Task- and resting-state fMRI studies in multiple sclerosis: From regions to systems and time-varying analysis. Current status and future perspective

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ABSTRACT

Multiple sclerosis (MS) is a neurological disorder affecting the central nervous system and features extensive functional brain changes that are poorly understood but relate strongly to clinical impairments. Functional magnetic resonance imaging (fMRI) is a non-invasive, powerful technique able to map activity of brain regions and to assess how such regions interact for an efficient brain network. FMRI has been widely applied to study functional brain changes in MS, allowing to investigate functional plasticity consequent to disease-related structural injury. The first studies in MS using active fMRI tasks mainly aimed to study such plastic changes by identifying abnormal activity in salient brain regions (or systems) involved by the task. In later studies the focus shifted towards resting state (RS) functional connectivity (FC) studies, which aimed to map large-scale functional networks of the brain and to establish how MS pathology impairs functional integration, eventually leading to the hypothesized network collapse as patients clinically progress. This review provides a summary of the main findings from studies using task-based and RS fMRI and illustrates how functional brain alterations relate to clinical disability and cognitive deficits in this condition. We also give an overview of longitudinal studies that used task-based and RS fMRI to monitor disease evolution and effects of motor and cognitive rehabilitation. In addition, we discuss the results of studies using newer technologies involving time-varying FC to investigate abnormal dynamism and flexibility of network configurations in MS. Finally, we show some preliminary results from two recent topics (i.e., multimodal MRI analysis and artificial intelligence) that are receiving increasing attention. Together, these functional studies could provide new (conceptual) insights into disease stage-specific mechanisms underlying progression in MS, with recommendations for future research.

1. Introduction

Multiple sclerosis (MS) is a neuroinflammatory and neurodegenerative disease of the central nervous system (CNS), commonly featuring severe cognitive and motor impairments. In the past decades, magnetic resonance imaging (MRI) has been largely applied to improve the understanding of the pathophysiology of MS. Structural MRI techniques provided accurate maps of macro- and microscopic tissue damage of the CNS occurring in this condition. (Enzinger et al., 2015; Filippi et al., 2017) However, associations between structural MRI injury and clinical findings remain still suboptimal. (Filippi et al., 2019) This might be due to the presence of a variable extent of functional brain plasticity across disease phases: at early MS stages, adaptive mechanisms might play a role in maintaining an efficient brain function despite an increasing structural damage, while later on in the disease, maladaptive mechanisms may be prevalent and lead to worsening of developing clinical symptoms. (Schoonheim et al., 2010; Rocca et al., 2016).

Functional MRI (fMRI) is a non-invasive technique allowing to

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explore CNS function by exploiting the blood-oxygenation level dependent (BOLD) effect. (Ogawa et al., 1990) Such an effect permits to map the vascular response to neuronal activation by using differences of MRI signal due to changes of deoxyhemoglobin concentration, cerebral blood flow, and volume. FMRI can be applied to highlight cerebral activity evoked by the performance of a given task (Friston et al., 1995; Ogawa et al., 1993) or, alternatively, to investigate spontaneous signal fluctuations occurring at low frequency during resting state (RS) conditions. (Biswal et al., 1995; Biswal et al., 2010) Task-related fMRI experiments have been principally used to map activation of specific brain regions and circuits during the performance of various tasks. (Ogawa et al., 1993; Kim et al., 1993; Cordes et al., 2000) RS fMRI studies usually aim at reconstructing functional connectivity (FC) networks, i.e., patterns of spatially distinct brain regions subserving different functions. (Biswal et al., 2010; Fox et al., 2005) RS fMRI has the advantage of avoiding confounds due to subjects' inability to comply with the task, and can therefore be applied to people with MS and severe disability. Thanks to this versatility, fMRI is a powerful tool to investigate plasticity mechanisms in the brain, and is therefore suitable to map *in vivo* functional reorganization occurring in MS, which could drastically improve our understanding of clinical impairments.

This narrative review aims at summarizing the main findings from studies that used fMRI to investigate brain plasticity across different MS disease stages. We searched PubMed with the terms "functional MRI", "fMRI", "resting state fMRI", "functional networks", "multiple sclerosis". Only articles published in English were considered. This search produced approximately 1500 results, from which clinical trials, review articles, technical reports and *meta*-analyses were excluded. From remaining results (approximately 600), the final reference list was generated on the basis of originality and relevance to the broad scope of this review. Our review is structured as follows: in section 2, we discuss findings from studies applying task-based fMRI in people with MS to map abnormalities of brain activity in strategic regions and circuits subserving sensory, motor and cognitive functions. In section 3, we present results of studies applying RS fMRI to explore the brain as an integrated system composed by interacting FC networks, and we give an overview of how the hypothesized large-scale network collapse might provide key insights into MS pathophysiology to explain the heterogeneous clinical manifestations driven by structural damage. In section 4, a summary of findings from longitudinal task-based and RS fMRI studies monitoring the effect of different interventions is given. In section 5, we introduce a novel way of analyzing functional connectivity, time-varying FC analysis, which helps to derive information about FC changes occurring at very fast time scales, and we will discuss how time-varying FC abnormalities characterize clinical and cognitive deficits of MS. Finally, in section 6, we present some new perspectives of fMRI analysis, including multimodal data integration and the use of machine learning to improve disease monitoring and prediction at an individual level.

2. Using fMRI to explore MS-related functional reorganization within salient regions and functional systems

Task-based fMRI experiments, using both sensorimotor and cognitive stimulations, have been widely applied in the last two decades to characterize cortical plasticity across the different phases of MS. Overall, widespread fMRI activation changes have been described across disease course, having both an adaptive and maladaptive role.

2.1. Exploring MS-related functional reorganization of the sensorimotor system

It is more than two decades that active fMRI has been successfully used to map brain plasticity in MS using sensory or motor tasks, both after an acute clinical attack (Rombouts et al., 1998; Mezzapesa et al., 2008; Werring et al., 2000) and in clinically stable people. (Rocca et al.,

2005; Rocca et al., 2002a; Rocca et al., 2003a; Rocca et al., 2002b) A list of relevant studies evaluating functional reorganization of the sensory and motor systems using task-based fMRI is provided in Table 1.

Studies using motor tasks mostly employed upper limb tasks, and results are generally concordant in showing significantly higher fMRI activity in all MS phenotypes compared to healthy controls (HC), (Rocca et al., 2005) especially - but not exclusively - in regions subserving the motor function and at early disease stages (Fig. 1). An increased activation of the primary sensorimotor cortex is a typical feature of people with clinically isolated syndrome (CIS) (Rico et al., 2011; Rocca et al., 2003b) and of people with non-disabling (Rocca et al., 2002a) or mildly disabling relapsing-remitting (RR) MS. (Reddy et al., 2002; Rocca et al., 2010; Rocca et al., 2004) However, during simple tasks, people with RRMS tend to activate not only classical motor regions, but also frontal and parietal areas devoted to motor control, (Reddy et al., 2002; Colorado et al., 2012; Lenzi et al., 2007) which are generally engaged in HC during more complex tasks, such as object manipulation (Filippi et al., 2004) or action observation (Rocca et al., 2008) (Fig. 1). In people with RRMS, an increased fMRI activity has been considered to play a compensatory role, since it was related to maintaining a good task performance despite the presence of widespread structural damage. (Rocca et al., 2002a; Rocca et al., 2004; Lenzi et al., 2007) During motor tasks, progressive MS phenotypes often present increased fMRI activations of high-order, integrative areas. (Rocca et al., 2003; Rocca et al., 2002a; Ciccarelli et al., 2006) This recruitment of additional areas may for instance indicate exhaustion of functional competence of classical motor circuits, possibly leading to a need to also bring in higher-order areas to maintain some measure of clinical functioning, or simply maladaptive changes due to a loss of inhibition (Fig. 1). However, decreased fMRI activity has also been detected in progressive MS, especially in case of high disability and poor task performance, which could indicate maladaptation, possibly due to structural disconnection of areas or regional metabolic exhaustion and/or neurodegeneration. (Ciccarelli et al., 2006).

Aforementioned patterns have since been extensively replicated in additional work. Abnormally high and widespread activation -more evident with increasing age- was confirmed by multicenter motor fMRI studies. (Rocca et al., 2009; Wegner et al., 2008) Also, a decreased deactivation of the motor circuit (Manson et al., 2008; Petsas et al., 2013) and increased deactivation of the default-mode network system was found during motor tasks. (Petsas et al., 2013) Overall, patterns of increased fMRI activations, both in primary motor and associative regions, were obtained by studies investigating motor functions using different tasks, such as motor imagery, (Tacchino et al., 2017) hand writing, (Bonzano et al., 2021; Saini et al., 2004) grip force (Alahmadi et al., 2021; Strik et al., 2021) and joystick tasks. (Boonstra et al., 2020) A few studies also detected selective associations between increased motor fMRI activity and higher upper limb (Reddy et al., 2002; Wegner et al., 2008) or lower limb (Ciccarelli et al., 2006) clinical impairment.

Studies of the visual system were less consistent than those employing sensorimotor tasks, showing mixed findings of decreased (Rombouts et al., 1998) or increased (Werring et al., 2000; Colorado et al., 2012; West et al., 2021) activity in occipital cortices, probably depending from disease stage and from closeness to clinical attacks.

FMRI activity is also influenced by the presence of fatigue, which has been consistently related to the presence of abnormal recruitment of a fronto-striatal circuit (Bonzano et al., 2017; Pardini et al., 2013) and impaired modulation of fMRI activity over time. (Rocca et al., 2016; Svolgaard et al., 2018).

More advanced methods have also been used to further elaborate underlying cellular mechanisms. Recent studies using calibrated fMRI (West et al., 2021; Hubbard et al., 2017) showed that abnormal task-related fMRI activation is due to both altered cerebral blood flow and oxygen consumption. This was seen during visual (Hubbard et al., 2017) and finger tapping (West et al., 2021) tasks, where increased blood flow/ oxygen consumption were detected in the central region of task

Table 1

Summary of the most important functional magnetic resonance imaging studies using sensory and motor active tasks to investigate brain activation in people with multiple sclerosis (MS).

Study	Subjects	Task	Main findings
Active sensorimotor tasks			
Rocca et al. 2002	14 people with RRMS 15 HC	Flexion-extension of the last four fingers of the right, dominant hand	People with MS showed increased fMRI activation in several contralateral and bilateral regions of the sensorimotor network, correlated with structural damage
Reddy et al., 2002	14 people with RRMS 8 HC	Task 1: flexion–extension of the last four fingers Task 2: flexion–extension of the third finger (actively or passively)	Increased fMRI activity was present in RRMS people in ipsilateral premotor, motor and parietal cortex with increasing EDSS score and with increasing hand motor impairment (assessed using FT). Brain activity patterns differed according to structural injury and hand disability
Rocca et al., 2002b	30 people with PPMS 15 HC	Task 1: flexion–extension of the last four fingers of the right, dominant hand Task 2: flexion–extension of the right foot Task 3: tasks 1 & 2 together	People with PPMS showed increased fMRI activation vs HC of brain regions within both traditional motor planning and execution regions, and several multimodal cortical regions in the temporal, parietal, and occipital lobes
Rocca et al., 2003a	13 people with SPMS 15 HC	Task 1: flexion–extension of the last four fingers of the right, dominant hand Task 2: flexion–extension of the right foot	During hand movement, people with SPMS showed more significant activations of fronto-parietal regions. During foot movement, people with SPMS had more significant activations of sensorimotor cortex and thalamus. Increased fMRI activation correlated with structural damage
Rocca et al., 2003b	16 people with CIS 15 HC	Flexion-extension of the last four fingers of the right, dominant hand	People with CIS had more significant fMRI activations of primary and secondary sensorimotor cortex, correlated with axonal injury
Filippi et al., 2004	16 people with RRMS 16 HC	Task 1: flexion–extension of the last four fingers of the right, dominant hand Task 2: manipulation of various daily-life objects	Regions activated by people with MS during the performance of the simple motor task (cerebellar, parietal and frontal regions) were part of more complex pathways, recruited by HC when performing the object manipulation task
Rocca et al., 2004	76 people with MS 15 HC	Flexion-extension of the last four fingers of the right, dominant hand	People with MS and lesions in the pyramidal tract had more significant activations of contralateral/ipsilateral sensorimotor regions and ipsilateral precuneus. Pyramidal tract lesion load correlated with primary sensorimotor activity
Saini et al., 2004	14 people with RRMS 11 HC	Writing "8″ repeatedly on a paper in a cursive manner	During the writing task, people with MS had higher fMRI activity in bilateral motor cortex. They also had lower FC between motor regions and contralateral cerebellum, and higher FC with the ipsilateral cerebellum
Rocca et al., 2005	57 people with MS and different phenotypes 15 HC	Flexion-extension of the last four fingers of the right, dominant hand	Early in MS disease course, increased and more widespread activation of areas typically devoted to motor tasks was found. With increasing disability and in progressive MS, bilateral activation of these regions was seen, as well as recruitment of areas that HC use for novel/complex tasks
Ciccarelli et al., 2006	14 people with PPMS 18 HC	Auditory-cued and passive dorsi-plantar flexion of the right foot	People with PPMS showed greater fMRI activation than HC with passive ankle movements in temporal, insular and subcortical regions. fMRI response to active and passive ankle movements in frontal regions was lower in patients with higher EDSS score and greater lesion load. Cerebellar activation was inversely correlated with T25FW
Lenzi et al., 2007	18 people with RRMS 18 HC	Right index finger to thumb opposition	Greater fMRI activity was found in people with MS in motor, cingulate, thalamic and insular regions during a motor task. A positive correlation between ipsilateral motor cortex activity and corpus callosum damage was detected
Rocca et al., 2008	16 people with RRMS 14 HC	Task 1: flexion–extension of the last four fingers of the right, dominant hand Task 2: mirror neuron system task: observation of a movie showing the hand of another subject performing task 1	During the simple motor task, people with MS had more significant fMRI activation of sensorimotor regions, as well as of several visual, parietal and frontal areas that HC

