Cognitive phenotypes in Multiple Sclerosis: underlying changes in structural connectivity

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Abstract

Background: Patients with multiple sclerosis (MS) frequently show difficulties in episodic memory, attention, information processing speed and executive functions. Some of them have selective deficits of a given cognitive domain, and different cognitive phenotypes involving memory or processing speed disturbances have been described.

Aim: To analyze the underlying patterns of damage in structural networks according to the cognitive phenotypes observed in a large sample of MS patients.

Methods: A cohort of 183 patients (age: 43.1±10 years; disease duration: 12.1±9.3 years; Expanded Disability Status Scale, EDSS: 2 (0-6.5)) was assessed by the Brief Repeatable Battery-Neuropsychology (BRB-N). Whole brain structural connectivity was obtained from diffusion magnetic resonance imaging and mean fractional anisotropy (FA) in each connection was compared among patients groups.

Results: Thirty-two patients (18%) showed memory impairment (z-score of Selective reminding test-delayed or Spatial recall tests-delayed below -1.5), 29 (16%) patients had attention deficits (below -1.5 z-score in Symbol Digit Modalities Test or Paced Auditory Serial Addition Task) and 21 (11%) had global impairment. The remaining 101 (55%) patients were cognitively preserved (CP). Patients with global impairment were older, more frequently secondary-progressive MS, and had higher EDSS score. Global cognitive impairment patients displayed a disruption of the network efficiency ($p<0.001$) compare to the other phenotypes. Also, differences among groups were observed in 12.4% (corrected $p<0.05$) of the brain connections, mainly involving frontal and parietal areas, and insula. While connectivity was similar in patients with memory and attention phenotypes compared with CP patients (decreased FA in 6% of connections), those with global impairment displayed widespread reduction in connectivity (decreased FA in 63% of connections).

Conclusions: In contrast to patients with global impairment, those with predominant memory or attention deficits have similar brain connectivity to that seen in CP patients, suggesting that they are at an early stage of cognitive disability and do not have specific patterns of network modifications. Furthermore, the results reinforce the importance of the frontoparietal network damage in the development of cognitive deficits in MS.

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1. Introduction

1.1 Multiple Sclerosis

Multiple Sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS) and is one of the main causes of neurological disability among young adults. According to the MS Atlas, currently more than 2.3 million people around the world have MS and, specifically, in Spain there are 46,000 people who suffer it (Multiple Sclerosis International Federation, 2013). This disease generally appears between the second and fourth decades of life and the onset of symptoms is around 30 years old on average (Kurtzke, 2005). In addition, epidemiological studies have shown that is more common in women, with a rate of 2:1 (Sadovnick & Ebers, 1992). Consequently, it is a pathology that can affect daily life functions, therefore, it's important to increase our knowledge of the physiopathological mechanisms underlying this disease, to progress on treatments, with a final goal of boosting quality of life for people with MS.

Although the cause of MS remains unknown, most studies suggest a complex etiology involving genetic, environmental and immunological factors that interact with each other (Fernandez & Rodriguez-Antigüedad, 2010). MS is characterized by the presence of sclerotic plaques, which represents the final phase of a process that involves inflammation, demyelination and remyelination, depletion of oligodendrocytes, astrocytosis, and neuronal and axonal degeneration(Compston & Coles, 2008). These physiopathological mechanisms lead to focal lesions in both white matter (WM) and grey matter (GM), and diffuse damage in normal-appearing tissue (Filippi et al., 2012). Cerebral damage can be studied through Magnetic Resonance Imaging (MRI) techniques, however, the presence of focal lesions observed in conventional MRI is poorly associated with the clinical and cognitive behaviour of the patients (Mollison et al., 2017), probably due to its insensitivity to diffuse tissue damage.

MS is a heterogeneous disease, both in its presentation and evolution within different clinical courses or phenotypes (Fig. 1). These phenotypes are important for the communication, prognosis, design and recruitment of clinical trials and for treatment (Lublin et al., 2014).

- Clinically Isolated Syndrome (CIS): It is recognized as the first clinical presentation of the disease (80%) (Compston & Coles, 2008). It shows an acute or subacute episode of neurological disturbance due to a single WM lesion that could be MS, but has yet to fulfil criteria of dissemination in time (Miller, Barkhof, Montalban, Thompson, & Filippi, 2005).

- Relapsing-Remitting MS (RRMS): It is the most common form of the disease, around 85-90% of cases has this form. It is defined by the presence of relapses, followed by stages of partial or total recovery, with a stable course in between (Juárez, 2010).

- Primary Progressive MS (PPMS): This form is present in 10-15% of patients. In this case, patients experience a slow and progressive symptomatology progression from the beginning of the disease, sometimes with relapses of neurological dysfunction. Lately, it has been suggested that PPMS is a part of the spectrum of progressive MS phenotype(Lublin et al., 2014).

- Secondary Progressive MS (SPMS): There is a gradual neurological deterioration regardless of the occurrence of outbreaks. It usually appears after an initial relapsing disease course, with or without relapses during the progressive course (Lublin et al., 2014).

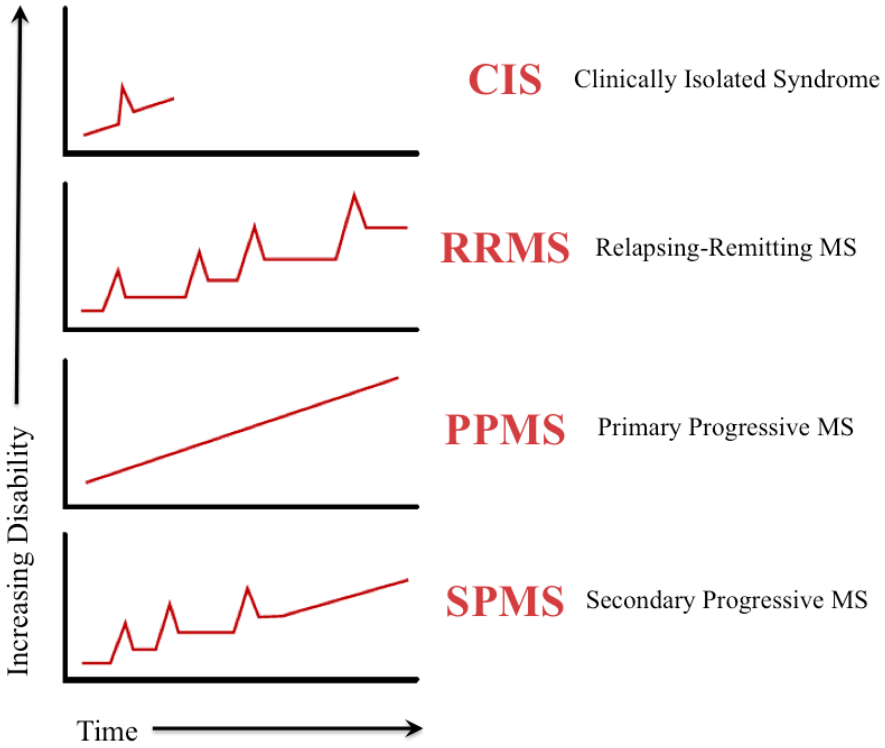

*Figure 1.*MS clinical phenotypes. Figure adapted from MS progression types (2009, March 11). Recovered from https://commons.wikimedia.org/wiki/File:Ms_progression_types.svg.

Due to the variability in the localization of lesions and the processes of neuronal degeneration, people with MS may experience fatigue, sensory, motor, cerebellar, visual, spinal, sexual and, cognitive and psychiatric disorders (Cruz, 2014). This is a polymorphic clinical semiology with an unpredictable evolution. The disabling effect of MS, in particular, physical dysfunction, cognitive impairment, fatigue and depression, trigger significant detriment to the quality of life in patients (Olascoaga, 2010). In addition, the results of a study made by Benito-Leon, Morales & Rivera-Navarro (2002), shows that MS patients perceive their quality of life differently according to severity, duration, and clinical course, where depression and anxiety play a key role.

1.2 Cognitive dysfunction in Multiple Sclerosis

As previously stated, cognitive dysfunction plays a very important role in the symptomatology of MS, with a frequency range between 40% and 65% of MS patients (Benedict, Bruce, et al., 2006; Deloire et al., 2005). Patients with cognitive worsening may have more problems on everyday activities as on social and emotional function, the ability to do household tasks, maintenance of gainful employment, and overall quality of life (Chiaravalloti & Deluca, 2008). These consequences can be present at any phase of the disease, from initial stages to the most advanced periods, significantly affecting the quality of life of the patients, their families, and carers' (Amato et al., 2013; Benito-Leon et al., 2002; Chiaravalloti & Deluca, 2008; Patti, 2009). Accordingly, recognizing the weight of cognitive functioning in MS becomes essential to understand these alterations, the effect they cause on people, and the capacity to benefit from therapy, which allows for a more global vision of the development of the disease.

Although cognitive deficits vary widely among patients, the most frequently impaired domains include attention, memory, information processing speed (PS), executive functions and visual perceptual functions (Chiaravalloti & Deluca, 2008; Winkelmann, Engel, Apel, & Zettl, 2007). It also must be taken into account that cognitive functions are interrelated; each impaired function may affect the other function's performance.

- Learning and episodic memory: This memory function appears to be the most consistently impaired cognitive domain in MS and is seen in 40-65% of patients (Rao et al., 1993). Research has shown that MS patients have difficulty with acquisition of new knowledge as opposed to retrieval from long-term storage(Chiaravalloti & Deluca, 2008). However, a decrease in the PS capacity may influence in the acquisition of new information.

- Attention: Attention deficits are reported in 25% of MS patients, implying impaired performance accuracy and reaction times in patients with prominent deficits on attention functions (Nebel et al., 2007). According to Winkelman & colleagues (2007), cognitive impaired patients execute all attention tasks more slowly than cognitive unimpaired patients, but with a similar number of errors in both groups.

- Information PS: This might be an initial marker of cognitive impairment in MS (Nocentini et al., 2006). With learning and memory difficulties, information PS, is one the most common deficit in MS and, appears to be a major feature of the cognitive profile associated with MS (Chiaravalloti & Deluca, 2008; Rogers & Panegyres, 2007).

- Executive functions: Executive dysfunction occurs less frequently than memory or PS disability, as it is only seen in 19% of MS patients (Winkelmann et al., 2007). Poor performance is caused by deficits in concept formation, feedback utilization and problem solving strategies (Rogers & Panegyres, 2007).

- Visuoconstructive and visuospatial abilities: Compared to studies on long-term memory and information processing speed, there has been little work done on visual perceptual processing. However, depending on the test system, up to 19% of MS patients show poor performance compared to controls (Winkelmann et al., 2007). According to Chiaravalloti and DeLuca (2008), not only difficulties in primary visual processing in MS can have a detrimental effect on visual perceptual processing.

