the intervention and control group at baseline.

		Intervention group (n = 20)	Control group (n = 20)		
		Mean (SD)	Mean (SD)	*F/U/X²*	*p*
Age (years)		44.05 (9.73)	43.20 (6.73)	0.10	0.750
Education (years)		13.25 (2.88)	13.90 (3.19)	173.00	0.459
Gender, n (%)	Males	8 (40.00)	7 (35.00)	0.11	0.744
	Females	12 (60.00)	13 (65.00)		
Disease duration (years)		10.25 (7.92)	10.15 (5.42)	<0.01	0.963
MS subtype, n (%)	RR	14 (70.00)	16 (80.00)	1.24	0.537
	PP	1 (5.00)	0 (0.00)		
	SP	5 (25.00)	4 (20.00)		
EDSS, median (range)		3.75 (1.00-6.00)	2.25 (0.00-6.50)	3.10	0.086
TAP		23.15 (3.94)	24.25 (3.71)	0.83	0.369
GDS		6.25 (3.34)	5.15 (3.27)	160.00	0.274
FSS		46.50 (16.92)	39.75 (18.24)	154.50	0.218
VAS		31.82 (28.44)	20.60 (24.72)	142.50	0.117

SD = standard deviation; F = MANOVA; U = Mann-Whitney U test; X^2 = Chi-square test; MS = multiple sclerosis; RR = relapsing-remitting; PP = primary progressive; SP = secondary progressive; EDSS = Expanded Disability Status Scale; TAP = Word Accentuation Test; GDS = Geriatric Depression Scale; FSS = Fatigue Severity Scale; VAS = Mental Fatigue Visual Analogue Scale.

With regards to repeated measures MANOVA for brain functional connectivity, significant Group x Time interactions were found within the DMN and the HMN following the cognitive intervention (Table 14). Within the DMN, a bidirectional change was found in the functional connectivity between the anterior cingulate cortex and the left anterior middle temporal gyrus (Figure 12a). Specifically, the intervention group showed a decreased functional connectivity between both nodes of the DMN following the intervention, while an increased functional connectivity was detected in the control group over time. Within the HMN, functional connectivity changes were detected between the left hippocampus and the left gracile lobule of the cerebellum (Figure 12b). Just as in the DMN, the intervention and the control group respectively showed a decreased and an increased functional connectivity between these nodes of the HMN. Effect sizes were large for brain connectivity changes within both cognitive networks.

Table 14. Repeated measures MANOVA Group x Time interactions for brain functional connectivity.

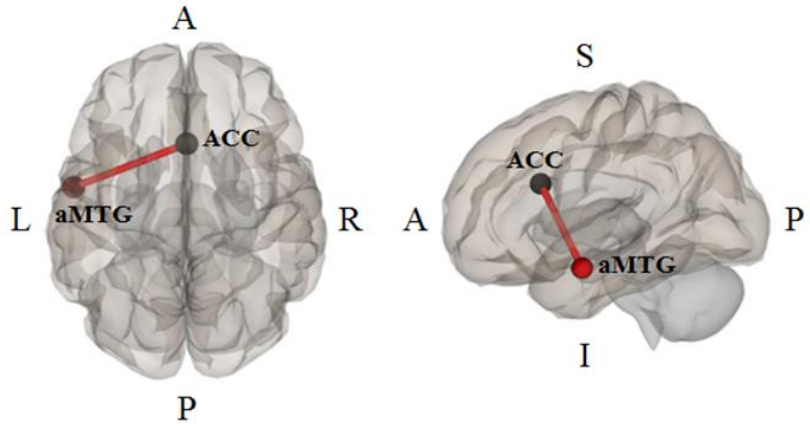
			Intervention Group	Control Group			
			Mean (SD)	Mean (SD)	F	p_{FDR}	η_p^2
DMN	ACC - left aMTG	Baseline	0.12 (0.15)	-0.01 (0.17)	9.80	0.044	0.21
		Follow-up	0.05 (0.19)	0.15 (0.17)			
HMN	Left HP - left CB	Baseline	0.10 (0.18)	-0.09 (0.14)	16.23	0.035	0.30
		Follow-up	-0.08 (0.20)	0.03 (0.22)			

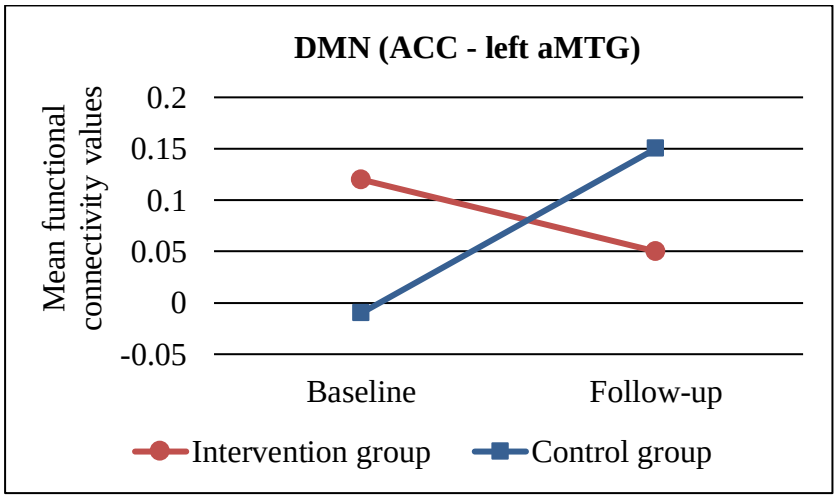
SD = standard deviation; F = repeated measures MANOVA; p_{FDR} = p value corrected with FDR; η_p^2 = partial eta-squared; DMN = default mode network; ACC = anterior cingulate cortex; aMTG = anterior middle temporal gyrus; HMN = hippocampal memory network; HP = hippocampus; CB = cerebellum. Means and standard deviations represent functional connectivity values.

In relation to repeated measures MANOVA for brain structural connectivity, significant Group x Time interactions were not noticed for any of the anisotropy (FA) or diffusivity indexes (MD, AD and RD).

Figure 12. Repeated measures MANOVA Group x Time interactions for brain functional connectivity.

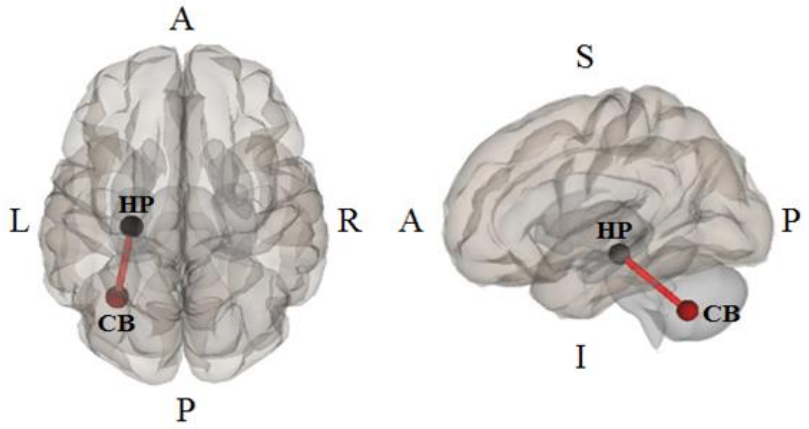
a) DMN functional connectivity changes between the ACC and the left aMTG:

