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**Corpus Callosum Damage to Account for Cognitive, Affective and Social-Cognitive
Dysfunctions in Multiple Sclerosis: A Model of Callosal Disconnection Syndrome?**

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Corpus Callosum Damage to Account for Cognitive, Affective and Social-Cognitive Dysfunctions in Multiple Sclerosis: A Model of Callosal Disconnection Syndrome?

Abstract

The corpus callosum (CC) is the major commissure interconnecting the two hemispheres and is particularly affected in multiple sclerosis (MS). In the present review, we aimed to investigate the role played by callosal damages in the pathogenesis of MS-related dysfunctions and examine whether a model of callosal disconnection syndrome is a valid model for MS. For this purpose, we will first review structural and functional evidence of callosal pathology in MS. Second, we will account for the potential role of CC abnormalities in MS-related dysfunctions. Finally, we will report data concurring with a ‘multiple disconnection hypothesis’ that has been proposed to explain those dysfunctions, and we will examine evidence pointing towards MS as a ‘callosal disconnection syndrome’. We will end by discussing the contribution of this interpretation to the understanding of MS and MS-related deficits.

Keywords

Multiple Sclerosis, Corpus Callosum, Connectivity, Cognitive Impairment, Disconnection Syndrome, ‘Callosal Disconnection Syndrome’.

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system manifested by multifocal demyelination and axonal loss. This disease is characterized by heterogeneous clinical manifestations, including sensorimotor and cerebellar symptoms, affective disturbances, impaired cognition and participation in social activities(1). While the etiology of neurocognitive dysfunction in MS is most commonly multifactorial, linked to multiple cumulative damages in the central nervous system, this review supports the idea that disconnection of cortical areas by White Matter (WM) damage—and particularly callosal damages—is a key mechanism underlying MS-related dysfunctions.

The Corpus Callosum (CC) is the largest and the most important WM-tract interconnecting the two cerebral hemispheres. The size, amount of myelination and density of the fibers in callosal or peri-callosal areas ensure the proper functioning of the brain structures they connect. Therefore, normal cognition and behavior depend, at least in part, on the integrity of the CC, as it mediates the interhemispheric communication among the specific brain areas underpinning higher level motor and cognitive functions.

In MS, the CC is frequently compromised in patients. Lesions in callosal or peri-callosal regions are common findings in both autopsy and imaging studies(2). The frequent involvement of CC-damage in patients and its impact on MS-related dysfunction has led some authors to consider this structure as a sensitive and specific indicator of the disease(3). A growing amount of evidence thus suggests that the reduced CC integrity that accompanies MS plays some part in MS-related dysfunctions.

In this paper, we aimed to review the current knowledge about the role played by callosal damages in the pathogenesis of MS-related dysfunctions. Given the fact that the CC is the major pathway interconnecting the two hemispheres—and is also particularly affected in

MS, including in the earliest clinical stages of the disease—the exploration of the role of CC-damage is of particular interest in relation to our understanding of the disease.ⁱ

2. Structural and functional alterations of the CC in MS

2.1 Structural imaging Data

CC atrophy or lesions in callosal or peri-callosal areas assessed by Magnetic Resonance Imaging (MRI) techniques are common findings in patients with MS. The prevalence of CC-damages in this pathology was confirmed since the early 1960s(4). Some authors found intra and peri-callous damages in more than 50% of patients, and global callous atrophy in more than 40%(5). Furthermore, CC atrophy has been shown to increase with the progression of the disease, with a loss of approximately 2% of callosal area per year(6), which is 10 times greater than the loss observed in healthy individuals. Recently, Petracca et al.(7) highlighted the presence of a topographic pattern of CC involvement in MS: CC-damages seem to mainly affect the splenium and the posterior portion of the CC body and develop following a postero–anterior gradient over time.

If several studies show the frequent involvement and the importance of CC-damages in MS, it also appears to be an early phenomenon. Callosal anomalies have been identified during the early phase of the disease, in patients with mild disability. For example, Barkhof et al.(8) found an overall CC atrophy of about 20% in Relapsing-Remitting MS (RR-MS) patients, with a median EDSS¹ of 3 and less than five years of disease duration. In patients with clinically isolated syndromes (CIS), Ranjeva et al.(9) showed that CC is affected as early as three months after the first clinical onset. Further, some studies suggested that these

¹ *Expanded Disability Status Scale*

damages would be most extensive in early disease courses. For example, Granberg et al.(10) revealed that the annual callosal atrophy rate decreased with disease duration in MS-patients.

Structural callosal anomalies in MS have also been assessed by advanced neuroimaging techniques, such as Diffusion Tensor Imaging (DTI) tractography. DTI allows to examine structural integrity of WM-tracts at the microstructural level when no lesion is yet visible at conventional MRI. This technique is particularly relevant to assess *normal-appearing* CC integrity. Using DTI techniques, many studies reported diffusion abnormalities of the CC in MS-patients, such as decreased fractional anisotropy or increased mean diffusivity²(11). These studies provide additional knowledge by assessing the integrity of the CC microstructure in MS: if CC-damages appear to be an early marker of the disease, microstructural abnormalities were also found in *normal-appearing* CC—thus may be present even in the absence of atrophy or detectable size alterations.

Recently, advanced high-gradient strength multi-shell diffusion MRI was proposed to outperform conventional DTI as a marker of microstructural changes in MS-patients. This diffusion metric enables separating intra and extra-axonal diffusion compartments and is thus more sensitive to axonal integrity as compared to conventional DTI metrics. Although protocols based on this technique are still scarce in MS, Huang et al.(12) reported increased axon diameter and decreased axon density in the normal-appearing CC of patients compared to controls. If further research is needed, high-gradient diffusion MRI holds promise as a novel imaging technique for monitoring MS progression and understanding its underlying pathophysiology.