Table 1 (*continued*)

Study	Subjects	Task	Main findings
			activated during the mirror neuron system task
Wegner et al., 2008	56 people with MS 60 HC	Flash light-cued flexion–extension of the last four fingers of the right, dominant hand	Increased fMRI activation was found in people with MS in the bilateral motor circuit, with a stronger modulatory effect of age in MS *vs* HC. Increased activation in fronto-striatal regions correlated with higher 9HPT scores.
Manson et al., 2008	56 people with MS 60 HC	Flash light-cued flexion–extension of the last four fingers of the right, dominant hand	In the same MS group as (Wegner et al., 2008), decreased task-associated deactivation was found during a motor task in regions specialized to hand movement control
Rocca et al., 2009	61 people with MS 74 HC	Flash light-cued flexion–extension of the last four fingers of the right, dominant hand	Increased effective connectivity was found during a motor task among regions of the sensorimotor network, which correlated with lesional and corticospinal tract damage
Rocca et al., 2010	17 people with BMS 15 people with SPMS 17 HC	Flexion-extension of the last four fingers of the right, dominant hand	Increased fMRI activity in classical motor regions was found in both people with BMS and PMS. Compared with people with BMS, SPMS had increased activations of inferior frontal and middle occipital regions
Rico et al., 2011	15 people with CIS 10 HC	Auditory-cued flexion–extension of the fingers of one hand	In people with CIS, during a simple movement task, fMRI activity was detected in the anterior cingulate cortex, usually involved in complex movements
Petsas et al., 2013	31 people with MS 15 HC	Passive flexion–extension of the metacarpo-phalangeal joints	The ipsilateral motor cortex was more activated during active and passive movements, with a gradient across phenotypes (SPMS > RRMS > HC). Motor regions were less deactivated and DMN areas were more deactivated in RRMS, but not in SPMS *vs* HC
Pardini et al., 2013	14 people with RRMS	Finger to thumb opposition with the right hand (index, medium, ring and little fingers)	During the finger tapping task, temporal accuracy of task execution was higher in fatigued MS and correlated with higher cerebellar and orbitofrontal fMRI activity Compared to HC, people with MS

Table 1 (*continued*)

Study	Subjects	Task	Main findings
Faivre et al., 2015	13 people with RRMS 14 HC	Auditory-cued flexion–extension of the fingers of one hand	presented higher fMRI activation during a motor task (especially when executed with non-dominant hand) and higher RS FC. Levels of hyper-activation and hyper-connectivity at RS were inter-related
Rocca et al., 2016	79 people with MS 26 HC	Flexion-extension of the last four fingers of the right, dominant hand	Fatigued MS people showed reduced activation of sensorimotor, temporal and basal ganglia regions, and increased frontal activation compared to non-fatigued MS. Time-modulation analysis showed reduced fMRI activity over time in non-fatigued MS only
Hubbard et al., 2016	25 people with RRMS 20 HC	Press and release both thumb-buttons at presentation of a checkerboard stimulus	Amplitude of the BOLD response in the visual and motor cortex was reduced in people with MS *vs* HC, and correlated with microstructural damage
Bonzano et al., 2017	14 people with RRMS	Finger to thumb opposition with the right hand (index, medium, ring and little fingers)	fMRI activity in basal ganglia regions (known to be involved in fatigue) and amygdala was high during the non-demanding finger tapping task, decreased during the execution of the highly demanding finger tapping task, and returned to baseline after a resting period
Tacchino et al., 2017	17 people with CIS 20 people with RRMS 20 HC	Squeeze (and imagine to squeeze) a foam ball with the dominant and non-dominant hand	Reduced performance of motor imagery varied according to disease stage (i.e., in CIS *vs* RRMS), and inversely associated with fMRI activations of occipital, frontal and parietal regions (which were stronger with the non-dominant hand)
Svolgaard et al., 2018	44 people with RRMS 25 HC	Press a pincer grip a force sensitive device, and produce a force matching that showed on a screen	In people with MS, during the precision grip task, fMRI activity of the cerebellum was proportional to fatigue. Linear increase of activity over time in premotor and frontal regions was impaired in MS according to fatigue severity
Boonstra et al., 2020	59 people with MS 15 HC	Task 1: play a paddle under a ball to bounce it up Task 2: watch a ball	FMRI activation was higher, during the joystick task, in patients with MS and

Table 1 (*continued*)

Study	Subjects	Task	Main findings
		moving on the screen Task 3: move the joystick to the left and right, while the ball is frozen on the screen	tremor than in HC and non-tremor MS, in parietal, premotor and supplementary motor cortex. Higher fMRI activation was associated with lower tremor severity
Alahmadi et al., 2021	14 people with RRMS 14 HC	To squeeze a rubber ball with varying grip force levels using the right hand	In response to the variable grip force task, fMRI activation was increased in MS *vs* HC both in anterior and posterior BA4. However, non-linear analysis showed abnormal non-linear responses to increasing grip forces in MS in posterior BA4
Bonzano et al., 2021	18 people with MS 18 HC	Writing a sentence in cursive	Hand-writing elicited fMRI activity was lower in people with MS *vs* HC in temporal, parietal, insular and basal ganglia regions. Preserved fMRI activity in these regions was associated with better writing performances
Strik et al., 2021	28 people with RRMS 17 HC	To follow a target force line by squeezing and releasing the right fingers, or by pulling up and down the right foot	During the lower limb force matching task, lower fMRI activity was detected in people with MS *vs* HC in cerebellar, occipital and superior parietal cortices. Reduced activity was associated with more erroneous/delayed lower limb tracking
West et al., 2021	32 people with RRMS 17 HC	Auditory-cued press-release of bilateral thumb buttons	Calibrated fMRI during the finger tapping task showed a significant increase of blood flow and oxygen consumption in the central region activated by the task. Poor MS performers at the 9HPT, compared to remaining people, had lower blood flow and oxygen consumption in the surrounding region
Visual tasks			
Rombouts et al., 1998	9 people with RRMS and ON 8 HC	Red light stimulation of both eyes simultaneously, then of each eye, separately	Upon stimulation, people with MS showed reduced activation of the affected eye (33% on average) and unaffected eye (61% on average) compared to HC
Werring et al., 2000	7 people with MS recovering from ON 7 HC	Red photic stimulation to the whole visual field	Extensive fMRI activation of visual, parietal, insular and thalamic regions was found when stimulating the recovered eye. FMRI activation of visual

Table 1 (*continued*)

Study	Subjects	Task	Main findings
			and insular regions was found when stimulating the unaffected eye
Colorado et al., 2012	22 people with RRMS 23 HC	Visual task: focus on a red crosshair, and press a key at the beginning of the flashing checkerboards Motor task: visually-cued flexion–extension of the last four finger of left or right hand Memory task: 0-back and 2-back task	During visual, motor and working memory fMRI tasks, an enhanced fMRI activity of regions belonging to the cognitive control system (dorsolateral prefrontal and anterior cingulate cortices) was found in people with MS *vs* HC
Hubbard et al., 2017	12 people with MS	Press and release both thumb-buttons at change in the luminance of the fixation cross	Calibrated fMRI demonstrated altered cerebral blood flow and oxygen consumption in the visual cortex during the visual task, which was associated with microstructural damage of occipital tracts

Abbreviations: CIS = clinically isolated syndrome; MS = multiple sclerosis; RR = relapsing-remitting; PP = primary progressive; SP = secondary progressive; ON = optic neuritis; HC = healthy controls; FC = functional connectivity; RS = resting state; BA = Brodmann area; DMN = default-mode network; FT = finger tapping; 9HPT = nine-hole peg test; T25FW = timed 25 foot walk; BOLD = blood-oxygenation level dependent.

activation, while the surrounding region was characterized by an opposite behavior, especially in people with MS and upper limb impairment. (West et al., 2021) This reinforces the notion that impairment in recruiting supplementary areas might be among the reasons explaining poor performances of people with MS.

2.2. Exploring MS-related functional reorganization in cognitive systems

A list of relevant studies evaluating functional reorganization within circuits involved in different cognitive functions using task-based fMRI is provided in Table 2. The mostly investigated cognitive domains are sustained attention, information processing speed and working memory, thanks to the use of fMRI tasks based on the paced auditory serial addition test (PASAT), (Audoin et al., 2003; Chiaravalloti et al., 2005; Forn et al., 2006; Hillary et al., 2003; Mainero et al., 2004; Nelson et al., 2017; Staffen et al., 2002) symbol digit modalities test (SDMT), (Forn et al., 2013; Leavitt et al., 2012) N-back (Cader et al., 2006; Rocca et al., 2014; Sweet et al., 2006; Sweet et al., 2004; Vacchi et al., 2017; Wishart et al., 2004; Penner et al., 2003) task and Go-NoGo (Koini et al., 2016; Loitfelder et al., 2011) task.

Results of these studies were concordant between cognitive but also motor tasks in showing abnormal fMRI activity in people with MS *vs* HC. Specifically, during the PASAT task there was a set of regions, belonging to the attention and working memory circuits, mostly showing increased fMRI activation, including the medial and dorsolateral prefrontal cortices, (Audoin et al., 2003; Chiaravalloti et al., 2005; Forn et al., 2006; Mainero et al., 2004; Staffen et al., 2002) inferior frontal gyri, (Chiaravalloti et al., 2005) angular gyri and other parietal areas, (Chiaravalloti et al., 2005; Mainero et al., 2004; Staffen et al., 2002; Forn et al., 2012) and the cerebellum. (Audoin et al., 2003; Forn et al., 2012) Overall, increased fMRI activity was more evident in people with MS with intact task performance or no cognitive impairment (Fig. 1), (Forn et al., 2006; Mainero et al., 2004; Penner et al., 2003) even if some evidence of higher, erratic activity in regions outside the classical
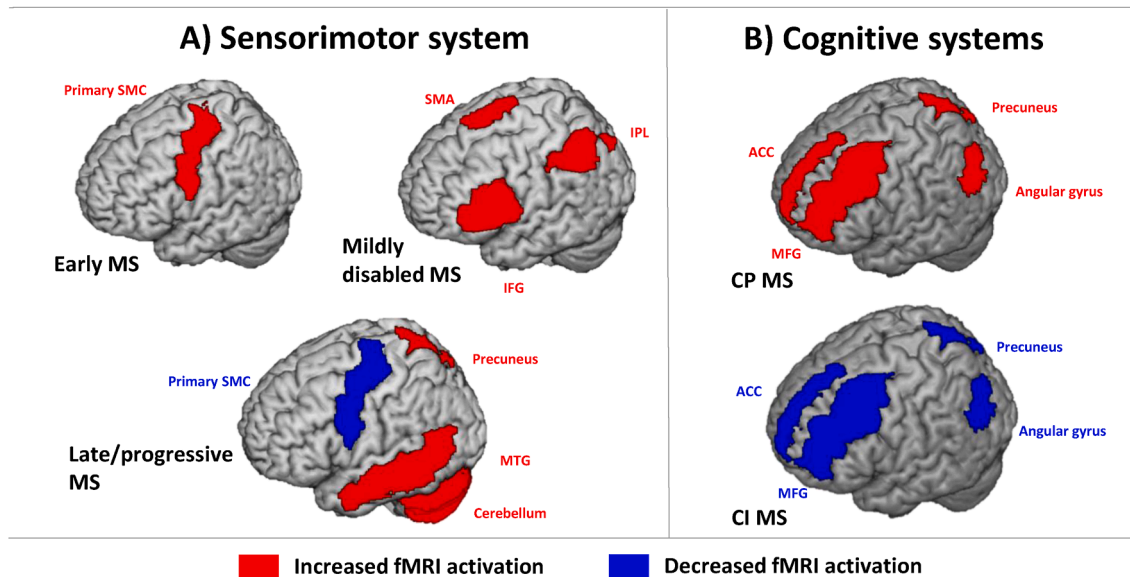
Task-related fMRI studies in MS

Fig. 1. Schematic representation of findings from the main studies using task-based functional magnetic resonance imaging (fMRI) to investigate reorganization of brain activity in people with multiple sclerosis (MS). A) During upper limb motor tasks, the sensorimotor system usually shows an increased fMRI activation of primary sensorimotor regions in early MS, which is followed by increased activation of supplementary motor areas and fronto-parietal areas devoted to motor control in mildly disabled people with MS. At later disease stages and in progressive MS, a decreased fMRI activity in the classical motor circuit is detected, together with increased fMRI activations of high-order, integrative areas. B) During cognitive tasks, an increased fMRI activity of fronto-parietal regions is usually detected in people with MS and intact task performance or no cognitive impairment. The same circuit shows decreased fMRI activity in people with MS and cognitive deficits. Abbreviations: SMC = sensorimotor cortex; SMA = supplementary motor area; IFG = inferior frontal gyrus; IPL = inferior parietal lobule; MTG = middle temporal gyrus; MFG = middle frontal gyrus; ACC = anterior cingulate cortex.

attention/working memory circuits was found in poor performers. (Chiaravalloti et al., 2005; Forn et al., 2012) During the N-back task, the most evident change of cortical activity found in people with MS compared to HC was a "saturation" effect, consisting in abnormally high fronto-parietal fMRI activity at low task complexity (i.e., at 1- and 2-back). (Cader et al., 2006; Rocca et al., 2014; Sweet et al., 2006; Penner et al., 2003; Amann et al., 2011) In addition, people presenting with cognitive deficits showed an impaired ability to increase task-specific fMRI activation with increasing task complexity (Fig. 1), as well as lowered proficiency to suppress default-mode network activity. (Rocca et al., 2014; Amann et al., 2011) Once again, regions mostly involved were the dorsolateral prefrontal, premotor and supplementary motor cortices, belonging to the working memory circuit, as well as medial and lateral parietal cortices, and abnormal fMRI activity was more evident in cognitively preserved than in cognitively impaired people with MS. (Rocca et al., 2014) However, also in this task, erratic activity outside the classic working memory circuit was described, (Wishart et al., 2004) which was more evident in people with secondary progressive (SP) MS compared to RRMS. (Vacchi et al., 2017) During the N-back task, fatigued MS people tended to exhibit increased activity in fronto-striatal-subcortical networks. (Spiteri et al., 2019).

