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Review

Pain in multiple sclerosis: A systematic review of neuroimaging studies

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ABSTRACT

Introduction: While pain in multiple sclerosis (MS) is common, in many cases the precise mechanisms are unclear. Neuroimaging studies could have a valuable role in investigating the aetiology of pain syndromes. The aim of this review was to synthesise and appraise the current literature on neuroimaging studies of pain syndromes in MS.

Methods: We systematically searched PubMed and Scopus from their inception dates to the 2nd of April 2013. Studies were selected by predefined inclusion and exclusion criteria. Methodological quality was appraised. Descriptive statistical analysis was conducted.

Results: We identified 38 studies of variable methodology and quality. All studies but one used conventional structural magnetic resonance imaging, and the majority reported a positive association between location of demyelinating lesions and specific neuropathic pain syndromes. Most investigated headache and facial pain, with more common pain syndromes such as limb pain being relatively understudied. We identified a number of methodological concerns, which along with variable study design and reporting limit our ability to synthesise data. Higher quality studies were however less likely to report positive associations of lesion distribution to pain syndromes.

Conclusions: Further high quality hypothesis-driven neuroimaging studies of pain syndromes in MS are required to clarify pain mechanisms, particularly for the commonest pain syndromes.

Contents

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1. Introduction

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS), which is associated with demyelination and neurodegeneration (Compston and Coles, 2008). Pain has been recognised as a symptom of MS since the first descriptions of the disease (Charcot, 1872) and can broadly be classified as nociceptive or neuropathic (O'Connor et al., 2008). It is common – the overall point prevalence of pain in MS is around 50% (O'Connor et al., 2008) – and it is often ranked by patients as one of the most distressing symptoms of the disease (Kalia and O'Connor, 2005). In spite of the prevalence and clinical importance of pain in MS, its mechanisms remain poorly understood.

Magnetic resonance imaging (MRI) plays a crucial role both in the diagnosis of MS (Polman et al., 2011) and in clinical research applications. It is widely used to study both inflammatory lesions and non-lesional tissue changes *in vivo* (Bakshi et al., 2008). MRI is also an important tool in the study of pain mechanisms, and it is likely to play an increasing clinical role in the future (Wise and Tracey, 2006). Positron-emission tomography (PET) and single-photon emission-computed tomography (SPECT) have, in addition, proved invaluable in the study of neurotransmitter systems involved in pain.

While neuroimaging is separately established as a mainstay in the investigation of both MS and pain, the study of pain syndromes in MS by neuroimaging remains a developing field. Improved understanding of neuroradiological findings in MS pain could improve our understanding of its mechanisms, and in turn contribute to development of therapies. In order to identify gaps in knowledge, and highlight future research priorities, our review summarises and appraises existing studies of neuroimaging correlates of MS pain (using MRI, PET or SPECT) and assesses the neuroradiological evidence for aetiology of MS-related pain syndromes.

2. Materials and methods

Our primary outcome of interest was the radiological evidence for the aetiology of any pain syndrome in MS. We analysed findings of available studies in light of detailed methodological assessment and emphasised results of high quality hypothesis-driven studies. We anticipated a low number of available studies, and therefore included any pain syndrome described as associated with MS.

We searched PubMed and Scopus from their inception dates (1977 and 1960, respectively) to the 2nd of April 2013. Keywords used for the PubMed search included the medical subject heading (MeSH) terms "pain" and "multiple sclerosis" along with "magnetic resonance imaging" or "positron-emission tomography" or "tomography, emission-computed, single-photon". Keywords used for the Scopus search included all entry terms of each MeSH term in PubMed and the MeSH terms themselves, combined in the same manner. We also hand-searched reference lists and consulted experts in the field to identify additional material.

We included all original English language studies examining neuroimaging correlates of pain in MS – using MRI, PET or SPECT imaging – in human adults. Three studies were excluded by the language criterion. We also excluded paediatric studies, studies of other demyelinating disorders, re-published data, and review articles.

We reviewed the titles and abstracts of identified studies and excluded duplicate references. Two reviewers (DS, PF) independently reviewed potentially relevant articles. Disagreements were resolved by consensus.

We then assessed quality of studies using the following 12 criteria relevant to our review objectives (adapted from Campbell et al., 2011): clearly stated research objective, recruitment procedure, and inclusion/exclusion criteria; description of sample demographics, participation rates, imaging protocol, and pain measurement instruments; image interpretation carried out without knowledge of subjects' pain status; participation rate above 70%; use of multivariate analysis; reporting of strength of effect, and acknowledgment of study limitations. Given the low number of identified studies, we did not exclude any studies on the basis of quality assessment. We also assessed the reporting of imaging methodology, clinical diagnostic criteria used, reported imaging findings, and methods used to investigate links between radiological findings and occurrence of pain syndromes. We conducted descriptive statistical analysis. We identified studies as case reports, case series, or investigational studies (defined here by any study with hypothesis-driven experimental design). This work was not submitted to an ethics committee because it is a systematic review of the literature.