In this context, the precocity and frequency of peri- and intra-callous damages have led some authors to consider the structural and functional evaluation of the CC as a diagnostic

² Decreased fractional anisotropy (FA) and increased mean diffusivity (MD) are DTI metrics suggesting alterations in the magnitude and directionality of water diffusion due to myelin and axonal damages.

and prognostic index in the follow-up of patients(13). Indeed, the early presence of callosal lesions among CIS patients would be predictive of their risk of conversion towards a clinically definite MS(14). In a longitudinal study including 158 MS-patients(14), the patients not fulfilling the Barkhof MRI diagnosis criteria had a fourfold increased risk of developing a clinically definite MS (relative risk of 3.8) when they had CC lesions. CC atrophy during the first year of treatment was found to be the best predictor of disease progression in a 9-year longitudinal study(15). The CC thus appears to be a useful target for detecting and monitoring progression of neurodegeneration in MS. For a full description of relevant articles identified regarding structural alterations of the CC in MS, please see the supplementary appendix in the online version of this article (Supplemental Table 1).

2.2 Functional Data

2.2.1 Electro-magnetic imaging approaches: EP and TMS Data

The use of evoked potentials (EP) to assess interhemispheric transfer (IHT) time, a functional index of callosal transmission, has been useful for investigating impaired connectivity in MS-patients, even at early-stage disease. As the CC constitutes the main pathway between hemispheres, protocols based on IHT time (as assessed by EP) allow the quantitative assessment of interhemispheric connectivity (and thus, callosal transmission). Indeed, a lateralized auditory, motor or visual stimulus first activates the contralateral hemisphere, and the ipsilateral one with a slight delay due to the IHT of information. Given the excellent temporal resolution of the EEG, a precise evaluation of the IHT time can be obtained by comparing the latency of recorded EP over each hemisphere. In such protocols, EP thus offer the opportunity to non-invasively assess impaired interhemispheric connectivity due to CC alterations in MS-patients. Hence, some authors used EP as an electrophysiological

probe of callosal dysfunction in their patients while others argued that EP investigations should be further explored for diagnosis and prognosis purposes in MS(16).

Studying callosal dysfunction in MS by using an EP paradigm often entails presenting a visual stimulus to one hemifield and then recording both contralateral and ipsilateral subsequent hemispheric responses—and thereby, allows to calculate callosal transmission between both hemispheres. Using a bi-manual coordination task, Larson et al.(16) reported a deficit in interhemispheric transmission in MS-patients compared to controls. Interestingly, deficits in bimanual motor coordination were found but only in MS-patients with EP evidence of inefficient callosal transmission (as shown by a reduced cross-callosal EP amplitude). This finding underlines the critical role of the CC in performance on tasks demanding interhemispheric interactions and reflects the decrease of callosal efficiency in MS-patients.

Callosal dysfunction in MS have also been investigated by measuring the Ipsilateral Silent Period (ISP) following Transcranial Magnetic Stimulation (TMS) of the primary motor cortex (M1), in order to examine interhemispheric transcallosal interactions between bilateral motor cortices. ISP corresponds to a brief reduction in the electromyogram activity following TMS applied to the M1 during a voluntary ipsilateral muscle activation. Previous studies have shown that ISP illustrates balanced inhibition between the two hemispheres—the extent to which homologous M1 areas mutually inhibit each contralateral side through the CC during motor task performance—and therefore, has been considered to reflect the functional integrity of the transcallosal fibers connecting corresponding motorcortices(17). Using this paradigm, several studies showed abnormal ISP measures in MS: some authors detected increased ISP onset latency or prolonged ISP duration in MS-patients compared to controls (see supplementary material). Schmierer et al.(18) observed ISP abnormalities in 80% of MS-patients in early stage disease (mean disease duration: 2.4 years) with moderate disability (EDSS ranging from 0 to 3.5). These results suggest that interhemispheric connections

between the motor cortices through the CC were damaged in patients, even at early stage disease.

2.2.2 Metabolic Imaging Approaches: fMRI data

Measures of fMRI local blood flow changes are associated with increased or decreased neural activity, thus allowing to visualize and estimate brain activity during motor, sensory or cognitive tasks. Using fMRI techniques, interhemispheric motor inhibition can be probed by examining asymmetric *blood oxygenation level dependent* (BOLD) activation patterns during unilateral hand movements. In normal functioning, fMRI studies revealed that BOLD activation of the contralateral M1 increases while the BOLD activation of the ipsilateral M1 decreases. These BOLD patterns have been proposed to express normal neuronal inhibitory control from contralateral M1 to ipsilateral M1 and reflect effective interhemispheric transcallosal communication.

Using this paradigm, several authors attempted to show that the reduced CC integrity that accompanies MS may disrupt interhemispheric balance: patients thus should demonstrate reduced inhibition between hemispheres compared to controls, reflected by greater BOLD activation of the ipsilateral motor cortices compared to controls. Several fMRI studies reported such results in MS-patients and suggested that this overactivation of the ipsilateral M1 in patients could be the result of reduced inhibitory inputs from the contralateral M1 subsequently to MS-induced CC-damages(19,20). For example, Manson et al.(19) analyzed impairments of transcallosal functional communication using fMRI techniques and their relation to structural measures of callosal damages in MS-patients. They showed that patients exhibited a loss of interhemispheric functional connectivity (measured by fMRI monitoring of the transcallosal interactions in the motor cortex) which was correlated with CC atrophy. Lenzi et al.(20) also showed that mean diffusivity (as assessed by DTI) in the CC was

positively correlated with the BOLD activation of the ipsilateral M1: the more severe the CC structural damage, reflected by increased diffusivity, the greater the activation in ipsilateral M1. These results are concordant with previous studies demonstrating that interhemispheric motor inhibition is completely absent in acallosal patients(21). It thus seems that the loss of interhemispheric motor inhibition in MS-patients (reflected by increased activation in ipsilateral M1) reflects, at least in part, functional CC-damages.

2.2.3 Neuropsychological assessments of IHT

Finally, neuropsychological tasks have been proposed to detect and quantify functional impairment of IHT in MS-patients (and thus, functional CC-damages). Typically, dichotic listening tasks are used to explore IHT of auditory information. Using this paradigm, a right-ear advantage/left-ear disadvantage effect usually emerges, at least in most right-handed individuals, when two different and competitive verbal auditory stimuli are presented simultaneously to both ears. The left-ear disadvantage is classically interpreted as the result of more indirect paths for left-ear stimuli, requiring a cross via the CC, from the acoustic cortex of the right hemisphere (where they were first contralaterally directed) to language-processing areas of the left hemisphere. Thus, left-ear dichotic listening marked disadvantage or deficit reflects alterations of the IHT of left-ear inputs to the left hemisphere, and thus CC abnormalities.

