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Functional Connectivity Alterations and Cognitive Impairment in Multiple Sclerosis

Multipl Sklerozda Fonksiyonel Bağlantısallık Değişimleri ve Bilişsel Bozukluk

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ABSTRACT

Multiple sclerosis (MS), one of the most common neurological causes of disability in young adults, is characterized by cognitive deficits in addition to balance-related symptoms, fatigue, and visual symptoms. Patients have difficulties in different cognitive domains such as memory, learning, executive functions, and attention, especially information processing speed. Current conventional imaging methods are insufficient to elucidate cognitive impairments. Structural alterations in the brain obtained by magnetic resonance imaging (MRI) do not have a high correlation in explaining all cognitive deficits. Therefore, connectivity-based approaches that address brain functions in a more holistic perspective come to the forefront in explaining cognitive functions. The relationship of cognitive deficits with large-scale functional networks through functional connectivity-based approaches via resting-state functional magnetic resonance imaging has begun to be investigated. Although functional connectivity (FC) studies are successful in explaining cognitive functions, the findings are not homogenous. The aim of this review is to analyse the contribution of functional connectivity-based approaches in understanding the clinical-imaging mismatch and to show that cognitive dysfunctions frequently seen in MS patients can only be partially explained by conventional structural imaging techniques. In this respect, this study is a narrative review based on a review of the literature published in the last fifteen years. While the importance of FC in explaining cognitive functions is mentioned, it is also emphasized that the findings of this study may be affected by individual factors such as cognitive reserve.

Keywords: Multiple sclerosis, cognitive impairment, functional connectivity, clinico-radiological paradox

ÖZ

Genç yetişkinlerde engelliliğin en yaygın nörolojik nedenlerinden biri olan multipl skleroz (MS), denge ile ilgili semptomlar, yorgunluk ve görsel semptomlara ek olarak bilişsel eksikliklerle karakterizedir. Hastalar başta bilgi işleme hızı olmak üzere hafıza, öğrenme, yürütücü işlevler ve dikkat gibi farklı bilişsel alanlarda zorluklar yaşamaktadır. Mevcut geleneksel görüntüleme yöntemleri bilişsel bozuklukları aydınlatmak için yetersizdir. Manyetik rezonans görüntüleme (MRG) ile elde edilen beyindeki yapısal değişiklikler, tüm bilişsel eksiklikleri açıklamada yüksek bir korelasyona sahip değildir. Bu nedenle, beyin işlevlerini daha bütüncül bir bakış açısıyla ele alan bağlantısallık temelli yaklaşımlar bilişsel işlevlerin açıklanmasında ön plana çıkmaktadır. Dinlenim durumu fonksiyonel manyetik rezonans görüntüleme aracılığıyla fonksiyonel bağlantısallık temelli yaklaşımlarla bilişsel eksikliklerin büyük ölçekli fonksiyonel ağlarla ilişkisi araştırılmaya başlanmıştır. Fonksiyonel bağlantısallık çalışmaları bilişsel işlevleri açıklamada başarılı olsa da bulgular homojen değildir. Bu derlemenin amacı, klinik-görüntüleme uyumsuzluğunu anlamada işlevsel bağlantı temelli yaklaşımların katkısını analiz etmek ve MS hastalarında sıklıkla görülen bilişsel işlev bozukluklarının geleneksel yapısal görüntüleme teknikleriyle yalnızca kısmen açıklanabildiğini göstermektir. Bu bakımdan, çalışma son on beş yılda yayınlanan literatürün gözden geçirilmesine dayalı bir naratif derlemedir. Bilişsel işlevlerin açıklanmasında fonksiyonel bağlantısallığın önemine değinilirken, bu çalışmanın bulgularının bilişsel rezerv gibi bireysel faktörlerden etkilenebileceği de vurgulanmaktadır.

Anahtar sözcükler: Multipl skleroz, bilişsel bozukluk, fonksiyonel bağlantısallık, klinik-radyolojik paradoks

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Introduction

Multiple sclerosis (MS) is a chronic, autoimmune disease affecting the central nervous system (CNS), resulting in the destruction of myelin sheaths and commonly impacting young adults aged 20 to 40 years (Naseri et al. 2021, Khan and Hashim 2025). The disease progresses with immune-mediated inflammation and axonal damage to the myelin sheath, resulting in delayed or blocked nerve conduction. According to 2021 reports, there are approximately 1.9 million people with MS worldwide; the incidence in women is approximately twice as high as that of men (women 32.3 vs. men 15.6/100,000) (Khan and Hashim 2025). Its prevalence is also high in Turkey: recent studies reported MS prevalence as approximately 96.4 per 100,000, with a female/male ratio of 2.1 (Öztürk et al., 2024).

