Multiple Sclerosis and Pain

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Abstract

In this chapter, we address a frequent and debilitating symptom—pain of one of the most common causes of neurological disability in the young adult: multiple sclerosis. We introduce multiple sclerosis and define the role of neuroimaging in the diagnosis of the disease and beyond. Pain syndromes in multiple sclerosis are described, as well as other comorbidities that may interfere or be associated with pain. We discuss the published literature in neuroimaging and pain in multiple sclerosis, and emphasize the impact of chronic pain in an already non-resilient brain.

Keywords

Plaque · Myelin · Lhermitte · Psychosocial · Default · Resting-state · Demyelination

1 Introduction to Multiple Sclerosis

Multiple sclerosis (MS) is a chronic neurological disease that causes serious morbidity and suffering, and is one of the most frequently observed neurological non-traumatic causes of progressive disability in the young adult.

MS is triggered by environmental factors in individuals with complex genetic risk profiles, and the disease process is of autoimmune inflammatory nature, mediated mainly by T-cells that attack antigens of oligodendrocytes and myelin sheaths [1]. This results in destruction of myelin and eventually of the axons and cell bodies in the central nervous system (CNS). The characteristic histopathological lesion is the plaque, which is a zone of demyelination. Such plaques may occur anywhere in the CNS, but are most frequently found in the spinal cord, particularly in the dorsal columns, in the brainstem, and in the white matter around the ventricles in the forebrain. Apart from the white matter lesions that are easily detected by imaging techniques,

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pathological studies showed that extensive cortical and deep gray matter areas are demyelinated in MS patients [2]. The plaque-centered view of the disease fails to explain clinical deterioration of the patients when they have reached the progressive stage of the disease. It was thus postulated during the past years that besides inflammation there is a neurodegenerative component of the disease that leads to progressive and global brain damage [3]. There is increasing evidence that the severity of the clinical manifestations of MS does not simply depend on the extent of tissue destruction, but rather represents a complex balance among tissue damage, tissue repair, and cortical reorganization.

The early course of the disease is characterized by episodes of neurological dysfunction that usually recover. However, over time the pathological changes become dominated by widespread microglial activation associated with extensive and chronic neurodegeneration, the clinical correlate of which is progressive accumulation of disability [1]. In most patients, clinical manifestations indicate the involvement of motor, sensory, visual, and autonomic systems but many other symptoms and signs can occur. MS first symptoms are frequently of the sensory type, like hypoesthesia (reduced sensitivity to cutaneous stimulation) or paresthesia (subjective cutaneous sensations experienced spontaneously) that starts in an extremity, and progress over days to involve an entire limb. Although pain is a common sensory abnormality of MS, it is rarely the presenting symptom. Symptoms usually remain stable for one or two weeks, and then resolve gradually. Other common symptoms at presentation are blurred vision, diplopia, vertigo, motor deficits, and ataxia. Few of the clinical features are disease specific, but particularly characteristic is Lhermitte's symptom (an electrical sensation running down the spine or limbs on neck flexion) and the Uhthoff phenomenon (transient worsening of symptoms and signs when core body temperature increases) [1]. The clinical evolution of MS is somewhat predictable, occurring usually in relapses in the first years of the disease, with remission of the symptoms and signs (relapsing-remitting—RR), and then becoming progressive with time (secondary progressive MS). There are also other more aggressive subtypes of the disease, like remittent-progressive MS (where the signs and symptoms of the disease do not abate completely after each relapse), and primary progressive MS, that lacks the characteristic episodic evolution, being progressive ad initium. An additional form of the disease is the denominated clinically isolated syndrome, representing the first neurological episode of the disease [4]. In all cases, the clinical course usually evolves over several decades. Death is attributable to MS in two-thirds of cases, and to the increased risk of infection and its complications in individuals with advanced neurological disability; the median time to death is around 30 years from disease onset, representing a reduction in life expectancy of 5–10 years [5].

1.1 Diagnosis of Multiple Sclerosis and the Role of Neuroimaging

There is no single clinical sign or symptom, or diagnostic test that is sufficient to diagnose MS. The diagnosis is mainly clinical, based on several criteria, in which neuroimaging has a key role.

Magnetic resonance imaging (MRI) is the neuroimaging method used in the context of MS, given its safety, availability, and high spatial resolution. Structural MRI can reveal focal or confluent lesions in the brain, both in the white and the gray matter, irreversible tissue loss (atrophy), and demonstrate inflammatory activity of the disease. Moreover, it facilitates the communication of neuroimaging results in a highly reproducible and accurate way, with reference to the brain anatomy, which is essential for the diagnosis and follow-up of the disease.

Magnetic resonance imaging reveals abnormalities in the white matter of more than 95% of patients [1]. The characteristic lesion demonstrated on MRI is the cerebral or spinal plaque. Pathologically, plaques consist of a discrete region of demyelination with a variable extent of axonal injury. Plaques suggestive of MS are

typically found on MRI in the periventricular region, corpus callosum, centrum semiovale, and, to a lesser extent, deep white matter structures and basal ganglia (Fig. 1). Multiple sclerosis plaques usually have an ovoid appearance, and lesions are arranged at right angles to the corpus callosum as if radiating from this area. When viewed on sagittal images, they are referred to as Dawson fingers (Fig. 2) [6].

The most common structural MRI sequence used in the diagnosis and follow-up of MS is T2-weighted turbo spin echo (TSE), which is able to demonstrate well the white matter demyelinating plaques (as hyperintense), both in the supra and infratentorial compartment, and edema (Fig. 3), whereas T1-weighted imaging has a better correlation with clinical disability by detecting hypointense lesions ("black holes") that relate to axonal loss (Fig. 4). Fluid-attenuated inversion recovery (FLAIR) has the highest sensitivity in the detection of lesions close to the cerebrospinal fluid (CSF) in the juxtacortical and the periventricular white matter, although being less sensitive in the evaluation of the structures of the posterior fossa like the cerebellum or the brainstem (Fig. 3) [7, 8]. The double inversion recovery (DIR) pulse sequence attenuates the signal of the CSF as well as of that of the white matter, improving the ability of MRI to detect cortical and juxtacortical lesions (Fig. 5).