Using this paradigm, several studies observed left-ear deficits on verbal dichotic listening tasks, suggestive of IHT dysfunction, which were correlated to the degree of callosal atrophy in MS-patients (see supplementary material). Other similar tasks exploring IHT of sensory and motor information have been used, such as crossed tactile finger localization tasks and alternate finger tapping tasks. Using these paradigms, Pelletier et al.(22) reported an association between impaired auditory, motor and sensory IHT and atrophy of the posterior

callosal region in patients. Overall, these studies demonstrate that neuropsychological testing can reveal behavioral impairments attesting for reduced interhemispheric communication in MS-patients, and underline the critical role of CC alterations in the magnitude of IHT dysfunction. For a full description of relevant articles identified regarding functional alterations of the CC in MS, please see the supplementary appendix in the online version of this article (Supplemental Table 2).

3. CC-damages and Cognitive Dysfunction in MS: Behavioral and Functional Data

In the last decades, numerous studies have investigated the relationship between CC-damages and cognitive dysfunction in MS. These studies highlighted an association between CC atrophy and global cognitive decline(23), impaired attention and information processing speed(10), impaired verbal fluency(24) or visual memory deficits(25). The relationship between CC-damages and cognitive dysfunction has also been shown in benign MS(27) and at the earliest stage of the disease, in patients with CIS(28). Mesaros et al.(26) showed, among patients classified as having the benign form of MS (i.e., low locomotor disability, with EDSS score ≤ 3 , after a relatively long disease duration: ≥ 15 years), that cognitively impaired patients had significantly higher CC lesion volume compared with cognitively preserved patients. In patients with CIS, Ranjeva et al.(27) reported poorer performance during the PASAT³, a processing speed and working memory test, that was associated with CC-damages. These findings provide evidence for a robust relation between cognitive dysfunction and structural abnormalities of the CC in MS, including at earliest phases of disease course or in patients with low locomotor disability.

³ *Paced Auditory Serial Addition Test*

Interestingly, not only did research show that CC-damages are associated with cognitive dysfunction, it also suggested that such damages could *contribute* to it—underlining the potential role of CC alterations in the pathogenesis of cognitive dysfunction in MS. A longitudinal study of Bodini et al.(28) showed that CC-damages (as assessed by DTI) predicted disability progression and cognitive deterioration after five years in patients with primary-progressive MS. Decreased fractional anisotropy along the entire CC predicted poorer cognitive performances at five years, particularly on measures of working memory and information processing speed. Caligiuri et al.(29) yielded similar results in RR-MS and showed that CC microstructural damages contribute to the development of cognitive dysfunction in patients. Cognitive impairment was mainly explained by FA reductions in the genu and splenium of CC. Huang et al.(12) replicated these findings with advanced imaging methods and showed that alteration in apparent axon diameter in the CC of MS-patients (as assessed by high-gradient diffusion MRI) is the strongest predictor of disability and cognitive dysfunction, reflected by SDMT⁴ and BVMT-R⁵ scores (measures of information processing speed and visual episodic memory). Recently, Winter et al.(30) used tract-specific MRI-measures to examine the relationship between neuropathology and cognitive dysfunction and showed that both verbal and visual immediate recall score differences were accounted for by the isthmus of the CC. Papathanasiou et al.(13) reported that CC atrophy best predicts cognitive decline in secondary-progressive MS-patients. As for CIS-patients, Yildiz et al.(31) also showed that progression of annualized CC atrophy is a predictive factor for cognitive dysfunction in patients.

Overall, these findings provide evidence for the potential role of structural CC abnormalities in cognitive dysfunction in MS: the more severe the CC structural damage, the

⁴ *Symbol Digit Modalities Test*

⁵ *Brief Visuospatial Memory Test - Revised*

greater seems to be cognitive deterioration. CC structural or functional assessments thus seem to offer key indices for cognitive dysfunctions in MS.

4. CC-Damages, Affective Information Processing and Social Cognition Deficits

4.1 Are CC-damages Related to Affective Information Processing Deficits in MS?

Alexithymia—an alteration of the ability to perceive, identify and verbalize one's proper emotions—has gained attention in the field of MS in the last decades(32). With a prevalence in MS-patients ranging from 10% to 53%(33), some authors suggested that alexithymia may arise from a disruption of the interhemispheric affective-cognitive communication mediated by the CC(33). This hypothesis derives from one important model of hemispheric specialization in emotion processing, which posits that the left hemisphere would be more specialized in linguistic abilities (i.e., in explicit/verbal emotional cognition), while the right hemisphere would be more specialized in implicit emotion arousal and experience(34). This model thus suggests that the IHT of the arousal experience from the right hemisphere to the verbally specialized left hemisphere would be necessary for the identification and expression of one's own emotional states. That is, IHT dysfunction would result in physiological arousal that could not be verbally identified, interpreted or communicated.

In this perspective, the prevalence of alexithymic symptoms would be the result of a deficit in interhemispheric communication due to CC-damages, a hypothesis that was later supported by several clinical and imaging studies, including on MS-patients. Indeed, Pelletier et al.(35) demonstrated a significant correlation between alexithymia and atrophy of the posterior segment of the CC in patients. Recently, Chalah et al.(33) reported that alexithymia was associated with lower volumes of the CC, deep white matter, bilateral pallidum and left

thalamus in patients. These findings are concordant with previous studies demonstrating that split-brain patients(36) or patients with CC agenesis(37) were found to be highly alexithymic. Overall, these results support the hypothesis of interhemispheric transfer dysfunction in alexithymic MS-patients, and extend the critical role of CC alterations to affective information processing deficits in patients.

Similarly, some authors highlighted deficits in MS-patients in comprehending emotional information from prosodic cues(38). Beatty et al.(39) showed that MS-patients identify emotional states expressed by prosodic cues less accurately than controls, and that these deficits were not related to hearing loss, aphasic deficits, cognitive impairment or depression. These difficulties may also be considered as a consequence of callosal anomalies and altered interhemispheric communication in patients. Indeed, some studies highlighted the distributed nature of neural networks involved in emotional information processing on the one hand(40), and the advantage of sharing information processing between the two hemispheres on the other(41).