When assessing cognitive functioning in MS patients, it has to be taken into account that cognitive deterioration in MS can be influenced by different factors (Krupp & Elkins, 2000). On the one hand, there are clinical characteristics of the disease that can affect this performance, as MS type, disease duration, fatigue or degree of disability (Gamazo, 2009). On the other hand, there are also psychological and psychiatric variables such as mood and related disorders (depression, anxiety, euphoria, etc.) that can hinder a correct evaluation of cognition functioning (Feinstein, 2004).

As previously mentioned, cognitive impairment is frequent in MS patients and, for now, we know little about the variability of the expression of cognitive deficit. It is important to highlight that cognition has typically been conceived as dichotomous; where studies characterize patients as cognitively impaired or non-impaired based on different tests measuring cognitive functions (Leavitt, Tosto, & Riley, 2018; Sumowski et al., 2018). This division has led to heterogeneous groups of impaired patients with different isolated or combined cognitive deficits. Leavitt et al. (2018) examined data from 128 RRMS patients and, from it, proposed adopting a novel classification taxonomy for cognitive phenotypes: non-impaired, isolated memory impairment, isolated PS impairment, and combined deficits in PS and memory. The description of the cognitive phenotypes and the identification of their underlying neural bases have become a key priority in the MS research (Sumowski et al., 2018).

1.3 Neuroimaging

The knowledge of how tissue damage contributes to cognitive deficits in MS is necessary to develop clinical and neuroimaging biomarkers that allow clinicians to monitor disease evolution, predict cognitive decline and define treatment response (Rocca, De Meo, & Filippi, 2016).

The non-conventional MRI techniques as diffusion tensor imaging (DTI), has become useful tools in defining parameters of demyelination and axonal loss (Li et al., 2013) in the MS pathology. It is a non-invasive imaging method that permits the procurement of anatomical information from connections in the neural network based on the movement of water molecules in organic tissue (Martínez-Heras, 2017). Thus, it allows researchers to exhaustively study the integrity of WM fiber pathways linking GM structures (Basser, Pajevic, Pierpaoli, Duda & Aldroubi, 2000). Diffusion characteristics as fractional anisotropy (FA), mean diffusion (MD), radial diffusion (RD) or axial diffusivity (AD) can be useful to understand WM matter damage. FA is commonly used as a structural

integrity marker (Beaulieu, 2002), MD is an average of the eigenvalues of the diffusion tensor (Le Bihan et al., 2001), while RD has been related to demyelination and AD to axonal damage in animal models (Song et al., 2003, 2005).

The DTI tractography studies with MS patients shows reduced FA and increased MD, RD and AD, as opposed to HV (Hulst et al., 2013; Llufriu et al., 2014) reflecting an impairment of the tissue integrity and a consequent decrement of network efficiency (Llufriu et al., 2014; Shu et al., 2011). Network connectivity changes have been associated with cognitive impairment (Llufriu et al., 2017; Shu et al., 2016). Recently, it has been proposed a disconnection theory for cognitive impairment in MS that could explain a series of disconnection mechanisms affecting several networks associated with cognition, where a specific cognitive deficit corresponds with a lesion in the WM of the anatomical location of that function (Dineen et al., 2009).

Recently, graph theoretical analysis provides a comprehensive and subtle method to characterise brain networks (Bullmore & Sporns, 2009).Graphs are simple mathematical models of a system consisting of a set of nodes (i.e., brain regions) and edges representing connections between them (i.e., structural and functional connections)(Bullmore & Sporns, 2012). Through this method, functional and diffusion-based MRI studies have found a disruption of the optimal balance between integration and segregation of network components resulting in a reduction of the system flow of information (He et al., 2009; Llufriu et al., 2017; Rocca et al., 2016). Global measures (e.g., global efficiency and path length) provide an indicator of the capability of the network to integrate information; while segregation measures (e.g., local efficiency, clustering or modularity) assesses processing information more locally (Fleischer et al., 2017). Overall, literature suggests a disrupted integrity in both structural and functional connectivity in MS patients provoked by damage to multiple tracts, thus providing new insights into the understanding of MS connectome.

1.4 Hypothesis and objectives

Due to the relevance of cognitive impairment, its repercussions on MS patient's daily lives and, the unknown underlying patterns of damage in structural networks according to these cognitive deficits; it is necessary to adopt a novel classification taxonomy for cognitive phenotypes and observe if it correlates with neural bases of these functions by neuroimaging techniques. In this study, we aimed to analyze the underlying patterns of damage in structural networks according to the cognitive phenotypes observed in a large sample of RRMS and SPMS patients. We hypothesized that there are different cognitive profiles in patients with MS and these differences can be observed in the results of neuropsychological tests and at the structural level by means of MRI. In order to study our hypothesis, we examined connectivity differences between MS patients and HV. Then, a proportional representation of predominant groups with the following cognitive phenotypes were evaluated: (1) CP, (2) memory-impaired only, (3) attention-

impaired only and (4) global-impaired. Moreover, we evaluated whether these cognitive differences were supported in a different structural networks.

Therefore, the main objective of the study was to analyze the underlying neural correlations to the different cognitive phenotypes in patients with MS, and to determine if there are different patterns of network damage in accordance with the dominant cognitive dysfunction. In addition, a secondary aim consisted in the study of the relation between demographic, clinical and network integrity variables with cognition impairment.

2. Methods

2.1 Participants

To evaluate cognitive phenotype representation, we examined data from 183 consecutively enrolled patients diagnosed with relapsing-remitting or secondary-progressive MS according to 2010 McDonald criteria (Polman et al., 2011). Patients were recruited from three different studies in the MS Unit at the Hospital Clinic of Barcelona:

- "Resonancia magnética no convencional como marcador predictivo de respuesta a terapia de primera línea en esclerosis múltiple", funded by TEVA Spain SLU (2013-2020).

- "Biomarcadores de resonancia avanzada en esclerosis múltiple: asociación con el perfil clínico evolutivo y sustrato genético", funded by Instituto de Salud Carlos III (2016-2018).

- "La integración sensitivo-motora como medida de evolución clínica en pacientes con esclerosis múltiple: un estudio neurofisiológico con correlación clínico-radiológica", funded by Hospital Clínic (2008-2009).

MS patients had to fulfill the following inclusion criteria to enter in the studies: (a) age between 18 and 65 years; (b) must be free from relapses in the last 30 days of the study; (c) had no history of any other neurologic or psychiatric condition interfering in the disease. In addition, a cohort of 42 healthy volunteers (HV) with age between 18 and 65 years andwithout previous or present history of neurological or psychiatric dysfunction was also enrolled. HV were recruited from the outpatient facility of the Neurology department via advertisements. The Ethics Committee of the Hospital Clinic of Barcelona approved the study and all participants signed an informed consent.

2.2 Clinical and cognitive assessment

Cognitive function was assessed with the Brief Repeatable Battery-Neuropsychology (BRB-N), which was developed by the Cognitive Function Study Group of the National Multiple Sclerosis Society as a tool to identify disturbances of cognitive domains in MS patients (Rao et al., 1990). It is one of the most widely used neuropsychological battery for MS; it is increasingly used as a research instrument in clinical studies to investigate the relationship between cognitive changes and MRI findings (Amato, Zipoli, & Portaccio, 2008; Bozzali et al., 2013; Huijbregts et al., 2004; Loitfelder et al., 2014; Sperling et al., 2001). The BRB-N evaluates diverse cognitive domains including:

- *Selective Reminding Test* (SRT): measures verbal learning process and long-term memory of a 12-word list. It distinguishes between short-term and long-term components of memory and examines also the consistency of retrieval from long-term memory (Boringa, Lazeron, Reuling, Adèr, Pfennings, Lindeboom, de Sonneville, et al., 2001). According to Huijbregts and colleagues (2004), the Long-Term Storage (LTS) score represents the sum of words recalled on two consecutive trials without reminding. The Consistent Long-Term Retrieval (CLTR) score is the sum of words recalled on all the subsequent trials without reminding. The Total Delay (SRTD) score is the number of words recalled after a delay of 10 minutes.

- *Spatial Recall Test* (SPART): was developed to assess visuospatial learning and memory. Subjects are instructed to recall the placement of 10 checkers that are randomly placed on a checkerboard (6X6). One score is the sum of correct responses in the three immediate recall trials (SPART) and the other score is delayed recall after 15 minutes (SPARTD) (Huijbregts et al., 2004).

- *Symbol Digit Modalities Test* (SDMT): is a symbol-number substitution test designed to examine speed of information processing and complex visual scanning and tracking. According to Boringa and cols. (2001), the subject examines a series of nine meaningless geometric symbols which are labelled 1 to 9 and, during 90 seconds, the participant has to substitute the symbols with its' corresponding number. The score is the number of correct substitutions. In our study, it was administered verbally to obtain a result independent of motor performance.

- *Paced Auditory Serial Addition Task* (PASAT): is a measure of sustained attention, information-processing speed, working memory and mental calculation. Subjects must add each new digit to the one immediately prior to it, and then, reports the outcome verbally. They must be able to rapidly refresh working memory content and resist interference from a previous response (Huijbregts et al., 2004). The score is the number of correct sums made out of the sixty possible (Gamazo, 2009).

- *Word List Generation* (WLG): a semantic verbal fluency test evaluating the spontaneous production of names of a given category within a limited amount of time (90 s). The subject is asked to give as many names of `vegetables and fruits' (version A) or `animals´ (version B) as possible during 90 s. The score is the number of correct names (WLGT) (Boringa et al., 2001).

The use of this battery has several advantages; it can be administered in approximately 30-45 minutes, depending on the speed with which the patient processes the information (Duque et al., 2012). It has a sensitivity of 71% and a specificity of 94% in discriminating cognitively intact from impaired MS patients as defined by the comprehensive battery (Boringa, Lazeron, Reuling, Adèr, Pfennings, Lindeboom, de Sonneville, et al., 2001). In addition, it has been translated into several languages and

its normative data is available in several countries, including Spain (Sepulcre et al., 2006).

The results of the cognitive tests were transformed to z-scores, derived from normative data obtained from a Spanish published healthy cohort and were stratified by age and educational level (Sepulcre et al., 2006) and alteration standards were placed at z-scores below -1.5 standard deviations (SD). From here, patients were divided according to their cognitive scores in CP, memory-impaired, attention-impaired (englobing PS, attention and working memory) and global-impaired (including memory and attentional deficits) phenotypes. Those patients with a z-score below to -1.5 in at least one of the following SRTD or SPARTD or in SDMT or PASAT were classified as memory-impaired group or attention-impaired group, respectively. Patients with z-scores below to -1.5 in SRTD or SPARTD and SDMT or PASAT were classified as global-impaired group. The remaining MS patients were classified as CP group.

Besides, MS global disability was evaluated using the *Expanded Disability Status Scale* (EDSS) (Kurtzke, 1983). It is an interval scale of physical disability in MS ranging from no disability (grade 0) to death due to MS (grade 10) (Sumowski et al., 2018).

We also assessed the cognitive reserve using the *Cognitive Reserve Questionnaire* (CRQ) (Rami et al., 2011) to include the protective effect of brain reserve against cognitive inefficiency (Sumowski et al., 2014)in the analysis. Cognitive reserve has been useful to explain the discrepancy between brain damage and clinical manifestations in neurodegenerative diseases(Borroni, Premi, Bozzali, & Padovani, 2012).