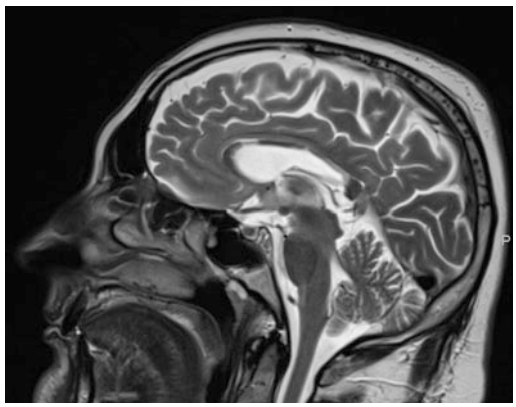

Fig. 1 Sagittal T2-weighted magnetic resonance image showing hyperintense lesions of multiple sclerosis in the corpus callosum. Note the associated atrophy of this commissure

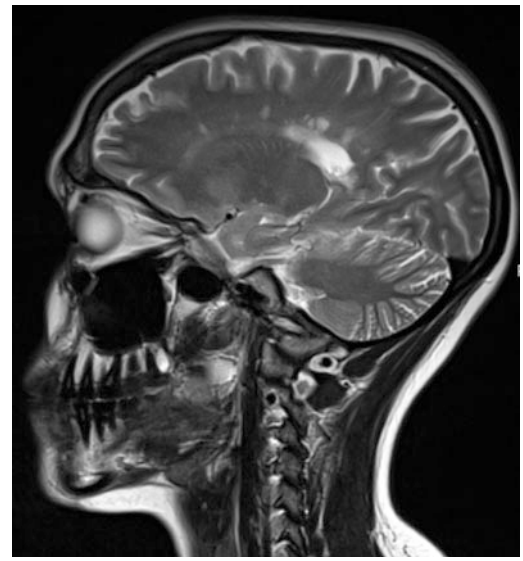

Fig. 2 Sagittal T2-weighted magnetic resonance image showing hyperintense lesions of multiple sclerosis radiating from the corpus callosum, referred to as "Dawson fingers"

Visualization of gray matter lesions may be further improved with the use of ultrahigh magnetic fields (7 T) [9].

Spinal cord MRI is used in studying sensory or motor symptoms in patients with spinal MS, including pain. Images of the spine in the sagittal plane correlate better with the extent of sensory impairments comparing with images in the axial plane [10], and usually include T2-weighted TSE, proton density (PD), and/or short-tau inversion recovery (STIR) sequences (Fig. 6).

Gadolinium-DTPA, a paramagnetic contrast agent that can cross only the disrupted blood–brain barrier, has been used to assess plaque activity, since the accumulation of gadolinium in plaques is associated with new or newly active plaques and with pathologically confirmed acute inflammation in MS (Fig. 7) [11]. Furthermore, gadolinium (Gd) enhancement patterns may provide clues to the diagnosis (and differential diagnosis) and underlying pathology of lesions. Concentric ring-enhancing lesions are thought to be related to accelerated disease activity and extensive tissue damage and may mark a type of inflammation characteristic of more aggressive

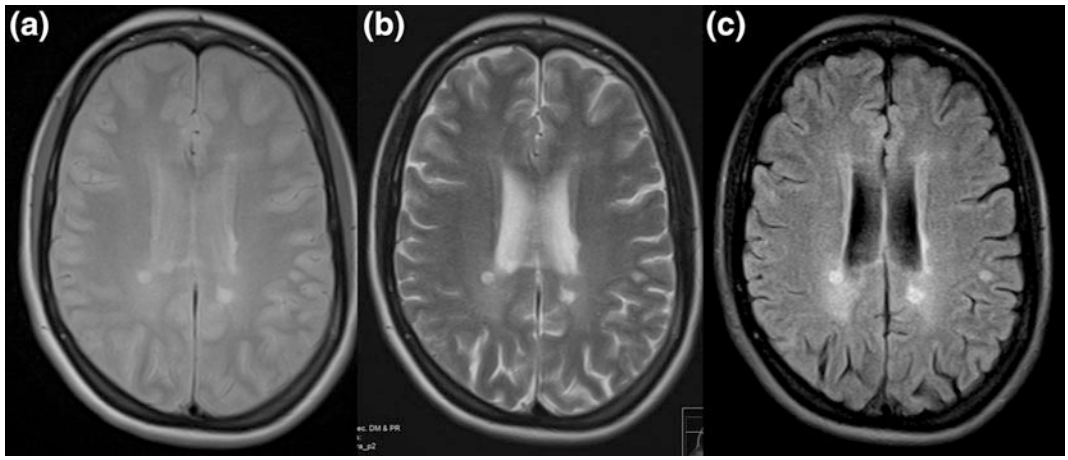

Fig. 3 Axial proton density (**a**), axial T2-weighted (**b**) and axial fluid attenuated inversion recovery (**c**) magnetic resonance images showing multiple, ovoid shaped, hyperintense foci consistent with multiple sclerosis plaques, located in the periventricular white matter

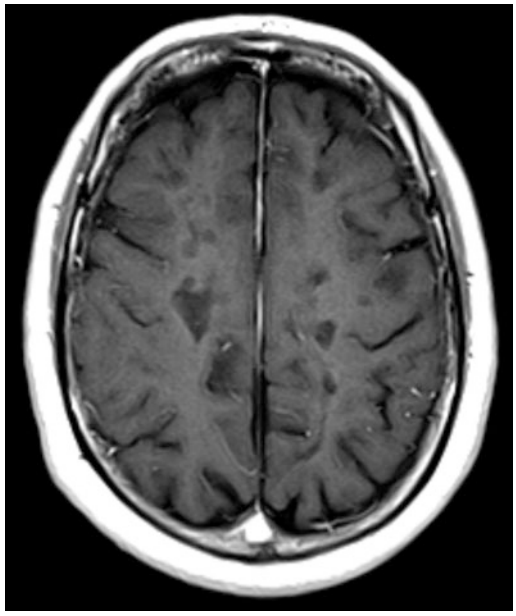

Fig. 4 Axial T1-weighted magnetic resonance image with contrast showing hypointense multiple sclerosis lesions in the centrum semiovale bilaterally, without gadolinium enhancement, the so called "black holes". These lesions are associated with axonal loss

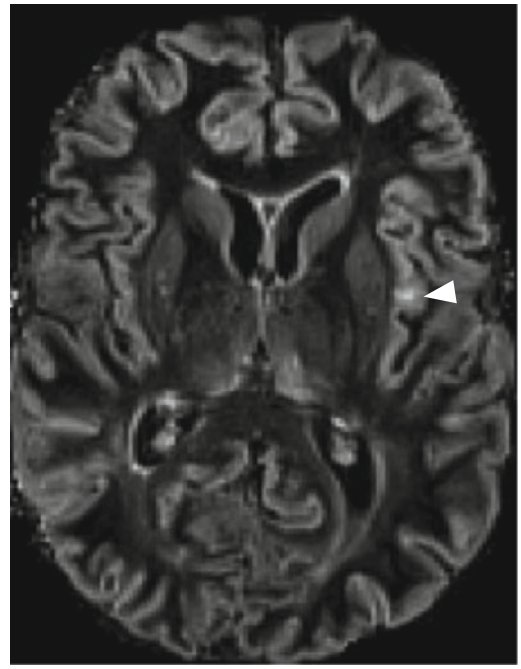

Fig. 5 Double inversion recovery magnetic resonance image revealing a multiple sclerosis plaque on the left insular cortex (*arrow*)

forms of disease [12]. Using higher doses of Gd, thinner slices or delayed imaging increases the sensitivity of Gd-enhanced MRI for the detection of active MS [13].