4.2 Are CC-damages Related to Social Cognition Deficits in MS ?

Social cognition is a multi-component construct that includes theory of mind (ToM), empathy, emotion recognition and mental state decoding. In MS, a recent meta-analysis identified both ToM and emotion recognition deficits in patients(42). Evidence also suggested that MS-patients showed a significantly lower level of self-reported empathy, as measured by Baron-Cohen's Empathy Quotient(43). However, the etiology of such deficits remains poorly documented. As for emotional information processing deficits, some authors suggested that social cognition deficits could be related to callosal anomalies and altered interhemispheric communication in patients(44–46). To our knowledge, only two studies specifically addressed

the relationship between CC-damages and social cognition deficits in MS and reported that CC alterations contribute to both ToM and emotion recognition deficits in patients(44,46). Social cognition performances were associated with multiple pathological WM findings, with largest effects observed for the CC(44,46), fornix(44), tapetum(44), uncinate fasciculus bilaterally(44,46), right fronto-occipital fasciculus(44,46), right inferior longitudinal fasciculus(46), and left inferior cerebellar peduncle(44). These results are concordant with previous studies demonstrating that patients with CC agenesis perform poorer than controls in facial emotion recognition tasks(47). CC-damages may thus be one of the underlying mechanism responsible for social cognition deficits in MS, but remains to be further investigated.

5. MS: A Model of Callosal Disconnection Syndrome?

If MS has been associated with cognitive, affective and social-cognitive dysfunctions, explaining this broad range of manifestations remains a major challenge. Recent years have witnessed an emerging scenario to account for the pathogenesis of MS-related dysfunctions, which would result from the disconnection of cognitively important processing regions(48). In this perspective, MS-related symptoms would derive from a ‘disconnection syndrome’, mainly through WM damage(49). Specifically, the presence of callosal pathology in MS-patients would disrupt inter-hemispheric connectivity and would impair performance on connectivity-demanding cognitive tasks. Thus, cognitive dysfunction in MS would be the result of connection disturbances between brain areas due to CC-damage.

Further, several authors argued that information processing speed (IPS) is the primary cognitive deficit underlying cognitive decline in MS-patients: this cognitive mechanism also appears to be highly associated with the degree of CC integrity in MS-patients. Indeed, the

cognitive domain that is most consistently affected in MS is IPS(1). Slowed IPS seem to influence the other cognitive domains in patients: Several studies reported an association between impaired IPS and impaired memory, executive functions, inhibition or flexibility. Interestingly, it appears that the differences between controls and MS-patients disappear after statistically controlling for shared variances between IPS and cognitive performances in various cognitive domains such as working memory(50), inhibition(51), planning(52) or flexibility(51). Once the influence of IPS is removed from such cognitive test scores, there are no longer significant group differences. These results suggest that performances on such cognitive tasks are highly dependent on IPS performances, which support other findings indicating that IPS appears to be the best index to discriminate MS-patients from controls(53). Thus, a growing number of authors consider IPS as a key deficit, which possibly underlies all other cognitive impairment in MS-patients(53).

Importantly, as suggested before, such deficit in IPS has been repeatedly found to correlate with structural and functional brain connectivity, and particularly CC integrity in patients. Using DTI, several authors reported poorer performance during the PASAT (a task reliant on processing speed) in MS-patients that were associated with microstructural CC-damages⁶. The fact that the CC emerges as the WM-tract that is the most consistently associated with IPS performance across cognitive tasks may not be surprising: the CC is the primary myelinic tract that ensures IHT and may constitute a major candidate to be one of the biological basis for IPS. These findings suggest the importance of CC integrity for maintained IPS performances across various cognitive domains through rapid transmission of information processed from one brain region to another, and show the critical role of CC-damage to explain and predict the observed deficits. These findings support the view of MS as a

⁶ For a full description of relevant articles identified regarding the association between IPS and CC-damages in MS, please see the supplementary appendix in the online version of this article, Supplemental Table 3

“callosal disconnection syndrome”: the lack of optimized communication between brain regions due to CC-damages leads to disconnection, which potentially drives cognitive decline.

If the role played by WM pathways in supporting complex cognitive processes has been advanced, it has also been proposed to subtend affective and social cognition processes(54,55). Social information is complex and multimodal and requires inter-hemispheric communication and cooperation. Consequently, efficient processing of social information must rely upon effective IHT of information between hemispheres—thus, relies (at least in part) upon the CC. However, only a few studies began to explore the impact of WM and CC-damage on social cognition performances in MS-patients(44,46), although one recent study identified specific functional connectivity substrates underlying social cognition in MS, suggesting that these symptoms may occur independently from those of other neurocognitive domains(56).

Studies on functional connectivity (FC) have lent strong support to the idea that CC plays a critical role in maintaining interhemispheric FC between hemispheres. Indeed, although other pathways of interhemispheric communication are also available (e.g., anterior commissure), studies reported that the surgical section of the CC drastically reduces the amount of communication between brain regions in monkeys(57) and humans(58). In MS, connectivity studies also investigated the relation between disconnection and dysconnectivity⁷ and suggested that disrupted FC may drive cognitive(59) and socio-cognitive impairments(56). Additionally, other authors showed that disrupted structural connectivity contributes to cognitive difficulties in MS(60). Yet, further studies are needed to explore the relationship between damage to connections (including those of the CC), network metrics and (socio)cognition.

⁷ See table 4 in the Supplementary Material

All in all, evidence points that MS should be considered as a model of callosal disconnection syndrome. Many of the deficits of MS-patients can be related to a disconnection syndrome caused by involvement of CC-damage. CC-damage may represent one of the most important mechanisms underlying the pathogenesis of MS-related impairments by interfering with the mainstream of the interhemispherical cooperation,

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Supplementary appendix for online publication

Literature search methodology

Aim: The main objective of this contribution is to provide a comprehensive synthesis focused on the role played by callosal damages in the pathogenesis of cognitive and social-cognitive dysfunctions associated with Multiple Sclerosis (MS). We first reviewed the role played by callosal alterations to account for MS-related impairment in patients. We then highlighted how the reviewed data sustain the possibility that CC damages represent an important factor underlying the pathogenesis of cognitive and social-cognitive dysfunction in MS by interfering with the connectivity between areas of both hemispheres—pointing towards MS as a model of ‘callosal disconnection syndrome’.