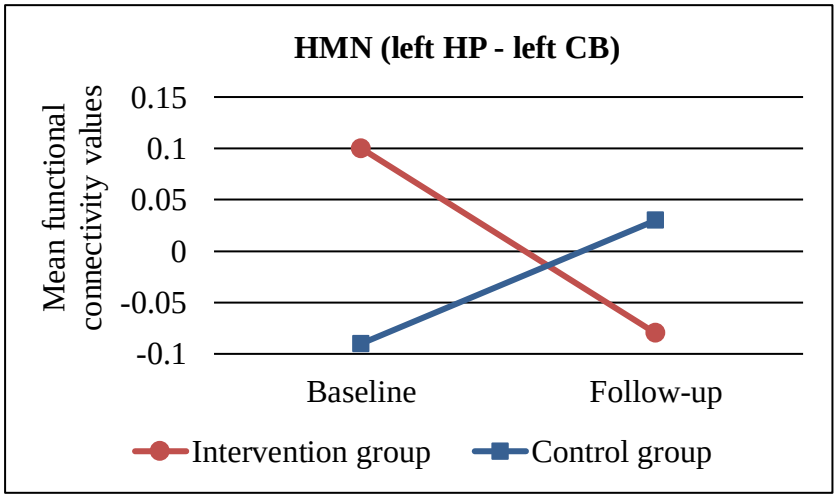




Seed (black circle) = anterior cingulate cortex; Target (red circle) = left anterior middle temporal gyrus; Red line = functional connectivity between the seed and the target. The graphic shows the mean functional connectivity values between the anterior cingulate cortex and the left anterior middle temporal gyrus presented by the intervention and the control group at each time point. DMN = default mode network; ACC = anterior cingulate cortex; aMTG = anterior middle temporal gyrus; A = anterior; P = posterior; L = left; R = right; S = superior; I = inferior.

b) HMN functional connectivity changes between the left HP and the left CB:





Seed (black circle) = left hippocampus; Target (red circle) = gracile lobule of the left cerebellum; Red line = functional connectivity between the seed and the target. The graphic shows the mean functional connectivity values between the left hippocampus and the gracile lobule of the left cerebellum presented by the intervention and the control group at each time point. HMN = hippocampal memory network; HP = hippocampus; CB = cerebellum; A = anterior; P = posterior; L = left; R = right; S = superior; I = inferior.

Prior to perform the correlational analyses between brain functional connectivity changes and cognitive improvements following the intervention, the efficacy of the REHACOP programme on improving cognitive functioning in the sample of this study was confirmed. Repeated measures MANCOVA showed significant Group x Time interactions in processing speed (F = 6.56, p = 0.015), working memory (F = 6.24, p = 0.017), episodic memory (F = 8.60, p = 0.006) and executive functioning (F = 4.98, p = 0.032). The intervention group specifically showed significant improvements following the cognitive

rehabilitation in all the aforementioned cognitive domains when compared to the control group. Effect sizes were large for processing speed (η_p^2 = 0.16), working memory (η_p^2 = 0.15) and episodic memory (η_p^2 = 0.20), as well as moderate for executive functioning (η_p^2 = 0.12).

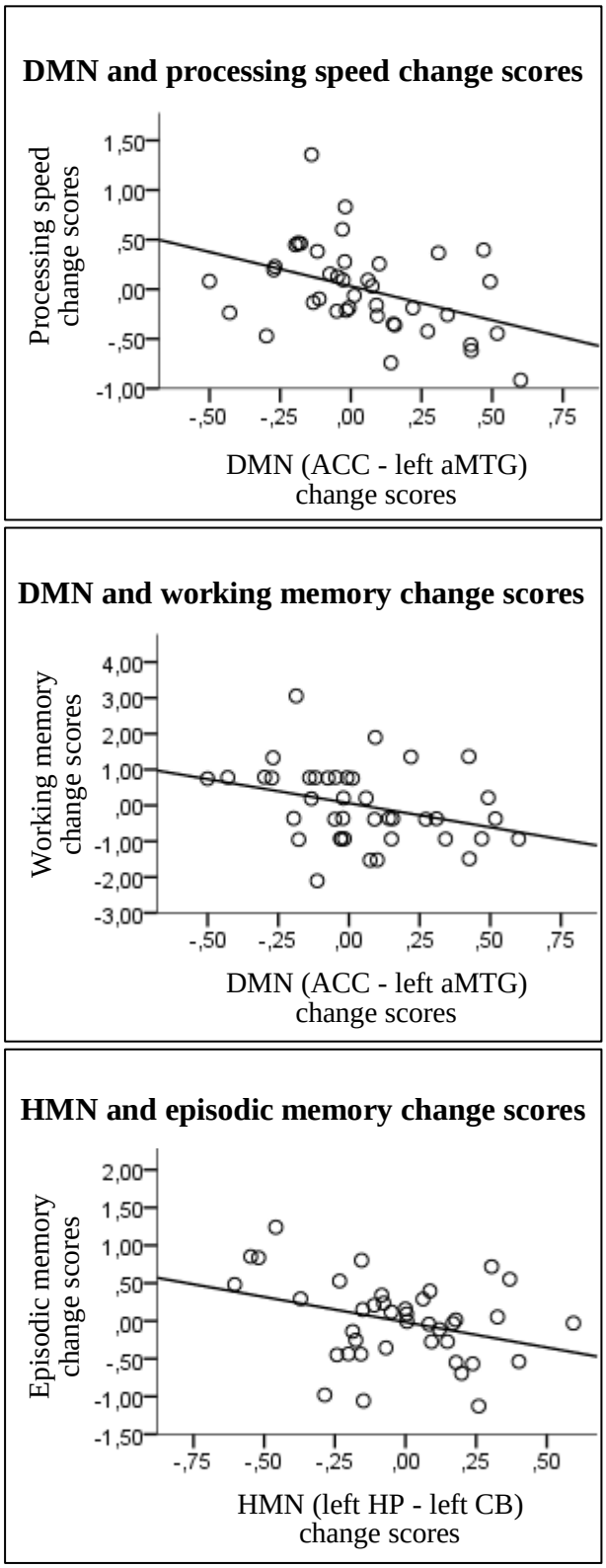
Functional connectivity changes within the DMN and the HMN significantly correlated with cognitive improvement. In particular, the functional connectivity change scores (follow-up minus baseline) between the anterior cingulate cortex and the left anterior middle temporal gyrus of the DMN were negatively associated with processing speed and working memory improvements (Table 15). Similarly, the HMN functional connectivity change scores (follow-up minus baseline) between the left hippocampus and the left gracile lobule of the cerebellum were negatively associated with episodic memory improvements (Table 15). These results pointed out that the lower the functional connectivity between these brain areas of the DMN (anterior cingulate cortex – left anterior middle temporal gyrus) and the HMN (left hippocampus – left cerebellum), the greater the cognitive improvement exhibited by MS participants in information processing (processing speed and working memory) and episodic memory, correspondingly (Figure 13).

Table 15. Correlation analyses between brain functional connectivity and cognitive change scores.