Not only is MRI an indicator of the anatomical dissemination of lesions, it can also show new plaques appearing over time. The core requirement for the diagnosis of MS is the

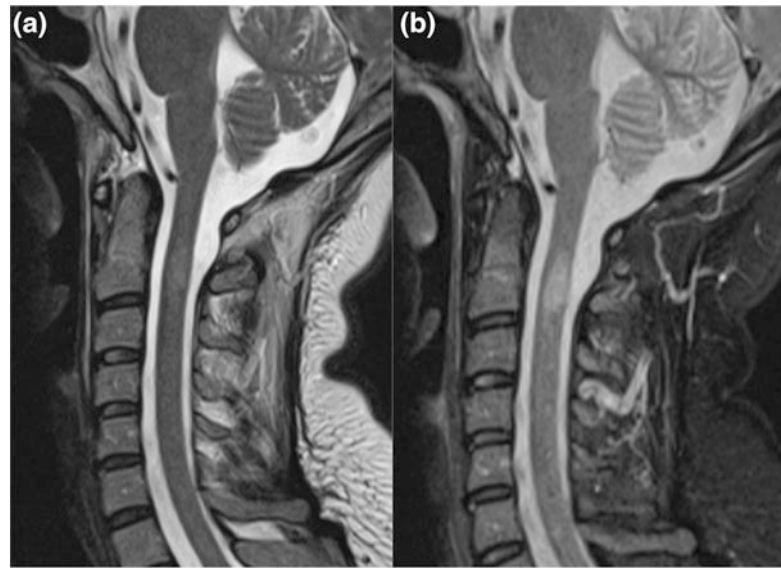

Fig. 6 T2-weighted turbo spin echo (**a**) and short-tau inversion recovery (**b**) sagittal magnetic resonance images showing a hyperintense multiple sclerosis plaque in the cervical spinal cord at the C2 level. Notice the higher sensitivity of the short-tau inversion recovery sequence compared to the T2-weighted sequence to detect lesions in the spinal cord

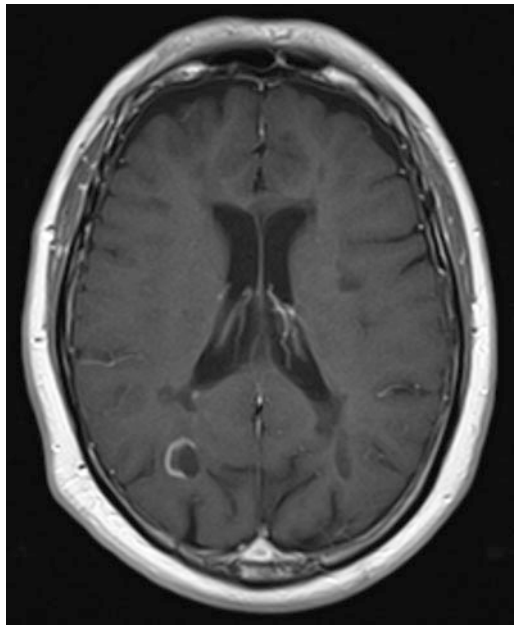

Fig. 7 Axial post-gadolinium T1-weighted magnetic resonance image showing a multiple sclerosis lesion enhancing with an open ring pattern, consistent with acute inflammation ("active" plaque)

demonstration of CNS lesion dissemination in time and space, based either in clinical findings or in a combination of clinical and MRI findings. Depending on the clinical presentation, a set of clinical, imaging, and paraclinical tests are needed to confirm the diagnosis of MS [14].

According to McDonald diagnostic criteria, dissemination in space is demonstrated with MRI by one or more T2 lesions in at least two of four MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord), or by other clinical attack implicating a different CNS site. For patients with brainstem or spinal cord syndromes, symptomatic MRI lesions are excluded from the criteria and do not contribute to lesion count. In its turn, dissemination in time is demonstrated with MRI by the simultaneous presence of asymptomatic Gd-enhancing and non-enhancing lesions at any time, or by a new T2 and/or Gd-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan, or by the development of a second clinical attack [14]. The McDonald diagnostic criteria are presented in Table 1.

It is important to note that characteristic radiological lesions can appear in individuals without clinical signs of the disease, and many older individuals have nonspecific white matter cerebral lesions, which should not be over-interpreted. At any age, lesions detected in the spinal cord are invariably abnormal. Inevitably, diagnostic criteria do not confer absolute protection against error, because other diseases

Table 1 Diagnostic criteria for multiple sclerosis

Clinical presentation	Additional data needed for MS diagnosis
• 2 or more attacks • Objective clinical evidence of 2 or more lesions with reasonable historical evidence of a prior attack	None; clinical evidence will suffice. Additional evidence (e.g., brain MRI) desirable, but must be consistent with MS
• 2 or more attacks • Objective clinical evidence of 1 lesion	Dissemination in space demonstrated by MRI or Await further clinical attack implicating a different site
• 1 attack • Objective clinical evidence of 2 or more lesions	Dissemination in time demonstrated by MRI or second clinical attack
• 1 attack • Objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space demonstrated by MRI or await a second clinical attack implicating a different CNS site and Dissemination in time, demonstrated by MRI or second clinical attack
• Insidious neurologic progression suggestive of MS	One year of disease progression and dissemination in space, demonstrated by two of the following: • One or more T2 lesions in brain, in regions characteristic of MS • Two or more T2 focal lesions in spinal cord Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

Adapted from Polman et al. [14], diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria
MS Multiple sclerosis; *CNS* Central nervous system; *MRI* Magnetic resonance imaging; *CSF* Cerebrospinal fluid; *IgG* Immunoglobulin G

can mimic MS. One of the limitations of using a conventional MRI measure in patients with MS is the discordance between the radiological extent of the lesions and the clinical presentation (clinical-radiological paradox), which other MRI techniques can help resolve [15].

1.2 Neuroimaging in Multiple Sclerosis Beyond the Diagnosis

In recent years, extensive MRI studies have had a major impact on MS, not only in diagnosis but also in the understanding of the disease [14]. By exploiting the natural history and histopathologic correlations, conventional and novel quantitative MRI techniques have demonstrated the ability to image underlying pathological processes in MS [16].

There are many MRI techniques that range from conventional MRI measures used in everyday clinical practice, to techniques more often used in investigating the mechanisms of the disease or as an outcome measure in clinical trials. Conventional MRI has contributed to the understanding of MS at the macroscopic level, but shows relatively weak relationships with clinical status [15]. Magnetic resonance imaging techniques that go beyond conventional anatomical imaging have demonstrated the ability to image underlying pathological processes in MS, and expand our knowledge on the true extent and nature of brain damage and plasticity in MS. These other measures are particularly useful in revealing diffuse damage in cerebral white and gray matter, and therefore are of help in resolving the dissociation between clinical and imaging findings. Advanced qualitative and quantitative MRI methods are thought to be more specific and sensitive for MS underlying pathology.

Quantitative MRI methods such as magnetization transfer ratio (MTR) are increasingly used to assess myelin content and axonal count in MS white matter, since MTR is significantly higher in remyelinated than demyelinated lesions [17]. Magnetization transfer contrast imaging (MTI) also increases sensitivity of Gd [18].

Diffusion-weighted imaging (DWI) is able to demonstrate differences in the magnitude and directionality of water diffusion, giving information about tissue integrity at a microscopic molecular level [19]. Diffusion tensor imaging (DTI) is the basis for white matter fiber tractography, a method to determine the pathways of anatomic white matter connectivity (Fig. 8). White matter tracts, which normally have a high degree of anisotropy due to their linear arrangement, appear with a decreased fractional anisotropy due to the injury of nerve axons or myelin sheaths. Normal-appearing white matter (NAWM) that is immediately adjacent to plaques seen on T2 imaging, may have abnormally reduced anisotropy due to either a less severe demyelization at the periphery of a centrifugally expanding plaque, or due to a continuous process of regression and repair in that area [20].