Psychological assessment was carried out through different questionnaires. At first, we used the *Hospital Anxiety and Depression Scale* (HADS) (Zigmond & Snaith, 1983), which was validated for use with MS patients by Honarmand and Feinstein (2009). Secondly, we used the *Modified Fatigue Impact Scale* (MFIS) that gathers information regarding the impact of fatigue on one's life. This is a modified form of the *Fatigue Impact Scale* (Fisk et al., 1994), which is composed by 21 items, assessing the impact of fatigue on cognitive, physical and social domains. This scale has demonstrated high internal consistency, with an overall coefficient alpha of 0.81 (Fisk et al., 1994).

Last of all, we used the *Short Form-36* (SF36) to address health concepts that are relevant to MS patients from the patient's perspective; Stewart and colleagues (1988) derive this from the General Health Survey of the Medical Outcomes Study. High levels of data quality support its' use as a health measure in patients with MS. There is no single overall score for the SF36, instead, it generates 8 subscales and two summary scores. The 8 subscales are: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role-limitations due to emotional problems, and mental health. The two summary scores are the physical component summary and the mental component summary.

All of them, HADS, MFIS and SF36, are structured, self-report questionnaire that the patient can generally complete with little or no intervention from an interviewer.

2.3 Magnetic resonance acquisition and processing

2.3.1 Structural magnetic resonance acquisition

MR images were acquired on a 3 Tesla Magnetom Trio (SIEMENS, Erlanger, Germany) scanner using a 32 channel phased-array head coil, including 3D-Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) structural, 3D-T2 fluid attenuated inversion recovery (FLAIR) and diffusion-weighted imaging sequence. The 3D-structural image had the following acquisition parameters: RT=1800 ms; TE=3.01 ms; TI=900 ms; 240 sagittal slices with 0.94 mm isotropic voxel size and 256x256 matrix size. The 3D-T2 FLAIR sequence parameters were: RT=5000 ms; TE=304 ms; TI=1800 ms; 192 sagittal slices with 0.94 mm isotropic voxel size and 6256x256 matrix size. High Angular Resolution Diffusion Imaging (HARDI) data was acquired with RT=14800 ms; TE=103 ms; 100 contiguous axial slices; 1.5 mm isotropic voxel size; 154x154 matrix size; b value=1000 s/mm^2; 60 diffusion encoding directions and a single baseline image acquired at 0 s/mm^2. In addition, field map images were generated to correct the distortions caused by field inhomogeneities (TE 1/TE 2=4.92/7.38 ms, with the same slice prescription, slice thickness and field of view as the HARDI sequence).

2.3.2 Anatomical parcellation

Cortical parcellation was done with the Desikan-Killiany atlas (Desikan et al., 2006) through the Mindboggle software (Klein et al., 2017) applied with FreeSurfer (freesurfer.net) resulting in 30 regions per hemisphere. Subcortical GM regions (8 per hemisphere) were segmented using the FIRST tool (fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST). Additionally, WM lesions were segmented with the Jim7 software (xinapse.com/j-im-7-software) on the 3D-MPRAGE sequence with 3D-FLAIR image as a reference to improve lesions identification and delineation. Then, lesion inpainting was applied to the 3D-MPRAGE image to enhance segmentation and registration in patients (Battaglini, Jenkinson, & De Stefano, 2012).

2.3.3 Whole brain structural connectivity

HARDI images were denoised (Veraart, Fieremans, & Novikov, 2016) and corrected for geometric distortions and head motion. The structural connectome was obtained using probabilistic streamlines by high-order fiber orientation distributions and anatomically-constrained tractography framework (Smith, Tournier, Calamante, & Connelly, 2012) provided in the MRtrix3 software package (http://www.mrtrix.org/). This approach preserves the principal fiber orientation directions, improving tract reconstructions in complex structural architecture and in areas of low FA, such as focal MS lesions. Thus, it may overcome the premature stop of the tracking process when the FA falls below a given threshold (Martínez-Heras et al., 2015). The WM and lesions mask were registered to undistorted HARDI images applying boundary-based registration (Greve & Fischl, 2009) in order to define the tractography seeding, and later on, generate a set of

three million streamlines. The default step size= 0.75; curvature= 45º and fiber orientation distribution amplitude threshold= 0.1 were used. Then, the 76 segmented ROIs were used to define the nodes of the network, and connections between them were obtained. Anatomical exclusion criteria postprocessing (Martínez-Heras et al., 2015)was applied to minimize the number of anatomically aberrant connections originated from the tractography. Brain structural networks were represented by 38x38 weighted connectivity matrices with 2850 connections liking pairs of nodes that represented mean FA values along each connection based on tracking results. Finally, only those connections present in about 60% of the HV group, were included in the analysis in order to reduce the number of false positive connections (de Reus & van den Heuvel, 2013).

Network connectivity was described with graph theoretical analyses from the Brain Connectivity Toolbox (https://sites.google.com/site/bctnet/) and included measures of segregation: local efficiency (the average of the inverse of the shortest path length in the network computed on node neighbourhoods), clustering coefficient (the fraction of node's neighbours that are neighbours of each other), transitivity (the ratio of triangles to triplets in the network) and modularity (the degree to which the network may be subdivided into clearly delineated groups); integration: global efficiency (the average of the inverse of the shortest path length in the network); centrality: betweenness centrality (the fraction of all shortest path in the network that contains a given node), and brain resilience: assortativity (a correlation coefficient between the degrees of all nodes on two opposite ends of a link) (Rubinov & Sporns, 2010). Nodal strength (the sum of weights of links connected to the node) was also obtained. Fig. 2 summarises the structural connectivity pipeline used in the study.

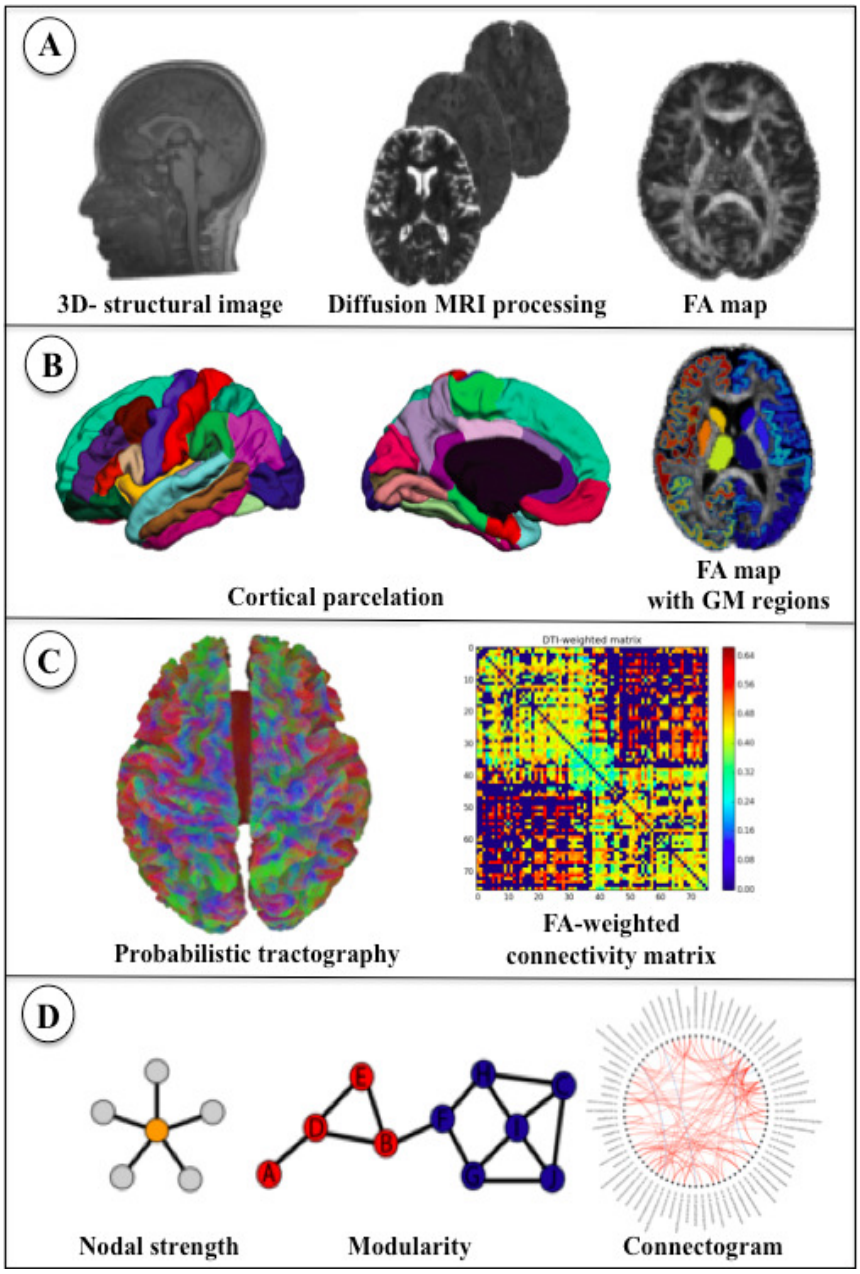

*Figure 2. Structural connectivity framework.*Adapted figure from Llufriu, S., Martinez-Heras, E., Solana, E., Sola-Valls, N., Sepulveda, M., Blanco, Y., … Saiz, A. (2017). Structural networks involved in attention and executive functions in multiple sclerosis. *NeuroImage: Clinical*, *13*, 288–296. https://doi.org/10.1016/j.nicl.2016.11.026.A) Diffusion MRI processing: FA maps were obtained through standard preprocessing of diffusion MRI processing. B) Nodes parcellation: Cortical parcellation was done with FreeSurfer and subcortical segmentation with FIRST tools from the 3D-structural image. Then, subcortical and cortical segmentation were registered to FA maps. C) Diffusion tractography: Probabilistic streamline fiber tracking by fiber orientation distribution including anatomical exclusion criteria postprocessing. Structural network reconstruction: Connections were assembled into FA-weighted connectivity matrices. D) Several graph theory metrics (i.e., nodal strength and modularity) were computed from the resulting matrices (Martínez-Heras, 2017). Connectogram included 30 cortical and 8 subcortical GM nodes and FA edges linking pairs of nodes. FA: fractional anisotropy; GM: grey matter.

2.4 Statistics

Data was checked for normality using Shapiro-Wilks test. Group differences between patients with MS and HV were performed with Chi-square tests for categorical variables, Kruskal-Wallis test for non-distributed variables and Student's t-test for independent samples in normal distributed data. Levene's tests for equality of variances was used to assess the homoscedasticity assumption. When this assumption was violated, we analysed MS groups differences with Welch correction, if not, we used one-way ANOVA or Kruskal-Wallis H test, as convenient. Multiple comparisons were done through Tukey HSD, Games-Howell, Dunnet's T3 tests or false discovery rate, as fitting. Moreover, we used Factorial ANCOVA, with age as covariant and gender and phenotype as fixed factors, in the analysis of whole graph metrics differences among MS patients phenotypes. Connectivity data was inspected for outliers, defined as values greater or lesser than 1.5*interquartile range from the median in the group of patients and in HVs, and were removed from the analyses.