The symptom spectrum of MS is very broad. The visual disturbances (e.g., blurred vision due to optic neuritis, double vision), motor system symptoms (muscle weakness, paresis), sensory loss (numbness, tingling), balance-coordination problems (ataxia, tremor), and brainstem findings (disturbance in visual pathways, swallowing or speech difficulties) are the common symptoms in MS (Khan and Hashim 2025). Bladder-bowel dysfunction, sexual dysfunction, and severe fatigue are also among the prevalent symptoms of MS. Psycho-emotional symptoms also play a significant role in the lives of patients; symptoms such as depression, anxiety, and chronic pain are other important findings that negatively affect quality of life (Gomez-Melero et al. 2024).

MS has three main clinical course subtypes: secondary progressive MS (SPMS), relapsing-remitting MS (RRMS), and primary progressive MS (PPMS). Most patients present with the relapsing-remittent form of the disease at its onset, characterized by relapses (attacks) and remission (Brochet et al. 2022). In the RRMS period, partial or complete neurological recovery is observed between relapses. The end of the relapsing-remitting phase, and some patients with RRMS may progress to SPMS form, which is a progressive phase over time (Scalfari et al. 2014). In SPMS, irregular attacks decrease; instead, gradually increasing disability develops. PPMS, on the other hand, shows a continuously worsening course from the onset.

MS has a wide range of symptoms and is a multifaceted disease involving both motor-sensory and cognitive-social dimensions (Gomez-Melero et al. 2024, Khan and Hashim 2025). Heterogeneity in the clinical subtypes of MS is not limited to motor and sensory symptoms and affects cognitive functions to varying degrees. Although deficits in cognitive abilities are not among the symptoms that patients complain about in the first place, impairment in cognitive abilities is reported in many individuals. It has been shown by studies that 40-70% of individuals with MS show various levels of cognitive impairment (Lechner-Scott et al. 2023). Moreover, the frequency of cognitive impairment is different in the subtypes: 30-45% of patients with RRMS and 50-75% of patients with SPMS (Benedict et al., 2020). Among cognitive functions, processing speed and episodic memory are reported to be the most frequently affected domains (Benedict et al. 2020). However, visual memory and higher cognitive functions such as executive functions, attention processes, and verbal fluency may also be impaired in many patients (Benedict et al. 2006a).

Interestingly, the intensity of cognitive symptoms observed in MS patients is frequently not well explained by conventional magnetic resonance imaging (MRI) measurements like lesion load or brain atrophy, a condition commonly known as the clinico-radiological paradox (Mollison et al. 2017). Some patients may exhibit severe cognitive impairment despite minimal lesion burden; others may remain cognitively preserved despite numerous lesions. This mismatch between lesions detected on imaging and symptoms demonstrates the inadequacy of conventional MRI findings. It has led researchers to connectivity-based approaches that address brain functions in a more holistic manner. Functional connectivity (FC) allows the measurement of the dynamic interaction of networks in the brain, thereby better understanding the effects of structural damage and compensatory mechanisms. Additionally, since cognitive functions are not dependent on a single brain region but occur through interactions between networks, FC reveals the complex interactions between these networks and enables us to understand cognition at a systemic level rather than examining individual regional lesions.

Furthermore, it is known that individual factors such as cognitive reserve influence the architecture of FC (Marques et al. 2016). It is the capacity to maintain cognitive functions despite brain damage (Stern, 2009). It has been demonstrated that individuals with high cognitive reserve can maintain their cognitive performance by more effectively utilising FC in brain networks (Franzmeier et al. 2017). Hence, when considering FC studies, it is important to take individual factors into account.

The aim of this narrative review is to demonstrate that cognitive dysfunctions frequently observed in MS patients are a phenomenon that can be explained in a limited way by conventional structural imaging methods and to evaluate the contributions of FC-based approaches in understanding this clinical-imaging mismatch. In this context, changes in FC patterns in major brain networks associated with cognitive processes (e.g., default mode network (DMN), frontoparietal network (FPN)) are systematically discussed through findings from resting-state functional magnetic resonance imaging (rs-fMRI) studies. The review aims to synthesise the current findings in this field with a holistic view and to guide future research on neuroimaging-based assessment of cognitive impairments. The literature search was conducted using the PubMed, Scopus, and ScienceDirect databases. The search strategy was developed using the keywords "multiple sclerosis", "cognitive impairment", "functional connectivity", "resting-state fMRI", "brain networks", and "cognitive reserve" either individually or in combination. The search was restricted to publications between 2010 and 2015. The studies include those written in English and published in national/international peer-reviewed journals.