Selection criteria: A systematic literature search was performed in PubMed, Scopus and Web of Knowledge with search strings containing ‘Corpus Callosum’, ‘Callosal’, ‘Connectivity’, ‘Disconnection Syndrome’ and ‘Cognitive Impairment’, ‘social-cognitive impairment’, ‘Social Cognition’, ‘Alexithymia’, ‘Interhemispheric Transfer’, ‘Processing Speed’, in combination with ‘multiple sclerosis’. No filters, publication date restrictions or language restrictions were used.

Databases searched: PubMed, Scopus and Web of Knowledge. In addition, the same search terms were used to search Google Scholar to ensure that no potentially relevant articles were missed.

Date of search: September 2020

Predefined search strings:

1. “*Corpus Callosum*” and its abbreviation (*CC*) combined with “*multiple sclerosis*”.
2. “*Disconnection Syndrome*” and “*callosal disconnection syndrome*” combined with “*multiple sclerosis*”.
3. Expressions referring to MS-related impairments (“*cognitive impairment*”, “*social cognition*”, “*interhemispheric transfer*”, “*processing speed*”) combined with “*multiple sclerosis*”.

If more than 100 results were retrieved in the PubMed search, “AND Corpus Callosum” was added to the search string to reduce the number of results to a more manageable number.

Screening: The retrieved abstracts were screened simultaneously and independently by two raters with regard to their relevance for this review. Any discrepancies or disagreements were discussed to reach consensus. If necessary, disagreements were referred to a third rater who served as a tiebreaker. All selected articles included were carefully read and their references scrutinised in order to identify other relevant studies. Only the papers investigating at least one measure of the CC were included.

Limitations: If papers providing contradictory or non-significant results were also included in the present review, the possibility of having missed eligible records cannot be completely ruled out—especially when studies were not associated with the keyword “corpus callosum” while still containing (potentially non-significant) results related to this structure. In the end, even if the interpretations and conclusions of the present review are based on a large body of evidence and articles providing strong support, this can constitute a selection bias. Besides, we did not retain studies that did not appear in peer-reviewed journals (such as conference papers, book chapters, dissertations...), which may also lead to the possibility of a publication bias. Finally, even if we focused on callosal damages to account for MS-related dysfunctions, the etiology of neurocognitive dysfunction in MS remains multifactorial, linked to multiple cumulative damages in the central nervous system. We examined the specific involvement of CC-damage in the pathogenesis of MS-related dysfunctions, but this does not mean that there is no other mechanism/structure involved to explain these dysfunctions. Ultimately, the clinical manifestations of the disease cannot be related to a callosal disconnection *only*: (1) other WM pathways of intra and interhemispheric communication may also be involved (e.g., U fibers, other commissural pathways and WM tracts); (2) as well as gray matter damage (e.g., prefrontal, hippocampal, entorhinal, thalamic, etc.). Thus, in the present work, we do not seek to deny the other potential mechanisms involved in MS-related dysfunctions—but rather attempt to account for the specific role of one particular structure that has been identified as a key mechanism underlying MS-related dysfunctions.

Table 1

Relevant articles identified regarding structural alterations of the CC in MS that were not referenced in the printed version of the article

| Reference | Results | Method | Population |
|--|---|--|---|
| Importance and precocity of CC damage | | | |
| Audoin et al., 2007 | CC atrophy appears over a period of one year after the first clinical onset. CC damages are associated with the progression of disability in patients: the authors showed a significant correlation between CC atrophy and EDSS scores during the follow-up period. | fMRI, DTI, MRS | 24 CIS MS patients |
| Barkhof et al., 1998 | The authors found an overall CC atrophy of about 20% in RR-MS patients, with a median EDSS of 3 and less than five years of disease duration. | Conventional MRI (T1/T2-weighted images) | 14 RR-MS patients |
| Cocozza et al., 2017 | 90.6% of MS patients exhibited CC anomalies. | Conventional MRI (FLAIR images) | 117 MS-patients |
| Gean-Marton et al., 1991 | 93% of patients exhibited CC anomalies. | Conventional MRI (Repetition time TR/ Time to Echo TE images) | 42 MS-patients |
| Kalincik et al., 2012 | The authors identified a 6-month decrease in the CC cross-sectional area and baseline volume of T2 lesions as predictors of clinically definite MS conversion. | Conventional MRI (FLAIR images) | 217 MS patients (2 years study) |
| Martola et al., 2006 | The mean annual CC area decrease is approximately 2%. | Conventional MRI (T1/T2-weighted images) | 37 MS-patients (9 years study) |
| Mesaros et al., 2009 | 98% of patients exhibited CC anomalies. Compared with controls, Benign MS had significantly different CC diffusivity and volumetry. Cognitively Impaired patients had significantly higher CC lesion volume. | Conventional MRI (Repetition time TR/ Time to Echo TE images), DTI | 54 BMS patients and 21 healthy controls |
| Ranjeva et al., 2003 | The authors showed that CC is affected in patients with CIS as early as three months after the first clinical onset. Diffusion abnormalities of the CC in MS patients with CIS (increased mean diffusivity) were observed before any atrophy is detected. | Conventional MRI (T1/T2-weighted and FLAIR images), MRS | 46 CIS MS patients |
| Pelletier et al., 2001 | RR-MS patients, in early stage disease and mild disability, exhibited CC anomalies (callosal area atrophy). CC damages are associated with the progression of disability in patients: the authors showed a significant correlation between CC measures and EDSS scores at baseline. | Conventional MRI (T1/T2-weighted images) | 30 RR-MS patients (5 years study) |