	DMN (ACC - left aMTG)		HMN (left HP - left CB)	
	r	*p*	*R*	*p*
PS	-0.41	0.009	-0.23	0.161
WM	-0.33	0.037	-0.05	0.755
EM	-0.13	0.419	-0.34	0.034
EF	-0.16	0.316	-0.31	0.054

DMN = default mode network; ACC = anterior cingulate cortex; aMTG = anterior middle temporal gyrus; HMN = hippocampal memory network; HP = hippocampus; CB = cerebellum; r = Pearson's r coefficient; PS = processing speed; WM = working memory; EM = episodic memory; EF = executive functioning.

Figure 13. Scatter diagrams between brain functional connectivity and cognitive change scores.



DMN = default mode network; ACC = anterior cingulate cortex; aMTG = anterior middle temporal gyrus; HMN = hippocampal memory network; HP = hippocampus; CB = cerebellum**.**

VI. Discussion

6. Discussion

6.1. Study I

The present study aimed to investigate the role of processing speed in MS cognitive impairment. It is noteworthy that this research is the first to examine whether such a broad array of cognitive deficits might occur mainly as a result of slowed processing speed in the disorder. The attained results showed the presence of processing speed, attention, verbal memory, visual memory, verbal fluency, inhibition and flexibility deficits in persons with MS, as compared with HC. Large effect sizes were observed for processing speed and visual memory, whereas the remaining cognitive domains showed moderate effect sizes. Interestingly, the cognitive differences initially observed between the MS and the HC group were no longer significant when the influence of processing speed was controlled, and small effect sizes were observed for all cognitive domains. These findings support the notion that those cognitive deficits exhibited by persons with MS in attention, episodic memory, verbal fluency and executive functioning might be explained to a large degree by slowed processing speed. Additionally, all these cognitive deficits seem to be specific to processing speed, given that when controlling for visual memory (selected as a control covariate) the between-group cognitive differences initially observed were still significant and effect sizes remained the same.

In relation to the obtained results for *attention*, cognitive differences between persons with MS and HC in this specific domain became non-significant after controlling for processing speed. Accordingly, slowed processing speed negatively affected attention performance in the BTA, despite this test does not involve a speeded or timed task. This finding is in contrast with a previous study focused on executive functioning, in which slowed processing speed was found to entail a negative impact exclusively on timed tasks (Leavitt, Wylie, Krch et al., 2014). This discrepancy between studies might be explained by

the fact that in the BTA the numbers and letters that make up the different strings are auditory presented at a rate of one item per second, and thereby the information has to be processed at a predefined and challenging pace (i.e. task performance indirectly involved a processing speed component). In line with this argument, an earlier study revealed that when persons with MS are allowed to complete visual sustained attention tasks at their own pace they perform as accurately as HC (Paul et al., 1998). Consequently, self-paced attention tasks might be more appropriate for assessing attention abilities in persons with MS than those including a predefined pace.

On the other side, in another study significant differences were detected between persons with MS and HC in alertness after controlling for the effect of processing speed (Roth et al., 2015), which is inconsistent with the results of the present study. A main difference between both studies relies on the MS sample, as in the study conducted by Roth et al. (2015) the same number of participants diagnosed with RRMS and SPMS were involved, while in this one most participants suffered from RRMS. In fact, when independent analyses were performed for each MS course in the study of Roth et al. (2015) those participants with SPMS still showed a significantly worse performance in alertness when compared to the HC, but, interestingly, significant differences were not detected between the RRMS and the HC group (Roth et al., 2015). These findings seem to indicate that slowed processing speed might specially underlie attention deficits in RRMS, whereas attention deficits (per se) might be more present in persons with SPMS. Given the above, the administration of self-paced attention tests could provide more objective information about attention performance in MS, especially when dealing with persons with RRMS.

Even though the direct role of slowed processing speed in *episodic memory* has not been specifically investigated in MS, diverse studies have explored this post-hoc (Arnett, 2004; Chiaravalloti et al., 2003; Chiaravalloti, Stojanovic-Radic et al., 2013; J. DeLuca et al.,

1994; J. DeLuca et al., 1998; Gaudino et al., 2001). The majority of these studies have supported a positive association between processing speed and episodic memory in persons with MS, indicating that the slower the processing speed the poorer the episodic memory performance. Moreover, in the study carried out by Arnett (2004) it was found that when the information to be learnt was provided at a rapid pace persons with MS recalled less items at immediate and delayed free recall than when the information was provided at a more leisurely rate. In the present study those verbal and visual memory deficits initially detected in the MS group, as compared with the HC, were no longer significant after controlling for processing speed. Therefore, the results of the present study are in line with previous ones in that slowed processing speed exerted a negative impact on episodic memory performance in MS.

It must be noted that most memory tests are indirectly affected by processing speed performance, as the information to be learned is usually provided at a specific pace (e.g. one stimulus per second) or presented within a predefined length of time (e.g. limited number of trials or exposure time). Actually, J. DeLuca et al. (1994) revealed that persons with MS were as able as HC to learn a word list, albeit they required a higher number of trials to reach the same degree of learning. In that study it was also observed that once the list of words was equally learned by both groups, significant differences were not detected in delayed free recall between persons with MS and HC (J. DeLuca et al., 1994). This study showed that episodic memory deficits might take place due to an inefficient initial learning, since once the words were learnt MS participants did not exhibit retrieval difficulties. Given all the above, the results of the present study suggest that slowed processing speed might lie beneath episodic learning deficits and, consequently, recall difficulties in MS. Clinically, this finding emphasizes the need for examining in depth the origin of memory impairments in order to select the most appropriate cognitive intervention for each patient.

A few studies have examined the presence of cognitive differences between persons with MS and HC in *verbal fluency* (Panou et al., 2008) and *executive functioning* (inhibition, flexibility and planning) (Denney & Lynch, 2009; Genova et al., 2013; Leavitt, Wylie, Krch et al., 2014; Owens et al., 2013) before and after controlling for processing speed. Findings derived from these studies pointed out that the cognitive differences originally observed between both groups became non-significant once the influence of processing speed was controlled (Denney & Lynch, 2009; Genova et al., 2013; Leavitt, Wylie, Krch et al., 2014; Owens et al., 2013). Accordingly, the results of the present study are consistent with previous literature and extend previous findings in that the same results have been noticed for executive functioning when controlling for the effect of common confounding variables in MS (motor impairment, premorbid IQ, depression and physical fatigue). This work also supports the notion that verbal fluency and executive functioning deficits are specific to processing speed, given that significant cognitive differences were still found between the MS and the HC group in both cognitive domains after controlling for visual memory.

In the present study, *working memory* was not significantly compromised in persons with MS. With regards to the MS literature, some studies have reported working memory deficits in persons with RRMS (Berrigan et al., 2013; Huijbregts et al., 2004; Parmenter et al., 2007; Potagas et al., 2008), while others have not detected such deficits (Archibald & Fisk, 2000; J. DeLuca et al., 2004; Schulz, Kopp, Kunkel, & Faiss, 2006). Discrepancies among studies might be due to the administration of tasks with different degrees of working memory and/or processing speed load. Thus, studies reporting working memory deficits have mainly administered neuropsychological tests involving greater processing speed and/or working memory loads [e.g. the Paced Auditory Serial Addition Test (PASAT) or the n-back 2 test] (Huijbregts et al., 2004; Parmenter et al., 2007; Potagas et al., 2008), compared to those not showing that deficits (e.g. the BD of the Wechsler Adult Intelligence Scale)

(Archibald & Fisk, 2000; J. DeLuca et al., 2004; Schulz et al., 2006). Moreover, studies using tests that involve an intermediate working memory load, such as the Letter Number Sequencing test, have provided contradictory results (Berrigan et al., 2013; J. DeLuca et al., 2004). Therefore, as previous studies have already suggested, neuropsychological tests with high working memory demands might be required to detect such deficits in RRMS samples (Parmenter et al., 2007), and those with high processing speed demands could lead to misdiagnose declines in processing speed as working memory deficits (Forn et al., 2008).