An adaptive increase of frontal, parietal and thalamic fMRI activations in people with MS *vs* HC was found also during the Go-NoGo (Koini et al., 2016; Loitfelder et al., 2011) and Stroop tasks, (Parry et al., 2003) which activate the sustained attention circuit. On the other hand, maladaptive activations outside such circuit, associated with higher levels of clinical disability, were also found, especially in people with SPMS. (Loitfelder et al., 2011) Finally, during episodic memory tasks a selective increase of fMRI activation in the hippocampus and anterior cingulate cortex (involved in the memory circuit) was detected, (Hulst et al., 2012) while selectively increased fMRI activation was seen in posterior parietal regions during face recognition/encoding tasks. (Jehna et al., 2011; Rocca et al., 2017) Once again, an effect of phenotype was observed contributing to the pattern of observed abnormalities, and

maladaptive activity in the frontal cortex detected in people with SPMS. (Rocca et al., 2017).

3. From segregation to integrated functional networks: The role of a large-scale network collapse to understand MS pathophysiology

While task-based paradigms can highlight which regions are active during specific tasks, this inherently does not hold information on how this active region is communicating with the rest of the brain. This is typically quantified by assessing FC, i.e., by correlating activation patterns of different regions. This information is (at least partly) independent from activation levels, since relatively inactive regions can still strongly communicate with other regions and *vice versa*. As mentioned, this approach has been applied mostly using RS fMRI paradigms, typically requesting participants to lie still with their eyes closed, and letting the mind wander. Early RS fMRI studies have shown increased FC in CIS, (Liu et al., 2016; Liu et al., 2017; Shu et al., 2016; Roosendaal et al., 2010) and decreased FC in progressive MS. (Rocca et al., 2010) This combination of findings led to the hypothesis (Schoonheim et al., 2010) that RS FC would follow the same indicated pattern as task-based activation, i.e., an early compensatory increase and a subsequent maladaptive decrease. However, subsequent work found confusing combinations of increased and decreased FC, often in the same patients' group. (Rocca et al., 2018) Although there are indications that specific connectivity patterns are peculiar to distinct disease-stages, (Meijer et al., 2018) longitudinal works remain rare. Most studies have performed RS fMRI studies during remission, given concerns of relapse-driven inflammation influencing signal stability, however, some relapse studies have been done. (Wu et al., 2020) Findings below explore disability and cognition, but it should be noted similar results have also been found for other symptoms such as fatigue (Manjaly et al., 2019) and social cognition. (Chalah and Ayache, 2020).

Table 2

Summary of the most important functional magnetic resonance imaging studies using cognitive active tasks to investigate brain activation in people with multiple sclerosis (MS).

Study	Subjects	Task	Main findings
PASAT/PVSAT tasks			
Staffen et al., 2002	21 people with RRMS 21 HC	PVSAT task	People with MS exhibited increased fMRI activation *vs* HC of the right hemispheric frontal cortex and of the angular gyrus
Audoin et al., 2003	8 people with MS 2 people with CIS 10 HC	PASAT task	Compared to HC, people with MS exhibited higher activity of frontopolar cortex, lateral prefrontal cortex and cerebellum. HC and CIS did not differ in terms of activation
Mainero et al., 2004	22 people with RRMS 22 HC	PASAT task Recall task: before fMRI, listen to 7 unrelated pairs of words. Try to recall the second word, when the first is presented on the screen	During both PASAT and recall tasks, RRMS people exhibited significantly greater brain fMRI activation than HC. Task-related fMRI changes were more significant in well-performer than in poor MS performers
Audoin et al., 2005	18 people with CIS 18 HC	PASAT task	In the subgroup of CIS with normal PASAT performance, fMRI showed larger activations in bilateral inferior frontal regions compared to HC. BA45 activation was inversely related to normal-appearing white matter damage
Au Duong et al., 2005	18 people with CIS 18 HC	PASAT task	People with CIS presented lower effective connectivity than HC from right BA46 to left BA46 and from left anterior cingulate to left BA46. They also had higher effective connectivity from right anterior cingulate cortex to right BA46, from left right to left anterior cingulate and *vice versa*
Chiaravalloti et al., 2005	11 people with MS 5 HC	PASAT task	HC and people with MS without working memory impairment showed fMRI activations lateralized to the left frontal hemisphere. Conversely, impaired MS people showed greater right frontal and right parietal activity *vs* HC
Forn et al., 2006	15 people with RRMS 10 HC	PASAT task	Well-performer MS people showed a stronger activation in the left prefrontal cortex when compared with HC
Forn et al., 2012	18 people with CIS 15 HC	PASAT task	CI CIS people had more significant fMRI activations and stronger effective connectivity in parietal, cerebellar and frontal regions than HC and CP CIS people
SDMT task			
		SDMT task	
Leavitt et al., 2012	16 people with MS 17 HC		During a modified SDMT task, people with MS showed more effective connectivity connections from multiple brain regions to the frontal cortex
Forn et al., 2013	18 people with CIS 15 HC	SDMT task	Compared to HC, people with CIS exhibited an enhanced deactivation of the "task-negative" (DMN) network, whereas no differences between groups were found when comparing the "task-positive" activity network
N-back task			
Penner et al., 2003	14 people with MS 7 HC	Task 1: 2-back task Task 2: tonic alertness task Task 3: incompatibility task	People with MS with mild cognitive impairment showed increased frontal and parietal fMRI activity *vs* HC in the three different attention tasks. Severely impaired MS did not show any additional prefrontal/premotor activation
Wishart et al., 2004	10 people with RRMS 10 HC	0-, 1-, and 2-back task	People with MS exhibited decreased activation *vs* HC in core prefrontal/parietal regions of working memory circuitry, and increased activation within and beyond typical working memory circuitry
Sweet et al., 2004	15 people with MS 15 HC	0- and 2-back	Compared to 0-back, during the 2-back condition people with MS and HC exhibited fMRI activity in inferior frontal, supplementary motor, premotor and dorsolateral prefrontal cortices. People with MS showed greater cortical activity than HC in sensorimotor cortices and several frontal regions
Sweet et al., 2006	15 people with RRMS 15 HC	0-, 1-, 2-, and 3-back task	People with MS exhibited significantly greater fMRI activity in anterior frontal regions compared to HC during a 1-back task, while superior frontal, cingulate, and parahippocampal regions were relatively less active at 2- and 3-back
Cader et al., 2006	21 people with RRMS 16 HC	0-, 1-, 2-, and 3-back task	At the N-back task, people with MS showed a smaller increase in activation than HC with greater task complexity. HC showed significantly greater FC between dorsolateral prefrontal and superior frontal/anterior cingulate activations

Table 2 (*continued*)

Study	Subjects	Task	Main findings
Amann et al., 2011	15 people with RRMS 15 HC	Working memory task: 1-, 2- and 3-back task Attention task: to react as quickly as possible by pressing a button to digit "2"	During attention and working memory fMRI experiments, HC showed a linear in- or decrease in fMRI activation paralleling the changing task complexity, while people with MS showed stronger activations at simple task levels and a saturation effect of (de-) activation at the highest task load
Rocca et al., 2014	42 people with RRMS 52 HC	0-, 1-, 2-, and 3-back task	Compared to HC and CI MS, people with CP MS had increased dorsolateral prefrontal fMRI recruitment. With increasing task difficulty, people with CI MS had reduced activations of fronto-parieto-temporal areas, as well as reduced deactivations of the DMN
Vacchi et al., 2017	12 people with CIS 38 people with RRMS 22 people with SPMS 24 HC	0-, 1-, 2-, and 3-back task	During the N-back load contrast, compared to HC, all MS phenotypes had decreased parietal and frontal activation. Increased activations in people with CIS *vs* the remaining groups were found in superior frontal/anterior cingulate cortices. People with SPMS selectively activated parahippocampal and superior temporal pole regions
Spiteri et al., 2019	40 people with MS 22 HC	1-, and 2-back task	Using a fatigue-inducing N-back task, effort-independent fatigue (i.e., fatigue not depending from task execution) was reflected by increased fMRI activity in fronto-striatal-subcortical networks. Effort-dependent fatigue (i.e., task-related fatigue) leaded to activity decreases in attention-related cortical and subcortical networks
Go-Nogo task			
Loitfelder et al., 2011	10 people with CIS 10 people with RRMS 10 people with SPMS 28 HC	Go-Nogo task	Widespread fMRI activation was found in frontal, parietal, insular, basal ganglia and cerebellar regions. Task performance was similar between phenotypes, but activation pattern deviated with disease progression. People with SPMS demonstrated the most abnormal network function
Koini et al., 2016	26 people with RRMS 32 HC	Go-Nogo task	Compared with HC, people with MS showed increased activation in a fronto-parietal network, including both thalami. Thalamic volume and

Table 2 (*continued*)

Study	Subjects	Task	Main findings
			thalamic activation were the best predictors of information processing speed and executive function scores
Stroop task			
Parry et al., 2003	10 people with MS 11 HC	Stroop task	Left medial prefrontal regions were more active in people with MS than in HC, while the inferior frontal cortex and basal ganglia were more active in HC than in MS
Rocca et al., 2012	17 people with RRMS 17 people with BMS 23 people with SPMS 18 HC	Stroop task	People with RRMS had abnormal fronto-parietal fMRI activations, people with SPMS had abnormal recruitment of cingulum and precuneus, and people with BMS had increased activation of the right prefrontal cortex, and increased interaction between frontal/parietal regions and cerebellum
Dobryakova et al., 2016	33 people with RRMS 18 people with BMS 33 people with SPMS 37 HC	Stroop task	People with MS exhibited connectivity abnormalities depending on phenotype, reflecting weaker shared connections, extra connections, connection reversal, and loss. In SPMS and BMS, but not in RRMS people, extra connections were associated with deficits in the Stroop task performance
Other tasks			
Hillary et al., 2003	8 people with MS 5 HC	To press a button if the presented letter was included in the previously presented string	Increased right prefrontal and temporal lobe activation was found in people with MS compared to HC during a working memory task
Lazeron et al., 2004	23 people with MS 18 HC	Planning condition: to respond about the minimum number of necessary moves to reach the target	People with MS and HC showed fMRI activity in frontal, parietal and cerebellar regions during the planning task. Although visual inspection suggested a larger extent of activation in MS, no formal differences were found. At ROI analysis, significantly larger cerebellar activation was found
Jehna et al., 2011	15 people with RRMS 15 HC	To indicate the gender of the presented subjects	People with MS demonstrated abnormally high fMRI activations during facial recognition compared to HC in the posterior and anterior cingulate cortices, precuneus and occipital fusiform gyrus
Hulst et al., 2012	50 people with MS 30 HC	Encoding phase: to decide whether images were "tropical" or "non-tropical" Retrieval phase: to	An episodic memory fMRI task elicited increased brain activation in parahippocampal and anterior cingulate

Table 2 (*continued*)

Study	Subjects	Task	Main findings
		indicate whether the picture was seen before	regions in CP MS people *vs* HC. CI MS showed decreased parahippocampal and prefrontal activation, as well as increased posterior cingulate/precuneus activation
Rocca et al., 2017	11 people with CIS 40 people with RRMS 24 people with SPMS 22 HC	To remember the presented faces for a subsequent test of face recognition outside the scanner	All subjects activated brain regions belonging to face perception and encoding network. Compared to HC/RRMS, people with CIS showed increased fMRI recruitment of posterior-visual areas. Thalami, parahippocampal gyri and anterior cingulum were more active in RRMS, while increased frontal recruitment was found in SPMS
Nelson et al., 2017	50 people with MS	Immediated (I) and delayed (D) memory task (MT)	During the DMT task, CP MS people had significantly greater working memory activation than CI MS in the left prefrontal cortex and supplementary motor area
Dobryakova et al., 2018	19 people with MS 14 HC	To guess whether the value on the front of the card was higher or lower than 5, to win a monetary bonus	During a gambling task with potential monetary gain (outcome condition) or not, a significant decrease of fatigue was found during the outcome condition, associated with abnormal fMRI activation of striatum and prefrontal cortex
Spirou et al., 2018	17 people with MS 13 HC	To guess whether the value on the front of the card was higher or lower than 5, to win a monetary bonus	During the same gambling task as in (Dobryakova et al., 2018), people with MS exhibited greater activation in the putamen, hippocampus, and posterior cingulate cortex during outcome anticipation compared to HC

Abbreviations: PASAT = Paced Auditory Serial Addition test; PVSAT = Paced Visual Serial Addition test; SDMT = symbol digit modalities test; CIS = clinically isolated syndrome; RR = relapsing-remitting; SP = secondary progressive; B = benign; CP = cognitively preserved; CI = cognitively impaired; MS = multiple sclerosis; HC = healthy controls; FC = functional connectivity; DMN = default-mode network; ROI = region of interest.