3. Results

We found 902 candidate publications (Fig. 1). Thirty-eight met the inclusion criteria (Alstadhaug et al., 2008; Andrade et al., 2012; Athanasiou et al., 2005; Balasa and Bajko, 2010; Bentley et al., 2002; Broggi et al., 2004; Burkey and Abla-Yao, 2010; Carrieri et al., 2009; Cordella et al., 2009; Cruccu et al., 2009; da Silva et al., 2005; Davey and Al-Din, 2004; Deppe et al., 2013; de Santi et al., 2009; Donat, 2012; Eldridge et al., 2003; Fragoso and Brooks, 2007; Gass et al., 1997; Gee et al., 2005; Gentile et al., 2007; González-Quintanilla et al., 2012; Haas et al., 1993; Hellwig et al., 2006; Kister et al., 2010; Leandri et al., 1999; Liu et al., 2008; Marchettini et al., 2006; Meaney et al., 1995; Minagar and Sheremata, 2000; Nakashima et al., 2001; Pichiecchio et al., 2007; Ramirez-Lassepas et al., 1992; Svendsen et al., 2011; Tanei et al., 2010; Tortorella et al., 2006; Tosi et al., 1998; Vilisaar and Constantinescu, 2006; Yetimalar et al., 2008). Of these, 16 were case reports (Alstadhaug et al., 2008; Andrade et al., 2012; Bentley et al., 2002; Burkey and Abla-Yao, 2010; Carrieri et al., 2009; Davey and Al-Din, 2004; Donat, 2012; Gentile et al., 2007; González-Quintanilla et al., 2012; Haas et al., 1993; Leandri et al., 1999; Liu et al., 2008; Pichiecchio et al., 2007; Tanei et al., 2010; Tosi et al., 1998; Vilisaar and Constantinescu, 2006), nine were case series (Athanasiou et al., 2005; Cordella et al., 2009; de Santi et al., 2009; Fragoso and Brooks, 2007; Hellwig et al., 2006; Marchettini et al., 2006; Meaney et al., 1995; Minagar and Sheremata, 2000; Nakashima et al., 2001), and 13 were investigational studies (Balasa and Bajko, 2010; Broggi et al., 2004; Cruccu et al., 2009; da Silva et al., 2005; Deppe et al., 2013; Eldridge et al., 2003; Gass et al.,

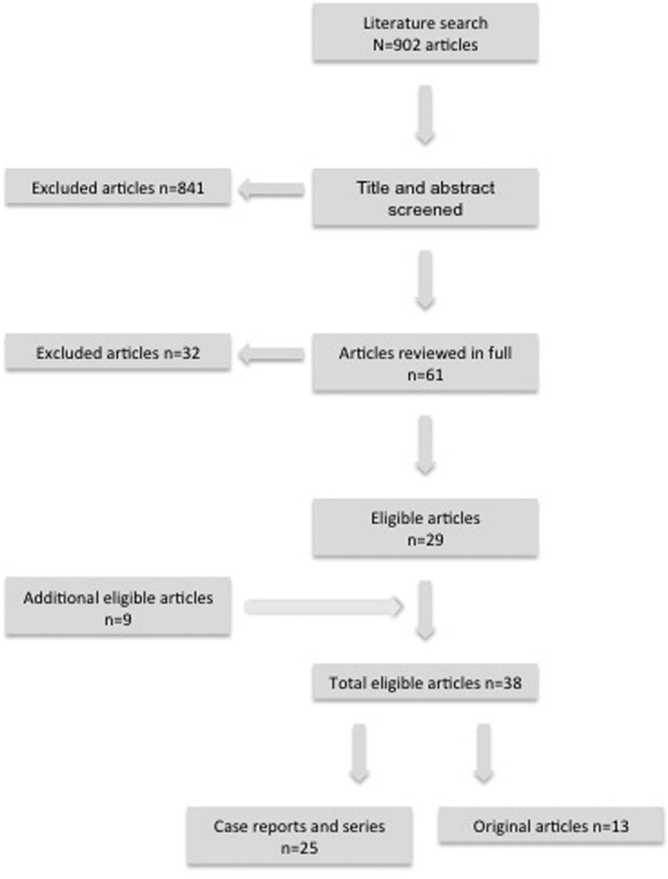

Fig. 1. Flow diagram of the review procedure.

Table 1
Characteristics of included investigational studies.