Cognitive Impairments in MS

Deficits in cognitive abilities in individuals with MS may be present in the early stages of the disease, before any neurological deficits are detected (Benedict et al. 2017). Cognitive impairments in MS are highly variable and vary from individual to individual (Benedict et al. 2020). However, studies generally show that information processing speed and memory (especially recall of newly learned information) are the cognitive domains most frequently affected.

Cognitive impairments in MS significantly impair occupational functioning, social life, and overall quality of life (Macías Islas and Ciampi 2019, Gomez-Melero et al. 2024). For example, Macías Islas and Ciampi (2019) conducted a study with a large European cohort, and it has been shown that only 35.8% of individuals with MS are able to remain in employment; the rest have to leave the labor market. They also reported that low mood and cognitive deficits (especially memory, attention, and slowed processing speed) are the most frequent causes of work-related difficulties in patients with MS. Patients who do not work or experience poor performance may be expected to have reduced economic independence, and their social participation and life satisfaction may be negatively affected.

The studies on quality of life reveal that cognitive dysfunction is an important determinant (Gomez-Melero et al. 2024). Although the physical symptoms of MS (motor limitation, visual impairment, etc.) reduce quality of life, additional factors such as cognitive decline, depression, pain, and fatigue worsen overall function and psychosocial status. In brief, cognitive dysfunction in MS leads not only to irregularity in neuropsychological test scores, but also to a significant loss of daily functioning and social participation.

Learning and Memory

In learning and memory, people with MS often have difficulty in grasping and encoding new information, whereas long-term retention of learned information is usually relatively well preserved (Benedict et al. 2020). As is well known, there are many subtypes of memory, and in MS, deficits occur especially in the learning/repeating of new verbal and visual information. Studies focusing specifically on these abilities report that patients with MS have reduced verbal memory performance, such as learning word lists, and reduced visual memory performance, such as learning shapes/numbers (Benedict et al. 2020). However, deficits in verbal memory are reported to be more frequent and profound (Rogers and Panegyres 2007).

Attention and Information Processing

Attentional processes are frequently impaired in MS. The studies have reported that 12-25% of patients have significant difficulties with attention (Benedict et al. 2020). Attention is divided into subcomponents such as sustained, selective, and divided, and there are different studies showing that all subcomponents are affected (Oreja-Guevara et al. 2019). Impairments are particularly prominent in complex tasks requiring selective attention and divided attention; simple focusing ability is largely preserved in most patients (Benedict et al. 2020). In addition, the decline in attention tests often coincides with a decline in overall information processing speed, which may mean that in a patient whose cognitive processing speed is very slow, attention tests may also be expected to be adversely affected. However, cognitive processing speed is one of the most affected functions in MS and has been shown to be the main marker of cognitive impairment in MS (Van Schependom et al. 2015). According to Migliore et al. (2018), 40–70% of MS patients do, in fact, have slower information processing. Therefore, a common approach to cognitive screening in MS is to focus primarily on speed tests.

Executive Functions

Executive functions (high-level skills such as planning, problem solving, multitasking, cognitive flexibility, and inhibition control) may also be impaired in MS. The most common impairments in this cognitive domain are found in working memory, mental flexibility, planning, categorization, and behavioral reasoning (Beatty and Monson 1994, Rao 1995). Problems in this domain are usually associated with progressive stages of the disease. Although less frequent than other cognitive functions, deficits in executive functions are reported in 15-28% of patients (Benedict et al. 2020).

Deficits in executive functions are observed in different MS subtypes. Planning and reasoning are better preserved in RRMS patients compared to cognitive flexibility, inhibition, and abstraction ability (Cerezo et al. 2015). Executive dysfunction is reported to be significantly higher in patients with PPMS than in patients with RRMS (Ruet et al. 2013).

Structural Connectivity Alterations and Cognition in MS

MRI is an important imaging technique that is formally part of the diagnostic criteria for MS patients and is used to determine the level of brain damage (Polman et al. 2011). In clinical practice, conventional MRI techniques are commonly used to assess and exclude other neurological conditions in a variety of diseases, not just MS (Messina and Patti 2014).