Myelin-selective MRI studies the MRI-visible water component associated with myelin. Since MS lesions show diffusely reduced NAWM when compared to healthy controls, this technique was validated as a measure of myelin density with the potential to quantitatively define the role of myelin-specific pathology in MS (Fig. 9) [21].

Magnetic resonance spectroscopy (MRS) provides insights into neurodegeneration, tissue repair, and oxidative stress in MS by detecting a range of chemical shifts that depict changes in white matter (Fig. 10) [22]. Phosphorus MRS can convey information on phospholipid metabolism, and proton MRS can generate information about other metabolic components, such as N-acetyl aspartate (NAA, a neuronal marker), creatine phosphate (Cr, an energy marker), choline (Cho, membrane components), and lactic acid (Fig. 10). Chronic MS is associated with a reduced NAA/Cr ratio within the brain, implying loss of neurons or axons. Because these findings can be correlated with disability scores, the use of MRS may prove valuable in monitoring patients after treatment and in prognosis [23].

Functional neuroimaging allows the study of the brain functions in humans in vivo. A subset of patients with MS experiences minimal clinical impairment despite significant lesions on MRI. Functional MRI (fMRI) studies detect changes in

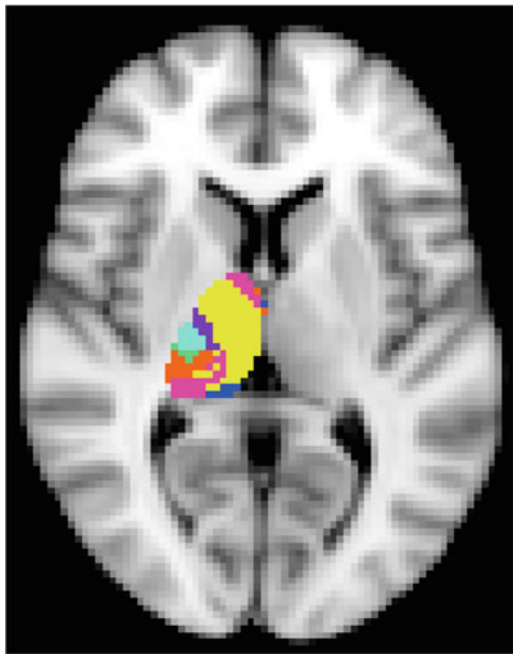

Fig. 8 Segmentation of the nuclei of right thalamus using the magnetic resonance diffusion tensor imaging technique and white matter fiber tractography

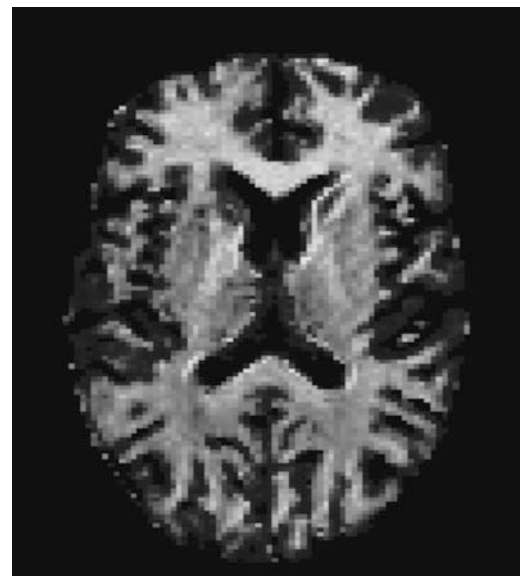

Fig. 9 Myelin water fraction map. The myelin-selective magnetic resonance imaging (MRI) techniques reveal the MRI-visible water component associated with myelin

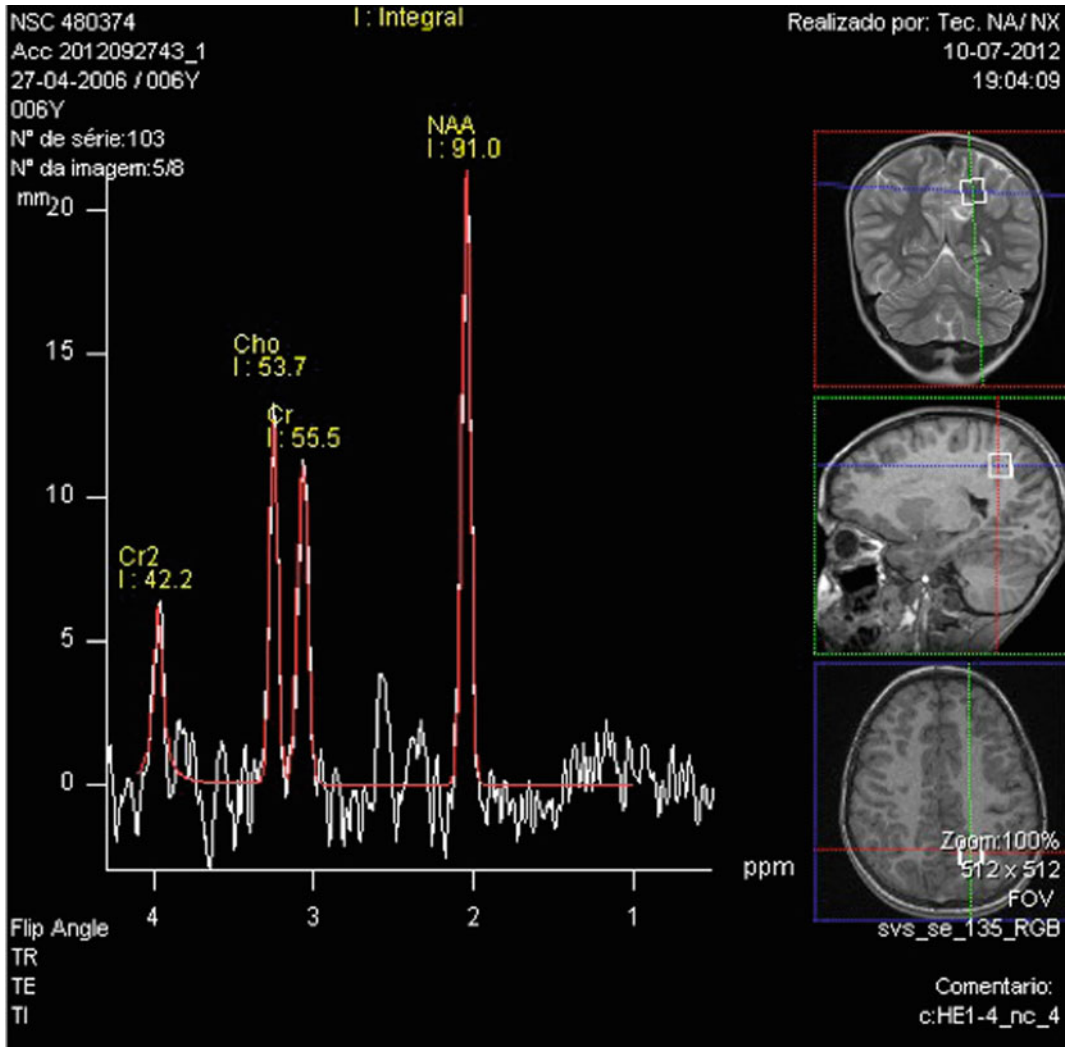

Fig. 10 Normal magnetic resonance proton spectroscopy showing the N-acetyl aspartate (NAA, a neuronal marker), creatine phosphate (Cr, an energy marker), and choline (Cho, membrane components) peaks

blood flow related to energy use by brain cells. These studies suggest that increased cognitive control recruitment in the motor system may limit the clinical manifestations of the disease in such cases [24].