Author (year)	Country	Type of study	Study population (n=)	Main study focus	Assessment of pain	Imaging	Main findings
Balasa (2010)	Romania	Retrospective, cross-sectional	20 patients with TN (10 with MS and 10 without MS)	Evaluation of clinical differences in TN presentation and pharmacological treatment response in patients with and without MS	International Headache Society Classification (2004), Barrow Neurological Institute score of clinical pain intensity	MRI (1 T), no image acquisition or reading protocols defined	MS patients had earlier onset TN, probably secondary to lesions in the trigeminal pathways, with overlapping characteristics and treatment response when compared to non-MS TN
Cruccu (2009)	Italy	Retrospective, cross-sectional	130 MS patients (50 with TN, 30 with sensory trigeminal disturbances, and 50 controls)	Causes and mechanisms of MS-related TN	International Headache Society Classification (2004), neurological examination including sensory and trigeminal reflex testing	MRI, dedicated image acquisition protocol (although not specified), voxel-based brainstem analysis, read by neuroradiologists	The onset ages of MS and trigeminal symptoms were older in the TN group, and most patients in the TN and non-TN groups had abnormal trigeminal reflexes. In the TN group the highest probability of brainstem lesion was in the pontine trigeminal primary afferents
Deppe (2013)	Germany	Retrospective	1 MS patient and 100 healthy controls	Investigate diffusion tensor imaging abnormalities in the thalamus related to a central pain syndrome comparing with controls	Describes the pain syndrome only as "episode of central pain and abnormal somatosensory and thermal sensations on the right hand side of the body"	MRI (3 T), well described imaging protocol and post-processing, data was obtained from a pilot study for a clinical trial, ROI analysis of the thalami	Temporary increase of the fractional anisotropy in the thalamus contralateral to the pain; a causative role is suggested
Gee (2005)	United States of America	Retrospective, cross-sectional	277 MS patients	To determine if the prevalence of migraine-like headache in MS patients was associated with plaques in the brainstem or other locations	International Headache Society Classification (1988), tailored questionnaire	MRI, contradictory information regarding image acquisition protocol, field strength and scanners; predefined reading protocol	The presence of a midbrain plaque was associated with an increased likelihood of headache with migraine characteristics; lesions in other locations and lesion load were not associated with headache prevalence
Kister (2010)	United States of America	Cross-sectional	204 MS patients	To assess the relative frequency of migraine in MS and to compare clinical and radiographic characteristics in MS patients with and without migraine	International Headache Society Classification (2004), tailored questionnaire to characterise headache and comorbidities adapted from the American Migraine Prevalence and Prevention Study, migraine severity assessed with Migraine Disability Assessment tool	MRI (0.6, 1.5 and 3 T), image acquisition protocol defined (T2-w and pre- and post-contrast T1-w), images read by a neurologist and an expert in MS neuroradiology	Migraine frequency was threefold higher in MS patients than in controls, and was more symptomatic; no difference in number or distribution of plaques, or enhancing lesions between migraine and no-migraine groups
Ramirez-Lassepas (1992)	United States of America	Retrospective, cross-sectional	11 MS patients	To study radicular pain as presenting MS symptom	–	Myelography, computed tomography or MRI; no image acquisition or reading protocols defined	Acute radicular pain in the absence of demonstrable root compression may not be an uncommon presenting symptom in MS and may be associated with trauma; in two patients plaques in the spinal cord explained the symptoms

Svendsen (2011)	Denmark	Cross-sectional	25 MS patients with sensory disturbances (13 with pain and 12 without pain)	To study location of plaques in MS patients with sensory disturbances with and without pain, and to ascertain if deafferentiation of spinothalamic tract was more common in the patients with pain	Structured pain interview, pain location in body map, neurological examination including bedside sensory examination	MRI (1.5 T), image acquisition protocol defined (brain — sagittal T1-w and T2-w and axial FLAIR, spine — sagittal T1-w and STIR axial T2-w), read by a neuroradiologist according to defined reading protocol	No association between central pain and site of demyelination was found; central pain was associated with allodynia, suggesting central hyperexcitability
Tortorella (2006)	Italy	Retrospective	58 patients with migraine and 79 MS patients (37 with and 42 without migraine)	Evaluate if red nucleus, substantia nigra and periaqueductal grey matter were involved by MRI-detectable structural abnormalities in migraine patients, and to investigate their frequency and extent in MS patients with migraine	International Headache Society Classification (2004)	MRI (1.5 T), defined image acquisition protocol (axial PD/T2-w), read by two observers using a defined reading protocol	Brainstem lesions were frequent in non-MS migraine, but did not seem associated with aura; demyelinating lesions in the red nucleus, substantia nigra and periaqueductal grey matter might be among the factors responsible for migraine in MS
Broggi (2004)	Italy	Cross-sectional, prospective	35 MS patients who underwent MVD for TN	To clarify the role of MVD in the treatment of TN in MS	Post-operative presence and intensity of residual facial pain and subsequent treatment for TN	MRI (0.5 or 1.5 T), defined image acquisition protocol (axial PD/T2-w, axial or coronal FLAIR; in 23 patients additional axial T2-w or coronal T2-w thin slices, coronal T1-w post-contrast, and 3D TOF angiography)	Results of MVD in TN in MS seemed to be less satisfactory than in the idiopathic group, suggesting a central mechanism in MS TN
da Silva (2005)	Brazil	Retrospective, cross-sectional	275 MS patients	Review of incidence of trigeminal involvement on MRI, as well as clinical correlation in patients with MS	Search for trigeminal symptoms in medical records and medical attendances	MRI (1 T), defined image acquisition protocol (axial FLAIR, PD/T2-w, and T1-w before and after contrast)	High clinically silent incidence of trigeminal involvement in MS, including simultaneous central and peripheral demyelination
Gass (1997)	UK and Germany	Cross-sectional?	6 MS patients with TN	Lesion localisation in MS patients with TN	Neurological examination	MRI (1.5 T), defined image acquisition protocol (including axial PD/T2-w)	Brainstem lesions involving the trigeminal fibres were demonstrated, without neurovascular contacts
Yetimalar (2008)	Turkey	Retrospective, cross-sectional	21 MS patients (11 with pain syndromes including headache, brachalgia and throat pain)	Description of patients with unusual symptoms that were primary manifestations of MS	International Headache Society Classification (2004), neurological examination	MRI (1.5 T), use of contrast	Possible correlations between clinical disturbances and neuroradiological abnormalities of some unusual primary manifestations of MS
Eldridge (2003)	UK	Retrospective	9 MS patients with TN	To assess whether MVD was a safe and efficacious treatment for patients with TN and MS	Review of medical records	MRI (1.5 T), protocol defined (conventional MRI and angiography, with and without contrast)	MVD provided good initial pain relief, but recurrence rate was higher than in idiopathic TN

MS — multiple sclerosis; TN — trigeminal neuralgia; MRI — magnetic resonance imaging; MVD — microvascular decompression; T — tesla; T1-w — T1-weighted; T2-w — T2-weighted; PD — proton density; FLAIR — fluid attenuation inversion recovery; STIR — short T1 inversion recovery; TOF — time-of-flight.