3.1. Exploring RS FC abnormalities related to disability

A list of relevant studies evaluating RS FC modifications occurring in people with MS in relation with disability is provided in Table 3. In principle, it could be hypothesized that mechanisms associated with clinical disability (which is mostly quantified by the expanded disability status scale [EDSS] score and mainly driven by physical impairment) would be more straightforward compared to the complex interplay of many brain regions involved in cognitive processing, but results demonstrated that this was not necessarily the case. In fact, contrasting findings showed the involvement of many RS networks in explaining clinical disability in MS. (Rocca et al., 2012) Indeed, many studies have

Table 3

Summary of the most important resting state (RS) functional magnetic resonance imaging studies analyzing brain functional connectivity (FC) in people with multiple sclerosis (MS) in relation to clinical disability.

Study	Subjects	Main findings
Faivre et al., 2012	13 people with MS 14 HC	Increased RS FC was seen for many networks, no decrease. MSFC was related to increased FC of fronto-parietal and salience networks
Rocca et al., 2012	85 people with MS 40 HC	MS showed decreased RS FC within and between many networks, but also increased FC of executive control and auditory networks. Decreased RS FC was related to higher EDSS score
Dogonowski et al., 2013	27 people with RRMS 15 people with SPMS	Premotor RS FC was positively related to EDSS score, but in RRMS only
Schoonheim et al., 2014	128 people with MS 50 HC	Ventral stream decreased eigenvector centrality related to worse cognition, sensorimotor decreases related to worse EDSS scores. Regions with altered centrality showed increased thalamic RS FC
Zhong et al., 2016	26 people with MS and motor impairment 17 people with MS and no motor impairment 20 HC	Right hand impairment was explored. Impaired people with MS showed lower SMN RS FC. FC was retained in a multivariate model explaining hand motor disability, assessed by using the 9HPT
Sbardella et al., 2017	54 people with MS 24 HC	Dentate nucleus RS FC was higher with fronto-parietal areas in people with MS compared to HC. Increased RS FC was related to better cognition, but worse EDSS score
d'Ambrosio et al., 2017	187 people with MS 94 HC	Different thalamic subnuclei FC profiles were investigated. Increased thalamic RS FC with temporal areas was seen in people with MS and CI. Decreased thalamic RS FC with caudate and cingulate cortex was related to worse 9HPT scores, while higher thalamus-insula RS FC was related to better 9HPT scores
Zhong et al., 2017	25 people with MS and motor impairment 26 people with MS and no motor impairment 21 HC	Upper limb impairment groups, evaluated using 9HPT, were explored. Support vector machines were able to distinguish subgroups based on structural and RS FC measures
Tona et al., 2018	25 people with MS 20 HC	RS FC of the dentate nucleus was explored, showing both increased and decreased FC compared to HC. Worse balance (determined by means of center of pressure scores) was related to lower dentate-caudate RS FC
Meijer et al., 2018	121 people with early RRMS 122 people with late RRMS 53 people with SPMS 96 HC	Early RRMS showed no RS FC changes. Late RRMS and SPMS showed increased deep GM RS FC, which was related to both cognition and EDSS scores. SPMS showed decreased within-cortex RS FC compared to early RRMS, which was only related to EDSS scores
Tommasin et al., 2018	119 people with MS 42 HC	Higher frontal and lower cerebellar RS FC was related to worse EDSS scores. A peculiar contribution of cerebellar RS FC

(*continued on next page*)

Table 3 (*continued*)

Study	Subjects	Main findings
		decrease was identified in multivariate models
Rocca et al., 2018	215 people with MS 98 HC	MS showed a complex mixture of increased and decreased RS FC within the main large-scale networks. Lower thalamic RS FC was especially related to less severe CI, while other networks mainly showed relations of reduced FC with worse CI and EDSS/functional system scores
Zurita et al., 2018	107 people with MS 50 HC	Multivariate models including RS FC were better able to distinguish MS from HC than MS subgroups based on EDSS scores. Functional measures were more important than diffusion-based measures for the classification
Bollaert et al., 2018	29 people with MS	In this one-group correlation study, T25FW was related to temporo-occipital RS FC
Fu et al., 2019	26 people with MS 23 HC	Postcentral RS FC was both increased and decreased depending on which cortical area and was related to the Fugl-Meyer sensory score and EDSS score
Pinter et al., 2019	180 people with MS	Subgroups based on lesion/atrophy severity indicate that patients with predominant white matter damage show increased SMN RS FC compared to those with predominant GM damage (atrophy). Lower SMN FC was related to worse EDSS
Carotenuto et al., 2020	19 people with MS 24 HC	RS FC of specific neurotransmitter networks were related to cognitive impairment, disease duration and EDSS scores
Cordani et al., 2020	366 people with MS 134 HC	Decreased RS FC was seen in people with MS compared to HC. Decreased RS FC of frontal/executive and cerebellar areas was related to 9HPT performance
Tommasin et al., 2020	119 people with MS 42 HC	Within-network RS FC was higher in people with MS than in HC for DMN, FPN and ECN, and was related to less severe EDSS scores, better 9HPT and T25FW scores and milder PASAT impairment. Between-network FC and whole-brain RS FC were also lower, but related to worse impairments at the same tests
Dekker et al., 2021	295 people with MS 96 HC	Event-based model showed an early involvement of DMN centrality changes related to more severe EDSS scores and cognitive progression
Chiang et al., 2021	20 people with MS	RS FC of areas frequently showing atrophy based on *meta*-analysis was evaluated. Deviation from optimal in this model was related to EDSS score
Cordani et al., 2021	250 people with RRMS 114 people with PMS 144 HC	RS FC related to clinical disability only in people with PMS, where increased FC of motor areas predicted EDSS. Conversely, in people with RRMS, EDSS score was only predicted by structural damage
Pasqua et al., 2021	119 people with MS 42 HC	Increased cerebellar RS FC related to lower cognitive impairment and physical

Table 3 (*continued*)

Study	Subjects	Main findings
		disability, assessed by using EDSS, 9HPT and T25FW scores
Strik et al., 2021	185 people with MS patientsand low disability (EDSS score ≤ 3.5)37 people with MS and high disability (EDSS score ≥ 6.0) 82 HC	People with high EDSS score showed higher network efficiency (based on RS FC) of the primary sensorimotor cortex (S1), pallidum and premotor cortex, of which only S1 was significant in a multivariate model. S1 RS FC was increased with prefrontal and secondary sensory areas
Giannì et al., 2021	36 people with MS 39 HC	Thalamo-cortical RS FC was higher, while intra-thalamic FC was lower in people with MS compared to HC. Finger movement speed was impaired and related to both abnormalities of thalamic RS FC
Rocca et al., 2021	233 people with MS 77 HC	At clinical follow-up, 45% of MS patients progressed, 16% of RRMS evolved to SPMS. Decreased DMN RS FC and increased SMN RS FC predicted clinical worsening, defined basing on EDSS score increase over time. SPMS conversion was mostly predicted by GM atrophy. Adding network measures improved prediction
Schoonheim et al., 2022	512 people with MS 161 HC	Thalamic RS FC was explored. EDSS was related to increased thalamus-SMN FC, which was especially high in people with MS and more severe disability. Thalamic RS FC was related to cortical network atrophy, but not thalamic atrophy, nor lesions

Abbreviations: RR = relapsing-remitting; SP = secondary progressive; P = progressive; CI = cognitively impaired; MS = multiple sclerosis; HC = healthy controls; MSFC = multiple sclerosis functional composite; EDSS = expanded disability status scale; T25FW = timed 25 foot walk; GM = grey matter; SMN = sensorimotor network; 9HPT = nine-hole peg test; DMN = default mode network; FPN = fronto-parietal network; ECN = executive control network; PASAT = paced auditory serial addition test.

related abnormal RS FC within the sensorimotor system to disability, (Pinter et al., 2019) for instance showing that both increased and decreased RS FC of the motor cortices, cerebellum and other areas explain physical and motor impairment. (Dogonowski et al., 2013; Zhong et al., 2016; Tona et al., 2018; Fu et al., 2019; Cordani et al., 2021; Tommasin et al., 2018) This suggests a co-occurrence of adaptive and maladaptive mechanisms within sensorimotor networks (SMN), which may vary according to patients' clinical characteristics. Of note, lower RS FC was found to be associated with more severe upper limb clinical impairment, (Cordani et al., 2020; Zhong et al., 2017) while preserved upper limb function has been associated with higher RS FC in motor and extra-motor regions. (d'Ambrosio et al., 2017; Pasqua et al., 2021; Tommasin et al., 2020) Interestingly, the involvement of extra-SMN regions has also become apparent, such as occipito-temporal areas. (Bollaert et al., 2018) Also, cognitive networks like the default-mode network (DMN) and fronto-parietal network (FPN) (Cordani et al., 2020; Tommasin et al., 2020; Faivre et al., 2012) have been shown to play a role. Some studies even found effects of specific structures to relate differently to cognition and disability based on the affected cortical area. (Rocca et al., 2018; Carotenuto et al., 2020) The same applies to RS FC patterns of structures like the cerebellum (Pasqua et al., 2021; Sbardella et al., 2017) and thalamus. (d'Ambrosio et al., 2017; Giannì et al., 2021; Schoonheim et al., 2022) Together, these findings have lead the field to re-evaluate the complexity of physical disability,

which is influenced by injury of several mechanisms and systems.

3.2. Exploring RS FC abnormalities related to cognition

A list of relevant studies evaluating RS FC modifications occurring in people with MS in relation with cognition is provided in Table 4. Historically, the field of cognition in MS has evolved drastically, moving from the PASAT, a sub-test of the multiple sclerosis functional composite (MSFC), to more expansive research batteries. (Benedict et al., 2020) The field of RS FC has evolved drastically as well, moving from individual connections to network analysis. In stark contrast to the cognitive task literature, RS fMRI studies identifying FC changes related to preserved/better cognitive performance remain rare. (Loitfelder et al., 2012; Prakash et al., 2011) Most of RS FC correlates of cognitive dysfunction revolve around a dysfunctional DMN, a collection of regions commonly de-activated during specific tasks. (Bassett and Sporns, 2017) Interestingly, RS FC of the DMN has been observed to be increased in some studies, (Tommasin et al., 2020; Hawellek et al., 2011; Has Silemek et al., 2020; Meijer et al., 2017; Veréb et al., 2022; Soares et al., 2021) but decreased in others, (Rocca et al., 2010; Leavitt et al., 2014; Bonavita et al., 2011; Janssen et al., 2013; Jandric et al., 2021; Louapre et al., 2014) a finding that might be explained by the fact that both phenomena can co-occur at the same time. (Conti et al., 2021) However, regardless of directionality, almost all DMN changes were related to the severity of cognitive impairment, indicating that both a hyper- and hypo-connected DMN would indicate an inefficient network for cognition. Later insights into the DMN have placed these findings in clearer context. Initially, the DMN was seen as a "default state" of the brain where the network would reside in when doing nothing, leading to the controversial term "task-negative network". (Spreng, 2012) Next, it was seen as a purely "intrinsic" system, featuring cognitively relevant processes but not actively processing during a cognitive task. Later on, however, it became clear that the DMN does have a crucial role in cognitive processing, namely the integration of higher-order extrinsic and intrinsic information over long timescales. (Yeshurun et al., 2021) Such a role could also explain why the DMN has been related to so many neurological and psychiatric disorders beyond MS, especially in relation to impaired cognition.

Of course, cognitively relevant RS FC changes in MS are not limited to the DMN. Ongoing work has identified the involvement of many networks, (Cruz-Gómez et al., 2014; Sbardella et al., 2015; Marchesi et al., 2021) among which a prominent role is played by the FPN, (Tommasin et al., 2020; Meijer et al., 2017; Marchesi et al., 2021; Wojtowicz et al., 2014; Petracca et al., 2017; Riccitelli et al., 2020) that also exhibit a combination of increased and decreased RS FC related to cognitive dysfunction. (Jandric et al., 2021) The FPN, also known as the central executive network (CEN), is a network classically related to active cognitive processing, coordinating behavior, attention, working memory and executive functioning. (Marek and Dosenbach, 2018) For this reason, it has also been named as the "task-positive" network, together with the dorsal attention network (DAN). (Spreng, 2012) The DMN and FPN contain most of the strongly connected regions, i.e., the functional hubs of the brain. (Bassett and Sporns, 2017) Despite their rather different role, the DMN and FPN both show similar patterns in MS, consisting of a disturbed RS FC especially with non-hub regions. (Meijer et al., 2017) This hub disruption could lead to an altered balance between the DMN and FPN, as both should normally be highly flexible and form opposing systems. (Douw et al., 2016) Together, these large-scale RS FC changes could lead to the hypothesized "network collapse" in MS (Fig. 2), where normal network flexibility is lost, with probable detrimental effects on cognitive processing. (Schoonheim et al., 2015).