The obtained results indicate that processing speed plays an essential role in the performance and understanding of a wide range of cognitive deficits in MS. The current study not only reinforces preceding findings concerning the lack of significant differences between persons with MS and HC in verbal fluency (Panou et al., 2008) and executive functioning (inhibition and flexibility) (Genova et al., 2013; Leavitt, Wylie, Krch et al., 2014) once the effect of processing speed is controlled, but also extends the same pattern of results to attention, verbal memory and visual memory. Therefore, these results specifically conform to the Relative Consequence Model posed by J. DeLuca et al. (2004), which proposes that persons with MS present a central processing speed decline that results in other cognitive deficits.

A possible explanation for these results might rely on the underlying neuropathology of MS. Specifically; white matter demyelination constitutes a main feature of the disorder, which, in turn, results in a reduced speed of information transmission along the neuronal axons (Filippi, Rocca et al., 2012; Lubetzki & Stankoff, 2014). In line with this, the white matter integrity decrease of distinct brain tracts (corpus callosum, fornix, forceps minor and major, superior and inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, corona radiata and thalamic radiation), presumably caused (at least in part) by demyelination processes, has been related to processing speed deficits in the disorder (Genova et al., 2013;

Roosendaal et al., 2009; Yu et al., 2012). Moreover, different studies have revealed that some of these white matter tracts are also involved in the performance of working memory, verbal memory, visual memory (Dineen et al., 2009) and executive functioning (Genova et al., 2013) tasks in MS. Consequently, the relevant role that processing speed exerts on the performance of a wide range of cognitive domains could be mainly explained by the occurrence of demyelination processes in the MS brain.

Diverse clinical implications may arise from the present study. The attained findings underscore the relevance of carefully examining the source of the cognitive deficits noticed through neuropsychological testing to prevent potential misdiagnoses. The proper identification of the origin of these deficits is critical for making the most well-informed treatment decisions possible in each particular case. Well-informed intervention decisions would ensure the implementation of cognitive interventions specifically aimed at improving the deficit in need of treatment. These decisions would also facilitate the management of other difficulties that are frequently related to MS cognitive impairment, such as the decreased ability to perform daily life (Goverover, Haas, & DeLuca, 2016; Kalmar et al., 2008) and professional tasks (Strober, Chiaravalloti et al., 2014), the reduced participation in social and leisure-time activities (Hakim et al., 2000) and the poor self-perceived health status (Ruet, Deloire, Hamel et al., 2013). Additionally, cognitive-behavioral therapies intended to treat the emotional distress presented by persons with MS (Chiaravalloti & DeLuca, 2008) would also be better-guided if those cognitive deficits leading to daily difficulties are correctly identified. Consequently, intervention decisions based on the proper identification of the source of the cognitive deficits would favor the implementation of more effective interventions, which, in turn, would further improve MS patients' cognitive performance, daily functionality and quality of life.

Several limitations can be noticed in relation to this study. First, the MS sample consisted primarily of persons with RRMS, and so the findings of this study might not be generalizable to persons suffering from progressive courses of the disorder. With regards to the cognitive assessment, a standardized neuropsychological battery for MS was not administered. The utilization of a standardized battery, for instance the Brief Repeatable Battery of Neuropsychological Tests (Rao, 1990) or the Minimal Assessment of Cognitive Function in Multiple Sclerosis (Benedict et al., 2006), could have facilitated the comparability of the attained results with the literature and, at the same time, their understanding by the MS clinical and research community. In this line, it must be also pointed out that working memory was assessed by means of the BD, whereas the letter number sequencing test might have been a more appropriate test to identify deficits in this cognitive domain. Additionally, two specific components of executive functioning (inhibition and flexibility) were evaluated in this study. However, executive functioning constitutes a multidimensional concept, as it encompasses many other cognitive processes such as attainment of objectives, resolution of problems, planning, organizing, error detection, self-monitoring, reasoning, formation of concepts and so on. Accordingly, upcoming studies ought to examine the effect of slowed processing speed in these other cognitive processes in MS. Other constraint, in reference to the manual dexterity assessment, relies on the fact that the MRC and the EDSS LAS were utilized. However, the administration of the Nine-Hole Peg Test (Cutter et al., 1999) would have been more appropriate, given that it provides a more objective assessment and constitutes a benchmark test for assessing manual dexterity in MS (Feys et al., 2017). Finally, the present study utilized a cross-sectional design, while longitudinal studies are better able to investigate causal links. Thereby, longitudinal studies should be conducted to further elucidate the causal relationship between slowed processing speed and other cognitive deficits in persons with MS.

Future studies should address the aforementioned limitations. Moreover, studies including MRI would shed light on how processing speed interferes in the relationship between different cognitive processes and brain structure, as some studies focused on executive functioning have already investigated (Genova et al., 2013; Leavitt, Wylie, Krch et al., 2014). Finally, because slowed processing speed adversely affects the performance of several cognitive domains in MS, the efficacy of processing speed cognitive interventions on the improvement of different domains should be investigated.

6.2. Study II

The present study aimed to assess the efficacy of an integrative group-based cognitive rehabilitation programme, the REHACOP, on improving cognitive functioning as well as daily functionality in persons with MS. Specifically, the intervention group exhibited significant cognitive improvements in processing speed, working memory, episodic memory and executive functioning, with moderate to large effect sizes, when compared to the control group. Additionally, the intervention group also showed a trend toward a significant improvement for theory of mind and daily functionality, with moderate effect sizes, when compared to the control group. These findings support the efficacy of integrative group-based cognitive rehabilitation interventions in persons with MS. In addition, this is one of the first RCTs to show that group-based cognitive interventions may improve cognitive performance in persons with MS. This takes on special relevance on account of the advantages that this approach can bring in a clinical context over an individual setting, as it is more time-efficient and cost-effective.

Until recently processing speed has not been commonly included as an intervention target in MS cognitive rehabilitation studies (Mitolo et al., 2015). However, the few RCTs targeting this cognitive domain in the disorder have mostly supported a positive effect of

cognitive rehabilitation on processing speed performance (Charvet et al., 2017; Filippi, Riccitelli et al., 2012; Gich et al., 2015; Hancock, Bruce, Bruce, & Lynch, 2015; Messinis et al., 2017). For instance, Charvet et al. (2017) conducted a class I study in which significant cognitive improvements were detected for processing speed, working memory and executive functioning in response to cognitive rehabilitation. Specifically, the Brain HQ cognitive rehabilitation programme that is targeted at addressing multiple cognitive domains (attention, processing speed, working memory and executive functioning) was implemented in such study (Charvet et al., 2017). Two additional studies have also revealed cognitive improvements in processing speed, as well as in other cognitive domains, in response to the RehaCom computerized cognitive rehabilitation programme (Filippi, Riccitelli et al., 2012; Messinis et al., 2017). Another clinical trial implemented the MS-line! cognitive intervention, which mainly aims to improve processing speed, working memory, language, executive functioning (logical thinking, reasoning and problem-solving), math skills and spatial orientation, and showed significant cognitive enhancements in processing speed, working memory, visual memory, verbal fluency and naming in persons with MS (Gich et al., 2015). Given all the above, the results of the present study are consistent with the existing literature. This study adds to the growing body of evidence that behavioral cognitive interventions constitute a worthwhile approach for improving information processing speed in persons with MS.