We performed logistic regression analyses to further explore the probability of association between demographic and clinical characteristics (disease duration, depression and anxiety, and cognitive reserve) and structural network integrity (global efficiency) with cognitive impairment in patients with MS. Data was transformed (value * 10) to obtain Odds ratio (OR) to quantify estimated change in the odds of cognitive worsening associated per 0.1 units of clinical and network integrity marker. All models had Likelihood ratio test with $p<0.001$.

Statistical analyses referring to demographic, clinical, neuropsychological and graph theory variables were performed using SPSS (V20.0). Connectivity matrices variables were computed through R statistical software (www.R-project.org) using Car (Fox, 2011) and FSA (Ogle, 2018) packages. The significance level was set at $p<0.05$.

3. Results

3.1 Demographic, clinical and neuropsychological results

MS subjects and HV were similar in age and gender: 130 (71%) of MS patients and 27 (64%) of HV were female (p>0.05); MS patients mean age ± standard deviation (SD) was 43.0 ± 10.0 years and HV mean age was 37.8 ± 11.3 years (p>0.05).

Percent representation of the four cognitive phenotypes is summarized in Fig. 3 Of the full sample, 32 patients (18%) showed memory impairment (z-score of Selective reminding test-delayed or Spatial recall tests-delayed below -1.5), 29 (16%) patients had attention deficits (below -1.5 z-score in Symbol Digit Modalities Test or Paced Auditory Serial Addition Task) and 21 (11%) had global impairment. The remaining 101 (55%) patients were CP.

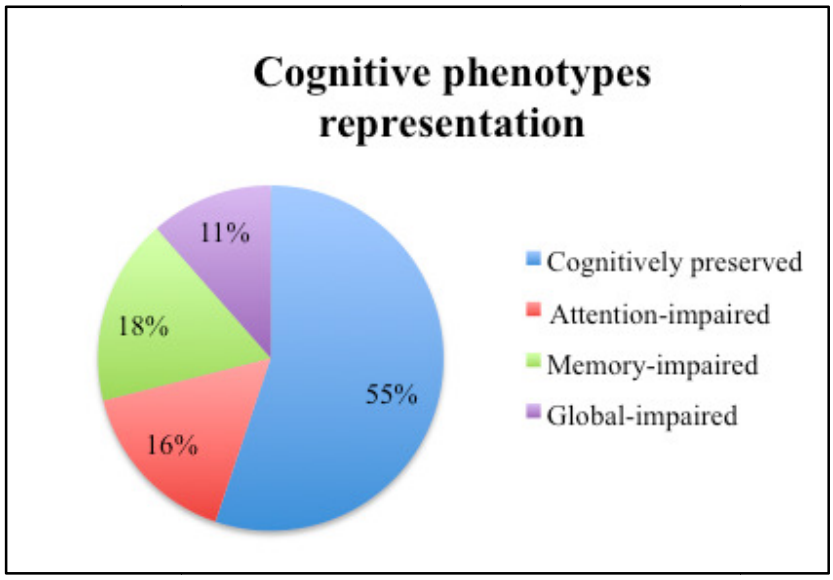

Figure 3. Percent representation of cognitive phenotype groups in full sample of 183 RRMS and SPMS patients.

Demographic, clinical and neuropsychological data from MS patients phenotypes are summarised in Table 1.

Table 1.
Demographic, clinical and cognitive characteristics of the MS patients phenotypes included in the study.

	CP (n =101)	Memory-impaired (n =32)	Attention-impaired (n =29)	Global-impaired (n =21)	*p* value
Female, n (%)	73 (72)	21 (66)	23 (79)	13 (62)	0.504[a]
Age (years)	42.6 (9.1)	46.5 (9.8)	38.4 (9.8)	46.5 (12.3)	0.004[b]
Type of education, n (%):					
Primary school	7 (7)	3 (10)	0 (0)	2 (10)	0.007[a]
Secondary school	44 (43)	10 (31)	9 (31)	14 (67)	
Graduate	37 (37)	9 (28)	8 (28)	3 (14)	
Post-graduate	13 (13)	10 (31)	12 (41)	2 (9)	
Type of MS, n (%):					
RRMS	96 (95)	29 (91)	26 (90)	14 (67)	0.001[a]
SPMS	5 (5)	3 (9)	3 (10)	7 (33)	
Disease duration (years)	11.2 (8.9)	13.7 (9.5)	10.1 (8.9)	16.5 (10.5)	0.048[b]
Median EDSS score (range)	2.0 (0-6.5)	2.0 (1-6)	2.0 (0-6.5)	4.0 (0-6.0)	0.009[d]
HADS score (range)	9.2 (0-28)	10.7 (0-27)	11.0 (0-25)	15.9 (3-28)	0.002[b]
Median MFIS score	9 (4.8)	8 (5.6)	7 (5.6)	11.5 (5.2)	0.064[b]
SF36 (mental) score	46.19 (13.59)	47.98 (12.21)	44.89 (14.90)	42.12 (12.30)	0.593[b]
SF36 (physical) score	41.82 (12.72)	43.37 (14.62)	43.25 (14.30)	35.36 (11.60)	0.228[b]
Cognitive reserve score	15.7 (3.9)	15.7 (3.9)	16.0 (4.0)	12.8 (3.9)	0.014[b]
SRT-D z-score	-0.08 (0.83)	-1.33 (1.17)	-0.33 (0.84)	-2.31 (1.05)	<0.001[c]
(10/36)-D z-score	0.18 (0.99)	-1.56 (1.22)	-0.27 (1.07)	-1.31 (1.00)	<0.001[b]
SDMT z-score	0.48 (0.83)	0.11 (0.65)	-1.22 (1.38)	-1.30 (0.70)	<0.001[c]
PASAT z-score	0.06 (0.84)	0.13 (0.74)	-2.04 (1.23)	-1.99 (1.52)	<0.001[c]

Continuous variables are given as mean (SD). EDSS = Expanded Disability Status Scale; HADS = Hospital Anxiety and Depression Scale; MFIS = Modified Fatigue Impact Scale; PASAT = Paced Auditory Serial Addition Test; RRMS = relapsing remitting multiple sclerosis; SDMT = Symbol Digit Modalities Test; SF36 = 36-Item Short Form Survey; SRT-D = Selective Reminding Test - Delayed; SPMS = secondary progressive multiple sclerosis; 10/36-D = Spatial Recall Test (10/36) Delayed.
[a] Chi square test; [b]ANOVA; [c]ANOVA Welch; [d]Kruskal-Wallis H Test.

Results from cognitive assessment were significantly different among groups, multiple comparison displayed that each group showed worst scores in those cognitive tests that define the group.

3.2 Structural connectivity results

3.2.1 Structural connectivity differences between MS patients and HV

MS patients showed a statistically significant reduction in most graph theory metrics compared to HV (p<0.04); nodal strength, global and local efficiency, clustering coefficient and increased shortest path length. By the other side, transitivity, modularity and assortativity were not different between groups (Supplementary material, Table. S1).

In terms of network connectivity, there were also significant differences on FA-weighted connectivity matrices between MS patients and HV. We identified statistically significant differences (adjusted p<0,05) in 902 out of the 1550 connections evaluated (58,2%). Most differences were due to reduction of FA in patients (887 connections), while only few (15 connections) showed an increased FA in patients compared to HV.

3.2.2 Structural connectivity differences among MS cognitive profiles

In reference to graph network metrics, we found significant differences among MS patients groups according to cognitive profiles in most measures (p=0.001, Table 2). The multiple comparison analysis revealed that statistically significant differences were mainly observed between global-impaired phenotype and the others (p<0.001).

Table 2.
Differences between MS patients phenotypes on the whole network graph theory properties.

	CP (n =101)	Memory-impaired (n =32)	Attention-impaired (n =29)	Global-impaired (n =21)	*p* value
Nodal strength	12.0236 (1.36)	11.6992 (1.78)	11.7325 (1.53)	9.8219 (2.20)	<0.001
Global efficiency	0.2940 (0.02)	0.2955 (0.02)	0.2890 (0.02)	0.2637 (0.03)	<0.001
Local efficiency	0.3669 (0.02)	0.3704 (0.02)	0.3648 (0.02)	0.3438 (0.03)	0.001
Clustering coefficient	0.2637 (0.01)	0.2650 (0.01)	0.2620 (0.01)	0.2463 (0.02)	0.001
Transitivity	0.2484 (0.01)	0.2487 (0.02)	0.2464 (0.02)	0.2291 (0.02)	0.001
Modularity	0.2141 (0.03)	0.2222 (0.04)	0.2135 (0.03)	0.2726 (0.57)	<0.001
Assortativity	0.0093 (0.03)	0.0077 (0.02)	0.0153 (0.03)	0.0159 (0.03)	0.880
Shortest path length	3.8088 (0.24)	3.8071 (0.27)	3.8276 (0.19)	4.3606 (0.64)	<0.001

Statistics by Factorial ANCOVA. Continuous variables are given as mean (SD).

MS cognitive groups comparison analyses displayed that FA was different in 192 out of 1550 connections (12,4%) (Supplementary material, Table. S2). Results from multiple comparisons among MS patients phenotypes follow below:

a) Attention-impaired vs. memory-impaired groups: 19 (1.2%) connections were significantly different between these groups, especially involving bilateral postcentral cortex (adjusted $p<0.05$). The left postcentral was connected with precentral, superior frontal and supramarginal from the left hemisphere and with posterior cingulate, postcentral, precuneus and superior parietal from the right hemisphere. Decreased mean FA in 17 connections from the attention-impaired group was found in comparison of memory-impaired group (Fig. 4).

b) Attention-impaired vs. CP groups: Mean FA in attention-impaired group was significantly decreased in 3 (0.2%) connections compared to CP group, mainly involving right hippocampus (adjusted $p<0.05$).

c) Memory-impaired vs. CP groups: Reduced mean FA was significantly different in 12 (0.8%) connections between CP and memory-impaired groups. Bilateral postcentral, left precuneus, right inferior parietal, left rostral middle frontal and right superior frontal were the most different nodes on significant connections (adjusted $p<0.05$).

d) Attention-impaired vs. global-impaired groups: 63 (4.1%) connections were significantly different between attention-impaired and global impaired groups, mainly involving, superior frontal, superior parietal, precuneus and insula from the right hemisphere (adjusted $p<0.05$).

e) Memory-impaired vs. global-impaired groups: 144 (9.3%) connections were significantly different between these two groups, involving specially right posterior cingulate, right superior frontal and right insula, left paracentral and bilateral precuneus and superior parietal cortex (adjusted $p<0.05$).

f) Global-impaired vs. CP groups: 120 (7.7%) connections were significantly different between global-impaired and CP groups. Left inferior parietal cortex and right posterior cingulate, right precuneus, right superior frontal, right superior parietal and right insula (adjusted $p<0.05$) were the most affected nodes in connections (Fig. 5).