One aspect that still deserves further investigations is why some studies find increased and others decreased RS FC in core brain functional networks. While some methodological choices may play a role, it has to be noted that investigating specific structures like the

Table 4

Summary of the most important resting state (RS) functional magnetic resonance imaging studies analyzing brain functional connectivity (FC) in people with multiple sclerosis (MS) in relation to cognition.

Study	Subjects	Main findings
Roosendaal et al., 2010	14 people with CIS 31 people with MS 41 HC	CIS showed no CI, but increased RS FC in many networks. MS showed CI but no RS FC changes compared to HC. RS FC changes were related to white matter damage
Rocca et al., 2010	33 people with SPMS 24 people with PPMS 24 HC	Lower RS FC was found in progressive MS in anterior DMN areas, most pronounced in cognitively impaired vs preserved people with MS. DMN reductions were related to PASAT and word list scores, and to white matter damage
Roosendaal et al., 2010	25 people with MS 30 HC	In memory-preserved people with MS, hippocampal connectivity was reduced, in relation to hippocampal atrophy
Hawellek et al., 2011	16 people with MS 16 HC	DMN showed increased RS FC in relation to the severity of CI. Results were especially significant for inferior parietal, posterior cingulate and medial prefrontal cortex
Prakash et al., 2011	45 people with MS	In this one-group correlational study, higher hippocampal connectivity was related to better relational memory
Bonavita et al., 2011	18 cognitively impaired people with MS 18 cognitively preserved people with MS 18 HC	Reduced ACC-DMN RS FC was worst in cognitively impaired compared to preserved people with MS, but was also seen in all people with MS vs HC. RS FC was not related to lesions or global atrophy, but did relate to local atrophy
Loitfelder et al., 2012	31 people with MS 31 HC	Rest phases of a task were used to analyze ACC RS FC with task-related areas. Increased ACC RS FC was related to better processing speed performance
Schoonheim et al., 2012	30 people with MS 30 HC	Results showed worst RS FC and cognitive changes in male people, showing reduced connectivity which was related to visuospatial memory
Janssen et al., 2013	28 people with MS 28 HC	DMN and attention network integration (within-network RS FC) was reduced and related to the severity of CI
Cruz-Gómez et al., 2014	30 cognitively impaired people with MS 30 cognitively preserved people with MS 18 HC	Cognitively impaired people with MS showed reduced RS FC compared to preserved MS across all resting state networks. Preserved people with MS showed lower RS FC in the FPN compared to HC. RS FC was related to atrophy and lesions
Louapre et al., 2014	15 cognitively impaired people with MS 20 cognitively preserved people with MS 20 HC	RS FC was increased in cognitively preserved people with MS vs HC, but decreased in cognitively impaired vs preserved MS. Results were mainly seen in the DMN and attention networks
Gamboa et al., 2014	16 people with MS 20 HC	Increased network modularity was related to worse PASAT performance
Leavitt et al., 2014	20 memory impaired people with MS 23 memory preserved people with MS	Memory impairment was related to lower DMN RS FC
Schoonheim et al., 2014	128 people with MS 50 HC	Ventral stream decreased eigenvector centrality related to worse cognition, sensorimotor decreases related to worse EDSS scores. Regions with altered centrality showed increased thalamic RS FC

Table 4 (*continued*)

Study	Subjects	Main findings
Tona et al., 2014	48 people with MS 24 HC	Worse PASAT scores were related to lower thalamic RS FC with thalamus, cerebellum and widespread cortical areas
Wojtowicz et al., 2014	18 people with MS 16 HC	Worse reaction time parameters were related to reduced RS FC of (pre) frontal areas
Hulst et al., 2015	57 people with MS 28 HC	Increased RS FC between hippocampus and posterior cingulate cortex was related to memory impairment. Hippocampal activation was not related to hippocampal RS FC
Sbardella et al., 2015	30 people with MS 24 HC	People with MS showed reduced RS FC in five networks and changes to between-network FC. RS FC changes were related to white matter damage and processing speed
Schoonheim et al., 2015	108 cognitively preserved people with MS 22 mild cognitively impaired people with MS 27 cognitively impaired people with MS	Thalamic RS FC was increased with cortical areas, but only in cognitively impaired people with MS. Multivariate regression included thalamic volume, RS FC and MD as predictors of CI
Rocca et al., 2016	246 people with MS 55 HC	Graph analytical properties based on RS FC patterns were able to differentiate cognitively impaired from preserved people with MS, but were not related to phenotype. Global network properties were altered by changing patterns and locations of hubs
Petracca et al., 2017	25 people with PPMS 20 HC	CI was related to reduced RS FC and increased within-region variability of BOLD amplitude. Cortical lesions were related to the severity of functional changes
Sbardella et al., 2017	54 people with MS 24 HC	Dentate nucleus RS FC was higher with fronto-parietal areas, which was related to better cognition, but worse motor performance
d'Ambrosio et al., 2017	187 people with MS 94 HC	Different thalamic subnuclei RS FC profiles were seen. Increased thalamic RS FC with temporal areas was seen in people with MS and CI. Decreased thalamic RS FC with caudate and cingulate cortex was related to worse motor performance, while higher thalamus-insula RS FC was related to better motor performance
Eijlers et al., 2017	87 cognitively impaired people with MS 65 mild cognitively impaired people with MS 180 cognitively preserved people with MS 96 HC	Eigenvector centrality, a graph measure indicating hubness based on RS FC profiles, was increased within DMN networks in people with MS and mild and severe CI. Cognitively preserved people with MS only showed changes in occipital and sensorimotor areas, which was related to disability
Meijer et al., 2017	87 cognitively impaired people with MS 65 mild cognitively impaired people with MS 180 cognitively preserved people with MS 96 HC	Hub networks (DMN and FPN) showed increased RS FC with the rest of the brain, but no within-network alterations. Higher hub RS FC was related to worse cognition. DMN RS FC increases were related to attention, processing speed and working memory, while increased FPN FC was related to attention
González Torre et al., 2017	64 people with MS 18 HC	Memory impairment was related to higher RS FC for posterior

Table 4 (*continued*)

Study	Subjects	Main findings
		hippocampus and cortical areas. People with MS and no impairment already showed some increased RS FC
Meijer et al., 2018	121 people with early RRMS 122 people with late RRMS 53 people with SPMS 96 HC	Early RRMS showed no RS FC changes. Late RRMS and SPMS showed increased deep GM RS FC, which was related to both cognition and disability. SPMS showed decreased within-cortex RS FC compared to early RRMS, which was only related to disability
Rocca et al., 2018	215 people with MS 98 HC	People with MS showed a complex mixture of increased and decreased RS FC *vs* HC. Lower thalamic RS FC was especially related to less severe CI, while other networks mainly showed relations for reduced RS FC with worse CI and disability
Meijer et al., 2018	330 people with MS 96 HC	Processing speed impairment was related to increased RS FC. CI variations in people with similar severities of structural damage could be related to the severity of increased RS FC
Cocozza et al., 2018	29 people with progressive MS 22 HC	Progressive MS showed reduced cerebellar RS FC for Crus II, but increased cerebellar FC for Lobule VIIb, which was related to memory impairment
Fuchs et al., 2019	74 people with MS 29 HC	Higher cognitive reserve was related to normal RS FC and cognition. This effect attenuated the impact of structural disconnection on CI
Karavasilis et al., 2019	31 people with MS 16 HC	Memory impairment was related to reduced hippocampal RS FC
Lin et al., 2019	64 people with MS 26 HC	Thalamic subnuclei showed different patterns of RS FC alterations, which were related to CI
Carotenuto et al., 2020	19 people with MS 24 HC	RS FC of specific neurotransmitter networks were related to CI
Has Silemek et al., 2020	33 people with MS 29 HC	Decreased structural FC was related to increased RS FC and worse cognitive performance. Effects were mostly seen in the DMN
Meijer et al., 2020	133 people with MS 48 HC	In people with MS and a long disease duration, structural connectivity loss was worst in long-distance connections, and was related to a more abnormal RS FC. Both functional and structural RS FC changes related to worse CI
Riccitelli et al., 2020	37 people with benign MS 50 HC	Increased RS FC in fronto-temporo-parietal regions was seen in MS, but was not included as a predictor of worse CI in a multivariate model
Wu et al., 2020	17 people with MS and relapse 24 people with MS in remission 23 HC	People with MS undergoing a relapse had more severe RS FC changes, which were related to worse PASAT scores compared to remitting people with MS and HC
Tommasin et al., 2020	119 people with MS 42 HC	Within-network RS FC was higher in MS for DMN, FPN and ECN and were related to less severe disability and PASAT impairment. Lower between-network and whole-brain RS FC was also lower, but related to worse impairments
Bizzo et al., 2021	28 people with MS 28 HC	Better cognitive reserve was related to lower RS FC of the dorsal anterior insula with cuneus and parieto-occipital areas
Jandric et al., 2021	55 cognitively impaired people with MS 47 cognitively	Decreased DMN but increased FPN FC was found in cognitively impaired *vs* preserved people with MS,

Table 4 (*continued*)

Study	Subjects	Main findings
	preserved people with MS 27 HC	combined with altered cerebral blood flow and structural disconnection
Dekker et al., 2021	295 people with MS 96 HC	Event-based model showed early involvement of DMN centrality changes related to disability and cognitive progression
Marchesi et al., 2021	116 people with MS 65 HC	RS FC of working memory, ECN, salience network and DMN related to worse Wisconsin card sorting outcomes
Pasqua et al., 2021	119 people with MS 42 HC	Increased cerebellar RS FC related to lower cognitive and physical disability
Soares et al., 2021	21 people with MS 17 HC	Lower RS FC was related to white matter lesion load and information processing
Buyukturkoglu et al., 2021	181 people with early MS	Machine learning approaches were able to differentiate low- and high-performing SDMT groups. Predictors included measures of atrophy, white matter damage and hub RS FC
Conti et al., 2021	84 cognitively impaired people with MS 192 cognitively preserved people with MS 102 HC	Regression models included atrophy and FA-based disconnection, but did not include RS FC as measures of importance for explaining CI
Veréb et al., 2021	24 people with MS 25 HC	The significantly increased leftward laterality of the angular gyrus in MS related to higher BVMT-R scores

Abbreviations: CIS = clinically isolated syndrome; SP = secondary progressive; PP = primary progressive; CI = cognitive impairment; PASAT = paced auditory serial addition test; EDSS = expanded disability status scale; SDMT = symbol digit modalities test; BVMT-R = brief visuospatial memory test- revised; GM = grey matter; DMN = default mode network; FPN = fronto-parietal network; ECN = executive control network; ACC = anterior cingulate cortex; PCC = posterior cingulate cortex; MD = mean diffusivity; FA = fractional anisotropy; BOLD = blood-oxygenation level dependent.

hippocampus, (Roosendaal et al., 2010; Hulst et al., 2015; González Torre et al., 2017; Karavasilis et al., 2019) thalamus, (Rocca et al., 2018; Conti et al., 2021; Tona et al., 2014; Schoonheim et al., 2015) and cerebellum, (Pasqua et al., 2021; Sbardella et al., 2017; Cocozza et al., 2018) led to similar results as large-scale network analysis, again showing both increased and decreased RS FC related to cognitive impairment, but with some more specificity in the association with distinct symptoms. Even investigations of small sub-structures, such as individual thalamic nuclei, showed a similar variation of increased and decreased RS FC. (d'Ambrosio et al., 2017; Lin et al., 2019) Interestingly, cortical areas showing altered RS FC with these individual structures are mostly part of the DMN and FPN. Taken together, previous literature is concordant in showing extensive RS FC changes with different directionalities, mostly associated to MS cognitive dysfunction. Combined with task studies, the field currently hypothesizes that beneficial changes in brain function might solely appear in the form of hyperactivation, and that RS FC patterns should remain as normal as possible. The prowess of maintaining a normal connectivity patterns to preserve cognition was also related to cognitive reserve, in the form of higher levels of education. (Fuchs et al., 2019; Bizzo et al., 2021) Since an abnormally low (or high) RS FC within critical large-scale networks is essential to explain cognitive deficits, the focus of recent research was to find the best way to quantify "network deviance". One way to do this was to quantify how strong functional connections deviates from those derived from an healthy control network, and put such deviations in relationship with cognitive impairment. (Meijer et al., 2018; Meijer et al., 2020) However, this approach does have limited information, as it cannot describe precise network functions.

3.3. Advanced network analyses

Studies mentioned in the previous section assessed RS FC in the main large-scale functional networks of the brain with different approaches. These include independent component analysis and seed-to-voxel correlation analysis, with a consequent variability of included regions and associated connectivity scores. One possible way to overcome such limitations might be to integrate raw RS FC measures into a more complex system, and analyze "whole-network" features rather than individual connections. (Schoonheim et al., 2015) In the field of network neuroscience (Bassett and Sporns, 2017) this can be done using graph theoretical analysis. Here, the brain is represented as a network (graph) of interconnected brain regions (nodes). This approach is interesting because it allows to analyze several graph parameters, quantifying the level of integration (e.g., path length) and segregation (e.g., clustering coefficient), how integrated sub-networks are into the entire network (e. g., modularity) or how hub-like a region is (e.g., centrality). Early work in MS showed a more random path length, (Hardmeier et al., 2012) indicating a loss of network efficiency in relation to cognitive dysfunction, especially in men. Modularity analyses showed that more segregated subnetworks are related to worse PASAT performance. (Gamboa et al., 2014).