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| Petracca et al., 2020 | The authors highlighted an earlier involvement of the posterior regions, followed at a later stage by involvement of the anterior portions of the CC. CC damage appears to develop following a postero–anterior gradient. This pattern seems to replicate the topography of regional gray matter progression over time. | Conventional MRI (T1/T2-weighted images) | 55 MS-patients (13 RRMS, 20 SPMS, 22 PPMS) and 24 controls |
| Microstructural alterations | | | |
| Braley et al., 2012 | SP MS-patients had significantly lower genu, body, and splenium FA values than those with RRMS, indicative of microstructural CC tissue damage. | DTI | 22 RRMS patients; 25 SPMS patients |
| Cicarelli et al., 2003 | Patients showed decreased FA and increased MD in the normal-appearing CC relative to controls. | DTI | 39 MS patients and 21 controls |
| Ge et al., 2004 | Patients showed significantly lower FA and higher MD in the normal-appearing CC, but not in frontal and occipital NAWM regions, compared to controls. | DTI | 15 RRMS patients; 12 controls |
| Harrison et al., 2011 | The authors examined the impact of MS on longitudinal changes in microscopic fiber tract damages (3 scans over 2 years). Changes were most rapid in the corpus callosum, where FA decreased 1.7% per year. | DTI | 78 MS patients (2 years study) |
| Hasan et al., 2005 | FA in the MS group was significantly decreased in the anterior and posterior midbody subdivisions of the CC, but no significant differences were detected in the splenium and genu. | DTI | 26 RRMS-patients and 32 controls |
| Oh et al., 2004 | Patients showed decreased FA and increased apparent diffusion coefficients in the normal-appearing CC relative to controls. | MRS | 47 RRMS patients and 15 controls |
| Rimkus et al., 2011 | Patients showed decreased FA and increased MD compared to controls. Cognitive dysfunction in patients was associated with DTI changes in the CC. | DTI | 23 RRMS patients and 12 controls |
| Rueda et al., 2008 | The authors reported robust diffusion abnormalities in all regions of the normal-appearing CC. Patients showed lower FA values compared to controls in all CC regions (rostrum, anterior body, posterior body and splenium). | DTI | 57 RRMS patients and 47 controls |
| Sigal et al., 2012 | CC volume and DTI metrics differed significantly between MS patients and controls. Patients showed decreased FA and increased apparent diffusion coefficients in the normal-appearing CC relative to controls. | DTI | 30 RRMS patients and 30 controls |

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| Xu et al. 2020 | The authors conducted a meta-analysis to determine microscopic fiber tract damage differences between MS patients and controls across 15 studies. Patients showed decreased FA (whole CC, genu and splenium), increased MD (whole CC, genu and splenium) and increased AD (whole CC) in the normal-appearing CC relative to controls. | DTI | 461 MS-patients and 365 controls from 15 studies were included. |
| Warlop et al., 2008 | Patients showed decreased FA and increased transverse and longitudinal diffusivity in the normal-appearing CC relative to controls. | DTI | 16 RRMS patients and 16 controls |
| CC as a prognostic index | | | |
| Giorgio et al., 2013 | The authors examined white matter lesion location and frequency that predict conversion of CIS to clinically definite MS. High lesion frequency was found in the converting group in projection, association, and commissural WM tracts, with larger clusters being in the CC, corona radiata, and cingulum. | Conventional MRI (T1/T2-weighted images) | 1165 CIS patients |
| Jafari et al., 2009 | The Barkhof criteria and CC lesions were strongly associated with conversion to clinically definite MS. | Conventional MRI (T1/T2-weighted and FLAIR images) | 158 MS patients |
| Odenthal et al., 2017 | Patients who converted to MS by 5-year had a significantly smaller mean Corpus Callosum Area (CCA) at follow-up. Greater CCA reduction was associated with higher annualized relapse rate over follow-up. | Conventional MRI (T1/T2-weighted and FLAIR images) | 100 MS patients (5 years study) |
| Vaneckova et al., 2012 | CC atrophy predicts future clinical deterioration. CC atrophy during the first year of treatment is the best predictor of disability | Conventional MRI (T1/T2-weighted images) | 39 MS patients (9 years study) |
| Yaldizli et al., 2010 | CC damages are associated with the progression of disability in patients: the authors showed a significant correlation between CCI (Corpus Callosum Index) and (1) disease duration and (2) EDSS scores at diagnosis. | Conventional MRI (T1/T2-weighted images) | 533 MS-patients at diagnosis and 169 MS patients at follow-up |

Note. AD = Axial Diffusivity; CC = Corpus Callosum; CIS = clinically isolated syndromes; DTI = Diffusion Tensor Imaging; FA = Fractional Anisotropy; FLAIR: Fluid Attenuated Inversion Recovery; fMRI = functional Magnetic resonance imaging; MD = Mean Diffusivity; MRI = Magnetic resonance imaging; MRS = Magnetic resonance Spectroscopy; PPMS = primary progressive MS; RRMS = Relapsing Remitting MS; SPMS = Secondary Progressive MS

Table 2

Relevant articles identified regarding functional alterations of the CC in MS that were not referenced in the printed version of the article

| Reference | Results | Method | Population |
|---|---|-------------------|----------------------------------|
| Evoked potentials (EP) Paradigm | | | |
| Burnison, Larson & Brown (1995) | The authors reported prolonged interhemispheric transmission latencies and reduced cross-callosal amplitudes in MS patients compared to controls. | EP | 28 MS patients and 30 controls |
| Fling et al., (2008) | The authors reviewed the relationship between corpus callosum integrity and functional bimanual performance in MS. | Literature Review | |
| Transcranial Magnetic Stimulation (TMS) Paradigm | | | |
| Boroogerdi et al., 1998 | The authors examined inhibition of the ongoing EMG activity of the first dorsal interosseus muscle after transcranial magnetic stimulation of the ipsilateral motor cortex. Transcallosal conduction time was delayed in patients compared with controls, showing that the interhemispheric functional connections between the motor cortices through the CC was damaged in patients. | EMG, TMS | 24 MS patients and 24 controls |
| Höppner et al., 1999 | The authors showed abnormalities in the transmission time of interhemispheric interactions by a prolonged latency in onset and duration of the ISP in patients compared with controls. Increase of onset latencies and durations were positively correlated with the summed area of CC lesions. | EMG, TMS | 34 MS patients and 12 controls |
| Jung et al., 2006 | ISP duration was significantly longer in RRMS patients compared to controls, but no significant differences were detected for iSP onset latency. ISP duration did not correlate with MRI abnormalities of the CC | EMG, TMS | 49 RRMS patients and 20 controls |
| Neva et al., 2016 | The authors showed prolonged transcallosal inhibition (as measured by iSP) that positively correlated with increasing disability in patients (as measured by EDSS). | EMG, TMS | 26 MS patients and 11 controls |
| Schmierer et al., 2000 | The authors investigated corticospinally mediated (central motor latencies, amplitudes) and transcallosally mediated (onset latency and duration) stimulation effects. TMS disclosed abnormalities of | EMG, TMS | 50 RRMS patients |