Arterial spin labeling (ASL) measures cerebral perfusion using arterial water as an endogenous tracer. Brain perfusion changes have been reported in NAWM and in cortical and subcortical gray matter of MS patients [25].

MRI at ultrahigh magnetic fields (7 T) has advantages in relation to higher signal-to-noise ratio and improved image contrast and resolution, although not without technical challenges. Imaging at 7 T was demonstrated to be safe and well tolerated, and provides high-resolution anatomical images within or near the cortical layer [26]. This might prove useful for confidently classifying the location of lesions in relation to the cortical/subcortical boundary [27]. Moreover, ultrahigh field imaging has greater sensitivity to localize iron deposition [28]. New iron-based MRI contrast agents are able to track peripheral macrophages, providing complementary information

on MS-related active inflammation [29]. Magnetic resonance iron-imaging has already established a link between iron deposition, gray matter damage, and clinical status [30].

FOCUS POINT: Although MRI alone cannot be used to diagnose MS, it is key in the differential diagnosis, for confirming MS and monitor disease progression.

2 Pain, Other Comorbidities, and Quality of Life in Multiple Sclerosis

2.1 Pain in Multiple Sclerosis

Pain is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [31]. The physiological purpose of pain is to protect the individual, warning of tissue damage, and most pain resolves rapidly as soon as the painful stimulus is removed. However, chronic pain may develop from poorly treated acute pain as a result of changes in the function of the CNS: the pain persists and has no protective role as it extends beyond the expected period of healing [32]. Chronic pain has traditionally been determined by an arbitrary interval of time since onset; the two most commonly used periods being 3 months and 6 months from its beginning [32]. Increasing evidence supports the idea that chronic pain could be understood not only as an altered perceptual state, but also as a consequence of maladaptive peripheral and central neuronal reorganization [33].

Pain can be classified as nociceptive when it arises from actual or threatened damage to non-neural tissue, and is due to the activation of nociceptors, i.e., a sensory receptor that is capable of transducing and encoding noxious stimuli. In turn, pain is defined as neuropathic when it is caused by a lesion or disease of the somatosensory nervous system, either in its peripheral elements (peripheral neuropathic pain) or in the CNS (central neuropathic pain) [34].

Pain is described by MS patients as one of their most important symptoms [35]. Pain is common in MS, but prevalence reports in the literature are heterogeneous. A recent systematic review and meta-analysis proposes that pain affects around 63% of adults with MS [36], comparing with the estimated 19% prevalence of chronic pain in the general population [37]. Pain in the MS population includes several pain syndromes and different mechanisms that are described in detail in the following section. Headache, followed by extremity neuropathic pain, are the most common types of pain, and trigeminal neuralgia (TN) the least frequent. Other pain syndromes include back pain, painful spasms, and the Lhermitte sign [36].

Although both neuropathic and nociceptive pain mechanisms may be in the origin of pain in MS, neuropathic pain is thought to be more prevalent than nociceptive pain [36]. In MS, causality of neuropathic pain may be difficult to establish due to the temporal and spatial complexity of the CNS lesions. The relationship between MS-related pain to disease evolution is uncertain. Headache has been described as appearing prior to MS onset [38] or related scarcely with relapses of the disease [39]. However, there is not any solid hypothesis concerning the natural history of pain during the disease course.

FOCUS POINT: Clinicians should routinely enquire MS patients about pain, and characterize existing pain syndromes.

2.2 Neuropsychiatric Abnormalities in Multiple Sclerosis

Neuropsychiatric abnormalities in MS are also frequent, and may interfere or be associated with pain; they can be broadly divided in disorders of mood, affect, and cognition [40].

Depression is the most pressing neuropsychiatric problem in MS [41], affecting nearly one in two patients during their lifetime [42], a figure three times the prevalence rate in the general population [43]. Rates of depression in MS may

exceed those in other chronic medical [44] or neurological illnesses [45].

Depression and pain often co-occur in individuals with MS [46]. This coexistence can be explained by the overlap of central nociceptive and affective pathways [47], as well as the sharing of underlying neurotransmitters, with both norepinephrine and serotonin implicated in mood disorders and in the processing of pain. Moreover, there are several potential psychological and behavioral links between the two, such as the fact that pain intensity is associated with fatigue, anxiety, and sleep disturbances, which in turn are related with higher levels of depression [48]. Neuroimaging offers important clues as to the pathogenesis of depression, but psychosocial factors cannot be ignored and emerge as equally important predictors [41].

Other described concerns of mood and affect are bipolar affective disorder, euphoria, involuntary emotional expression disorder (episodes of crying or laughing that are unrelated to or out of proportion to the eliciting stimulus) and psychosis [35, 41].

2.3 Neuropsychological Abnormalities in Multiple Sclerosis

Multiple sclerosis-related cognitive dysfunction is highly prevalent, and may, as well as depression, interact with pain. In neuropsychological studies 40–65% of MS patients have shown cognitive impairment [49]. Multiple sclerosis patients do poorly in the Iowa Gambling Task (a psychological task thought to simulate real-life decision-making), probably reflecting altered decision-making capacity and emotional reactivity [50]. Their performance may relate to an increased sensitivity to immediate reward in addition to an impaired ability to evaluate the long-term consequences of decisions [51].

Pain and cognitive changes have been studied across various animal models of MS. In these models the onset of pain and cognitive dysfunction occur early, and do not coincide with the pattern of motor deficits. This is likely underpinned by a number of different mechanisms including changes in glutamate transmission, glial cell activation, and increased levels of pro-inflammatory cytokines. Changes in pain and cognition have been described as belonging to a cluster of symptoms and have been linked through centrally driven processes. In particular, the overactive immune response can induce a state of "sickness-like behaviors" that can influence both pain and cognition. Investigating the mechanism of inflammatory sickness behaviors in MS could lead to a better understanding of the links between pain and cognition [52].

FOCUS POINT: Neuropsychiatric and Neuropsychological abnormalities in MS are frequent and may interfere or be associated with pain. Depression and cognitive dysfunction are highly prevalent in MS.

2.4 Pain and Quality of Life

Pain is linked with adverse MS disease outcome —longer disease duration and higher disability [53]—and it has been associated not only with neuropsychiatric or neuropsychological factors but also with psychosocial and demographic factors, such as female sex, increased age, and lower educational level [54]. These problems often co-occur and are likely to have bidirectional effects, amplifying the impact on overall health-related quality of life (QOL) of MS patients and providing support for a biopsychosocial model of pain in MS [55].