Several RCTs have studied the effects of working memory rehabilitation in persons with MS (Amato et al., 2014; Charvet et al., 2017; Filippi, Riccitelli et al., 2012; Gich et al., 2015; Grasso et al., 2017; Hancock et al., 2015; Hildebrandt et al., 2007; Huiskamp, Dobryakova, Wylie, DeLuca, & Chiaravalloti, 2016; Solari et al., 2004). Most of these studies, as well as the present one, have described working memory improvements in response to cognitive rehabilitation (Amato et al., 2014; Charvet et al., 2017; Filippi,

Riccitelli et al., 2012; Gich et al., 2015; Hancock et al., 2015; Hildebrandt et al., 2007). Thus, a recent study implemented a cognitive rehabilitation focused on processing speed and working memory, and revealed cognitive improvements in both cognitive domains as assessed with the PASAT (Hancock et al., 2015). Hildebrandt et al. (2007) also reported verbal and working memory improvements in those persons with MS attending a cognitive intervention named VILAT-G 1.0, which was specifically targeted at improving both cognitive domains. Several studies have also shown working memory enhancements following more integrative interventions (Charvet et al., 2017; Filippi, Riccitelli et al., 2012; Gich et al., 2015). It must be noted that, in contrast to the present study, the above mentioned RCTs have implemented the cognitive rehabilitation in an individual setting. Consequently, this work not only increases the evidence for the efficacy of working memory rehabilitation in persons with MS but also extends it to group-based cognitive interventions.

The existing RCTs on the efficacy of episodic memory rehabilitation in MS have been mainly focused on the utilization of internal memory aids (Basso, Lowery, Ghormley, Combs, & Johnson, 2006; Chiaravalloti, DeLuca, Moore, & Ricker, 2005; Chiaravalloti, Moore, Nikelshpur, & DeLuca, 2013; Chiaravalloti & DeLuca, 2015; Goverover, Chiaravalloti, Genova et al., 2018; Mani, Chohedri, Ravanfar, Mowla, & Nikseresht, 2018; Moore, Peterson, O'Shea, McIntosh, & Thaut, 2008; Thaut, Peterson, McIntosh, & Hoemberg, 2014), or on memory training (in combination with internal/external aids or not) (Hildebrandt et al., 2007; Messinis et al., 2017; Solari et al., 2004; Stuifbergen et al., 2012; Stuifbergen et al., 2018). Importantly, most of these studies sustain the efficacy of memory rehabilitation in MS (Basso et al., 2006; Chiaravalloti et al., 2005; Chiaravalloti, Moore et al., 2013; Chiaravalloti & DeLuca, 2015; Goverover, Chiaravalloti, Genova et al., 2018; Hildebrandt et al., 2007; Mani et al., 2018; Messinis et al., 2017; Moore et al., 2008; Stuifbergen et al., 2012; Thaut et al., 2014).

For instance, two class I studies have supported the efficacy of the modified Story Memory Technique (Chiaravalloti, Moore et al., 2013) and the Self-Generation Learning Program (Goverover, Chiaravalloti, Genova et al., 2018) for improving verbal memory (learning and long-term recall). Messinis et al. (2017) used the RehaCom programme to train attention, processing speed, episodic memory and executive functioning, and revealed significant improvements in verbal long term storage and delayed recall, visual delayed recall, processing speed, verbal fluency, inhibition and flexibility. Another study described cognitive improvements in verbal learning as well as an increase in the use of mnemonic strategies in persons with MS following their participation in the MAPSS-MS programme for attention, memory and problem solving (Stuifbergen et al., 2012). A recent Cochrane review has additionally revealed significant effects of memory rehabilitation on immediate and long term memory (das Nair, Martin, & Lincoln, 2016). A second Cochrane review has also showed significant improvements in verbal learning as well as in verbal and visual long-term recall for cognitive training interventions in combination with internal or external aids (Rosti-Otajärvi & Hämäläinen, 2014). Therefore, the results of the present study are consistent with previous literature on the effects of memory rehabilitation. Importantly, the present results support that group-based cognitive interventions are effective in improving episodic memory performance.

Most published RCTs, as well as the present study, coincide that cognitive rehabilitation might improve executive functioning in persons with MS (Charvet et al., 2017; Filippi, Riccitelli et al., 2012; Grasso et al., 2017; Mani et al., 2018; Messinis et al., 2017). Thus, a class I study showed an enhancement in cognitive flexibility (TMT-B) in response to the Brain HQ cognitive training programme (Charvet et al., 2017). A recent study has also revealed cognitive improvements in categorization [Wisconsin Card Sorting Test (WCST)] as well as in behavioral regulation and metacognition (Behaviour Rating Inventory of Executive

Function) following the implementation of a cognitive intervention focused on attention, memory, executive functioning and psychoeducation (Mani et al., 2018). Likewise, the RehaCom programme has also been found to improve categorization (WCST), inhibition (ST) and flexibility (TMT-B) in persons with MS (Filippi, Riccitelli et al., 2012; Messinis et al., 2017). Another study also described a significant improvement in the ST in those participants attending the Attention Processing Programme, which is aimed at training attention, information processing and executive functioning (Grasso et al., 2017). Nevertheless, it must also be renowned that a class I study did not detect significant improvements in the WCST after the implementation of the MAPSS-MS (Stuifbergen et al., 2012). Similarly, another RCT failed to find cognitive improvements in the TMT-B in response to the MS-Line! programme (Gich et al., 2015). Discrepancies among studies could be attributed to differing conceptualizations of the cognitive processes that are encompassed within executive functions (e.g. categorization, self-regulation, problem solving, reasoning, inhibition, flexibility...), and consequently to the diverse approaches employed to rehabilitate executive functioning. Despite these differences, it seems that cognitive rehabilitation might be a useful approach for improving executive functioning in persons with MS.

To my knowledge, this is the first study aiming at improving theory of mind performance in persons with MS. Specifically; a trend toward a significant improvement was encountered for this cognitive domain after the intervention, with a moderate effect size. These results might be indicative of a lack of statistical power to detect theory of mind improvements due to the utilization of a limited sample size. Moreover, significant differences between the MS and the HC group were not detected in relation to this cognitive domain at baseline (data not shown), which could have also favored the absence of statistically significant results. Furthermore, previous studies have demonstrated the efficacy of the REHACOP programme for addressing theory of mind deficits in Schizophrenia (Peña

et al., 2016) and Parkinson's disease (Peña et al., 2014). Taken together, all these findings suggest that REHACOP, and accordingly cognitive rehabilitation interventions, might improve theory of mind deficits in MS. Nonetheless, further research is needed to confirm this notion in persons with MS suffering from theory of mind deficits while using greater sample sizes.