Postmortem studies on the brains of individuals with MS have shown that demyelination can occur in all regions of the CNS, white matter (WM) and grey matter (GM) (Staugaitis et al. 2012). GM atrophy is a marker of disease-related degeneration and manifests itself during the early stages of the disease course (Pirko et al. 2007). MRI is used to measure GM volume. The assessment of GM atrophy and the distribution of atrophy are associated with cognitive impairments. For example, Amato et al. (2007) reported that in RRMS patients, cortical atrophy was associated with cognitive abilities such as impaired verbal memory, verbal fluency, and attention, and that after a 2.5-year follow-up, the alteration in cortical volumes was deeper in patients with cognitive impairment. Another study found a relationship between cortex volume and verbal and visual memory and information processing speed, and suggested that third ventricle width, which reflects thalamic atrophy, may be a marker of cognitive impairment (Benedict et al. 2006b).

The microstructural integrity of WM tracts can be examined by diffusion tensor imaging (DTI). The diffusion of water molecules in the brain is measured by using this technique (Le Bihan 2003). WM integrity is revealed by multiple measurements with DTI, including the most used ones, mean diffusivity (MD) and fractional anisotropy (FA). In clinical practice, the variability of FA in various neurological conditions, including MS, is useful as an indicator of white matter pathology (Sbardella et al. 2013).

For some WM tracts, including the corpus callosum, cingulum, and posterior thalamic tract, a reduction in FA and an increase in MD have been observed previously; these abnormalities are associated with

impairments in various neuropsychological tests (Dineen et al. 2009, Yu et al. 2012). For example, Hulst et al. (2013) evaluated FA values in their study comparing MS patients with and without cognitive impairment. They observed that several brain regions with decreased FA in both MS groups, including the superior and inferior longitudinal fasciculus, the corpus callosum, forceps major, corticospinal tracts, fornix, and cingulum, were significantly worse in MS patients with cognitive impairment. Impaired WM integrity was also reported in the brainstem, cerebellum, thalamus, uncinate fasciculus, and cortical brain regions.

Although changes in WM and GM explain cognitive abilities up to a certain point, it has been emphasized by many studies that a multimodal imaging strategy is required to accurately explain cognitive impairment in MS, to monitor its course, and to evaluate the results of therapeutic treatments, rather than relying solely on a single MR modality (Preziosa et al. 2016). For this reason, the importance of FC in predicting cognitive impairment at the clinical threshold level and the importance of structural connectivity and FC coupling have been highlighted in recent studies (Koubiyr et al. 2021).

Functional Connectivity Alterations and Cognition in MS

Clinically, conventional MRI lesion load is indispensable in the diagnosis and monitoring of MS; however, it may be insufficient to completely explain cognitive symptoms and functional impairments (Mahmoudi et al. 2025). FC studies are one of the best methods to fill this gap, and alterations in FC may provide information about the cognitive and neurological course of the disease (Tona et al. 2014). For instance, fMRI has been the only imaging modality documented to reveal compensatory or pathological reorganizations beyond visual and motor pathways in MS (Mahmoudi et al. 2025). Therefore, resting-state functional magnetic resonance imaging (rs-fMRI) studies are of great importance in MS research and can shed light on both the understanding of disease mechanisms and future clinical applications.

rs- FC is the coherence of synchronised activity between functionally related brain regions (Mahmoudi et al. 2025). It arises in the absence of any task or stimulus and originates from spontaneous fluctuations in low-frequency signals (Biswal and Kannurpatti 2009). In other words, anatomically separate areas that show temporally correlated fluctuations are within a common functional network (such as visual, auditory, or DMN). It may allow us to understand brain function at the network level, beyond the activities of individual regions, and to study disturbances in this intrinsic brain organisation in MS.

The studies indicate that there is a relationship between impairments in cognitive function and large-scale networks like the DMN and FPN (Meijer et al. 2017, Wojtowicz et al. 2014, Hawellek et al. 2011). It has been argued that impairment in FC plays a role in differentiating MS patients with cognitive impairment from patients without cognitive impairment and from individuals who are completely healthy (Mahmoudi et al. 2025). Furthermore, FC alterations have shown promise in differentiating between other MS subtypes. For instance, a study found that patients with RRMS with preserved cognitive abilities exhibited increased FC in bilateral FPN compared to both healthy individuals and those with cognitive impairment (Louapre et al. 2014). Therefore, an increasing number of FC studies are elucidating aspects that are difficult to explain with conventional imaging techniques, such as cognitive abilities.

Functional Connectivity, Cognitive Impairments and Psychosocial Effects in MS

In MS, besides cognitive impairment, psychiatric symptoms such as depression, anxiety, and fatigue, as well as the psychosocial effects caused by these symptoms (e.g., decline in quality of life, impairment in social functioning), are also common (Liu et al. 2009). FC studies conducted in recent years suggest that these clinical findings may be associated with changes in specific brain networks. It has been demonstrated that alterations observed in networks closely associated with cognitive processes, such as the DMN and FPN, are linked to levels of depression and fatigue (Bonavita et al. 2017, Høgestøl et al. 2019, Jaeger et al. 2019). For example, Høgestøl et al. (2019) reported significant correlations between connectivity alterations in the DMN and depression and fatigue scores in their study with RRMS patients. These findings suggest that cognitive and psychosocial disorders may arise through common neural mechanisms.