Overall, trajectories of network changes in MS seem to follow the scheme presented in Fig. 2. At early disease stages, or when structural damage is still limited, network abnormalities mainly consist in a loss of long-range connections and increased local efficiency/modularity as well as hyperactivation, which together may have a compensatory role and help to maintain preserved cognitive abilities. Later on in the disease, as structural damage progresses, a failure of functional compensation occurs, characterized by severe loss of connections and network efficiency and hypoactivation. This leads to a "network collapse" (Schoonheim et al., 2015) and cognitive impairment, although this concept likely also applies to other clinical symptoms such as disability.

Hub analyses indicated vastly altered hub patterns related to cognitive impairment (both in terms of spatial location and strength). (Rocca et al., 2016; Buyukturkoglu et al., 2021) Centrality analyses showed that specific subsystems of the whole-brain functional network were related to specific MS disease features, for instance DMN and ventral stream changes were related to cognition, while sensorimotor changes were related to disability. (Schoonheim et al., 2014; Eijlers et al., 2017; Dekker et al., 2021) Of note, segregation (quantified by means of the inverse of path length) was associated to disability, indicating that increasing connectivity within the motor system leads to a loss of normal "local efficiency". Effects were centered around the thalamus and primary sensorimotor cortex. (Strik et al., 2021) As this field continues to grow with new measures developed continuously, the search for an optimal measure of "efficiency" continues.

4. fMRI to explore changes over time of activation patterns and RS FC in MS

Longitudinal fMRI studies have been performed to monitor changes over time of task-related fMRI activation or RS FC, and to monitor the effects of rehabilitative or pharmacological treatments. A list of relevant studies evaluating longitudinal task-based fMRI and RS FC changes occurring in people with MS is provided in Table 5.

4.1. Task-based studies

Longitudinal active fMRI studies have been performed to investigate several aspects of MS, including clinical recovery from relapses (Pantano et al., 2011; Reddy et al., 2000) or pseudo-tumoral lesions, (Mezzapesa et al., 2008) effects of pharmacological treatments, (Parry et al., 2003; Mainero et al., 2004; Rocca et al., 2007) and effects of motor and cognitive rehabilitation. (Bonzano et al., 2019; Cerasa et al., 2013; Chiaravalloti et al., 2012; Dobryakova et al., 2014; Ernst et al., 2012;
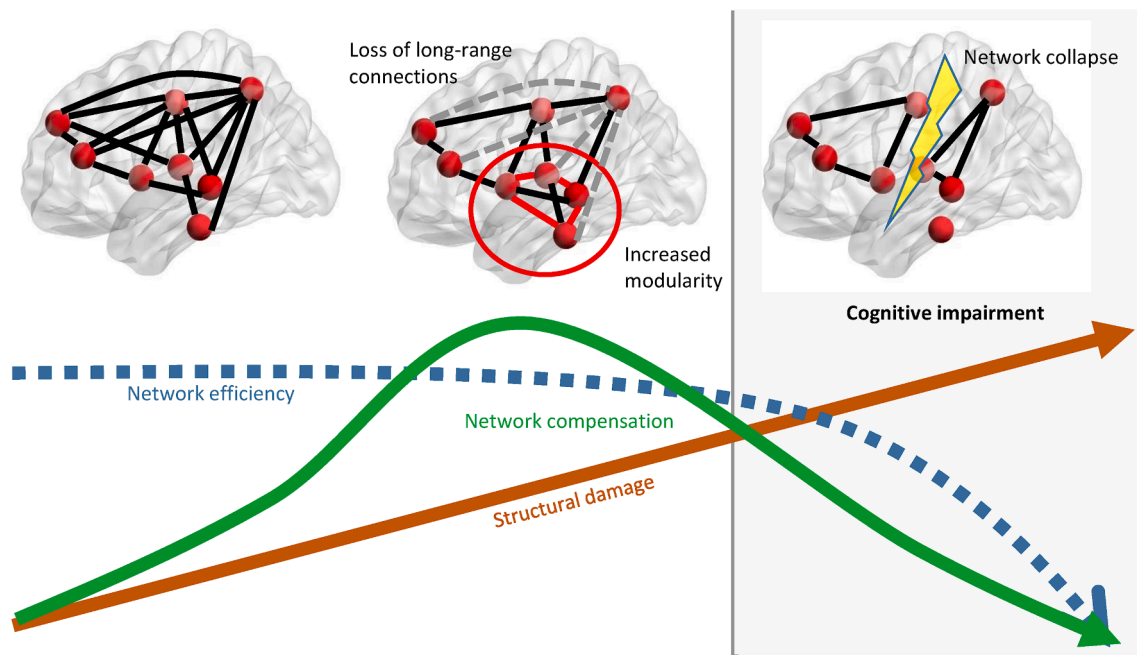
Fig. 2. Schematic representation of the behavior of network functional connectivity (FC), assessed using graph theoretical analysis, in relation to cognitive impairment in people with multiple sclerosis (MS) (see (Schoonheim et al., 2015) for details). At the beginning of the disease and/or when structural damage is still limited, network metrics show some compensatory abnormalities, mainly consisting in a loss of long-range connections and increased modularity, as well as regional hyperactivation, which contribute to maintain network efficiency. As disease and structural damage progresses, further loss of functional connections leads to a loss of network efficiency and eventually a network collapse and cognitive impairment.

Filippi et al., 2012; Huiskamp et al., 2016; Morgen et al., 2004; Péran et al., 2020; Rocca et al., 2019; Sastre-Garriga et al., 2011; Sulpizio et al., 2021; Tavazzi et al., 2018; Tomassini et al., 2012; Zuber et al., 2020) Also, observational studies simply monitoring how patterns of fMRI activation evolve over time in these patients have been performed. (Audoin et al., 2008; Loitfelder et al., 2014; Pantano et al., 2005).

Overall, results showed that at the time of an acute clinical relapse, people with MS experienced abnormally high baseline fMRI activity in homologous regions of the unaffected hemisphere, (Mezzapesa et al., 2008; Pantano et al., 2011; Reddy et al., 2000) which tended to return to normal levels during follow-up, (Mezzapesa et al., 2008; Reddy et al., 2000) especially in people with good clinical recovery. (Mezzapesa et al., 2008; Pantano et al., 2011; Reddy et al., 2000) A "normalization" of fMRI activation was also observed when administering symptomatic treatments such as rivastigmine and 3,4-diaminopyridine. (Parry et al., 2003; Mainero et al., 2004) On the other hand, reversible fatigue due to interferon-beta 1a treatment was associated with dynamic abnormal recruitment of fronto-thalamic pathways during motor tasks. (Rocca et al., 2007).

Studies using fMRI to monitor the effect of motor rehabilitation were all concordant in showing a more "efficient" pattern of fMRI activation at follow-up compared to baseline, mainly consisting in a decreased activity of high-order, integrative regions, (Péran et al., 2020; Tomassini et al., 2012; Zuber et al., 2020) a more focused activation of the sensorimotor network, (Morgen et al., 2004; Péran et al., 2020; Tavazzi et al., 2018; Zuber et al., 2020) and restoration of lateralization of sensorimotor network activity. (Bonzano et al., 2019) When increased brain activation was found at follow-up *vs* baseline, as in the case of an action-observation training (AOT), (Rocca et al., 2019) such an increase was correlated with amelioration at motor scores following treatment. (Rocca et al., 2019).

Findings from studies assessing fMRI changes after cognitive rehabilitation mainly showed increased fMRI activation at follow-up *vs* baseline, which involved superior and inferior parietal regions, temporal and hippocampal regions, the dorsolateral prefrontal cortex and the precuneus, (Cerasa et al., 2013; Chiaravalloti et al., 2012; Dobryakova et al., 2014; Ernst et al., 2012; Filippi et al., 2012; Huiskamp et al., 2016; Sastre-Garriga et al., 2011) in coherence with the trained cognitive functions, i.e., attention, information processing speed, working memory and executive functions. (Cerasa et al., 2013; Chiaravalloti et al., 2012; Dobryakova et al., 2014; Ernst et al., 2012; Filippi et al., 2012; Huiskamp et al., 2016; Sastre-Garriga et al., 2011) Increased fMRI activation was probably observed in all these studies because enrolled people with MS were cognitively impaired, and showed abnormally low fMRI activity at study entry. In fact, increased fMRI activity was beneficial in all cases, since it was correlated with improved cognitive functions after rehabilitation. (Cerasa et al., 2013; Chiaravalloti et al., 2012; Dobryakova et al., 2014; Ernst et al., 2012; Filippi et al., 2012; Huiskamp et al., 2016; Sastre-Garriga et al., 2011) As such, these studies provide key insights seemingly confirming the adaptive nature of hyperactivation in MS.

Finally, observational studies using motor (Pantano et al., 2005) and cognitive (Audoin et al., 2008; Loitfelder et al., 2014) fMRI paradigms showed patterns of functional reorganization resembling those obtained during motor and cognitive rehabilitation, with decreased sensorimotor activation over time in younger people with MS, or in people with less severe structural damage, (Pantano et al., 2005) and with increased fronto-parietal activation over time in people with MS improving their cognitive performances. (Audoin et al., 2008) However, some maladaptive increments of fMRI activity in the inferior parietal lobule, correlated with worse SDMT performance, have also been described. (Loitfelder et al., 2014).

4.2. RS FC studies

Longitudinal patterns of RS FC changes in relation with MS clinical disability have been investigated in two studies so far. (Faivre et al., 2016; Cui et al., 2017) The first was performed by Faivre et al., showing that a higher RS FC at baseline was related to preserved motor function, but that this mechanism was lost over time, suggesting that longitudinal RS FC decreases are associated to a loss of beneficial plastic changes, or to maladaptation. (Faivre et al., 2016) The second, by Cui et al., showed

Table 5

Summary of the most important task-based and resting state (RS) functional magnetic resonance imaging (fMRI) studies analyzing longitudinal changes over time of brain activation and functional connectivity (FC) in people with multiple sclerosis (MS).

Task-based fMRI studies			
Study	Subjects	Task	Main findings
Reddy et al., 2000	1 MS after the new onset of hemiparesis from relapse	Index finger-thumb opposition	Clinical improvement was associated with recovery of N-acetylaspartate, and with reduction of abnormally large fMRI activation with movement
Parry et al., 2003	5 people with MS 4 HC	Stroop task	BOLD signal intensity change was 56% lower after rivastigmine administration in left medial prefrontal regions compared with placebo for the patients
Morgen et al., 2004	9 people with MS 9 HC	Visually-cued thumb flexion–extension	Before training, thumb movements elicited more prominent fMRI activation of the contralateral premotor cortex in people with MS than in HC. After training, unlike HC, people with MS did not exhibit task-specific fMRI reductions
Mainero et al., 2004	12 people with RRMS	Index finger-thumb opposition	FMRI activity was higher after receiving 3,4-diamionopyridine than under placebo in the ipsilateral sensorimotor and supplementary motor cortex
Pantano et al., 2005	18 people with MS 9 HC	Finger to thumb opposition with the right hand (index, medium, ring and little fingers)	People with MS exhibited greater bilateral fMRI activation than HC at baseline and follow-up. In younger MS people and in those with lower structural damage, follow-up fMRI activity decreased vs baseline in motor and cerebellar areas
Rocca et al., 2007	22 people with RRMS	Task 1: flexion–extension of the last four fingers of the right hand Task 2: flexion–extension of the right hand and right foot	After interferon-beta 1a injection, people with MS with reversible fatigue showed an abnormal recruitment of the fronto-thalamic circuitry
Mezzapesa et al., 2008	12 people with RRMS 15 HC	Flexion-extension of the last four fingers of the right hand	In people with MS and a pseudo-tumoral lesion, baseline ipsilateral sensorimotor cortex fMRI activity was higher with the impaired than the unimpaired hand. FMRI recovery in the

Table 5 (*continued*)

Task-based fMRI studies			
Study	Subjects	Task	Main findings
			contralateral primary sensorimotor cortex at follow-up was found in clinically improved MS people
Audoin et al., 2008	13 people with CIS 19 HC	PASAT task	People with MS improving at PASAT performance after one year showed larger increase in fMRI activation between month 0 and month 12 in the right lateral prefrontal cortex compared to stable/worsening people
Pantano et al., 2011	32 people with RRMS (19 after onset of a clinical relapse, 13 stable)	Flexion-extension of the last four fingers of the right hand	During a motor task, patients acquired within 48 h from the beginning of a clinical relapse showed a significant difference of fMRI activation in the ipsilateral precentral gyrus compared to stable MS people, indicating reduced deactivation. Longitudinal changes in precentral gyrus activity over two months were significantly greater in relapsing than in stable MS people
Sastre-Garriga et al., 2011	15 people with MS 5 HC	PASAT task	After cognitive rehabilitation, people with MS and cognitive impairment increased their fMRI activation in several cerebellar areas
Filippi et al., 2012	20 people with RRMS (10 treatment group, 10 control group)	Stroop task	In a group of people with MS undergoing 12-week cognitive rehabilitation, fMRI demonstrated modifications of activity of the posterior cingulate cortex/precuneus and dorsolateral prefrontal cortex compared to a control group
Ernst et al., 2012	8 people with RRMS 15 HC	Evocation of unique personal past events	After undergoing a facilitation session to potentiate autobiographic memory functions, people with MS showed significant increase of fMRI activations in occipital, temporal and precuneus regions during a memory task
Tomassini et al., 2012	23 people with MS 12 HC	Visuomotor task: to track vertical movements of a computer-controlled bar	People with MS undergoing two sessions of the visuomotor task (session I: short-term practice; session II: longer-term practice, after 2 weeks of daily