Cognitive interventions aim not only to improve cognitive performance but also daily functionality and quality of life (Mitolo et al., 2015; Sumowski et al., 2018). Some RCTs in MS have investigated the effects of cognitive rehabilitation on daily living activities; however, these studies have yielded inconsistent results. For instance, Goverover, Chiaravalloti, Genova et al. (2018) reported daily functionality improvements in the Functional Behavior Profile after the implementation of the Self-generation technique. Similarly, in another study those persons with MS attending an intervention focused on the modified Story Memory Technique showed functional improvements, as assessed with the Functional Assessment of Multiple Sclerosis (Chiaravalloti, Moore et al., 2013). In contrast, other studies have failed to show such improvement in response to the MAPSS-MS (Stuifbergen et al., 2018), the attention processing programme (Amato et al., 2014) or the RehaCom (Campbell et al., 2016). Importantly, a recent Cochrane review did not detect memory cognitive rehabilitation effects on daily functionality (das Nair et al., 2016). Given these inconsistencies among studies, further research examining the effects of cognitive rehabilitation on daily functionality is required in MS. In the present study a trend toward a significant improvement was detected for daily functionality in response to the cognitive intervention. The lack of a significant improvement might have been caused by two main factors. First, the improvement observed in daily functionality did not reach the statistical significance despite that a moderate effect size was observed. Hence, a greater sample size might be required to statistically detect such improvement. Second, both study groups

(intervention and control) obtained almost the maximum score at baseline in the Lawton's IADLs (maximum score = 8). In addition, most MS participants scoring below the maximum score referred that they were not able to perform the corresponding daily tasks because of motor impairment, not because of cognitive difficulties. Consequently, the possibility of detecting functional improvements following the cognitive intervention in this study was very limited.

The present study failed to show a significant effect of cognitive rehabilitation on attention and verbal fluency. The absence of significant improvements for attention is in contrast with most of the RCTs published on this topic (Amato et al., 2014; Cerasa et al., 2013; De Giglio et al., 2015; Filippi, Riccitelli et al., 2012; Hancock et al., 2015; Messinis et al., 2017; Pusswald, Mildner, Zebenholzer, Auff, & Lehrner, 2014). For instance, Amato et al. (2014) carried out a class I study in which the treatment group showed significant improvements in sustained attention after receiving a cognitive intervention specifically aimed at attention abilities (focused, sustained, selective, alternating and divided attention). Another class I study also reported significant improvements in attention and executive functioning, following the implementation of a cognitive intervention also focused on attention (concentration, divided attention and vigilance) (Cerasa et al., 2013). Similarly, different cognitive interventions intended to address multiple cognitive domains, including attention abilities, have also described an enhancement in attention performance (De Giglio et al., 2015; Filippi, Riccitelli et al., 2012; Hancock et al., 2015; Messinis et al., 2017). Moreover, a Cochrane review has also revealed significant improvements in attention following the implementation of cognitive training interventions in combination with internal or external aids (Rosti-Otajärvi & Hämäläinen, 2014). The presence of inconsistent findings between this study and previous literature might rely on the use of different cognitive tests in order to assess attention abilities. Thus, previous studies have mainly utilized cognitive tests

such as the SDMT, the TMT-A, the PASAT or the ST, which might depend on more complex cognitive processes such as processing speed, working memory, mental arithmetic or cognitive inhibition. Conversely, in the present study the BTA was administered that, in spite of being influenced by processing speed, might be a more specific measure of attention. In this line, it must be also noted that in the present work significant cognitive improvements were also detected in the SDMT and the TMT-A (as part of the processing speed composite score) as well as in the ST (as part of the executive functioning composite score), and therefore when considering these tests our results are consistent with the literature.

While several RCTs in MS have included verbal fluency tests in the neuropsychological assessment, to the best of my knowledge, none of these trials has implemented a cognitive intervention aiming at improving this cognitive domain. Accordingly, the large majority of these trials have failed to show significant improvements in verbal fluency in response to cognitive rehabilitation (Amato et al., 2014; Cerasa et al., 2013; Grasso et al., 2017; Hancock et al., 2015; Messinis et al., 2017; Pusswald et al., 2014; Stuifbergen et al., 2012; Stuifbergen et al., 2018). Thus, only two previous studies have reported significant improvements in verbal fluency (Gich et al., 2015; Parisi et al., 2013). Interestingly, in one of these studies the MS-line! cognitive rehabilitation programme was implemented, which included different word-based exercises that may have indirectly trained such cognitive domain. In the present study, the absence of significant improvements in verbal fluency might be explained by an insufficient training of this cognitive domain, given that only two cognitive sessions were intended to improve verbal fluency performance. A complementary explanation could be based on the lack of statistical power to detect this improvement, given that the obtained effect size for this cognitive domain was nearly moderate. Therefore, the combination of these two factors might contribute to the explanation of the absence of significant results for verbal fluency in the present study.

In conclusion, MS participants attending the REHACOP cognitive rehabilitation presented statistically significant cognitive improvements in processing speed, working memory, episodic memory and executive functioning. Accordingly, the current work provides preliminary evidence for the effectiveness of the REHACOP integrative group-based cognitive rehabilitation programme in persons with MS. Moreover, these findings reinforce the notion that albeit the REHACOP was originally intended for persons with psychotic disorders (Ojeda & Peña, 2012; Peña et al., 2016) it also seems to be effective in neurodegenerative conditions, such as Parkinson's disease (Peña et al., 2014) and MS.

Several limitations in relation to the present RCT should be stated. The study was not blinded. Nor was an active control group included, which constrains the possibility of differentiating the effects of the cognitive intervention from those due to the social involvement in group sessions or the receipt of a greater attention by the neuropsychologist. Another aspect is that suffering from cognitive impairment was not considered as an inclusion criterion. The influence of having included MS participants with different cognitive status was statistically controlled in repeated measures MANCOVA. Nevertheless, in order to assess the efficacy of cognitive interventions it would is advisable to only consider cognitively impaired participants. On the other side, despite having carried out a random allocation of the MS participants to the different study conditions, significant cognitive differences were detected between the intervention and the control group at baseline. These differences are controlled by default in repeated measures MANOVA/MANCOVA (Van Breukelen, 2006); however, the use of groups with equivalent baseline characteristics would have been more suitable. Finally, the sample size of the study was small, which might have influenced the lack of significant improvements especially in those cognitive domains showing moderate effect sizes such as theory of mind and daily functionality. Notwithstanding these limitations, this study has revealed significant improvements in a

broad range of cognitive domains, which points out that the REHACOP cognitive rehabilitation programme might be an effective tool for addressing MS cognitive deficits. Together with the accumulative scientific evidence about the effectiveness of cognitive remediation treatments in MS, this study supports the need for adding neuropsychological rehabilitation interventions to standardized clinical treatment protocols in the disorder.

The above mentioned limitations should be addressed in future studies. Further research should also analyze the effects of the REHACOP programme in other relevant aspects such as depressive/anxiety symptoms, subjective perception of cognitive difficulties, general self-efficacy or quality of life. Future studies should also investigate the predictors of response to cognitive rehabilitation, that is to say, which persons with MS will benefit most from this therapeutic approach. Additionally, a long-term prospective follow-up study might aid to determine the maintenance of the benefits derived from the cognitive intervention over time.