Cognitive Domains and Alterations in Functional Connectivity Networks

Since cognitive impairments are frequently observed in MS patients, FC provides important evidence in explaining cognitive dysfunctions such as processing speed, attention, and memory. Rs-fMRI studies have revealed many abnormal network dynamics linked to cognitive performance. The canonical resting state FC networks and related cognitive functions are illustrated in Figure 1.

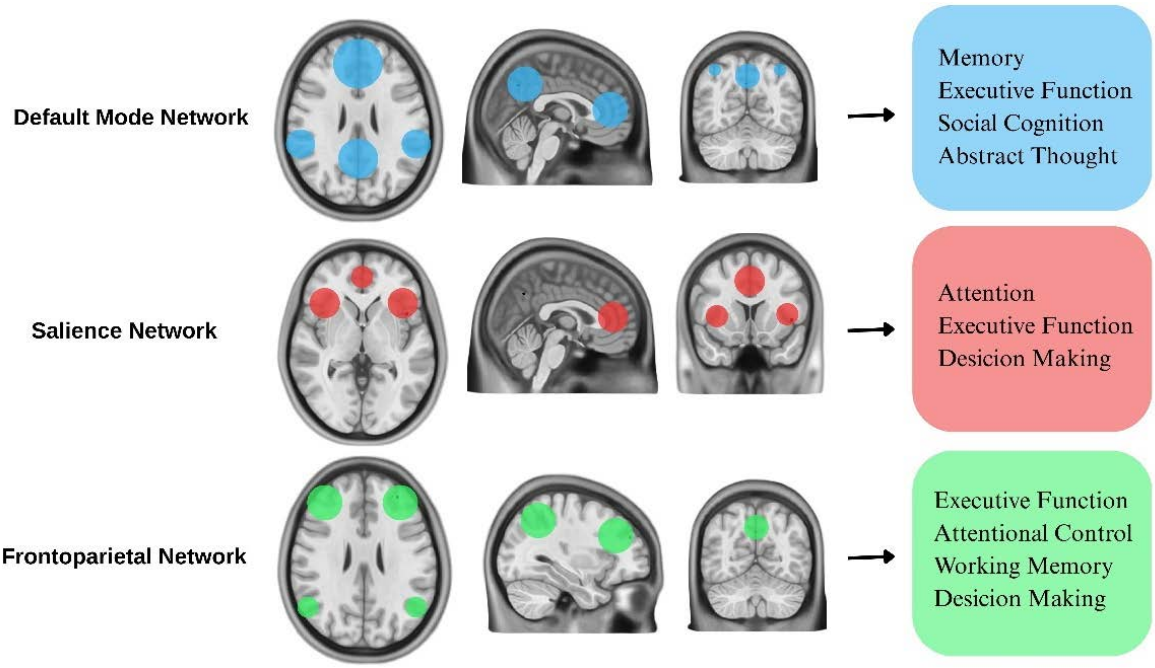

Figure 1. Canonical resting state functional connectivity networks and related cognitive domains.
Brain slices were obtained from the Montreal Neurological Institute/International Brain Mapping Consortium (MNI/ICBM) 152 standard template, and network regions were manually illustrated (Mazziotta et al. 2001).

Attention is one of the cognitive functions that are frequently affected in individuals with MS and has been frequently included in FC studies. In MS patients, impairments in attention in rs-fMRI studies are often associated with FC alterations in networks such as the FPN and DMN and the dorsal attention network in task-based fMRI studies. Meijer et al. (2017) aimed to link cognitive deficits in MS patients with findings of intra-network connectivity, connectivity with the rest of the brain, and inter-network connectivity in large-scale networks. Only MS patients with cognitive deficits showed increased FC of both DMN and FPN with the rest of the brain. Elevated FC with the rest of the brain was linked to poorer cognitive performance, that is, attention for FPN and both information processing speed and working memory performances for DMN.

Another study provides a cognitive rehabilitation program that improves attention, information processing, and executive functioning skills in RRMS patients for 12 weeks and aimed to show network-based changes (Parisi et al. 2014). The researchers found that the anterior cingulate cortex (ACC), part of the salience network (SN), the left dorsolateral prefrontal cortex, part of the executive control network (ECN), the right posterior cingulate cortex (PCC), and the right inferior parietal lobule, part of the DMN, increased or remained stable in rs-FC in the rehabilitated RRMS group.