1997; Gee et al., 2005; Kister et al., 2010; Ramirez-Lassepas et al., 1992; Svendsen et al., 2011; Tortorella et al., 2006; Yetimalar et al., 2008). Characteristics of included investigational studies are detailed in Table 1. On quality assessment, the mean number of criteria fulfilled by the included investigational studies ($n = 13$) was six (range 3–12). Only Kister et al. (2010) fulfilled all the criteria. Four studies (Gee et al., 2005; Kister et al., 2010; Svendsen et al., 2011; Tortorella et al., 2006) fulfilled seven or more of the twelve criteria (Table 2).

3.1. Reporting of image acquisition methods

All identified studies used conventional structural MRI but one, which investigated pain in MS using diffusion tensor imaging (DTI) (Deppe et al., 2013). No studies used functional MRI, SPECT or PET. There were significant deficiencies in the description of imaging methodology in many studies (Table 3 summarises frequency of description of each aspect of imaging acquisition). We found that field strength was specified in 15 studies (39% of all studies). Of these 15 studies, one tesla scanners were used in two studies (Balasa and Bajko, 2010; da Silva et al., 2005), 1.5 T scanners were used in nine studies (Eldridge et al., 2003; Gass et al., 1997; Gee et al., 2005; Meaney et al., 1995; Nakashima et al., 2001; Pichiecchio et al., 2007; Svendsen et al., 2011; Tortorella et al., 2006; Yetimalar et al., 2008), and 3 T scanners were used in two (of the most recent) studies (Andrade et al., 2012; Deppe et al., 2013). Scanners of varying strengths were employed in two studies: 0.6, 1.5 and 3 T (Kister et al., 2010), and 0.5 and 1.5 T (Broggi et al., 2004). Of all the included studies, MRI protocols were stated only in 14 (37%) (Andrade et al., 2012; Athanasiou et al., 2005; Broggi et al., 2004; da Silva et al., 2005; Deppe et al., 2013; Donat, 2012; Eldridge et al., 2003; Gass et al., 1997; González-Quintanilla et al., 2012; Haas et al., 1993; Kister et al., 2010; Meaney et al., 1995; Svendsen et al., 2011; Tortorella et al., 2006). Of the 14 studies that did describe the MRI protocol used, only nine of these described all the sequences (Broggi et al., 2004; da Silva et al., 2005; Deppe et al., 2013; Gass et al., 1997; Haas et al., 1993; Kister et al., 2010; Meaney et al., 1995; Svendsen et al., 2011; Tortorella et al., 2006), and only four described all the sequence parameters of all the sequences (da Silva et al., 2005; Gass et al., 1997; Svendsen et al., 2011; Tortorella et al., 2006). Imaging methodology was relatively better described in the 13 investigational studies, although four did not describe MRI protocols, and reading methods were described in only five studies.

3.2. Diagnosis of multiple sclerosis

Criteria used to confirm the diagnosis of MS were explicitly stated in only 16 of the 38 studies (2010 revisions to the McDonald criteria — Polman et al., 2011 (Deppe et al., 2013; González-Quintanilla et al., 2012); revised McDonald — Polman et al., 2005 (Andrade et al., 2012; Cruccu et al., 2009; Fragoso and Brooks, 2007; Gentile et al., 2007; Kister et al., 2010); McDonald — McDonald et al., 2001 (Balasa and Bajko, 2010; Carrieri et al., 2009; Hellwig et al., 2006; Yetimalar et al., 2008); Poser — Poser et al., 1983 (Broggi et al., 2004; Hellwig et al., 2006; Leandri et al., 1999; Meaney et al., 1995); Rose — Rose et al., 1976 (Ramirez-Lassepas et al., 1992)). The type of MS in subjects was not fully described in 14 studies (Athanasiou et al., 2005; Balasa and Bajko 2010; Burkey and Abla-Yao, 2010; Cruccu et al., 2009; Donat, 2012; Eldridge et al., 2003; Fragoso and Brooks, 2007; González-Quintanilla et al., 2012; Kister et al., 2010; Marchettini et al., 2006; Meaney et al., 1995; Minagar and Sheremata, 2000; Ramirez-Lassepas et al., 1992; Yetimalar et al., 2008). It was relapsing–remitting in 16 ((Alstadhaug et al., 2008; Andrade et al., 2012; Bentley et al., 2002; Carrieri et al., 2009; Deppe et al., 2013; de Santi et al., 2009; Gentile et al., 2007; Haas et al., 1993; Hellwig et al., 2006; Leandri et al., 1999; Liu et al., 2008; Nakashima et al., 2001; Pichiecchio et al., 2007; Tanei et al., 2010; Tosi et al., 1998) (Minagar and Sheremata, 2000) – one case). Six studies included patients with various MS subtypes (Broggi et al., 2004; da Silva et al., 2005; Gass et al., 1997; Gee et al., 2005; Svendsen et al., 2011; Tortorella et al., 2006).