This deterioration in QOL is manifest in daily activities, energy/vitality, mood, work, social relations, and enjoyment of life [46]. Individuals with MS who experience pain are significantly more likely to be unemployed than individuals with MS who are pain free [56], as well as a consuming more health care [54].

Psychosocial factors are more strongly associated with pain intensity than demographic and clinical variables [57]. This underlines the fact that psychosocial aspects are not additional to the experience of pain, but part of it; these factors influence how individuals react to and report pain, and result in coping strategies which may

be helpful or destructive in maintaining function, particularly in chronic pain. Even though the phenotype of chronic central pain of MS does not differ psychophysically from other central neuropathic pain [58], the assessment of psychosocial factors is thus important [40].

3 Pain Syndromes in Multiple Sclerosis

Pain syndromes in MS are varied and may coexist, and may be of central neuropathic and/or nociceptive nature. Truini and co-workers recently proposed a mechanism-based classification of pain in MS, distinguishing five pain categories: nociceptive, neuropathic, psychogenic, mixed, and idiopathic [59]. Nine types of MS associated pain syndromes were identified, and their possible mechanisms are detailed in Table 2. These include headache, ongoing extremity pain, Lhermitte's phenomenon, painful tonic spasms, musculoskeletal pains, spasticity pain, pain associated with optic neuritis, TN, and treatment-induced pains [59].

Headache and ongoing extremity pain, as previously seen, are the most common types of pain in MS. Headache includes tension headache, migraine, cluster headache, or chronic daily headache [60]. Headache generally precedes the onset of MS and is not significantly modified by the disease.

Ongoing extremity pain is a kind of dysesthetic pain occurring in MS, described by patients as a "continuous burning pain" (searing, burning, tingling, piercing, electric-like), usually located in the lower extremities, mostly bilateral and that worsens with exposure to heat or weather changes [58].

Lhermitte's phenomenon is a transient short-lasting sensation related to neck movement felt in the back of the neck, lower back, or in other parts of the body usually observed in the initial stages of the disease and in patients with primary progressive MS [61].

Painful tonic spasms are seizure-like, involuntary dystonic spasms, usually brought on by movement or also by touch, hyperventilation, or emotions. They usually occur several times a day and last for less than two minutes [62].

Musculoskeletal pain, a nociceptive pain, is most often seen in the hips, legs, and arms when muscles, tendons, and ligaments remain immobile for a long time result of irregular, asymmetric movement patterns and postures, and changes in muscle strength, tone (spasticity), or length (contracture). However, it may also be a manifestation of central pain [58]. Secondary musculoskeletal pain can also be caused by treatment drugs.

Retrobulbar optic neuritis is the first symptom of MS in 20% of cases [63]. It is characterized by blurred vision or the complete loss of vision and color vision deficiency and contrast sensitivity that decrease proportionally to visual acuity loss. In most cases, it is accompanied by pain originating from behind the eye, that may even involve the whole head, and frequently preceding the disturbances of visual acuity.

Trigeminal neuralgia is a rare neuropathic pain syndrome in MS that appears in the trigeminal innervation area, spontaneously, or caused by stimuli in specific trigger areas of the face or mouth. It is characterized by paroxysms of shooting, piercing, stinging, electric-like pain, normally with a sudden onset, and often accompanied by a characteristic facial grimace [64].

Because in MS, and even in the same patient, pain may have various pathophysiological mechanisms (Table 2), it manifests with heterogeneous sensory disturbances [65]. Further refining mechanisms behind pain in MS through clinical examination, dedicated questionnaires, and procedures such as quantitative sensory testing, pain-related evoked potentials, and skin biopsy have led to the development of the so-called sensory profiles [66]. The clustering of sensory abnormalities (for example, hypo and hypersensitivity to mechanical and thermal stimuli) in a somatosensory phenotype, points to certain pathophysiological dysfunctions in afferent processing. These sensory pain-related abnormalities in patients with neuropathic pain can form different patterns, allowing sensory profiling of patients. Subgroups of patients with different somatosensory profiles may also

Table 2 Mechanism-based classification of pain in multiple sclerosis

Types of pain	Possible mechanisms
Neuropathic pains	
Ongoing extremity pain	Deafferentation pain secondary to lesions in the spino-thalamo-cortical pathways
Trigeminal neuralgia	Paroxysmal high-frequency discharges ectopically generated by intra-axial inflammatory demyelination and extra-axial mechanical demyelination of the trigeminal primary afferents
Lhermitte's phenomenon	Paroxysmal neuropathic pain due to high-frequency ectopic impulse generated by demyelination of the dorsal column primary afferents
Nociceptive pains	
Pain associated with optic neuritis	Nerve trunk pain originating from endoneural inflammation intraneural nociceptors of the nervi nervorum
Musculoskeletal pain	Nociceptive pain related to postural abnormalities secondary to motor disturbances
Back pain	Consequence of postural anomalies
Migraine	Nociceptive pain favored by predisposing factors or secondary to midbrain/periaqueductal gray matter lesions
Tension-type headache	Probably coexisting conditions
Treatment-induced pains	Interferon beta (flu-like symptoms, myalgias, and headache), glatiramer acetate (pain at the injection site), corticosteroids (osteoporosis and secondary pain)
Mixed pains	
Painful tonic spasms	High-frequency discharges ectopically generated by demyelinating lesions in the cortico-spinal pathways induce tonic spasm which, in turn, induce ischemic muscle pain
Spasticity pain	Mixed pain secondary to lesions in the central motor pathways but mediated by muscle nociceptors

Adapted from Truini et al. [59], a mechanism-based classification of pain in multiple sclerosis

respond differently to treatment [67]. Cruccu and co-authors defend that neuropathic pain should be classified according to these sensory profiles rather than etiology [65], so it could minimize the pathophysiological heterogeneity within study groups and clinical trials, thus making it easier to identify a positive treatment response and opening the way to new therapeutic approaches of pain in MS.

In this context, neurophysiologic testing becomes important in associating a specific type of sensory disturbance to specific afferent pathway damages. Evoked potentials can be useful neurophysiologic studies for evaluation of MS, including laser evoked potentials (LEP) and somatosensory evoked potentials (SEP).

Ongoing extremity pain is associated with LEP abnormalities that suggest that this type of pain is related to nociceptive pathway damage. Since MRI shows cervical or thoracic spinal cord damage, ongoing extremity pain may arise from spinothalamic tract lesions with deafferentation of thalamic nuclei [66]. Distinctively, Lhermitte's phenomenon is associated with SEP abnormalities, implying that this type of pain is related to non-nociceptive Ab-fiber pathway damage. Cervical spinal cord lesions as assessed by MRI imaging and the reported pain due to neck movement build up to the conclusion that the Lhermitte's phenomenon probably arises from a demyelinating lesion in the dorsal columns of the cervical spinal cord [66].

FOCUS POINT: Headache and ongoing extremity pain are the most common types of pain in MS. Neurophysiologic characterization of pain syndromes in MS and correlation of results with lesion location, as demonstrated by MRI, may be important for treatment selection.