Moreover, many studies on the relationship between FPN and DMN and information processing speed are reported. Indeed, in a population of different MS subtypes with cognitive impairment, it has been shown that these two networks increase their FC with the rest of the brain and that this is associated with worse information processing speed (Meijer et al. 2017). This study also focused on FC differences in different MS subtypes and found that only in RRMS patients did increased FC in the DMN correlate with poorer information processing speed. Therefore, FPN and DMN may be important for attention and information processing speed.

Table 1. The studies that have associated cognitive dysfunction with resting state FC networks

Study	Functional Network	MS Subtype	Cognitive Domain	Main Findings
Leavitt et al. (2014)	DMN	RRMS (33), PPMS (4), SPMS (6)	Memory	Memory-intact patients showed ↑ DMN FC
Sumowski et al. (2013)	DMN	RRMS (28), SPMS (6)	Memory	↑ DMN activity linked to better memory
Van Geest et al. (2018)	DMN	RRMS (33), Control (19)	IPS	The dynamic FC difference of the DMN predicts IPS scores of MS patients
Manca et al. (2018)	DMN, SN, FPN	RRMS (40), SPMS (25)	IPS	IPS performance was found to be low in those with high SN and DMN FC, and high in those with high left FPN FC.
Marchesi et al. (2022)	DMN, WMN, SN, ECN	MS (139), Control (72)	Executive Function	MS patients showed ↓ left WMN, right WMN RS FC for worse performance; ↓ ECN, ↑ DMN, and SN rs- FC for better performance
Louapre et al. (2014)	DMN, FPN, DAN	RRMS (15 cognitively impaired, 20 cognitively preserved)	General cognition	Cognitively impaired MS patients showed ↓ integration in DMN and attention related networks (left/ right FPN, DAN)
Cruz-Gómez et al. (2014)	DMN, FPN, SN	RRMS (30 cognitively impaired,30 cognitively preserved), control (18)	General cognition	Cognitively impaired MS patients showed ↓ FC in DMN, FPN and SN
Rocca et al. (2018)	DMN, DAN, SMN, Visual/ Sensory Network, Cerebellum Network, Thalamic Network, Amygdala Network	CIS (13), RRMS (119), SPMS (41), Bening MS (29), PPMS (13), control (13)	General cognition	At global level, cognitively impaired MS patients showed ↓ rs-FC in DMN and DAN. At regional level, there was a ↓ in rs- FC in parietal, frontal, and cerebellar regions of cognitive, sensory, and motor networks.
Meijer et al. (2017)	DMN, FPN	RRMS (243), SPMS (53), PPMS (36), control (96)	General cognition	Cognitively impaired MS patients showed ↑ connectivity both the DMN and FPN. ↑ connectivity correlated with worse cognitive performance, namely attention for the FPN as well as IPS and WM for both networks.

DMN; default mode network, RRMS; relapsing remitting multipl sclerosis, PPMS; primary progressive multiple sclerosis, SPMS; secondary progressive multiple sclerosis, ↑; increase, FC; functional connectivity, IPS; information processing speed, SN; salience network, FPN; frontoparietal network, ECN; executive control network, ↓; decrease, WMN; working memory network, rs; resting state, DAN; dorsal attention network, CIS; clinically isolated form, WM; working memory

In addition to attention and information processing speed, memory is one of the cognitive skills affected in MS and has also been addressed in rs-FC studies. A study investigated how memory impairment in MS causes alterations in DMN (Leavitt et al. 2014). An increase in DMN FC was observed in MS patients with intact memory function, while no similar increase was observed in patients with memory impairment. Therefore, DMN FC correlated with memory performance, meaning that higher DMN FC indicates better memory performance. There have also been studies addressing the effect of computerised cognitive

training, which focuses on memory skills, on FC. In one of these studies, a 4-week memory-based training was applied to juvenile MS patients (Hubacher et al. 2015). In the group of patients with juvenile MS, a smaller change in FC between subcomponents of the DMN was found after memory-based training.

Dysfunction in executive functions also influences FC networks. As is well known, executive functions consist of many components, such as set shifting, working memory, and attention. Marchesi et al. (2022) associated the performance of these different components of executive functions with related FC networks. In a study conducted with individuals with MS who had different levels of executive function, poorer performance in working memory was associated with decreased working memory network (WMN) FC, whereas higher performance was linked to lower ECN, higher DMN, and SN FC. Low performance on attention was associated with lower left WMN and DMN rs-FC, while better performance was correlated with higher left WMN and ECN rs-FC. Finally, worse performance in set shifting was associated with lower left WMN rs-FC, and better performance was associated with higher ECN rs-FC. The studies having associated cognitive impairments in MS with resting-state FC networks are summarized in Table 1.