3.3. Pain syndromes and lesion localisation

All studies examined either neuropathic pain or headache (studied pain syndromes are detailed in Table 4). We found no studies investigating nociceptive/somatic pain or psychogenic pain. Most studies ($n = 28$, 74% of total) focused on headache or facial pain syndromes, and the remainder on bodily pain (eight studies, 21% of total), except for two studies (6%), which included both patients with headache/facial pain and those with body pain (Svendsen et al., 2011; Yetimalar et al., 2008).

All studies detailed the location of lesions thought to be responsible for pain syndromes. Table 5 describes lesion locations in the 25 included case reports and series. Of these, 21 describe demyelinating lesions in areas thought likely to be responsible for a pain syndrome (Table 5) whereas four did not find demyelinating lesions thought likely to be responsible (Athanasiou et al., 2005; Carrieri et al., 2009; Davey and Al-Din, 2004; Minagar and Sheremata, 2000). Most authors assigned lesions as the likely cause of pain syndromes by anatomical location. Relatively few investigators further studied the age or evolution of the lesion in relation to the pain syndrome by use of either serial imaging or intravenous contrast (Table 5). Lesions were identified in the CNS (*i.e.* central neuropathic pain) in 21 studies; of these, lesions were located in the spinal cord in six studies ((Alstadhaug et al., 2008; Burkey and Abla-Yao, 2010; Tosi et al., 1998) (de Santi et al., 2009) — three cases (Hellwig et al., 2006) — four cases: only two documented with MRI (Marchettini et al., 2006) — five cases), in the brainstem in 13 studies ((Bentley et al., 2002; Donat, 2012; Gentile et al., 2007; González-Quintanilla et al., 2012; Haas et al., 1993; Leandri et al., 1999; Liu et al., 2008; Tanei et al., 2010) (Meaney et al., 1995; Nakashima et al., 2001; Vilisaar and Constantinescu, 2006) — one case (Fragoso and Brooks, 2007) — two cases (Cordella et al., 2009) — five cases), in the thalamus in one study (Deppe et al., 2013) and in multiple locations throughout the pyramidal tract in another study (Andrade et al., 2012).

3.3.1. Headache and facial pain

The classification of headache disorders used was not specified in four of the 10 investigational studies studying headaches (Broggi et al., 2004; da Silva et al., 2005; Eldridge et al., 2003; Gass et al., 1997), and in the remaining six studies the criteria used were those of the International Headache Society 1988 (Headache Classification Committee of the International Headache Society, 1988) (Gee et al., 2005) or of the International Headache Society 2004 (Headache Classification Subcommittee of the International Headache Society, 2004) (Balasa and Bajko, 2010; Cruccu et al., 2009; Kister et al., 2010; Tortorella et al., 2006; Yetimalar et al., 2008).

All identified brainstem lesions corresponded to headache disorders, except for a lesion in the cerebral peduncle (among other lesions identified in the pyramidal tract) in a case of painful tonic spasms (Andrade et al., 2012). Spinal cord lesions corresponded to headache disorders in two studies (Alstadhaug et al., 2008; de Santi et al., 2009) (Table 5). Lesions including both the peripheral and the CNS were described in one study (brainstem and trigeminal nerve — Pichiecchio et al., 2007). Three studies found incidental structural lesions, which were unrelated to MS but felt to explain headache or facial pain (Athanasiou et al., 2005; Eldridge et al., 2003; Meaney et al., 1995).

3.3.2. Neuropathic body pain

Five different body pain syndromes were identified, all neuropathic: pseudo-radicular pain (Marchettini et al., 2006; Ramirez-Lassepas et al., 1992; Tosi et al., 1998), dysesthetic pain (Burkey et al., 2010; Deppe et al., 2013; Hellwig et al., 2006), painful itching (Hellwig et al., 2006), painful tonic spasms (Andrade et al., 2012) and visceral pain (Marchettini et al., 2006). All lesions thought to explain the body pain syndromes were located in the spinal cord (Table 5), except for the painful tonic spasms where lesions were identified in the pyramidal tract in the brain (Andrade et al., 2012) (Table 5).

3.4. Treatment of pain

In seven of the studies (21% of total), although neuroimaging was used to study pain syndromes in MS, the main focus of the study was an invasive pain treatment. These studies addressed microvascular decompression for trigeminal neuralgia (TN) (Athanasiou et al., 2005; Broggi et al., 2004; Eldridge et al., 2003), CNS stimulation (Burkey and Abla-Yao, 2010; Cordella et al., 2009; Tanei et al., 2010), and intrathecal administration of a steroid (Hellwig et al., 2006).

4. Discussion

Our findings suggest that the number of studies examining neuroradiological correlates of MS pain is low and that methodology and quality of these studies are variable. The majority of included articles are case reports or series, and therefore are of limited value for clinical practice or for research (Vandenbroucke, 2001). Specifically, we found only 13 hypothesis-driven investigational studies. In turn, of these identified investigational studies, only one met all of our quality criteria (Kister et al., 2010), and five (Deppe et al., 2013; Gee et al., 2005; Kister et al., 2010; Svendsen et al., 2011; Tortorella et al., 2006) over half. We identified several aspects of methodology that could be improved in our included studies.