4 Neuroimaging and Pain in Multiple Sclerosis

Studies investigating pain in MS with neuroimaging methods are scarce. A recent systematic review of neuroimaging studies in MS reports that most of the published articles are case reports/series aimed at describing associations between demyelinating lesions and pain syndromes, with limited impact for the knowledge of pain mechanisms in MS and for patient management [68].

More evidence on pain mechanisms in MS is warranted, considering the high relevance and impact of pain in this disease, and how little is known about its pathophysiology. In the case of central neuropathic pain, a single CNS lesion in a strategic location can be in its origin. On the other hand, it is recognized that the remainder of the lesion load and hidden pathology on conventional MRI—in the cortex and in NAWM—may contribute to MS pain and associated comorbidities.

Most neuroimaging studies in pain in MS investigated headache and facial pain [68]. Studies of migraine [69], as well as unclassified headache [70], identified abnormalities in the brainstem, a finding in line with the putative role of the brainstem in pain transmission pathways in central neuropathic pain in MS. Apart from the lesion location, the T2 lesion burden on brain MRI does not seem to account for any differences in the migraine status [71].

Studies characterizing TN and trigeminal autonomic cephalalgias (TACs) in MS focused on abnormalities associated to the trigeminal nucleus and nerve. Interestingly, there appears to be some radiological overlap between findings in these groups of headaches, which are traditionally viewed as distinct in etiology. The controversy remains, whether MS lesions in the trigeminal pathways account for TN [72–74], or if there is a simultaneous role of central and peripheral trigeminal damage [75, 76].

The role of cervical spinal imaging in investigating headache etiology (particularly, though not exclusively, when occipital, and thus hypothetically related to a cervical dermatomal distribution of pain) are also of notice [77, 78]. Cervical MRI with Gd in patients with sudden paroxysmal occipital pain might reveal a new active or new T2-weighted demyelinating C2 cervical lesion which may signal relapse of MS [78].

More frequent pain syndromes in MS, such as limb pain, have been relatively understudied, comparing, for example, with headache [68]. Considering limb and radicular pain, the limited data available suggest, as might be suspected on a neuroanatomical basis, that a spinal location of an MS plaque should be considered. Dorsal lesions in the thoracic and/or cervical cord have been associated with limb pain [79–81].

Although thalamic or cortical lesions are known to be responsible for pain syndromes, such as in post-stroke pain [82], no difference has been found regarding the presence of lesions in the thalamus, capsula interna and thalamo-cortical projections in MS patients with or without pain (Fig. 11) [83]. These studies may potentially suggest a role of spinal lesions in either directly disturbing sensory afferent pathways, or perhaps in contributing to the imbalance between spinothalamic and other sensory pathways, or dysfunction of descending inhibitory pathways [83].

FOCUS POINT: The spinal cord is a frequent origin of central pain in MS. Thalamic lesions, although common in MS, are not frequently associated with pain.

It is of note that the previously discussed describes only potential associations, rather than established causation. Moreover, pain present at multiple body sites cannot be presumed to be associated with identical radiological abnormalities as those identified in the limited studies of well-localized pain at a single site [68]. Furthermore, the current literature of neuroimaging studies of pain in MS is methodologically poor [68]. Studies tend to give emphasis to white matter pathology in MS, although histopathological and MRI research has shown that lesions are often located in the gray matter, especially in the cerebral cortex [1]. Likewise, it is important to take into account MS normal-appearing brain damage. The use of functional or molecular

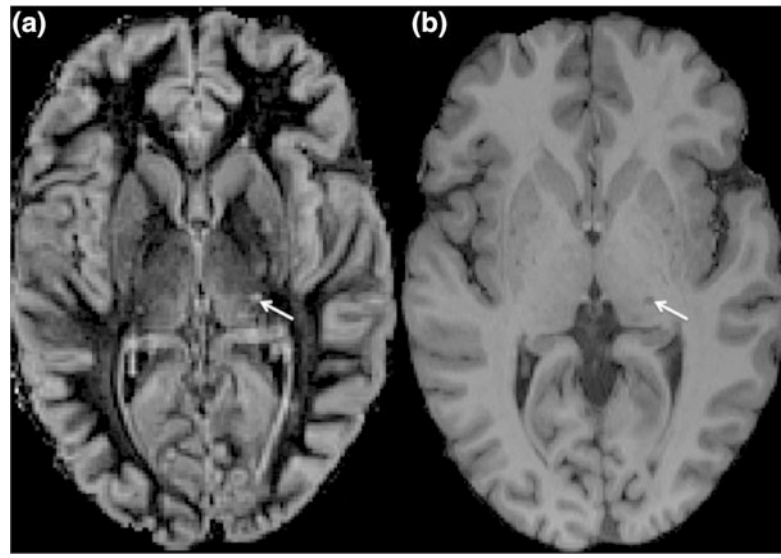

Fig. 11 Double inversion recovery (**a**) and axial T1-weighted magnetic resonance images (**b**) identifying a thalamic lesion (*arrows*) in a multiple sclerosis patient with a thalamic pain syndrome. Notice that thalamic lesions, although common in multiple sclerosis, are not frequently associated with pain in this disease

imaging techniques, serial imaging, and/or the use of intravenous contrast medium complemented by electrophysiological techniques can contribute as well to the establishment of a temporal association (and hence possible causality) between the lesion and the specific pain syndromes, bringing time to space resolution to the study of pain in MS.

Neuroimaging methods, in particular functional and advanced structural MRI techniques, are ideal to study pain noninvasively in these patients, given their already substantial contributions to both the MS and pain research fields. Functional neuroimaging is able to provide insight on critical brain regions for pain processing and to the understanding of how cognitive, emotional and contextual factors modulate the pain experience in MS. The ASL technique can measure changes in the regional cerebral blood flow (CBF) in brain areas that have been previously associated with pain perception, like the secondary somatosensory, insular and cingulate cortices [84], proving itself suitable to study pain conditions that are difficult to investigate with current fMRI, such as chronic pain. Resting-state fMRI is an MRI technique that has several potential advantages over task-activation fMRI in terms of its clinical applicability, particularly for ongoing pain states [85]. In the systematic review of Seixas and colleagues, only one study was identified investigating pain in MS using nonconventional MRI [68].

FOCUS POINT: More studies investigating pain in MS with neuroimaging methods are needed. The majority of the published articles are only case reports/series describing associations between MS plaques and pain.

4.1 Chronic Pain in Multiple Sclerosis

Neuroimaging techniques, besides allowing the study of lesion topography and its association with pain, offer as well a window to the evaluation of the consequences of chronic pain in the CNS in MS. There is evidence of brain structural and functional dysfunction in chronic pain. Studies in animal models have demonstrated that chronic pain is accompanied by molecular, neuronal, and structural changes in the brain and also in the spinal cord [86]. Chronic pain can be understood not only as an altered functional state, but also a consequence of neuronal reorganization [33, 87].