6.3. Study III

The present study aimed to examine brain functional and structural connectivity changes following the implementation of the REHACOP cognitive rehabilitation programme in persons with MS. Results specifically showed significant functional connectivity changes involving the DMN and the HMN. Thus, the intervention group presented a decreased functional connectivity between the anterior cingulate cortex and the left anterior middle temporal gyrus of the DMN following the cognitive rehabilitation, while an increased functional connectivity was observed between these brain areas in the control group. Similarly, the intervention group also exhibited a decreased functional connectivity between the left hippocampus and the left cerebellar hemisphere of the HMN in response to the cognitive rehabilitation, whereas the control group showed an increased functional

connectivity between such nodes over time. DMN and HMN functional connectivity decreases were respectively associated with the observed cognitive improvements in information processing (processing speed and working memory) and episodic memory after the intervention. Accordingly, this work offers preliminary evidence for the efficacy of the REHACOP cognitive rehabilitation programme on inducing adaptive brain functional connectivity changes in persons with MS.

Previous studies examining functional connectivity changes within the DMN in response to cognitive interventions have reported inconsistent outcomes in MS. Thus, initial studies recurrently reported brain functional connectivity increases within this network following cognitive rehabilitation (Bonavita et al., 2015; Filippi, Riccitelli et al., 2012; Leavitt, Wylie, Girgis et al., 2014; Parisi et al., 2014), whereas subsequent works have shown that functional connectivity decreases may occur as well (Ernst et al., 2016a; Ernst et al., 2016b). For instance, in two early studies the RehaCom programme was found to increase the functional connectivity of the posterior nodes of the DMN, including the posterior cingulate cortex, the precuneus, and the inferior parietal gyrus (Bonavita et al., 2015; Filippi, Riccitelli et al., 2012). In one of these studies, the observed functional connectivity increases were additionally related with working memory and executive functioning improvements, as assessed with the PASAT and the WCST (Filippi, Riccitelli et al., 2012). In a third study in which the RehaCom programme was also implemented and the anterior cingulate cortex was specifically seeded, this DMN hub showed a functional connectivity increase with the inferior parietal gyrus in the intervention group, as well as a functional connectivity decrease with the inferior temporal lobe in the control group (Parisi et al., 2014). In such study, the functional connectivity increase observed in the intervention group was associated with an improvement in the performance of the PASAT (Parisi et al., 2014). In another study a functional connectivity increase was also found between the posterior cingulate cortex

(selected as a seed) and the thalamus in response to the modified Story Memory Technique (Leavitt, Wylie, Girgis et al., 2014).

In contrast, in a later study both functional connectivity increases and decreases were observed within the DMN in response to a mental visual imagery facilitation programme intended to improve autobiographical memory performance (Ernst et al., 2016b). Functional connectivity increases specifically involved the right posterior cingulate cortex [Brodmann area (BA 30)], left precuneus (BA19) and left middle temporal gyrus, while functional connectivity decreases were found in the bilateral precuneus (BA 7), right posterior cingulate cortex (BA23) and left angular gyrus. In another study, in which the same mental visual imagery programme was implemented only functional connectivity decreases were noticed, particularly in the bilateral cingulate cortex and right precuneus of the DMN (Ernst et al., 2016a). Regrettably, these studies did not examine the association between functional connectivity and cognitive changes after the implementation of the facilitation programme (Ernst et al., 2016a; Ernst et al., 2016b). However, a recent study examining the thalamic resting-state network after the implementation of the Dr. Kawashima's Brain Training has revealed that not only functional connectivity increases but also decreases can be associated with cognitive improvements. Thus, in that study, the thalamus presented functional connectivity increases with posterior nodes of the DMN and decreases with cerebellum, which were respectively associated with processing speed and working memory improvements (De Giglio, Tona et al., 2016). Therefore, the present study not only strengthens the notion that functional connectivity decreases in response to cognitive interventions can also be adaptive (i.e. be associated with cognitive improvements), but also constitutes the first one to reveal these findings concerning the DMN.

In the present study functional connectivity changes within the DMN were specifically noticed between the anterior cingulate cortex and the anterior middle temporal

gyrus. Previous DMN studies have not described functional connectivity changes between these two specific nodes. However, the literature has shown functional connectivity changes in distinct brain regions depending on the implemented cognitive rehabilitation programme and rs-fMRI protocol (Chiaravalloti et al., 2015). Specifically, the anterior cingulate cortex is widely recognized as a key brain area in the management and processing of information (Margulies et al., 2007). In addition, the middle temporal gyrus has been found to be engaged in processing written or spoken linguistic information (Vorobyev et al., 2004). Some fMRI studies have additionally described the participation of these two brain nodes in the performance of working memory tasks in persons with MS (Hampson, Driesen, Skudlarski, Gore, & Constable, 2006; Mainero, Pantano, Caramia, & Pozzilli, 2006). Accordingly, it could be assumed that functional connectivity changes between these two specific brain nodes might modulate written information processing speed and working memory performance, as suggested by the observed significant correlations between the DMN functional connectivity and cognitive changes following the intervention.

Repetitive cognitive task training has been commonly found to produce performance enhancements as well as brain activity decreases in HC (Kelly & Garavan, 2004). This activity decreases are thought to reflect a greater brain neural efficiency. That is, the refinement of the functional network required for the accomplishment of the task, which is accompanied by an improvement of the trained cognitive ability in the absence of strategy changes (Kelly & Garavan, 2004). Interestingly, these activity decreases commonly involve brain regions located in the frontal lobe that are implicated in attention and executive control cognitive processes, such as the anterior cingulate cortex (Kelly & Garavan, 2004). Therefore, it is suggested that processing speed and working memory stimulation by means of the REHACOP programme might have given rise to cognitive improvements in both cognitive domains, as well as to a more efficient functional connectivity between the anterior

cingulate cortex and the anterior middle temporal gyrus. Particularly, this decrease could be indicative of a lower requirement of effortful information processing, meaning a lower involvement of the anterior cingulate cortex, in processing speed and working memory performance.

On the other side, only one previous study has examined the presence of functional connectivity changes within the HMN in response to cognitive rehabilitation in persons with MS (Leavitt, Wylie, Girgis et al., 2014). In that study the hippocampus showed an increased functional connectivity with several brain areas (the precentral and the postcentral gyrus, the cingulate cortex and the insula) following the implementation of the modified Story Memory Technique (Leavitt, Wylie, Girgis et al., 2014). Possible correlations between functional connectivity and cognitive changes were not examined in that study (Leavitt, Wylie, Girgis et al., 2014). In the present one, the intervention group showed a functional connectivity decrease between the left hippocampus and the homolateral gracile lobule of the cerebellum in response to the cognitive intervention, while the control group presented a functional connectivity decrease between such brain nodes over time. Consequently, the results of the present work are in contrast with those reported by Leavitt, Wylie, Girgis et al. (2014), since functional connectivity changes were observed in the opposite direction (decreases vs. increases). A significant relationship was also noticed in the present study between the described HMN functional connectivity decrease and episodic memory improvements after the cognitive rehabilitation. Therefore, this study constitutes the first to show that functional connectivity decreases within the HMN in response to a cognitive can be adaptive in MS.