Firstly, we identified that the focus of identified studies on specific pain syndromes did not closely reflect clinical estimates of the prevalence of these pain syndromes in MS. All identified studies investigated neuropathic pain syndromes, despite frequent observations in cross-sectional studies that both nociceptive and neuropathic pains are common in MS (Polman et al., 2011). There was also an emphasis on investigation of headache disorders and facial pain (74% of all studies), in particular TN. This emphasis is at odds with estimates of prevalence of pain syndromes in MS — for example TN is reported in 1–5% of MS patients, as compared to an overall pain prevalence of approximately 50% (Polman et al., 2011). Other cranial pain syndromes examined in included studies (such as occipital or glossopharyngeal neuralgia (Carrieri et al., 2009; de Santi et al., 2009; Minagar and Sheremata, 2000; Vilisaar and Constantinescu, 2006)) are even less common. These observations could suggest that studies identifying neuroradiological correlates of neuropathic pain syndromes in general, and headache or facial pain syndromes in particular, are disproportionately represented by the current literature (Bax and Moons, 2011).

Table 2
The quality assessment criteria used in the systematic review of the literature.

Original studies	Quality assessment criteria										
	Research objective	Recruitment procedure	Inclusion/exclusion criteria	Population demographics	Participation rates	Pain measures	Imaging protocol	Strength of effect	Multivariate analysis	Limitations discussed	Participation over 70%
Balasa (2010)	Yes	Yes	No	No	No	Yes	No	No	No	No	No
Broggi (2004)	Yes	Yes	No	Yes	No	Yes	Yes	No	No	No	No
Crucu (2009)	No	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	No
Deppe (2013)	Yes	Yes	Yes	Yes	No	No	Yes	No	No	Yes	No
Eldridge (2003)	Yes	Yes	No	Yes	No	No	Yes	No	No	No	No
Gass (1997)	Yes	Yes	No	Yes	No	No	Yes	No	No	No	No
Gee (2005)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No
Kister (2010)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ramirez-Lassepas (1992)	No	Yes	No	Yes	No	No	No	No	No	Yes	No
Da Silva (2005)	Yes	Yes	No	Yes	No	No	Yes	No	No	Yes	No
Svendsen (2011)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No
Tortorella (2006)	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	No
Yetimalar (2008)	Yes	Yes	No	Yes	No	No	Yes	No	No	No	No

The included headache studies largely aimed to examine neuroradiological correlates of specific headache subtypes. Small studies of migraine and unclassified headache including one to two subjects (Fragoso and Brooks, 2007; Haas et al., 1993) identified abnormalities in relation to the brainstem, in keeping with the putative role of the brainstem in pain transmission pathways. Larger investigational studies including those by Gee and colleagues ($n = 277$) (Gee et al., 2005) and Tortorella and colleagues ($n = 79$) (Tortorella et al., 2006) (quality assessments ten and eight, respectively, from a maximum of 12) also suggested that the presence of brainstem demyelination might be associated with the occurrence of migraine. In contrast, Kister and colleagues ($n = 204$) (quality assessment 12) compared MS groups with and without migraine, and found no differences in the number or distribution of lesions in the brain (including the brainstem) between the two groups (Kister et al., 2010).

Studies characterising TN and trigeminal autonomic cephalalgias (TACs), in contrast, focused on abnormalities related to the trigeminal nucleus and nerve. Interestingly, there appears to be an overlap in radiological findings between TN and TACs, though this observation may not be generalisable to patients without MS. Regarding TN, two of the identified studies (Broggi et al., 2004; Eldridge et al., 2003) focused on treatment. Separate studies supported the roles of both central demyelination (Balasa and Bajko, 2010; Broggi et al., 2004; Cruccu et al., 2009; Gass et al., 1997) and peripheral mechanisms (da Silva et al., 2005; Eldridge et al., 2003). Despite the preponderance of headache and facial pain studies described in our review, differing methodology impairs synthesis of results. Both peripheral and central mechanisms in TN related to MS are described, and the relative importance of each is not easily quantified. Studies of microvascular decompression further suggest that in some cases outcome for patients with demonstrated neurovascular contact is relatively poor than that for patients without MS (Broggi et al., 2004; Eldridge et al., 2003). This has been interpreted as supporting a dual mechanism of TN pain in at least some MS patients.

Neuropathic extremity pain of central origin (typically a chronic "burning" pain affecting the lower limbs) is thought to be one of the most common pain syndromes in MS (O'Connor et al., 2008). Our included studies examined differing types of limb pain, and the hypothesis that spinal lesions may be causative in limb or radicular pain has been proposed in several studies. In particular, in case reports or series (Burkey and Abla-Yao, 2010; Hellwig et al., 2006; Tosi et al., 1998), dorsal cord lesions in the thoracic and/or the cervical cord have been linked to limb pain, perhaps by directly disturbing sensory afferent pathways, or by disrupting descending inhibitory pathways (Svendsen et al., 2011). This hypothesis is further supported by one investigational study that was assessed as relatively poor quality by our criteria ($n = 11$, quality assessment three, from a maximum of 12) (Ramirez-Lassepas et al., 1992). Svendsen et al., however, using a better study design including spinal and brain MRI ($n = 25$, quality assessment eight) found no association between the site of demyelination and the presence of chronic central neuropathic pain (Svendsen et al., 2011).