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| | corticospinally mediated responses in 62% and of transcallosal inhibition in 80% of the patients. | | |
| Neuropsychological assessments of Interhemispheric Transfer (ITH) | | | |
| Barkhof et al., 1998 | The total area of the CC was smaller in patients than in controls. Impairment of IHT in MS patients was correlated to the degree of callosal atrophy (splenium). | Conventional MRI (T1/T2-weighted images), Neurophysiological evaluation (DL) | 14 RRMS patients and 14 controls |
| Bonzano et al., 2008 | The authors showed significant differences in the performance of repetitive bimanual finger opposition movements between MS patients and controls. Bimanual finger motor performance correlated with microstructural changes (lower FA values) in different regions of the CC in MS patients, supporting the conclusion that deficits in bimanual motor coordination is related to callosal dysfunction in MS. | DTI, Neurophysiological evaluation (motor task) | 14 MS patients and 10 controls |
| Gadea et al., 2002 | Impairment of IHT in MS patients was correlated to the degree of callosal alteration (only for the non-forced condition of the DL task). | Conventional MRI (T1/T2-weighted images), Neurophysiological evaluation (DL) | 25 RRMS patients and 25 controls |
| Pelletier et al., 1993 | IHT was impaired in patients with MS (for all functional tasks explored) and proportional to both degree of callosal atrophy and diffusion of white-matter lesions (as assessed by a semiquantitative evaluation of hemispheric brain MRI hyperintensities). Performance on DL task was predominantly associated with atrophy of the posterior CC region, finger tapping with the anterior CC region, and cross-localization with midanterior and posterior regions. | Conventional MRI (T1/T2-weighted images), Neurophysiological evaluation (DL, crossed tactile finger localization task, and an alternate finger tapping task) | 90 MS patients and 25 controls |
| Pelletier et al., 2001 | Compared with controls, patients showed greater callosal atrophy and functional impairment of IHT (for all modalities explored) at baseline that worsened during the 5-year study. The authors reported an | Conventional MRI (T1/T2-weighted images), Neurophysiological | 30 RRMS patients and 25 controls (5 years study) |

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| | association between the severity of impaired auditory, motor and sensory IHT and callosal atrophy in MS patients. | evaluation (DL, crossed tactile finger localization task, and an alternate finger tapping task) | |
| Rao et al., 1989 | Impairment of IHT (as assessed by the Verbal Dichotic Listening Task and the Object Naming Latency Task) was found only in the MS patients with CCA. The left ear suppression was found only for MS patients with CCA. They also were slower in responding to stimuli presented in the left visual field compared with in patients without CCA. | Conventional MRI (T1/T2-weighted images), Neurophysiological evaluation (DL, Object Naming Latency Task) | 28 MS patients with CCA, 16 MS patients without significant CCA, and 64 controls |
| Reinvang et al., 1994 | Impairment of IHT (as assessed by dichotic listening) was correlated to the degree of callosal atrophy in the forced-left condition in MS patients. | Conventional MRI (T1/T2-weighted), Neurophysiological evaluation (DL) | 22 MS patients |

Note. CC = Corpus Callosum; CCA = Corpus Callosum Atrophy; DL = Dichotic Listening; DTI = Diffusion Tensor Imaging; EMG = electromyogram; EP = Evoked Potential; FA = Fractional Anisotropy; ISP = Ipsilateral Silent Period; IHT = Interhemispheric Transfer; RRMS = Relapsing Remitting MS; TMS = Transcranial Magnetic Stimulation.

Table 3

Relevant articles identified regarding the association between processing speed and CC damages in MS that were not referenced in the printed version of the article

| Reference | Results | Method | Population |
|--------------------------|--|---|----------------------------------|
| Abel et al., 2020 | Reduced IPS performances (as assessed by the SDMT) was associated with increased microstructural abnormalities (as assessed by myelin water measures) in the superior longitudinal fasciculus, CC and cingulum. | Myelin water imaging, Neurophysiological evaluation | 73 MS patients |
| Bester et al., 2013 | Deficits in IPS (as assessed by the SDMT and PASAT) were associated with the T2 lesion volume of the anterior thalamic tracts. The association between DTI-derived metrics of the CC tracts and IPS performances did not reach significance. | DTI, Neurophysiological evaluation | 26 BMS patients and 24 controls |
| Bozzali et al., 2013 | The authors observed a correlation between patients' ACM and the number of correct responses in the PASAT (a processing speed and working memory test), which are found in the anterior portion of the CC, in the right hippocampus, and in the cerebellum (IX lobules). | Conventional MRI (diffusion-weighted images), Neurophysiological evaluation | 25 RRMS patients and 25 controls |
| Dineen et al., 2009 | Reduced FA in the CC correlated with normalized PASAT scores. | DTI, Neurophysiological evaluation | 37 MS patients |
| Gonçalves et al., 2018 | The corpus callosum index (CCI) correlated with PASAT scores. | Conventional MRI (T1/T2-weighted and FLAIR images), Neurophysiological evaluation | 24 MS patients |
| Granberg, et al. (2015). | CC atrophy was strongly correlated with SDMT scores (after adjusting for disease duration, age and sex). | | |
| Hecke et al., 2010 | PASAT scores correlated with diffusion measures (FA, MD and RD) in the left cingulum and inferior longitudinal fasciculus, corona radiata (bilateral), forceps minor, genu of the CC, superior longitudinal fasciculus, interna and externa capsulae. | DTI, Neurophysiological evaluation | 20 MS patients |