Table 5 (*continued*)

Task-based fMRI studies Study	Subjects	Task	Main findings
			practice with the same task) showed an association between short-term improvements and lower sensorimotor, parietal and hippocampal fMRI activation
Chiaravalloti et al., 2012	16 people with MS (8 treatment group, 8 control group)	Word learning task Word recognition task	In people with MS undergoing behavioral treatment for memory deficits, greater activation was evident during performance of a memory task within a widespread cortical network involving frontal, parietal, precuneus, temporal and parahippocampal regions
Cerasa et al., 2013	23 people with MS (12 treatment group, 11 control group)	PASAT task	After a 6-week attention training, treated people with MS, compared with control people, showed enhanced performance in attention abilities, which was associated with increased fMRI activity in the cerebellum and in the superior parietal lobule
Loitfelder et al., 2014	13 people with RRMS 15 HC	Go-NoGo task	At baseline and after 20 months of follow-up, people with MS showed increased activation *vs* HC in the insular, parietal, occipital and cerebellar cortex. Over time, people with MS (but not HC) demonstrated fMRI activity increments in the inferior parietal lobule
Dobryakova et al., 2014	8 people with MS (6-month follow-up of the treated group in (Chiaravalloti et al., 2012)	Word learning task Word recognition task	Greater fMRI activity in parietal, occipital, cerebellar and prefrontal regions *vs* baseline was confirmed after 6 months from the end of training
Huiskamp et al., 2016	16 people with MS (7 treatment group, 9 control group)	0-, 1-, and 2-back task	During a N-back task, significant increases in fMRI activation were seen in the dorsolateral prefrontal cortex, supplementary motor area and inferior parietal lobule at follow-up in the treatment group. No significant changes were noted in the control group
Tavazzi et al., 2018	29 people with MS		After a 4-week neurorehabilitation,

Table 5 (*continued*)

Task-based fMRI studies Study	Subjects	Task	Main findings
		Plantar dorsiflexion of the left and right foot	people with MS showed a less widespread activation, and a more focused activation of sensorimotor areas. fMRI changes were not maintained after 3 months from rehabilitation end
Rocca et al., 2019	41 people with MS (20 action-observation training, 21 control training) 46 HC (23 action-observation training, 23 control training)	Right hand object manipulation	After 2 weeks of training, compared to HC-Control, action observation training HC had greater fMRI activation of the left precentral gyrus. Compared to MS-Control, MS undergoing action observation training had greater fMRI activation of bilateral inferior frontal and left insular regions, which correlated with improved motor scores
Bonzano et al., 2019	30 people with MS (15 training voluntary movements, 15 training passive movements)	Index finger-thumb opposition	After 8-week upper limb training based on voluntary movements, people with MS showed increased lateralization of fMRI activity compared to people with MS undergoing passive movement training
Peran et al., 2020	30 people with progressive MS	Mental simulation of actions, mime of actions and passive movements	After multidisciplinary rehabilitation, decreased fMRI activation was found in MS in circuits that are normally activated by the tasks
Zuber et al., 2020	24 people with relapse-onset MS 24 HC	Motor sequence learning task	After multidisciplinary rehabilitation, decreased fMRI activation was found in MS in the left cerebellum and right prefrontal lobe, which was maintained at longer-term follow-up
Sulpizio et al., 2021	9 people with MS (4 undergoing standard rehabilitation, 5 undergoing rehabilitation with a exoskeleton)	Go-NoGo task	After 6-week rehabilitation, the group treated using the exoskeleton showed decreased fMRI activation in inferior frontal regions compared to the standard rehabilitation group
RS fMRI studies			
Faivre et al., 2016	38 people with MS 24 HC		At baseline, RS FC was higher in people with MS *vs* HC and related to less severe disability. During follow-up, RS FC decreases were related to worse disability progression
Cui et al., 2017	20 people with MS 15 HC		Striatal subregions were explored, showing relations with EDSS for dorsal striatal-prefrontal and parietal connections. After 7 months, stable results were found

Table 5 (*continued*)

Task-based fMRI studies

Study	Subjects	Task	Main findings
Parisi et al., 2014	10 people with MS + treatment 10 people with MS - treatment		ACC-parietal RS FC increased during the program, while ACC-temporal RS FC decreased. ACC-parietal RS FC was related to improved PASAT performance
Leavitt et al., 2014	7 people with MS + treatment 7 people with MS - treatment		Hippocampal RS FC increases correlated with memory rehabilitation
Parisi et al., 2014	9 people with MS + treatment 9 people with MS - treatment		Longer-term follow-up compared to the previous paper. (Parisi et al., 2014) DMN RS FC predicted cognitive performance
Bonavita et al., 2015	18 cognitively impaired people with MS + treatment 14 cognitively impaired people with MS - treatment		Following cognitive rehabilitation, RS FC and cognitive performance was increased. Stroop improvement was related to increased PCC RS FC
Koubiyr et al., 2019	32 people with CIS 10 HC		Coupling of structure and function within modules declined after one year in patients with CIS preserved cognition.
Welton et al., 2020	37 people with MS 23 HC		Graph analytical parameters based on RS FC indicated that network segregation was positively related to processing speed, while integration was inversely related. Re-scan after one month showed good reliability
Huiskamp et al., 2020	15 intervention people with MS 14 waiting-list people with MS		Longitudinal increases in hippocampus-DMN RS FC were related to improved visuospatial memory, but only in people with MS undergoing exercise therapy
Meng et al., 2021	52 people with MS 36 HC		Cross-sectionally reduced effective connectivity of the dorsolateral prefrontal cortex was related to worse PASAT scores. Follow-up measurement after eight months was stable
Huiskamp et al., 2021	123 cognitively preserved people with MS 32 mild cognitively impaired people with MS 72 cognitively impaired people with MS 59 HC		DMN centrality was higher in cognitively preserved people with MS (cross-sectionally), while ventral attention network centrality longitudinally increased in cognitively preserved people with MS converting to mild cognitively impaired
Koubiyr et al., 2021	32 people with CIS 10 HC		Structural-functional coupling (assessed by means of correlation between connectivity strengths) went up after five years. Such increase related to cognitive and disability progression

Abbreviations: MS = multiple sclerosis; RR = relapsing-remitting; CIS = clinically isolated syndrome; HC = healthy controls; PASAT = paced auditory serial addition test; BOLD = blood-oxygenation level dependent; EDSS = expanded disability status scale; DMN = default-mode network; ACC = anterior cingulate cortex; PCC = posterior cingulate cortex.

that striatal RS FC was related to EDSS at baseline, and remained stable after 7 month follow-up. (Cui et al., 2017).

With regard to cognition, longitudinal RS FC patterns have been explored in ten studies. Of these, the first four published were all related to cognitive rehabilitation. Parisi et al. published two papers of the same three-month computerized cognitive rehabilitation trial involving attention, information processing and executive functions, and showed that within-DMN RS FC increased during the program and was related to improved PASAT performance. (Parisi et al., 2014) In addition, longer-term follow-up outcomes were predicted by DMN RS FC levels. (Parisi et al., 2014) Two subsequent studies by Leavitt et al. (hippocampal RS FC and memory rehabilitation) and Bonavita et al. (Bonavita et al.,

2015) (DMN RS FC and computerized cognitive rehabilitation of attention, executive and logical functions) also showed increasing RS FC following rehabilitation, in relation to improving cognitive performance. Such treatment effects were further explored in later studies, for instance Huiskamp et al., (Huiskamp et al., 2020) who related increasing longitudinal hippocampal-DMN RS FC to improved memory after an exercise rehabilitation.

Subsequent work has mostly focused on describing patterns of RS FC changes over time in relation to clinical progression. Welton et al. (Welton et al., 2020) showed that network segregation alterations related to processing speed remained stable after a one-month scan-rescan. Similarly, Meng et al. (Meng et al., 2021) showed that reduced frontal RS FC was related to worse PASAT performance, which remained stable after eight months. Longitudinal studies showing the actual progression of network changes related to worsening cognition remain rare. Koubiyr et al. (Koubiyr et al., 2021; Koubiyr et al., 2019) recently published on people with CIS, (Koubiyr et al., 2021) identified that the correlation between structural and functional connectivity was increased after five years, and was related to cognitive and disability progression. In addition, relations of more advanced modularity-based graph measures decoupled in people with CIS with preserved cognition after one year. (Koubiyr et al., 2019) The most recent paper investigating longitudinal network changes related to cognitive progression was performed by Huiskamp et al. (Huiskamp et al., 2021) This study investigated network patterns in different subgroups transitioning between cognitively preserved, mild cognitively impaired and cognitively impaired subgroups. Results showed that cognitively preserved and mild cognitively impaired people with MS with worsening cognition showed also increasing ventral attention (salience) network RS FC over time, while cognitively impaired people with MS mainly showed increased DMN RS FC. The ventral attention network is mainly composed of the insula and anterior cingulate cortex, whose role is especially related to balancing of intrinsic and extrinsic stimuli. (Uddin, 2015) As such, it is thought to be the balancing factor between the DMN and FPN, ensuring a normal network efficiency during different requirements. This suggests that different networks could be affected with evolving disease, perhaps starting with an overloaded salience system, leading towards DMN and FPN disruption. However, as mentioned previously, further longitudinal studies in MS remain crucially needed to be able to disentangle the distinct processes leading to clinical progression in the different disease stages.

5. Spatiotemporal profiles of functional reorganization: time-varying analysis of resting state functional connectivity

While MS functional network mapping continued, it became clear from work on the healthy brain that the balance between different networks shifts during specific cognitive requirements and that these shifts are clinically relevant. (Braun et al., 2015) Moreover, neurophysiological techniques have consistently shown that brain FC varies at very fast time scales also during resting conditions. This "dynamic" or "time-varying" reconfiguration of brain networks also became technically feasible to be evaluated in recent years. (Bassett and Sporns, 2017) Traditionally, FC among brain regions or networks has been assessed using the whole dataset of fMRI scans acquired during a session. This setting, which was used in all studies described in sections 2–4, relies on the assumption that FC is stationary across the whole fMRI examination. (Biswal et al., 2010) Time-varying connectivity (TVC, also termed "dynamic" FC) is a novel technique aiming at quantifying how variable FC is during the course of fMRI acquisition, and at detecting reoccurring connectivity patterns among functional brain networks or regions. (Hutchison et al., 2013; Calhoun et al., 2014) TVC usually consists in assessing FC over a series of shifting temporal segments of the fMRI acquisition (sliding windows), and then calculating summary metrics of FC dynamism over windows, or using clustering techniques to characterize reoccurring states of FC across windows. (Calhoun et al., 2014;

Valsasina et al., 2019) TVC has provided significant information on intrinsic functional brain properties, both in HC and in different psychiatric and neurological diseases, that complements data derived by static FC analysis. (Calhoun et al., 2014; Filippi et al., 2019; Hutchison et al., 2013; Valsasina et al., 2019).

This section summarizes findings of studies examining TVC abnormalities of people with MS (reported in Table 6), with a particular focus on disability and neuropsychological correlates of detected TVC modifications.

5.1. TVC analysis in MS: disability correlates

The first study assessing TVC abnormalities in MS was that from Leonardi et al., (Leonardi et al., 2013) who mainly found increased FC dynamism of parietal regions of the DMN, as well as decreased FC dynamism in frontal and subcortical regions in people with RRMS and mild-to-moderate disability. Similar results were obtained by Bosma et al., (Bosma et al., 2018) who showed increased FC variability in posterior DMN regions in people with MS vs HC, together with an association between higher TVC of salience-nociceptive networks and neuropathic pain. The first study depicting the presence of a significant association between clinical disability and TVC abnormalities in MS was that of Zhou et al., (Zhou et al., 2016) who found increased TVC (expressed as brain entropy) in angular, prefrontal and sensorimotor brain regions, this latter correlated with a higher EDSS score. Conversely, decreased entropy in parahippocampal and temporal regions were correlated with lower fatigue severity scores.

Recent TVC studies characterized heterogeneity of dynamic FC abnormalities across different MS phenotypes. This was achieved by using a more advanced TVC analysis, which looks at re-occurring states of FC patterns (also termed "states"), (Allen et al., 2014) and quantifies their temporal features, such as their occurrence and frequency of transitions. Using this approach, people with CIS showed, early after the first demyelinating attack, a decrease of TVC in the functional networks mostly affected by the attack. (Rocca et al., 2020) During the subsequent two years, however, TVC tended to increase in most of relevant networks, including the DMN, sensorimotor and cognitive networks. (Rocca et al., 2020) In RRMS, a study based on clustering techniques evidenced a widespread decrease of TVC in reoccurring states characterized by low FC, involving the sensorimotor, cerebellar and cognitive networks. (Hidalgo de la Cruz et al., 2021) However, a selective increase of TVC in middle/high-connected states was also detected. (Hidalgo de la Cruz et al., 2021) Such a pattern was confirmed by a recent study focusing on cerebellar connections, which found a selective increase of TVC between the cerebellum and basal ganglia in this phenotype. (Schoonheim et al., 2021) When looking at people with progressive MS, mixed patterns of TVC abnormalities were detected. Overall, decreased TVC in the DMN, (Hidalgo de la Cruz et al., 2021; Bommarito et al., 2021) as well as in sensorimotor and visual networks (Hidalgo de la Cruz et al., 2021) was found in progressive MS. However, more severe disability in people with MS was also characterized by abnormally high TVC in frontal/attention networks (Hidalgo de la Cruz et al., 2021) and between cerebellum and DMN, attention and basal ganglia networks, (Schoonheim et al., 2021) suggesting a maladaptive mechanism.