Taking into account all identified studies, culprit demyelinating lesions were most commonly reported in the brainstem, and less commonly in the spinal cord. This may as well be linked to our observations above that the majority of studies investigated headache or facial pain. Notably, among the included investigational studies, Svendsen et al. (2011) investigated corticothalamic involvement and found no statistically significant difference in thalamic or thalamocortical projection lesion load in MS patients with or without pain. Deppe and colleagues, using DTI, studied a patient with central pain and abnormal somatosensory and thermal sensations on the right side of the body, comparing with imaging data from 100 healthy volunteers (the subjects and patient were part of a pilot study for a clinical trial) (Deppe et al., 2013). The imaging technique and post-processing methods were well described. However, the authors suggest that the unilateral temporary increase of the fractional anisotropy found in the

Table 3
Descriptions of magnetic resonance imaging methodology.

MRI image acquisition	Papers
Scanner	Deppe (2013), Eldridge (2003), Gass (1997), Meaney (1995), Svendsen (2011)
Field strength	Andrade (2012), Broggi (2004), da Silva (2005), Deppe (2013), Eldridge (2003), Gass (1997), Kister (2010), Meaney (1995), Svendsen (2011), Tortorella (2006), Yetimalar (2008)
Sequences	
All the sequences used	Broggi (2004), da Silva (2005), Deppe (2013), Gass (1997), Haas (1993), Kister (2010), Meaney (1995), Svendsen et al., 2011, Tortorella (2006)
Some of the sequences used	Andrade (2012), Athanasiou (2005), Donat (2012), Eldridge (2003), González-Quintanilla (2012)
Sequence parameters	
All the sequences used and all its parameters	da Silva (2005), Gass (1997), Svendsen (2011), Tortorella (2006)
Some of the sequences used and/or some of the parameters	Athanasiou (2005), Broggi (2004), Deppe (2013), Haas (1993), Meaney (1995)

contralateral thalamus may have played a causative role, though the pain syndrome was poorly characterised. The relative lack of studies of corticothalamic involvement in MS-related pain may relate to a historical emphasis on white matter pathology in MS, despite ample recent evidence of grey matter involvement (Compston and Coles, 2008). Methods used for identification of culprit MS lesions also frequently relied on *a priori* anatomical hypotheses. This could in theory diminish the likelihood of identifying novel associations with a particular pain syndrome. In only a minority of cases was a temporal association between the lesion and the pain syndrome in question further studied by serial imaging and/or the use of intravenous contrast (Table 5). Furthermore, any possible role of MS-related damage in normal-appearing tissue was not considered, with the one exception of Deppe and colleagues' study (Deppe et al., 2013); no investigators explicitly studied transition from acute to chronic pain states.

In all but one of the studies, MRI was used (most frequently to analyse lesion location, or to investigate structural causes of pain). The description of image acquisition and reading protocols, and investigator blinding in the original studies was, however, in general insufficient. It was also not always clear who read and interpreted the images (Table 1), and only four investigational studies (Gee et al., 2005; Kister et al., 2010; Svendsen et al., 2011; Tortorella et al., 2006) described image interpretation blinded to subject pain status (Table 2). The complexity of imaging techniques such as MRI requires more rigorous methodology and reporting in order to ensure clarity and reproducibility. Poldrack and colleagues published comprehensive guidelines for the reporting of methods and results in fMRI that are relevant as well for structural MRI (Poldrack et al., 2008). Blinded assessment could also help to minimise potential for biased interpretation of images.

We identified no functional or molecular imaging studies of the CNS, despite the potential of these methods in studying pain mechanisms in health and disease (Tracey, 2007), and only one study (Deppe et al., 2013) investigated pain using non-conventional structural MRI (DTI). MRI is important in the diagnosis and investigation of MS due to its sensitivity, non-invasiveness and reproducibility. However, clinical–radiological correlations have not always been the expected, including in the pain research field. This discrepancy may reflect the difficulties of imaging the complete spectrum of MS pathological abnormalities that range from focal and diffuse white matter lesions, normal-appearing white matter damage, grey matter damage and vascular changes, in the brain and in the spinal cord. Several non-conventional MRI techniques are important in resolving non-focal, grey matter and vascular MS pathology. DTI, magnetisation transfer imaging (MTI) and proton spectroscopy can quantify and characterise normal-appearing tissue

Table 4
Types of pain syndromes studied.

Type of pain syndrome	Study
Headache disorders	
Migraine	Fragoso (2007), Kister (2010), Tortorella (2006)
Cluster headache and other trigeminal autonomic cephalalgias	Cluster headache — Gentile (2007) Cluster-like headache — Donat (2012), Leandri (1999) Cluster-tic syndrome — González-Quintanilla (2012) SUNCT — Davey (2004), Vilisaar (2006) Probable trigeminal autonomic cephalalgia with allodynia — Liu (2008)
Cranial neuralgias and central causes of facial pain	Glossopharyngeal neuralgia — Carrieri (2009), Minagar (2000) Occipital neuralgia — de Santi (2009) (2 cases) Painful third nerve palsy — Bentley (2002) Transverse colli neuralgia — de Santi (2009) (1 case) Trigeminal neuralgia — Athanasiou (2005), Balasa (2010), Broggi (2004), Cordella (2009), Cruccu (2009), da Silva (2005), Eldridge (2003), Gass (1997), Meaney (1995), Nakashima (2001), Pichiecchio (2007)
Other headache, cranial neuralgia, central or primary facial pain	Atypical trigeminal neuralgia/facial pain — Tanei (2010) Headache — Alstadhaug et al., 2008, Haas (1993)
Body pain	
Pseudo-radicular pain	Cervical — Tosi (1998) Sciatica — Marchettini (2006) Various levels — Ramirez-Lassepas (1992)
Dysesthetic pain	Burkey (2010), Deppe (2013), Hellwig (2006)
Pain and painful itching	Hellwig (2006)
Painful tonic spasms	Andrade (2012)
Visceral pain	Marchettini (2006)
Various	Svendsen (2011), Yetimalar (2008)