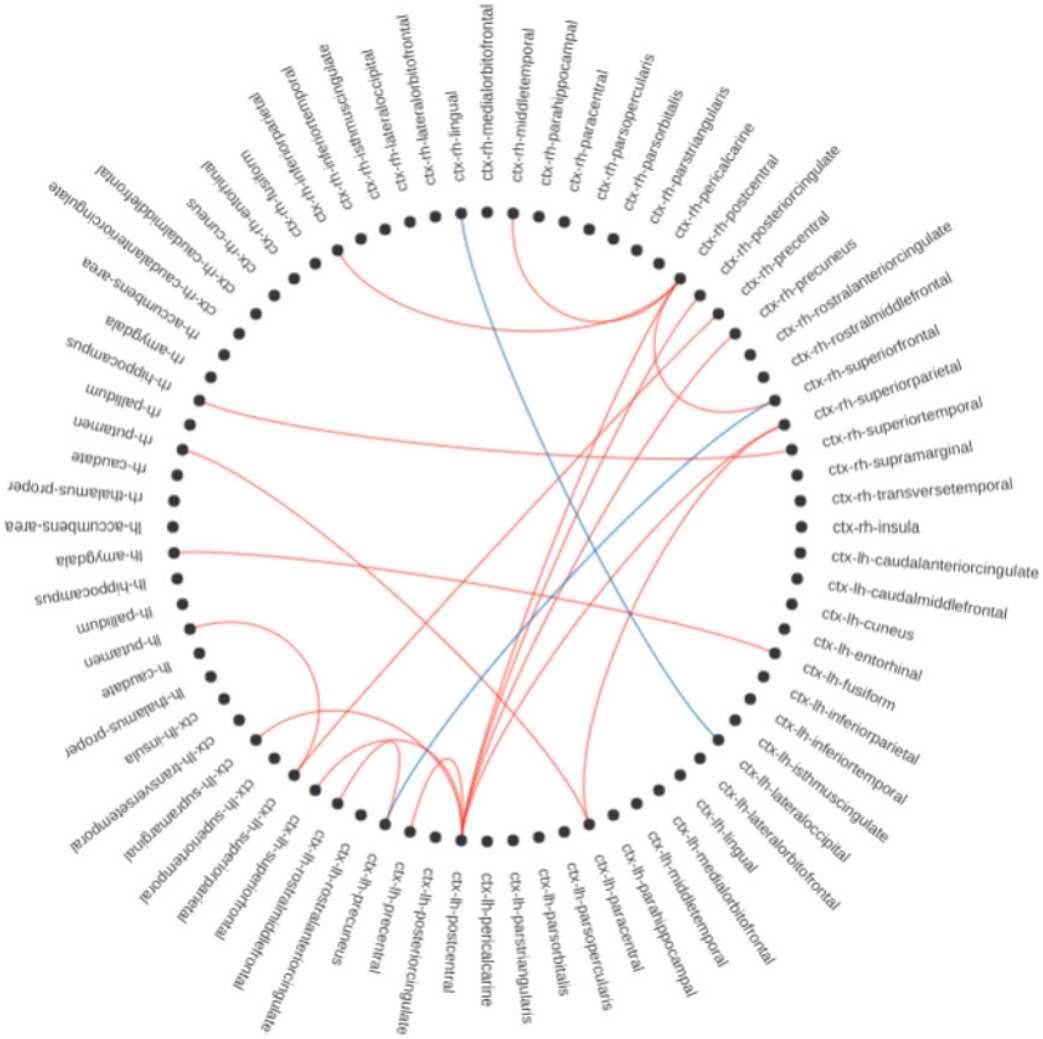

Figure 4. Group comparison for edge FA and nodal strength between attention-impaired and memory-impaired groups. Nodes are located in the corresponding vertices of the circle. Only edges showing significant differences (adjusted $p<0.05$) between cognitive groups are displayed as lines (reduction of edge FA is colored in red and increase in blue). ctx: cortex; lh: left hemisphere; rh: right hemisphere. This connectogram was developed by Bokeh from Python v2.7 (http:// bokeh.pydata.org/en/latest/).

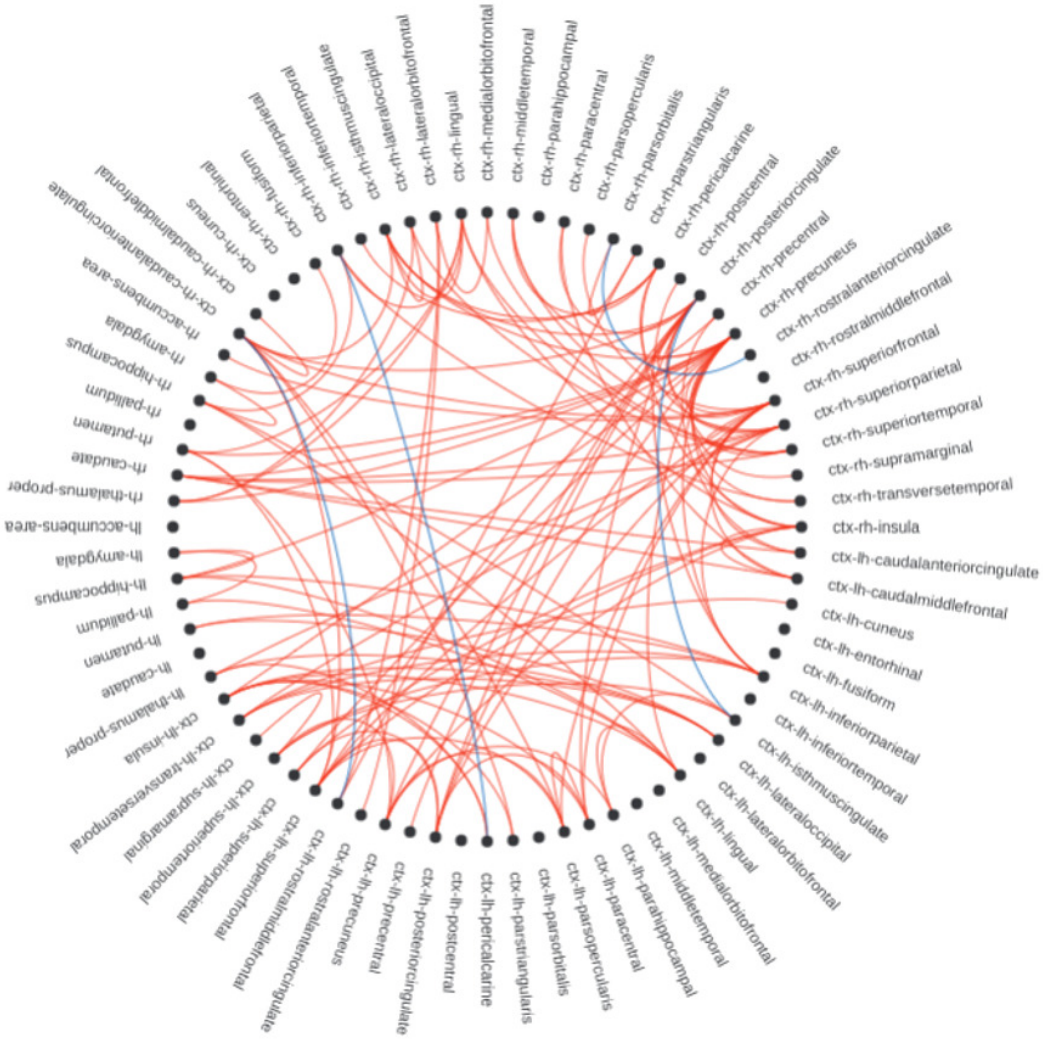

Figure 5. Group comparison for edge FA and nodal strength between global-impaired and CP MS groups. Nodes are located in the corresponding vertices of the circle. Only edges showing significant differences (adjusted $p<0.05$) between cognitive groups are displayed as lines (reduction of edge FA is colored in red and increase in blue). ctx: cortex; lh: left hemisphere; rh: right hemisphere. This connectogram was developed by Bokeh from Python v2.7 (http:// bokeh.pydata.org/en/latest/).

3.3 Logistic regression analyses

We next wanted to evaluate the predictive value of demographic and clinical characteristics and structural network integrity on cognitive impairment in MS. In order to achieve this, we created several models including the following variables as predictors: disease duration, depression and anxiety score from HADS, cognitive reserve score and global network efficiency. The logistic regression models were implemented on all those MS patients with a z-score below -1.5 in at least one of the cognitive tests (including attention-impaired, memory-impaired and global-impaired phenotypes). The results displayed that the OR of showing worse cognitive performance was 1.006 for every 0.1 increase in HADS score ($p < 0.01$) (Supplementary material, Table. S3).

4. Discussion

This study shows that cognitive impairment in MS is associated with damage in white matter (WM) connectivity. Patients with selective impairment in memory or attention had similar structural connectivity compared with cognitive preserved patients. On the contrary, patients with more global cognitive deficits had worse connectivity at the global level measured with whole brain graph theory metrics and, specially, in connections from the frontoparietal network (FPN) and insula. These results reinforce the importance of the FPN damage in the development of cognitive deficits in MS.Therefore, the results supports that cognitive impairment is driven by a certain level of brain damage, since severe cognitive deterioration appear when network connectivity changes are prominent.

Forty five percent of our sample showed cognitive impairment. Our results were in line with previous studies (Benedict, Cookfair, et al., 2006; Deloire et al., 2005; Leavitt et al., 2018). Leavitt et al. (2018) published the first study evaluating different cognitive phenotypes in MS and found these results: more than a half of the sample were CP patients and the memory-impaired group was the cognitive impaired phenotype with more percentage of patients (18.8%). Similar to these results, in our study also CP was the predominant group with 55% of the MS patients and the most consistently impaired cognitive domain was the memory function; which was present in 29% of MS patients, as reported by Chiaravalloti & DeLuca (2008). In contrast to the study of Leavitt and colleagues (2018), we found demographic and clinical differences among cognitive phenotypes. Patients in the attention-impaired group were younger than the others. Moreover, we also observed that the global-impaired group was older, had the highest percentage of patients with secondary progressive form of the disease and worse EDSS. All these results suggest that patients with global impairment are at a later phase of the disease.

Using improved tractography approaches, our findings confirm structural connectivity changes in a cohort of MS participants at several levels, both in whole brain graph theory metrics and in terms of connections compared to HV. Brain organization in healthy people is characterised by high clustering and high global efficiency, the presence of highly connected regions (hubs), and a modular organization (Mears & Pollard, 2016). On the opposite side, a disruption of the optimal balance between integration and segregation of the network components was detected in MS patients, as shown by a reduction of global and local efficiency and clustering coefficient as well as the increase of shortest path length when compared to HV. These results are consistent with other diffusion-based MRI studies where transitivity, global and local efficiency were significantly decreased in the MS patients when compared to the HV (He et al., 2009; Llufriu et al., 2017). In regards to network connectivity, the decrease of white matter WM FA in MS patients compared to HV in 58,2% of connections suggests that brain network suffers a widespread impairment in MS (Hulst et al., 2013; Llufriu et al., 2014, 2017). All in all, our study reinforces the existence of a disrupted integrity in structural connectivity and a decrement of network flow of information in MS participants.