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| Lin et al., 2008 | Mean apparent diffusion coefficient (ADC_{av}) and MT ratio were measured for the CC as defined by tractography. PASAT was correlated with mean MT ratio, ADC_{av} , CC area and total T2 lesion load, but not with T2 lesion load within the CC in patients. | DTI, MTI, Neurophysiological evaluation | 36 RRMS patients and 13 controls |
| Llufriu et al., 2012 | The ISP latency correlated with physical disability scores, IPS (as assessed by the SDMT) and executive cognitive domain tests. Even if the ISP latency correlated with the area of the CC and CC volume, the correlation between DTI indices and IPS measures did not reach significance. | DTI, Neurophysiological evaluation | 21 RRMS patients and 12 controls |
| Manca et al. 2018 | Although the authors reviewed partially different WM tracts association depending on the IPS test included, the CC emerged as the WM tract that most consistently correlated with IPS across tasks. Microstructural integrity of the CC was more consistently found to correlate with IPS performance. | Literature Review | |
| Mazerolle et al., 2013 | Reduced IPS performances (for both SDMT and CTIP) were associated with increased microstructural abnormalities in WM tracts. SDMT performance was associated with DTI metrics for the body (FA) and genu (FA, MD, RD) of the CC, the posterior thalamic radiation (FA, MD, RD), and the superior longitudinal fasciculus (MD, RD). Mean CTIP SRT performance was associated with DTI metrics for the body (FA, MD, RD), genu (FA, MD, RD), and splenium (MD) of the CC, as well as for the posterior thalamic radiation (RD), the uncinate fasciculus (FA), and the corona radiata (RD). | DTI, Neurophysiological evaluation | 20 RRMS patients and 20 controls |
| Mesaros et al., 2009 | The authors observed a significant correlation between PASAT scores and the majority of CC DT / MRI metrics (T2 lesion volume, FA, NAWM FA, NAWM MD). | DTI, Neurophysiological evaluation | 54 BMS patients and 21 controls |
| Ozturk et al., 2010 | Normalized PASAT scores were significantly correlated with callosal MRI indices (callosal FA, MD and perpendicular diffusivity) but not with age, whole-brain MRI indices, normalized callosal volume, or callosal lesion fraction. | DTI, Neurophysiological evaluation | 69 MS patients and 29 controls |

| | | | |
|-----------------------------|---|--|-------------------------------------|
| Rimkus et al., 2011 | The strongest correlations were observed between normalized SDMT scores with FA and normalized HVLT-delayed recall scores (a long-term memory test) with RD. The normalized SDMT scores also correlated with MD and RD. | DTI, Neurophysiological evaluation | 23 RRMS patients and 12 controls |
| Roosendaal et al. (2009) | Reduced FA in the left side of the body of the CC correlated with the <i>Letter Digit Substitution Test</i> scores (a processing speed of visual information test). | DTI, Neurophysiological evaluation | 30 MS patients and 31 controls |
| Sbardella et al., 2013 | The authors report correlations between DTI metrics and IPS (as assessed by the SDMT) in many WM bundles including the CC, internal capsule, posterior thalamic radiations, cerebral peduncles. A significant positive correlation was also found between Gray Matter volume in the orbito-frontal cortex (bilaterally) and the PASAT scores (2 seconds version). | DTI, Neurophysiological evaluation | 36 RRMS patients and 25 controls |
| Yu et al., 2012 | The authors reported correlations between reduced FA and impairment on several clinical neuropsychological tests, with the strongest correlations observed for the SDMT (a processing speed test). | DTI, Neurophysiological evaluation | 37 RRMS patients and 20 controls |

Note. ACM = Anatomical Connectivity Mapping, quantifying structural brain connectivity; BMS = patients with benign MS; CC = Corpus Callosum; CTIP = Computerized Test of Information Processing, a processing speed test; DTI = Diffusion Tensor Imaging; FA = Fractional Anisotropy; HVLT = Hopkins verbal learning tests; IPS = Information Processing Speed; ISP = Ipsilateral Silent Period; MD = Mean Diffusivity; MTI = magnetisation transfer imaging; NAWM, normal-appearing white matter; PASAT = Paced Auditory Serial Addition Test, a processing speed and working memory test; RD = Radial Diffusivity; MRI = Magnetic resonance imaging; RRMS = Relapsing Remitting MS; SDMT = Symbol Digit Modalities Test, a processing speed test.

Table 4

Relevant articles identified regarding the association between disconnection and dysconnectivity in MS that were not referenced in the printed version of the article

| Reference | Results | Method | Population |
|----------------------|--|---|----------------------------------|
| Golde et al., 2020 | The authors identified specific FC substrates underlying social cognition in MS, suggesting that these symptoms may occur independently from those of other neurocognitive domains | fMRI, DTI | 29 RRMS patients and 29 controls |
| He et al. 2009 | WM lesions were associated with aberrant neuronal connectivity, supporting the notion that MS is a disconnection syndrome | fMRI, DTI | 330 RRMS patients |
| Li et al., 2013 | Using DTI-based neuroconnectivity analysis, the authors showed a loss of communicability and alterations of fiber tract connections in patients. | DTI | 24 MS and 30 controls |
| Llufriu et al., 2017 | The authors showed structural connectivity changes in MS and identified strategic networks where connectivity is critical to preserve attention and executive performance in MS. These results highlight the relevance of brain networks integrity in preserving cognition. | DTI | 72 MS patients and 38 controls |
| Meijer et al., 2020 | Structural connectivity was estimated from DTI using probabilistic tractography (MRtrix 3.0) between pairs of brain regions. The structural network had a reduced efficiency and integrity in MS compared to controls. The long-range connections showed the largest reduction in FA. Damage to long-range connections was more strongly related to structural network efficiency and cognition. MS especially interrupts structural pathways connecting remote brain regions. | DTI | 133 MS patients and 48 controls |
| Pagani et al., 2020 | The authors evaluated whether modeling disconnection caused by lesions helps explain motor and cognitive impairment in MS., Correlations revealed nodes pertinent to motor and cognitive dysfunctions; these became slightly stronger after disconnection. Overall, modeling disconnection did not greatly change the picture of connectivity, suggesting that the brain is resilient to damage in MS lesions. | Conventional MRI (T1/T2-weighted and diffusion-weighted images) | 227 MS patients and 50 controls |

| | | | |
|-----------------------|---|-------------------|--------------------------------|
| Peterson et al., 2017 | The authors discuss the link between callosal structural damage and reduced interhemispheric inhibition: CC degeneration may represent a potential link between increased ipsilateral neural activity and poorer motor performance. | Literature Review | |
| Sjøgård et al., 2020 | Global network-level reductions in within- and cross-network rsFC were observed in the default-mode network. | MEG | 99 MS patients and 47 controls |

Note. FC = Functional Connectivity; fMRI = Functional Magnetic Resonance Imaging; MEG = magnetoencephalography; MRI = Magnetic Resonance Imaging; MS = Multiple Sclerosis; RRMS = Relapsing Remitting MS; rsFC = resting-state Functional Connectivity.

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ⁱ A complete description of the search methodology and limitations is presented in the supplementary appendix in the online version of this article.