5.2. TVC analysis in MS: Cognitive correlates

The field of cognitive analyses is still young. As mentioned in the static RS FC section, there are clear insights from earlier work leading to the hypothesis that the balance between DMN, FPN and salience networks is disrupted in cognitively impaired people with MS. Given the above-mentioned methodological innovation, TVC could provide unique insights into this hypothesis. The first study relating TVC to cognition in MS was by Lin et al., showing that reduced network variations was related to worse cognition. (Lin et al., 2018) Overall, as in static FC, also in TVC studies network abnormalities were more severe in

Table 6

Summary of the most important resting state (RS) functional magnetic resonance imaging (fMRI) studies analyzing time-varying functional connectivity (TVC) in people with multiple sclerosis (MS).

Study	Subjects	Main findings
Leonardi et al., 2013	22 people with RRMS 14 HC	Compared to HC, people with MS showed increased TVC in parietal regions and decreased TVC in prefrontal regions and amygdala
Zhou et al., 2016	34 people with RRMS 34 HC	Brain entropy was increased in people with MS vs HC in motor, executive control, coordination and memory regions; increased entropy correlated with higher clinical disability
Bosma et al., 2018	31 people with MS 31 HC	Compared to HC, people with MS had greater TVC, especially in the salience and nociceptive network. Abnormal TVC correlated with the presence of neuropathic pain
Lin et al., 2018	55 people with RRMS 15 HC	People with MS had lower network variations but higher flexibility of interhemispheric connections vs HC. A higher connectivity dynamism was associated with better cognitive scores
Van Geest et al., 2018	29 people with MS 18 HC	TVC of the DMN was increased in the task vs resting condition in people with MS compared to HC. Such increase was associated with better information processing speed scores
Van Geest et al., 2018	38 people with MS 29 HC	Decreased TVC in the hippocampus was associated with better cognitive performances at different memory tests
Huang et al., 2019	22 people with RRMS 22 HC	People with MS showed increased TVC between attention networks, but decreased TVC within attention networks, which was correlated with a higher lesion load
Eijlers et al., 2019	87 people with CI MS (MCI was excluded) 180 people with CP MS 96 HC	CI versus CP MS showed reduced centrality dynamics in DMN, FPN and visual networks. DMN and visual dynamics were anti-correlated in HC, but this was lost in CI
d'Ambrosio et al., 2020	62 people with RRMS 65 HC	People with CI MS had reduced TVC between subcortical network and DMN compared to CP MS, and spent less time in a connectivity state characterized by high FC strength
Rocca et al., 2020	50 people with CIS 13 HC	People with CIS exhibited decreased TVC in networks hit by the clinical attack, and increased FC dynamism over two-years of follow-up
Lin et al., 2020	25 people with RRMS 41 HC	In people with MS, higher stationary and dynamic interhemispheric FC between homologous regions was associated with higher scores at different neuropsychological tests
Cordani et al., 2021	41 people with MS 46 HC	Increased TVC in sensorimotor and cognitive networks was found in people with MS following two weeks of action-observation training and, to a lesser extent, following control training
Tijhuis et al., 2021	35 people with RRMS 19 HC	People with MS had higher global TVC compared to HC; in MS, TVC strength between the basal ganglia and DMN explained the presence/absence of fatigue
Hidalgo de la Cruz et al., 2021	128 people with MS 40 HC	People with MS exhibited overall lower TVC, but also marginal increase of TVC in sensorimotor and cognitive networks vs HC in middle/highly connected states. TVC abnormalities were more severe in progressive MS and in CI MS people
Bommarito et al., 2021	22 people with progressive MS 25 HC	Reduced TVC in the anterior DMN and increased TVC in the executive control network was found in people with

Table 6 (*continued*)

Study	Subjects	Main findings
Schoonheim et al., 2021	278 people with MS 41 HC	progressive MS compared to HC. Decreased anterior DMN TVC explained cognitive disability SPMS showed cerebellar connectivity changes, compared to RRMS and HC, including lower static FC in the fronto-parietal network and DMN, and higher TVC in dorsal and ventral attention, DMN and deep grey matter networks. Cerebellar atrophy and higher TVC explained disability and cognitive variance

Abbreviations: MS = multiple sclerosis; CIS = clinically isolated syndrome; RR = relapsing-remitting; SP = secondary progressive; HC = healthy controls; TVC = time-varying connectivity; FC = functional connectivity; DMN = default-mode network; CI = cognitively impaired; CP = cognitively preserved.

cognitively impaired people with MS. (Hidalgo de la Cruz et al., 2021) For instance, a higher RS TVC in the hippocampus was related to poorer cognition, (van Geest et al., 2018) which was also seen for homologous interhemispheric TVC. (Lin et al., 2020) More recently, the network neuroscience field gained interest in alterations of network balance occurring not only at rest, but also between task and rest, which was shown to provide crucial information on a person's cognitive ability, especially for the DMN and FPN. (Douw et al., 2016) In MS, higher TVC in task-states compared to rest was related to better cognitive functioning. (van Geest et al., 2018) Finally, centrality techniques (described in section 3.3) were also evaluated dynamically, showing that cognitive impairment in people with MS was related to a marked reduction of dynamic centrality in the DMN, FPN and visual systems. Relations between networks (i.e., dynamic network interplay) were lost in cognitively impaired MS, which could indicate an impaired proficiency for other networks to "reactivate" and/or "suppress" the DMN. (Eijlers et al., 2019) Finally, TVC states were also related to cognitive impairment, with evidence that patients with cognitive deficits had reduced deep GM and DMN dynamics, with less time spent in a highly connected state. (d'Ambrosio et al., 2020).

TVC abnormalities seem to have also some associations with other symptoms, such as fatigue. (Tijhuis et al., 2021) In a recent study, non-fatigued people with MS had a higher TVC between the basal ganglia and DMN compared to fatigued MS, (Tijhuis et al., 2021) suggesting that increased TVC in this circuit may protect against fatigue. Finally, it was recently shown that TVC can be used in longitudinal studies to monitor plasticity mechanisms occurring after rehabilitative treatments. In MS people undergoing AOT or control trainings, a significant increase of TVC was found in motor and cognitive networks, especially after AOT, (Cordani et al., 2021) which correlated with concomitant clinical improvements.

6. New perspectives for fMRI analysis

6.1. Multimodal data integration

MS is a complex condition, with several pathological processes contributing to clinical and cognitive disability. Therefore, it is likely that integrating information from different MRI modalities, sensitive to distinct pathological substrates, improves disease characterization across various stages. In line with this, recent studies have shown that multivariable models incorporating both functional and structural MRI measures of brain damage (these latter including voxel-based, (Cordani et al., 2020; Conti et al., 2021) region-based (Riccitelli et al., 2020; Hulst et al., 2015; Schoonheim et al., 2015; Fuchs et al., 2019) or source-based morphometry (Cordani et al., 2021; Rocca et al., 2021) of grey matter atrophy, as well as damage to white matter tracts derived from diffusion tensor MRI (Cordani et al., 2020; Conti et al., 2021; Marchesi et al.,

2021; Schoonheim et al., 2015; Cordani et al., 2021)) were able to explain motor impairment, (Cordani et al., 2020; Cordani et al., 2021) cognitive dysfunction (Conti et al., 2021; Marchesi et al., 2021; Riccitelli et al., 2020; Hulst et al., 2015; Schoonheim et al., 2015; Fuchs et al., 2019) and medium-term disease prognosis. (Rocca et al., 2021) Also, studies using advanced network analysis showed that there is a complex interplay between structural and functional network alterations, (Has Silemek et al., 2020; Jandric et al., 2021; Meijer et al., 2020; Koubiyr et al., 2021) with structural disconnection (assessed by means of diffusion-weighted MRI tractography between pairs of brain regions) and functional network abnormalities both contributing to cognitive impairment (Has Silemek et al., 2020; Jandric et al., 2021; Meijer et al., 2020) and medium-term disability progression. (Koubiyr et al., 2021).

Most of previous studies integrated structural MRI and fMRI using multivariate statistical models. However, a direct integration of structural MRI and fMRI while performing data post-processing might be beneficial to produce features improved by shared information between modalities. This is the aim of recently proposed methods, e.g., joint independent component analysis, (Sui et al., 2014) multilayer network analysis, (Kivela et al., 2014) or virtual brain modeling, (Ritter et al., 2013) which were already successfully applied to other neurological and psychiatric conditions. Such approaches hold great promise for an application to MS, since they might be more powerful than single-modality analyses to depict the different pathological substrates associated to this condition.

6.2. Application of artificial intelligence to fMRI data

Artificial intelligence (AI) is an emerging area of computer science, which is able to learn solving various tasks from training examples without an explicit human encoding of prior knowledge. Thanks to its good performance and versatility, AI is increasingly being applied to MRI data of people with MS. In particular, machine learning and deep learning techniques have been successfully employed for a variety of tasks, including lesion and brain tissue segmentation, analysis of different MRI data modalities, differential diagnosis with other white matter disorders and disease prognosis. (Vrenken et al., 2021) To date, most of studies applying AI to MRI data in MS used T2- and T1-weighted imaging, or advanced structural MRI techniques, such as susceptibility-weighted and diffusion-weighted imaging. (Vrenken et al., 2021; Moazami et al., 2021) Nevertheless, recent investigations showed promising results also when applying AI to fMRI data. For instance, Saccà et al. (Saccà et al., 2019) applied five different machine learning techniques to maps of the sensorimotor network (reconstructed by independent component analysis) in 18 people with early MS and 19 HC. Results showed that all five machine learning techniques were able to correctly classify people with MS from HC, with the best accuracies (85.7% in both cases) obtained using random forest and support vector machine. Another study (Buyukturkoglu et al., 2021) applied machine learning to different sets of data (the first one including only clinical and demographic data, the second including lesion information, the third including atrophy metrics, the fourth including diffusion tensor MRI metrics and the fifth one including RS FC measures) derived from 183 people with early MS, divided into "poor" and "good performance" groups according to their SDMT performance. Results showed that a composite classifier, including RS FC among core hubs of seven large-scale networks, together with other atrophy and diffusion tensor MRI features, reached the best classification performance between poor and good SDMT performers (area under the curve = 0.90). Finally, there was some preliminary evidence that different machine learning principles can be used to detect specific RS FC configurations allowing an accurate classification of 113 people with MS with different clinical phenotypes from HC (balanced accuracy of HC *vs* RRMS classification = 72.5%; HC *vs* progressive MS classification = 85.2%; RRMS *vs* progressive MS classification = 76%). (Rocca et al., 2021) These preliminary results encourage a more extensive application of AI to fMRI data of people with

MS, especially for further improvements of classification according to disease severity and for a better prediction of disease prognosis. On the other hand, some limitations should be kept in mind when planning to use AI on medical image data. First, there might be a strong dependence of algorithm performances from selected training data (and from training features, in case of machine learning analysis), leading to a bias in the results. Second, deep learning approaches are affected by the "black-box" issue: since they do not provide information on the features relevant for the classification/prediction task, it might be not easy to correctly interpret or generalize results. Finally, an extensive application of AI to medical data might raise ethical concerns, related to data ownership, security, privacy and AI-based decision making. (Safdar et al., 2020)

7. Conclusions

MS features a combination of adaptive and maladaptive functional brain changes, as seen by the large body of work using FMRI to map MS-related cortical reorganization. Active fMRI studies found abnormal activation patterns in people with MS *vs* HC during motor and cognitive tasks, with a trend towards possibly beneficial higher fMRI activity at early MS stages and maladaptive decreased fMRI activity later on in the disease, suggesting a disease phase-specific progressive exhaustion of adaptive mechanisms. Functional network architecture, as explored by RS FC, was also abnormal in people with MS *vs* HC, and was mainly characterized by a progressive collapse of long-range connections and impaired hub integration, driving motor and cognitive disability through a loss of network efficiency. TVC analysis provided significant information on intrinsic brain organization, complementary to that produced by static RS FC, and indicated a peculiar involvement of sensorimotor and salience networks, as well as of DMN and FPN, indicating a loss of network stability as patients progress. Finally, new interesting perspectives might be the use of multimodal MRI analysis approaches, for a better characterization of network abnormalities. More advanced methods of quantifying structure–function interaction, and the application of AI to fMRI data, may lead to optimized disease classification, monitoring and prognosis.

CRediT authorship contribution statement

Maria A. Rocca: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Menno M. Schoonheim:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Paola Valsasina:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Jeroen J.G. Geurts:** Conceptualization, Writing – review & editing. **Massimo Filippi:** Conceptualization, Writing – review & editing.

Declaration of Competing Interest

M.A. Rocca received speaker honoraria from Bayer, Biogen, Bristol Myers Squibb, Celgene, Genzyme, Merck Serono, Novartis, Roche, and Teva, and receives research support from the MS Society of Canada and Fondazione Italiana Sclerosi Multipla. M.M. Schoonheim serves on the editorial boards of Neurology and Frontiers in Neurology, receives research support from the Dutch MS Research Foundation and has served as a consultant for or received research support from Atara Biotherapeutics, Biogen, Celgene, Genzyme, MedDay and Merck. P. Valsasina received speaker honoraria from Biogen Idec. J.J.G. Geurts has served as a consultant for or received research support from Biogen, Celgene, Genzyme, MedDay, Merck, Novartis and Teva. M. Filippi is Editor-in-Chief of the *Journal of Neurology* and Associate Editor of

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