The hippocampus and the cerebellum are widely known to be implicated in episodic memory performance (Eichenbaum, 2000; Svoboda, McKinnon, & Levine, 2006; Weis, Klaver, Reul, Elger, & Fernández, 2004). However, the involvement of the cerebellum in memory processes seems to be more relevant as the memory demands or the task difficulty

increase (Desmond & Fiez, 1998). In this line, repetitive memory task training has been found to improve memory performance as well as to produce a decrease in the activation of the cerebellum, that is, a greater neural efficiency in HC (Kelly & Garavan, 2004). Accordingly, it is suggested that the functional connectivity decrease between the hippocampus and the cerebellum, given its association with episodic memory improvements, could be reflecting a lesser requirement of the cerebellum in episodic memory processes and, thereby, a greater brain neural efficiency following the cognitive intervention.

The literature on brain white matter structural connectivity changes in response to cognitive rehabilitation is very scarce (Campbell et al., 2016; De Giglio, Upadhyay et al., 2016; Filippi, Riccitelli et al., 2012). Despite this, the existing studies have reported inconsistent results. Thus, two studies have failed to show significant white matter structural connectivity changes after the implementation of the RehaCom programme (Campbell et al., 2016). Conversely, in the study conducted by De Giglio, Upadhyay et al. (2016) a decreased AD was noticed in the intervention group following a cognitive intervention with the Dr. Kawashima's Brain Training for attention, visuospatial processing, memory and calculation. This AD reduction was additionally associated with a better performance on the PASAT. It must be noted that some studies have also investigated the effects of cognitive interventions on other brain structural features, such as brain volume (Bonavita et al., 2015; Filippi, Riccitelli et al., 2012), lesion burden (Bonavita et al., 2015) or gray matter microstructure (Campbell et al., 2016; Filippi, Riccitelli et al., 2012). However, none of them detected brain structural changes after cognitive rehabilitation. Accordingly, the results of the present study are consistent with the great majority of the MS literature about the structural brain effects of cognitive rehabilitation. The implementation of cognitive interventions during more than three consecutive months might favor the stimulation of brain structural plasticity processes

in MS. However, further research is needed to better define the structural basis of cognitive rehabilitation (Campbell et al., 2016).

Two main findings must be stressed in relation to the present study. First, this work, along with the second study of this thesis, supports the notion that the REHACOP programme could be a meaningful tool to improve cognitive performance and induce brain functional connectivity changes in MS. Second, this study seems to point out that a more efficient functional connectivity within the brain resting-state networks can be associated with better cognitive performance following a neuropsychological intervention in MS and, thereby, this study contributes to an increasing understanding of the neurobiological mechanisms that may lie beneath these cognitive improvements in the disorder.

Some limitations concerning the present study can be discussed. The sample size was limited, and an active control group was not included. The latter limitation constrains the possibility of differentiating the effects derived from the cognitive intervention from those due to the social involvement in group sessions. Moreover, handedness was not considered as an inclusion criteria. Despite this, all participants except one, which was randomly allocated in the control group, were right-handed. Notwithstanding these limitations, the present work has revealed brain plasticity changes within two specific resting-state networks as well as their association with cognitive improvements following the intervention, which reinforces the efficacy of the REHACOP cognitive rehabilitation programme in the treatment of MS cognitive deficits.

Future research should deal with the aforementioned limitations. A long-term prospective follow-up study might aid to determine the maintenance of the brain changes derived from the cognitive rehabilitation over time. Further studies should also investigate the predictive role of brain functional connectivity changes in the long-term maintenance of those cognitive improvements observed following the cognitive intervention in persons with MS.

VII. Conclusions

7. Conclusions

7.1. Conclusions

The main conclusions of the present work can be summarized as follows:

Study I

i. MS participants presented deficits in a wide range of cognitive domains including processing speed, attention, episodic memory (verbal and visual), verbal fluency and executive functioning (inhibition and flexibility), as compared to healthy subjects.

ii. Those cognitive deficits initially observed in MS participants were no longer significant after controlling for the influence of processing speed, but remained significant after controlling for the effect of visual memory. These findings point out that processing speed decline might to a large extent underlie other cognitive deficits in MS, and underscore the need for identifying the precise source of the aforementioned cognitive deficits to better-inform intervention decisions.

Study II

i. MS participants receiving the REHACOP cognitive rehabilitation programme presented cognitive improvements in processing speed, working memory, episodic memory and executive functioning as compared to the control group. The present findings provide evidence for integrative group-based cognitive rehabilitation efficacy in persons with MS through the implementation of the REHACOP programme.

Study III

i. Those MS participants receiving the REHACOP programme exhibited brain functional connectivity decreases within the DMN and the HMN, while functional connectivity increases were observed within both networks in the control group over time.

ii. MS participants did not present brain structural connectivity changes in response to the cognitive intervention.

iii. Functional connectivity decreases within the DMN and the HMN following the cognitive rehabilitation were respectively associated with cognitive improvements in information processing (processing speed and working memory) and episodic memory. Accordingly, the REHACOP integrative group-based cognitive rehabilitation programme might not only improve cognitive performance, but also induce adaptive brain functional connectivity changes in persons with MS.

7.2. Conclusiones

Las principales conclusiones de este trabajo pueden resumirse de la siguiente manera:

Study I

i. Los participantes con esclerosis múltiple (EM) presentaron déficits en un amplio abanico de dominios cognitivos, incluyendo la velocidad de procesamiento, atención, memoria episódica (verbal y visual), fluidez verbal y funcionamiento ejecutivo (inhibición y flexibilidad cognitiva), en comparación con los sujetos sanos.

ii. Los déficits cognitivos detectados inicialmente en los participantes con EM dejaron de ser significativos tras controlar por la influencia de la velocidad de procesamiento, pero permanecieron siendo significativos tras controlar por el efecto de la memoria visual. Estos hallazgos señalan que el deterioro de la velocidad de procesamiento podría subyacer en gran medida a otros déficits cognitivos en la EM, y destacan la necesidad de identificar el origen exacto de estos déficits con el fin de mejorar la toma de decisiones terapéuticas.

Study II

i. Aquellos participantes con EM que recibieron la rehabilitación cognitiva con el programa REHACOP presentaron mejoras significativas en velocidad de procesamiento, memoria de trabajo, memoria episódica y funcionamiento ejecutivo en comparación con el grupo control. Estos hallazgos proporcionan evidencia a favor de la eficacia de la rehabilitación cognitiva integral aplicada en formato grupal mediante el programa REHACOP en personas con EM.

Study III

i. Aquellos participantes con EM que recibieron la intervención cognitiva con el programa REHACOP mostraron una reducción de la conectividad funcional cerebral en la red neuronal por defecto (RND) así como en la red de memoria hipocampal (RMH), mientras que el grupo control presentó un incremento de la conectividad funcional en ambas redes neuronales a lo largo del tiempo.

ii. Los participantes con EM no presentaron cambios estructurales en la conectividad cerebral en respuesta a la intervención cognitiva.

iii. Las reducciones de la conectividad funcional cerebral en la RND y la RMH tras la rehabilitación cognitiva se asociaron, respectivamente, con las mejoras cognitivas encontradas en procesamiento de la información (velocidad de procesamiento y memoria de trabajo) y memoria episódica. De acuerdo con esto, el programa de rehabilitación cognitiva integral REHACOP aplicado en formato grupal podría no solo mejorar el funcionamiento cognitivo, sino también inducir cambios adaptativos en la conectividad funcional cerebral en personas con EM.

VIII. References

8. References

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