MS Findings on Cognitive Reserve and Plasticity in Functional Connectivity

While certain relationships between cognitive dysfunctions and patterns of FC have been identified in MS, it is noteworthy that these relationships do not occur similarly in all patients. Some of the most important reasons for heterogeneity in studies related to cognitive dysfunction and FC in MS are age, gender, duration and type of disease, and cognitive reserve. Therefore, the discrepancy between neuropsychological performance levels and imaging findings may be explained not only by the extent of structural or functional impairments but also by individual differences. The most important of these differences is cognitive reserve, a concept that refers to the individual's cognitive capacity before the disease and the ability of brain networks to reorganize. It is known to have a protective role in MS-related cognitive impairment (Artemiadis et al 2020).

Some MS patients have intact cognitive function even with structural brain pathology in GM and WM (Sumowski and Leavitt 2013). When explaining this intact functioning, it is important to emphasize the concept of cognitive reserve. It refers to the capacity of individuals to maintain cognitive function despite brain damage caused by aging or neurological diseases (Stern 2009). Lifelong experiences such as educational level, occupational complexity, and history of mental stimulation are known to play an important role in the development of the reserve (Stern 2009), but the underlying physiological substrates have not been fully elucidated.

Cognitive reserve in the context of MS has become an important concept in linking cognitive deficits in MS to FC. Although rs-FC correlates with cognitive function and reflects coordinated activation patterns between functionally connected regions (Schoonheim et al. 2015), a significant portion of FC cannot currently be explained by existing structural alterations (Fuchs et al. 2019). Therefore, more information is needed on the influence of cognitive reserve on the process when explaining the interplay between structural network disruption and preservation of FC in the case of cognitive impairments in MS. For example, Fuchs et al. (2019) focused on the concept of cognitive reserve when describing the status of patients with MS who have a normal pattern of FC despite atrophy and destroyed grey matter. They found deficits in information processing speed and memory in individuals and associated them with structural differences; however, they did not observe an alteration in FC, which they explained with cognitive reserve.

Indeed, some recent studies have even tried to explain the FC between cognitive reserve and certain brain regions. Bizzo et al. (2021) focused on the dorsal anterior insula, which is involved in cognitive control and is an important hub for some networks, and aimed to relate its connectivity with the whole brain to cognitive reserve. In the study, RRMS patients were compared with controls, and participants' IQ, level of education, leisure activities, and occupational attainment were considered to assess cognitive reserve. As a result of the study, they found a relationship between FC in the insula and occipital regions and associated it with cognitive reserve.

As studies have shown, cognitive reserve appears to be an important individual factor in explaining both preserved cognitive functions despite structural alteration and preserved FC in some patient groups. Therefore, it is crucial to consider individual factors when addressing all these structural and FC changes and to explain some of the conflicting findings in FC.

Discussion

MS is primarily characterized by demyelinating lesions in the CNS; however, it also leads to widespread grey and white matter atrophy over time. These structural changes are known to be associated to some extent with the clinical course of the disease (Benedict et al. 2020). As a result of this atrophy, apart from the basic symptoms related to vision, motor skills, and balance, a spectrum of symptoms ranging from bladder dysfunction, sexual dysfunction, fatigue, depression, and deficits in cognitive abilities occurs.

It is estimated that 45-70% of MS patients experience impairment of cognitive functions (Meca-Lallana et al. 2021). When it is considered that deficits in cognitive abilities complicate the daily life of individuals, decrease their quality of life, and increase dependency on their caregivers, it is very important for both patients and their caregivers (Figved et al. 2007, Yazgan et al. 2021). For this reason, studies on the effects of cognitive impairment on patients with MS have continued to increase. However, the failure to find the expected linear relationship between the degree of structural damage and the level of cognitive impairment in many studies has raised an important problem defined as the clinical-radiological paradox (Barkhof 2002). . This contradiction has pointed to the necessity of more holistic and dynamic approaches to explain cognitive symptoms and has led researchers to methods that examine brain organisation at the system level, such as FC. This review comprehensively addresses cognitive dysfunction in MS, explaining it through FC findings, as well as through the clinical-radiological paradox and cognitive reserve framework. While the existing literature generally focuses on individual networks or a single methodology, this study discusses methodological, individual, and analytical differences in a comparative manner to explain the heterogeneity in FC findings.