As previously discussed, in MS neuropathic pain may originate from a single lesion in the somatosensory pathways, possibly the spinal cord, and evolve into chronic pain, burdening an already

MS-damaged CNS and leading to a cycle of structural and functional brain disruption (Fig. 12). This is the context that is perhaps unique to MS, which mechanisms can be captured using a state-of-the-art imaging protocol directed at the specificities of this demyelinating disease.

The fact that MS is a demyelinating disease and changes in white matter have been identified in chronic pain conditions, suggests a link to pain chronicity in altering vulnerable or non-resilient white matter. These plastic, probably maladaptive, brain changes may be a contribution of chronic pain, and furthermore, a consequence of pain originating in the spinal cord in MS [40].

Regarding functional brain plastic changes in long-standing pain, different chronic pain conditions seem to evoke distinct brain activity patterns, which may reflect not only pain but also processes related with each disease [88]. Pain alters brain dynamics beyond pain perception by distorting brain resting-state networks (RSNs) [89–91]. These networks are brain regions that are active when the individual is not focused on the outside world and the brain is at wakeful rest. This intrinsic neuronal activity is critical for the development of synaptic connections and maintenance of synaptic homeostasis [92]. The default-mode network (DMN) (Fig. 13), one of such networks, is deactivated during demanding cognitive tasks and involved in internal modes of cognition [93]. It includes the medial temporal lobe and the medial prefrontal cortex subsystems, converging on important nodes of integration including the posterior cingulate cortex highlighting the possible adaptive role of the DMN in planning the future and in social interactions often impaired, for example, in chronic pain states [94]. A DMN dysfunction in regions subserving the reward system, the caudate nucleus and nucleus accumbens, was reported in chronic MS pain, and may be associated with altered decision-making and planning [40]. It is important to further investigate the meaning and consequences of this dysfunction in the reward system, especially because cognition and emotion disorders are also prevalent in MS.

FOCUS POINT: Chronic pain is known to induce molecular, neuronal, and structural changes in the brain and the spinal cord, which can burden an already non-resilient CNS in MS.

5 Pain Management in Multiple Sclerosis

Pharmacological treatment of pain in MS is challenging, due to the many underlying pathophysiological mechanisms [59]. It has been described the potential for several drugs in its management, including antidepressants, anticonvulsants, dextromethorphan/quinidine, opioids/opioid antagonists, and cannabinoids. Regarding invasive pain treatment, the options to relief pain include microvascular decompression for TN, CNS transcutaneous electrical nerve stimulation (motor cortex stimulation, spinal cord stimulation, and posterior nucleus of the hypothalamus stimulation). Neuroimaging methods have a role in

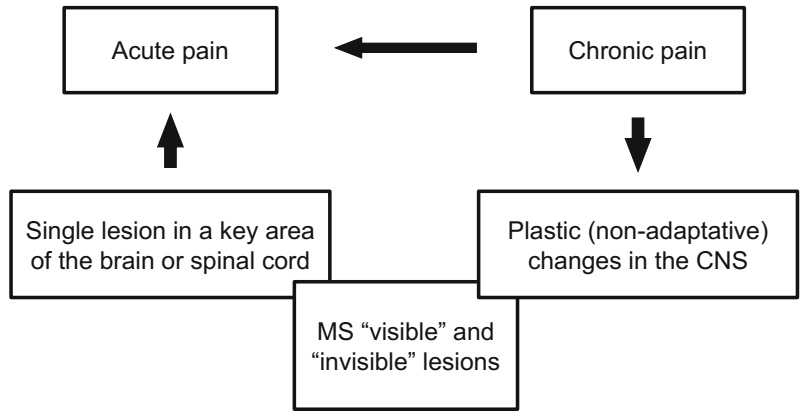

Fig. 12 The cycle of structural and functional central nervous system damage of pain associated with multiple sclerosis

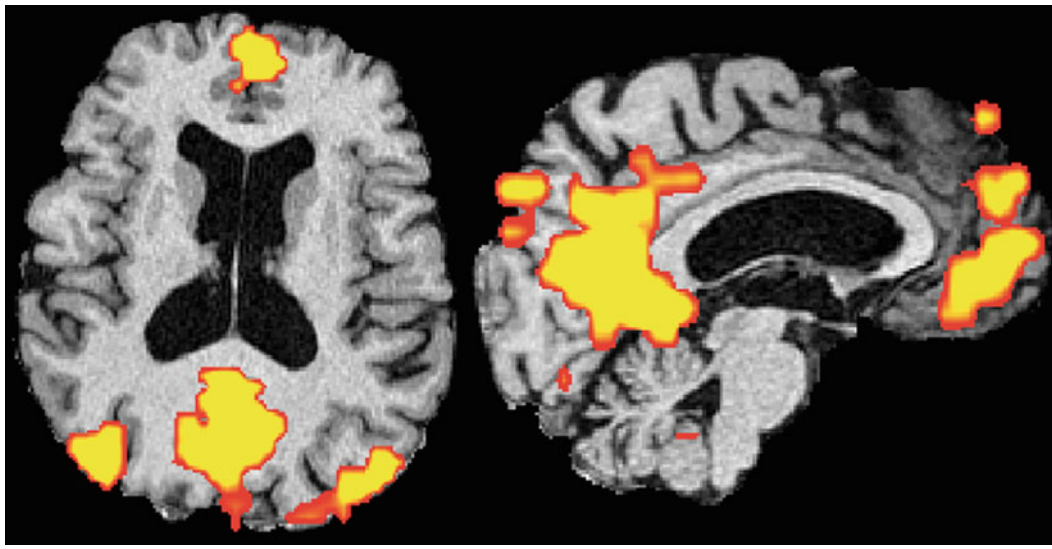

Fig. 13 The default-mode network. Regions belonging to the default-mode network include the medial prefrontal cortex, the anterior and posterior cingulate cortex, lateral and inferior parietal cortex, inferior and middle temporal gyri and mesial temporal lobe regions, the precuneus, the thalami, and cerebellar areas

invasive treatment planning, and as well as outcome measures in clinical drug trials.

6 Conclusions

Pain is a frequent and debilitating symptom of MS, which in turn is one of the most prevalent causes of neurological disability in the young adult. Pain in MS may be neuropatic or, less frequently, of nociceptive origin. Pain is still underrecognized in MS, and its mechanisms are poorly understood.

Neuroimaging techniques are key for the diagnosis and differential diagnosis in MS, and for disease follow-up. Magnetic resonance imaging, together with neurophysiological testing, has a role as well in the characterization of pain syndromes in MS, with an impact in the treatment of pain, in better targeting both drugs and interventions such as deep brain or cord stimulation.

Magnetic resonance imaging has been important in the research of pain mechanisms in humans. However, the literature is still scarce in publications investigating pain in MS using neuroimaging methods. More studies are needed, in particular addressing chronic pain and nociceptive pain of MS, and investigating the interaction of MS and comorbidities like depression and cognitive impairment. Neuroimaging methods can contribute further to the understanding of pain in MS, and to create opportunities for the recognition and effective treatment of pain in this disease.

Nonetheless, the complexity of MS, with lesions disseminating both in time and spatially in the CNS, and its invisible brain and cord damage, together with the technical complexity of the different MRI methods, warrant rigorous methodology for obtaining valid, reproducible and enlightening results in the investigation of pain syndromes in MS.

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