The main aim of this project was to analyse the underlying patterns of damage in structural networks, according to the cognitive phenotypes observed in MS patients. In our knowledge, this is the first time that network characteristics are analysed in these cognitive phenotypes. Patients with global cognitive impairment showed significant worse connectivity in comparison with patients with selective impairment of a cognitive function or with patients with preserved cognition. Specifically, subjects with global-impaired phenotype showed decreased nodal strength, global and local efficiency, clustering coefficient and transitivity, and increased modularity and path length compared with the others groups. Our findings support that cognitive worsening in MS patients is associated with changes in the network properties (Benedict et al., 2014; Dineen et al., 2009; Fleischer et al., 2017; Hulst et al., 2013; Llufriu et al., 2014). However, other clinical and pathological characteristics of the sample could influence cognitive performance. Also, these findings should be interpreted carefully since graph theory metrics are global measures with limited sensitivity to observe differences between cognitive phenotypes, creating a limitation in the study.

Besides graph theoretical analyses, we also found differences in connections. While patients with memory or attention impairment showed similar brain connectivity to that seen in the CP group, the global-impaired group connectivity was significantly different to CP group on 7.7% of connections mainly involving left inferior parietal cortex and right posterior cingulate, right precuneus, right superior frontal, right superior parietal and right insula. These results suggest that mild cognitive impaired groups are at an early stage of cognitive disability and do not have specific patterns of network modifications. Although MS diffuses tissue damage, we have observed the predominance of some highly connected GM regions, which are more susceptible to damage. These hubs are part of the FPN, and involve parietal superior, frontal cortex and precuneus. FPN includes highly connected regions that have been associated with functions like working memory, number manipulation or automatically captured attention, among others (Parlatini et al., 2017). Similar to previous studies, our results also suggest susceptibility in parietal and frontal areas in patients with MS (Llufriu et al., 2017). The results of the previous and the present study may have identified the FPN as a more susceptible track to brain damage in patients with MS.

Lastly, we wanted to further evaluate the influence of demographic, clinical and network efficiency variables in the risk of presenting cognitive impairment in MS. Therefore, we applied a logistic regression analysis to carry out our secondary aim of the study. The results displayed an association between cognitive impairment and depression and anxiety (as seen in HADS scores). This is in accordance with Krupp & Elkins (2000), who suggest that affective disorders can influence cognitive deterioration and obstruct a correct evaluation of cognitive performance (Feinstein, 2004).

The present study has strengths and limitations. First, we had a large cohort of MS patients but, when classifying them into MS phenotypes, the number of patients per group was reduced. Secondly, we have not taken into account GM brain damage produced in MS, which is an important feature of MS pathology, leading to massive brain atrophy (Filippi et al., 2012). Finally, future studies including all MS types, being

more focused on specific networks and analysing GM brain damage as well, are needed to understand this new cognitive phenotype classification.

This work has been submitted to the 34th annual congress of the European Committee for Treatment and Research in MS (ECTRIMS), 10-12 Oct., 2018, Berlin (Germany). Moreover, a related research paper is under preparation for its dissemination in international journal (Supplementary material, Annex IV).

5. Conclusions

The classification of patients with MS according to the type of cognitive impairment seems to be supported by the connectivity network differences between the global-impaired phenotype among the others. In contrast to patients with worst cognitive impairment, those with predominant memory or attention deficits have similar brain connectivity to those seen in CP patients. These results suggests that the accumulation of structural damage in the brain would lead to a collapse of the network and to the development of global cognitive deficits. Our study reinforces this view and exemplifies the key role of the FPN in cognitive performance.

Finally, highlight the prevalence of cognitive deterioration in MS, its relation to the decreased structural network connectivity and the importance of research to understanding this new taxonomy. Discriminating among these phenotypes may facilitate the development of effective targeted treatments for cognition in persons with MS.

References

Amato, M. P., Langdon, D., Montalban, X., Benedict, R. H., DeLuca, J., Krupp, L. B., … Comi, G. (2013). Treatment of cognitive impairment in multiple sclerosis: Position paper. *Journal of Neurology*, *260*(6), 1452–1468. DOI:10.1007/s00415-012-6678-0.

Amato, M. P., Zipoli, V., & Portaccio, E. (2008). Cognitive changes in multiple sclerosis. *Expert Review of Neurotherapeutics*, *8*(10), 1585–1596. DOI:10.1586/14737175.8.10.158.

Battaglini, M., Jenkinson, M., & De Stefano, N. (2012). Evaluating and reducing the impact of white matter lesions on brain volume measurements. *Human Brain Mapping*, *33*(9), 2062–2071. DOI:10.1002/hbm.21344.

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system - A technical review. *NMR in Biomedicine*, *15*(7–8), 435–455. DOI:10.1002/nbm.782.

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

Benedict, R. H., Cookfair, D., Gavett, R., Gunther, M., Munschauer, F., Garg, N., & Weinstock-Guttman, B. (2006). Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). *J Int Neuropsychol Soc*, *12*(4), 549–558.

Benedict, R. H., Morrow, S., Rodgers, J., Hojnacki, D., Bucello, M. A., Zivadinov, R., & Weinstock-Guttman, B. (2014). Characterizing cognitive function during relapse in multiple sclerosis. *Multiple Sclerosis Journal*, *20*(13),1745–1752. DOI:10.1177/1352458514533229.

Benito-Leon, J., Morales, J. M., & Rivera-Navarro, J. (2002). Health-related quality of life and its relationship to cognitive and emotional functioning in multiple sclerosis patients. *European Journal of Neurology*, *9*(5), 497–502. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12220381

Boringa, J. B., Lazeron, R. H., Reuling, I. E., Adèr, H. J., Pfennings, L., Lindeboom, J., … Polman, C. H. (2001). The Brief Repeatable Battery of Neuropsychological Tests: normative values allow application in multiple sclerosis clinical practice. *Multiple Sclerosis*, *7*(4), 263–267. DOI:10.1191/135245801680209385.

Borroni, B., Premi, E., Bozzali, M., & Padovani, A. (2012). Reserve mechanisms in neurodegenerative diseases: from bench to bedside and back again. *Current Medicinal Chemistry*, *19*(36), 6112–6118. DOI:10.2174/092986712804485737.

Bozzali, M., Spanò, B., Parker, G. J., Giulietti, G., Castelli, M., Basile, B., … Cercignani, M. (2013). Anatomical brain connectivity can assess cognitive dysfunction in multiple sclerosis. *Multiple Sclerosis Journal*, *19*(9), 1161–1168. DOI:10.1177/1352458512474088.

Bullmore, E., & Sporns, O. (2009). Complex brain networks: graph theoretical analysis of structural and functional systems. *Nature Reviews Neuroscience*, *10*(3), 186–198. https://doi.org/10.1038/nrn2575

Bullmore, E., & Sporns, O. (2012). The economy of brain network organization. *Nature Reviews Neuroscience*, *13*(5), 336–349. DOI:10.1038/nrn3214.

Chiaravalloti, N. D., & Deluca, J. (2008). Cognitive impairment in multiple sclerosis. *The Lancet*, *7*, 1139–1151.

Compston, A., & Coles, A. (2008). Multiple sclerosis. *The Lancet*, *372*(9648), 1502–1517.

De Reus, M. A., & van den Heuvel, M. P. (2013). Estimating false positives and negatives in brain networks. *NeuroImage*, *70*, 402–409. DOI:10.1016/j.neuroimage.2012.12.06.

Deloire, M. S., Salort, E., Bonnet, M., Arimone, Y., Boundineau, M., Amieva, H., … BROCHET, B. (2005). Cognitive impairment as marker of diffuse brain abnormalities in early relapsing remitting multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry*, *76*(4), 519–526. DOI:10.1136/jnnp.2004.045872.

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., … Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, *31*(3), 968–980. DOI:10.1016/j.neuroimage.2006.01.021.

Dineen, R. A., Vilisaar, J., Hlinka, J., Bradshaw, C. M., Morgan, P. S., Constantinescu, C. S., & Auer, D. P. (2009). dysfunction in multiple sclerosis, (2008). DOI:10.1093/brain/awn275.

Duque, P., Ibáñez, J., del Barco, A., Sepulcre, J., de Ramón, E., & Fernández-Fernández, Ó. (2012). Normalización y validación de la batería neuropsicológica breve como test neuropsicológico de referencia en la esclerosis múltiple. *Revista de Neurologia*, *54*(5), 263–270.

Feinstein, A. (2004). The neuropsychiatry of multiple sclerosis. *Canadian Journal of Psychiatry. Revue Canadienne de Psychiatrie*, *49*(3), 157–163. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med4&AN=15101497

Filippi, M., Rocca, M. A., Barkhof, F., Brück, W., Chen, J. T., Comi, G., … Lassmann, H. (2012). Association between pathological and MRI findings in multiple sclerosis. *The Lancet Neurology*, *11*(4), 349–360. DOI:10.1016/S1474-4422(12)70003-0.

Fleischer, V., Radetz, A., Ciolac, D., Muthuraman, M., Gonzalez-Escamilla, G., Zipp, F., & Groppa, S. (2017). Graph Theoretical Framework of Brain Networks in Multiple Sclerosis: A Review of Concepts. *Neuroscience*. DOI:10.1016/j.neuroscience.2017.10.033.

Greve, D. N., & Fischl, B. (2009). Accurate and robust brain image alignment using boundary-based registration. *NeuroImage*, *48*(1), 63–72. DOI:10.1016/j.neuroimage.2009.06.060.

He, Y., Dagher, A., Chen, Z., Charil, A., Zijdenbos, A., Worsley, K., & Evans, A. (2009). Impaired small-world efficiency in structural cortical networks in multiple sclerosis associated with white matter lesion load. *Brain*, *132*(12), 3366–3379. DOI:10.1093/brain/awp089.

Huijbregts, S. C. J., Kalkers, N. F., De Sonneville, L. M. J., De Groot, V., Reuling, I. E. W., & Polman, C. H. (2004). Differences in cognitive impairment of relapsing remitting, secondary, and primary progressive MS. *Neurology*, *63*(2), 335–339. DOI:10.1212/01.WNL.0000129828.03714.90.

Hulst, H. E., Steenwijk, M. D., Versteeg, A., Pouwels, P. J., Vrenkan, H., Uitdehaag, B. M., … Barkhof, F. (2013). Cognitive impairment in MS: Imapct of white matter integrity, gray matter volume, and lesions. *Neurology*, *80*(11), 1025–1032. DOI:10.1212/WNL.0b013e31828726cc.

Juárez, G. (2010). Neurorrehabilitación del paciente con esclerosis múltiple. *Revista Mexicana de Medicina Física y Rehabilitación*, *22*, 41–53.