FC studies have revealed that cognitive impairments in MS patients are associated not only with structural damage but also with altered dynamic functional interactions between brain regions. In MS patients, alterations in FC have been reported in different large-scale networks, especially in networks involved in high-level cognitive processing such as DMN and FPN (Rocca et al. 2010, Hawellek et al., 2011). Thus, FC changes in MS play a role in cognitive performance, enabling a deeper understanding of cognitive symptoms that cannot be explained by structural measures.

Although FC studies have revealed strong associations between various networks and cognitive performance, the direction and functional outcome of these connectivity changes are not always homogenous. This suggests that FC should be considered in a broader framework, including its interaction with cognitive reserve and brain plasticity. Moreover, the poor correlation between cognitive performance and structural damage suggests that not only anatomical impairments but also individual differences affect cognitive outcomes in MS. At this point, the concept of cognitive reserve provides an explanatory framework.

Cognitive reserve refers to an individual's capacity to maintain a functional status despite brain pathology and is associated with factors such as lifelong acquired intellectual enrichment (educational level, occupational complexity, mentally stimulating activities) (Stern 2009). Indeed, some study findings suggest that cognitive reserve preserves the FC of the brain network by compensating for the effect of the disruption of white matter tracts due to lesions in MS (Marques et al. 2016). Therefore, while FC offers a useful window to explain cognitive deficits in MS, it is also important to consider the existence of individual factors such as cognitive reserve and to address FC studies from this perspective. Consequently, factors such as individuals' life experiences and educational background may be factors that need to be controlled in this regard.

The heterogeneity of findings in FC studies in MS is not only due to clinical and individual differences, but also to the analysis approaches used. For example, independent component analysis is a data-driven

method that identifies functional components at the network level and reveals the holistic interactions of these components. In contrast, graph-based analyses approach the brain as a mathematical network model through nodes and edges, providing topological measures such as global efficiency, modularity, or hubness. These various perspectives on the methods explain the diversity of the results obtained and the difficulties in comparing them. Therefore, the methodological approach used has a significant impact on the findings and explains the heterogeneity in the literature from another perspective. In addition, the cross-sectional nature of FC studies, the variety of neuropsychological assessment tests used in the studies, and the fact that the studies generally include specific subtypes such as RRMS more frequently affect the generalizability and consistency of the findings.

Conclusion

Cognitive deficits, which are very common in MS, are one of the important symptoms affecting both the patient and the caregiver. Investigation of brain mechanisms is crucial to understand the cause of cognitive deficits, their neural substrates, and to detect deficits in the early stages. At this point, apart from conventional MRI, rs-fMRI, which allows us to examine FC, also provides critical information. Therefore, examining both structural and functional changes together seems to be more useful to relate MS symptoms to the brain. However, especially considering that FC is affected by individual factors such as experiences and years of education, it should be evaluated cautiously. Future studies evaluating structural and FC in MS should create homogeneous groups to minimize individual variation or covariates for possible life experiences that may affect cognitive reserve.

Although FC alone provides important information, it should be noted that it may be insufficient to explain the complex nature of cognitive impairments. When structural (cortical volume, white matter integrity using DTI), functional (resting-state and task-based connectivity), and metabolic methods (e.g., FDG-PET) are used together, a more comprehensive picture of both damage and compensatory processes can be obtained. Such multimodal approaches are considered critical, particularly for early diagnosis and determining the role of cognitive reserve at different stages of the disease.

Additionally, the development of cognitive impairments in MS is a dynamic process. Cross-sectional studies are valuable, but they are limited in tracking changes in FC over time in individuals. Longitudinal fMRI studies make it possible to observe changes in FC at different stages of the disease in the same individuals. This allows for clearer conclusions to be drawn about whether early FC changes can predict future cognitive decline or about the long-term protective effects of cognitive reserve. Also, these types of longitudinal data, particularly when integrated with advanced analytical methods (e.g., machine learning), can become more powerful in terms of personalized predictions.

In recent years, machine learning and artificial intelligence-based models have been increasingly used to predict clinical outcomes from neuroimaging data. Incorporating seed-based or network-level FC data into the model, along with structural and clinical indicators, may provide a powerful tool for personalized prognosis. Such approaches can enable early intervention by identifying which patients are at higher risk for cognitive impairment.

Consequently, the integration of multimodal methods, the widespread use of longitudinal designs, and the application of advanced analytical approaches will enable more accurate assessment of cognitive impairments in MS and contribute significantly to clinical practice. In this context, future studies may yield robust findings that will directly impact clinical management and patient care.

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