Klein, A., Ghosh, S. S., Bao, F. S., Giard, J., Häme, Y., Stavsky, E., … Keshavan, A. (2017). *Mindboggling morphometry of human brains*. *PLoS Computational Biology* (Vol. 13). DOI:10.1371/journal.pcbi.1005350.

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

Kurtzke, J. F. (2005). Epidemiology and etiology of multiple sclerosis. *Physical Medicine and Rehabilitation Clinics of North America*, *16*(2), 327–349. DOI:10.1016/j.pmr.2005.01.013.

Le Bihan, D., Mangin, J. F., Poupon, C., Clark, C. A., Pappata, S., Molko, N., & Chabriat, H. (2001). Diffusion Tensor Imaging: Concepts and Applications. *Journal of Magnetic Resonance Imaging*, *13*(4), 534–546. DOI:10.1002/jmri.1076.

Leavitt, V. M., Tosto, G., & Riley, C. S. (2018). Cognitive phenotypes in multiple sclerosis. *Journal of Neurology*, *265*(3), 562–566. DOI:10.1007/s00415-018-8747-5.

Li, Y., Jewells, V., Kim, M., Chen, Y., Moon, A., Armao, D., … Shen, D. (2013). Diffusion Tensor Imaging Based Network Analysis Detects Alterations of Neuroconnectivity in Patients with Clinically Early Relapsing-Remitting Multiple Sclerosis. *Human Brain Mapping*, *34*, 3376–3391. DOI:10.1002/hbm.22158.

Llufriu, S., Martinez-Heras, E., Fortea, J., Blanco, Y., Berenguer, J., Gabilondo, I., … Saiz, A. (2014). Cognitive functions in multiple sclerosis: impact of gray matter integrity. *Multiple Sclerosis Journal*, *20*(4), 424–432. DOI:10.1177/1352458513503722.

Llufriu, S., Martinez-Heras, E., Solana, E., Sola-Valls, N., Sepulveda, M., Blanco, Y., … Saiz, A. (2017). Structural networks involved in attention and executive functions in multiple sclerosis. *NeuroImage: Clinical*, *13*, 288–296. DOI:10.1016/j.nicl.2016.11.026.

Loitfelder, M., Fazekas, F., Koschutnig, K., Fuchs, S., Petrovic, K., Ropele, S., … Enzinger, C. (2014). Brain activity changes in cognitive networks in relapsing-remitting multiple sclerosis - Insights from a longitudinal fMRI study. *PLoS ONE*, *9*(4). DOI:10.1371/journal.pone.0093715.

Lublin, F. D., Reingold, S. C., Cohen, J. A., Cutter, G. R., Sørensen, P. S., Thompson, A. J., … Polman, C. H. (2014). Defining the clinical course of multiple sclerosis: The 2013 revisions. *Neurology*, *83*(3), 278–286. DOI:10.1212/WNL.0000000000000560.

Martínez-Heras, E., Varriano, F., Prčkovska, V., Laredo, C., Andorrà, M., Martínez-Lapiscina, E. H., … Llufriu, S. (2015). Improved framework for tractography reconstruction of the optic radiation. *PLoS ONE*, *10*(9), 1–16. DOI:10.1371/journal.pone.0137064.

Mears, D., & Pollard, H. B. (2016). Network science and the human brain: Using graph theory to understand the brain and one of its hubs, the amygdala, in health and disease. *Journal of Neuroscience Research*, *94*(6), 590–605. DOI:10.1002/jnr.23705.

Miller, D., Barkhof, F., Montalban, X., Thompson, A., & Filippi, M. (2005). Clinically isolated syndromes suggestive of multiple sclerosis , part I : natural history, pathogenesis, diagnosis, and prognosis. *Lancet Neurol*, *4*, 281–88. DOI:10.1016/S1474-4422(05)70071-5.

Mollison, D., Sellar, R., Bastin, M., Mollison, D., Chandran, S., Wardlaw, J., & Connick, P. (2017). The clinico-radiological paradox of cognitive function and MRI burden of white matter lesions in people with multiple sclerosis: A systematic review and meta-analysis. *PLoS ONE*, *12*(5), 1–16. DOI:10.1371/journal.pone.0177727.

Nebel, K., Wiese, H., Seyfarth, J., Gizewski, E. R., Stude, P., Diener, H. C., & Limmroth, V. (2007). Activity of attention related structures in multiple sclerosis patients. *Brain Research*, *1151*, 150–160. DOI:10.1016/j.brainres.2007.03.007.

Nocentini, U., Pasqualetti, P., Bonavita, S., Buccafusca, M., De Caro, M. F., Farina, D., … Caltagirone, C. (2006). Cognitive dysfunction in patients with relapsing-remitting multiple sclerosis. *Multiple Sclerosis Journal*, *12*(1), 77–87. DOI:10.1191/135248506ms1227oa.

Olascoaga, J. (2010). Calidad de vida y esclerosis múltiple. *Revista de Neurología*, *51*(5), 279-288. Retrieved from http://cat.inist.fr/?aModele=afficheN&cpsidt=23274346

Parlatini, V., Radua, J., Dell'Acqua, F., Leslie, A., Simmons, A., Murphy, D. G., … Thiebaut de Schotten, M. (2017). Functional segregation and integration within fronto-parietal networks. *NeuroImage*, *146*, 367–375. DOI:10.1016/j.neuroimage.2016.08.031.

Patti, F. (2009). Cognitive impairment in multiple sclerosis. *Multiple Sclerosis Journal*, *15*(1), 2–8. DOI:10.1177/1352458513498834.

Polman, C. H., Reingold, S. C., Banwell, B., Clanet, M., Cohen, J. A., Filippi, M., … Wolinsky, J. S. (2011). Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Annals of Neurology*, *69*(2), 292–302. DOI:10.1002/ana.22366.

Rao, S. M., Grafman, J., DiGiulio, D., Mittenberg, W., Bernardin, L., Leo, G. J., … Unverzagt, F. (1993). Memory dysfunction in multiple sclerosis: Its relation to working memory, semantic encoding, and implicit learning. *Neuropsychology*, *7*(3), 364–374. DOI:10.1037/0894-4105.7.3.364.

Rocca, M. A., De Meo, E., & Filippi, M. (2016). Functional MRI in investigating cognitive impairment in multiple sclerosis. *Acta Neurologica Scandinavica*, *134*(July), 39–46. DOI:10.1111/ane.12654.

Rogers, J. M., & Panegyres, P. K. (2007). Cognitive impairment in multiple sclerosis: Evidence-based analysis and recommendations. *Journal of Clinical Neuroscience*, *14*(10), 919–927. DOI:10.1016/j.jocn.2007.02.006.

Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: Uses and interpretations. *NeuroImage*, *52*(3), 1059–1069. DOI:10.1016/j.neuroimage.2009.10.003.

Sadovnick, A. D., & Ebers, G. C. (1992). Epidemiology of Multiple Sclerosis : A critical overview. *Le Journal Canadien Des Sciences Neurologiques*, *20*(1), 17–29. DOI:10.1017/S0317167100047351.

Sepulcre, J., Vanotti, S., Hernández, R., Sandoval, G., Cáceres, F., Garcea, O., & Villoslada, P. (2006). Cognitive impairment in patients with multiple sclerosis using the Brief Repeatable Battery-Neuropsychology test. *Multiple Sclerosis Journal*, *12*(2), 187–195. DOI:10.1191/1352458506ms1258oa.

Shu, N., Duan, Y., Xia, M., Schoonheim, M. M., Huang, J., Ren, Z., … Liu, Y. (2016). Disrupted topological organization of structural and functional brain connectomes in clinically isolated syndrome and multiple sclerosis. *Nature*, (July), 1–11. DOI:10.1038/srep29383.

Shu, N., Liu, Y., Li, K., Duan, Y., Wang, J., Yu, C., … He, Y. (2011). Diffusion tensor tractography reveals disrupted topological efficiency in white matter structural networks in multiple sclerosis. *Cerebral Cortex*, *21*(11), 2565–2577. DOI:10.1093/cercor/bhr039.

Smith, R. E., Tournier, J. D., Calamante, F., & Connelly, A. (2012). Anatomically-constrained tractography: Improved diffusion MRI streamlines tractography through effective use of anatomical information. *NeuroImage*, *62*(3), 1924–1938. DOI:10.1016/j.neuroimage.2012.06.005.

Song, S. K., Sun, S. W., Ju, W. K., Lin, S. ., Cross, A. H., & Neufeld, A. H. (2003). Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. *NeuroImage*, *20*(3), 1714–1722. DOI:10.1016/j.neuroimage.2003.07.005.

Song, S. K., Yoshino, J., Le, T. Q., Lin, S. J., Sun, S. W., Cross, A. ., & Armstrong, R. C. (2005). Demyelination increases radial diffusivity in corpus callosum of mouse brain. *NeuroImage*, *26*(1), 132–140. DOI:10.1016/j.neuroimage.2005.01.028.

Sperling, R., Guttmann, C., Hohol, M., Warfield, S., Jakab, M., Parente, M., … Weiner, H. (2001). Regional MRI lesion burden and cognitive function in MS : A longitudinal study. *Arch Neurol*, *58*(1), 115–121.

Sumowski, J. F., Benedict, R., Enzinger, C., Filippi, M., Geurts, J. J., Hamalainen, P., … Rao, S. (2018). Cognition in multiple sclerosis: State of the field and priorities for the future. *Neurology*, *90*(6). DOI:10.1212/WNL.0000000000004977.

Sumowski, J. F., Rocca, M. A., Leavitt, V. M., Dackovic, J., Mesaros, S., Drulovic, J., … Filippi, M. (2014). Brain reserve and cognitive reserve protect against cognitive decline over 4.5 years in MS. *Neurology*, *82*, 1776–1783.

Veraart, J., Fieremans, E., & Novikov, D. S. (2016). Diffusion MRI noise mapping using random matrix theory. *Magnetic Resonance in Medicine*, *76*(5), 1582–1593. DOI:10.1002/mrm.26059.

Winkelmann, A., Engel, C., Apel, A., & Zettl, U. K. (2007). Cognitive impairment in multiple sclerosis. *Journal of Neurology*, *254*(Suppl. 2), 35–42. DOI:10.1007/s00415-007-2010-9.

Zigmond, A.S. & Snaith, R.P. (1983).The hospital anxiety and depression scale. *Acta Psychiatr Scand 67*, 361–370.

Annex

Annex I.

Table S1.

Differences between MS patients and HV on the whole network graph theory properties.

	MS patients (n = 183)	Healthy volunteers (n = 42)	*p* value
Strength	11.6661 (1.71)	12.2699 (1.37)	0.041
Global efficiency	0.2899 (0.02)	0.3040 (0.02)	<0.001
Local efficiency	0.3644 (0.02)	0.3804 (0.02)	<0.001
Clustering coefficient	0.2615 (0.02)	0.2684 (0.01)	0.031
Transitivity	0.2459 (0.02)	0.2519 (0.02)	0.090
Modularity	0.2222 (0.04)	0.2227 (0.03)	0.480
Assortativity	0.0107 (0.03)	0.0083 (0.03)	0.562
Shortest path length	3.8745 (0.35)	3.6713 (0.22)	<0.001

Statistics by Mann-Whitney U Test for independent samples. Variables are given as mean (standard deviation).

Annex II.

Table. S2
Resume from multiple comparisons among MS patients phenotypes.

Phenotypes comparison	Connections with significant differences (%)	Mean FA	Most affected nodes on significantly different connections	
Attention-impaired vs. Memory-impaired	19 (1.2%)	Attention-impaired < Memory-impaired	Left postcentral ctx	- Left precentral ctx - Left superior frontal ctx - Left supramarginal ctx - Right posterior cingulate ctx - Right postcentral ctx - Right precuneus ctx - Right superior parietal ctx
Attention-impaired vs. CP	3 (0.2%)	Attention-impaired < CP	Right hippocampus	- Right amygdala - Right superior temporal ctx
Memory-impaired vs. CP	12 (0.8%)	Memory-impaired > CP	Left postcentral ctx	- Left rostral middle frontal ctx - Right posterior cingulate ctx
			Left precuneus ctx	- Left rostral middle frontal ctx - Right superior frontal ctx
			Right inferior parietal ctx	- Right postcentral ctx - Right transverse temporal ctx
			Right postcentral ctx	- Right middle temporal ctx - Right superior frontal ctx
Attention-impaired vs. Global-impaired	63 (4.1%)	Attention-impaired > Global-impaired	Right superior frontal ctx	- Left caudal anterior cingulate ctx - Left paracentral ctx - Left posterior cingulate ctx - Left superior frontal ctx - Right caudal anterior cingulate ctx - Right parsopercularis ctx - Right precuneus ctx
			Right superior parietal ctx	- Left transverse temporal ctx - Right caudate - Right isthmus cingulate ctx - Right pericalcarine ctx - Right posterior cingulate ctx - Right superior frontal ctx
			Right precuneus ctx	- Right superior temporal ctx - Right supramarginal ctx - Right transverse temporal ctx - Right insula ctx - Left posterior cingulate ctx - Right caudate

				- Right putamen - Right isthmus cingulate ctx - Right posterior cingulate ctx
			Right insula ctx	- Left precuneus ctx - Left superior frontal ctx - Left superior parietal ctx - Right lingual ctx
Memory-impaired vs. Global-impaired	144 (9.3%)	Memory-impaired > Global-impaired	Right superior parietal ctx	- Left inferior parietal ctx - Left paracentral ctx - Left postcentral ctx - Left precuneus ctx - Left transverse temporal ctx - Left insula ctx - Right insula ctx - Left thalamus proper - Right caudate - Right isthmus cingulate ctx - Right middle temporal ctx - Right pericalcarine ctx - Right posterior cingulate ctx - Right precuneus ctx - Right superior frontal ctx
			Right superior frontal	- Left caudal anterior cingulate ctx - Left caudal middle frontal ctx - Left paracentral ctx - Left posterior cingulate ctx - Left precuneus ctx - Left superior frontal ctx - Right accumbens area - Right caudal anterior cingulate ctx - Right parsopercularis ctx - Right postcentral ctx - Right posterior cingulate ctx - Right precuneus ctx
			Right precuneus ctx	- Left inferior parietal ctx - Left lingual ctx - Left paracentral ctx - Left postcentral ctx - Left posterior cingulate ctx - Left superior parietal ctx - Left superior temporal ctx - Left insula ctx - Right insula ctx - Right thalamus proper - Right putamen - Right caudal middle frontal ctx - Right posterior cingulate ctx

			Left paracentral ctx	- Left parsopercularis ctx - Right posterior cingulate ctx - Right precentral ctx - Right putamen ctx - Left superior parietal ctx - Right caudate ctx - Left insula ctx
			Left precuneus ctx	- Left superior temporal ctx - Right posterior cingulate ctx - Left putamen - Left transverse temporal ctx - Right postcentral ctx - Right putamen - Right insula ctx - Left insula ctx
			Right posterior cingulate ctx	- Left isthmus cingulate ctx - Left postcentral ctx - Left posterior cingulate ctx - Left precentral ctx - Left superior frontal ctx - Left superior parietal ctx - Right inferior parietal ctx - Right paracentral ctx
			Right insula ctx	- Left superior frontal ctx - Left superior parietal ctx - Right lateral occipital ctx - Right lingual ctx - Right pericalcarine ctx
Global-impaired vs. CP	120 (7.7%)	Global-impaired < CP	Right precuneus ctx	- Left inferior parietal ctx - Left lingual ctx - Left posterior cingulate ctx - Left superior parietal ctx - Left insula ctx - Left hippocampus - Right thalamus proper - Right caudate - Right putamen - Right isthmus cingulate ctx - Right middle temporal ctx - Right posterior cingulate ctx
			Right superior frontal ctx	- Left paracentral ctx - Left caudal anterior cingulate ctx - Left caudal middle frontal ctx - Left pars opercularis ctx Left posterior cingulate - Left superior frontal ctx - Right accumbens area - Right caudal anterior cingulate ctx

				- Right parsopercularis ctx Right posterior cingulate ctx - Right precuneus ctx
			Right posterior cingulate ctx	- Left precentral ctx - Left isthmus cingulate ctx - Left paracentral ctx - Left posterior cingulate ctx - Left precuneus ctx - Left superior frontal ctx - Right caudal anterior cingulate ctx - Right isthmus cingulate ctx - Right paracentral ctx
			Right superior parietal ctx	- Right caudate - Left inferior parietal ctx - Left transverse temporal ctx - Left thalamus proper - Right middle temporal ctx - Right pericalcarine ctx - Right posterior cingulate ctx - Right superior frontal ctx
			Left inferior parietal ctx	- Left putamen - Left transverse temporal ctx - Right postcentral ctx - Left superior temporal ctx - Left hippocampus
			Right insula ctx	- Left precuneus ctx - Left caudal middle frontal ctx - Left superior frontal ctx - Left superior parietal ctx - Right lingual ctx - Right pericalcarine ctx - Right precuneus ctx

Ctx = Cortex. Only results with an adjusted $p < 0.05$ were displayed.

Annex III.

Table. S3

Association results between demographic and clinical characteristics and structural network integrity among cognitive impaired MS patients.

	Cognitive worsening		
	n	OR (95% CI)	*p*-value
Disease duration, years	182	1.003 (0.999-1.006)	0.098
Cognitive reserve scale	179	0.996 (0.989-1.004)	0.310
HADS score	177	1.006 (1.001-1.010)	0.009
Global efficiency	173	0.291 (0.060-1.405)	0.124

CI = Confidence Interval; HADS= Hospital Anxiety and Depression Scale. Data was transformed (value * 10) to obtain ORs to quantify estimated change in the odds of cognitive worsening associated per 0.1 units of clinical and network integrity marker. All models had Likelihood ratio test with *p*-value <0.001.

Annex IV.

Congress dissemination

Abstract Preview - Step 3/4

- print version -

Topic: 21 Pathology and pathogenesis of MS - MRI and PET

Title: **Cognitive phenotypes in MS: underlying changes in structural connectivity.**

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Text: **Background:** Patients with multiple sclerosis (MS) frequently show difficulties in episodic memory, attention, information processing speed and executive functions. Some of them have selective deficits of a given cognitive domain, and different cognitive phenotypes involving memory or processing speed disturbances have been described.

Aim: To analyse the underlying patterns of damage in structural networks according to the cognitive phenotypes observed in a large sample of MS patients.

Methods: A cohort of 183 patients (age: 43.1±10 years; disease duration: 12.1±9.3 years; Expanded Disability Status Scale, EDSS: 2 (0-6.5)) was assessed by the Rao Battery. Whole brain structural connectivity was obtained from diffusion magnetic resonance imaging and mean fractional anisotropy (FA) in each connection was compared among patients' groups.

Results: Thirty-two patients (18%) showed memory impairment (z-score of Selective reminding test-delayed or Spatial recall tests-delayed below -1.5), 29 (16%) patients had attention deficits (below -1.5 z-score in Symbol Digit Modalities Test or Paced Auditory Serial Addition Task) and 21 (11%) had global impairment. The remaining 101 (55%) patients were cognitively preserved (CP). Patients with global impairment were older, more frequently secondary-progressive MS, and had higher EDSS score.

While connectivity was similar in patients with memory and attention phenotypes compared with CP patients (decreased FA in 6% of connections), those with global impairment displayed more widespread reduction in connectivity (decreased FA in 63% of connections). Patients with global impairment showed larger number of connections with reduced FA (adjusted p< 0.05) in frontal and parietal areas, and insula, compared with the other cognitive groups.

Conclusions: In contrast to patients with global impairment, those with predominant memory or attention deficits have similar brain connectivity to that seen in CP patients, suggesting that they are at an early stage of cognitive disability and do not have specific patterns of network modifications. Furthermore, the results reinforce the importance of the frontoparietal network damage in the development of cognitive deficits in MS.
Disclosure: ÷Disclosure: ES received travel reimbursement from TEVA; EMH, ELS, CM, NB declare nothing to disclose; MS received speaker honoraria from Sanofi and Biogen, and funding from the Generalitat de Catalunya (SLT002/16/00354); NSV receives funding from the Spanish Government (Instituto de Salud Carlos III, Spain, and Fondo Europeo de Desarrollo Regional [FEDER, FI16/00251], and the Predoctoral Grant for Health Research) and received speaker honoraria from Genzyme, Merck-Serono, Biogen-idec, Bayer; EML received speaking honoraria from Biogen, Genzyme and Novartis, travel reimbursement from Roche, Sanofi-Genzyme and TEVA, and funding from the Spanish Government (Instituto de Salud Carlos III [CM13/00150; MV15/00012; JR16/00006]), Fundació Marató TV3 (20142030), GMSI (2016) and Fundació Cellex Barcelona; YB: received speaking honoraria from Biogen, Novartis and Genzyme; EHML has received honoraria from Biogen, Roche, Novartis and Sanofi for speaking, and a travel reimbursement from Roche, Biogen, Novartis and Sanofi; AS received compensation for consulting services and speaker honoraria from Bayer-Schering, Merck-Serono, Biogen-Idec, Sanofi-Aventis, TEVA and Novartis; SL received speaker honoraria from Biogen Idec, Novartis, Teva, Genzyme and Merck, and research support from the Spanish Government (PI15/00587). ÷Funding: This work was funded by a Proyecto de Investigacion en Salud (FIS 2015. PI15/00587, SL, AS) integrated in the Plan Estatal de Investigación Científica y Técnica de Innovación I+D+I and co-funded by the Instituto de Salud Carlos III-Subdirección General de Evaluación and the Fondo Europeo de Desarrollo Regional (FEDER, "Otra manera de hacer Europa"); Red Española de Esclerosis Múltiple (REEM) (RD16/0015/0002, RD16/0015/0003, RD12/0032/0002, RD12/0060/01-02); TEVA SLU.

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