SUNCT — short-lasting unilateral neuralgiform headache with conjunctival injection and tearing.

Table 5
Location of candidate culprit multiple sclerosis lesions in the origin of pain as detected by magnetic resonance imaging in the case reports/series retrieved.

Study	Pain syndrome or location	Localisation of the lesions possibly explaining the pain syndrome	Basis of association (A/S/C)
Spinal cord			
Tosi (1998)	Radicular	Cervical (C5–C6) dorsal root entry zone and posterior horn	A, S
Alstadhaug et al., 2008	Headache (type not defined)	Posterior part of the upper cervical spinal cord	A, S
Burkey (2010)	Upper limb pain	Posterior columns from C2 to C4	A
Hellwig (2006)	Painful dysaesthesia at thoracic level and/or below	Posterior upper thoracic spinal cord; cord lesions at the level of C1, C4/5, Th3 (two cases)	A, C
de Santi (2009)	Occipital neuralgia	Right antero-lateral spinal cord at C2; C1, C2, C3 and D1–D2; C2–C3 lesion (three cases)	A, S, C
Marchettini (2006)	Back, leg, flank or abdominal pain	Spinal cord location of the lesions assumed; MRI was used to exclude other causes of pseudo-radicular or visceral pain (five cases)	n/a
Brain			
Andrade (2012)	Painful stereotyped involuntary posturing movements of the left upper limb	Pyramidal tract lesions (cerebral peduncle, internal capsule and corona Radiata)	A, S, C
Bentley (2002)	Painful third nerve palsy (including pupil)	Midbrain adjacent to right third nerve fascicle	A, S
Donat, 2012	Cluster-like headache	Right dorsal pons	A
González-Quintanilla (2012)	Cluster-tic	Left and right trigeminal root inlet and main sensory nucleus in the brainstem	A, S
Tanei (2010	Facial pain (non-TN)	Right dorsal pons and medulla oblongata	A
Haas (1993)	Headache (type not defined)	Periaqueductal grey	A, S, C
Liu (2008)	Probable TAC with allodynia and other symptoms	Right lateral tegmentum of the lower pons	A, S
Leandri (1999)	TAC	Root entry zone of the trigeminal nerve on the right	A
Gentile (2007)	Cluster headache/TAC with sensory symptoms	Left brachium pontis	A, S
Meaney (1995)	TN (unilateral or bilateral)	Root entry zone of both trigeminal nerves (one case out of seven cases described)	A
Nakashima (2001)	TN	Left trigeminal root entry zone (one case out of five cases described)	A
Fragoso (2007)	Migraine without aura	Brainstem (two cases)	A
Cordella (2009)	TN	Trigeminal root entry zone (five cases)	A
Pichiecchio (2007)	TN	Trigeminal root entry zone bilaterally and enhancement of trigeminal nerves	A/C
Vilisaar (2006)	SUNCT	Anterior pons, right cerebral peduncle and medulla (one case)	A

A — anatomically plausible lesion; S — serial imaging demonstrating emergence or disappearance of plaque in line with clinical pain syndrome; C — contrast enhancing plaque; n/a = not applicable; TN — trigeminal neuralgia; TAC — trigeminal autonomic cephalalgia; SUNCT — short-lasting unilateral neuralgiform headache with conjunctival injection and tearing; MRI — magnetic resonance imaging.

changes (Filippi et al., 2012). Double inversion recovery has improved the sensitivity of MRI to detect cortical lesions (Geurts et al., 2005), and the use of ultra-high-field scanners is promising (Filippi et al., 2012; Ropele et al., 2011). Brain tissue perfusion can be assessed as well with MRI (Ge et al., 2005; Inglese et al., 2007). Inter-patient variability of clinical manifestations might also be explained with functional CNS reorganisation and plasticity, which can be imaged with fMRI (Filippi and Rocca, 2011).

Our review had several limitations. We have included studies, as discussed above, which do not fully describe diagnostic criteria used in application of the diagnosis of MS. Therefore although all studies described the inclusion of only subjects with MS, the possibility of alternative pathology contributing to pain therefore needs to be remembered. We have, in addition, limited our study to articles published in English, and although only three studies were excluded using this criterion, it is possible that relevant data was not assessed.

5. Conclusion

We have found that neuroradiological studies of pain in MS are relatively low in number, and of variable design and quality. Some common pain syndromes were less frequently studied, and significant methodological issues relating to study design, execution and reporting were identified. We found that investigators using different study methodologies have reached differing conclusions regarding the neuroradiological correlates of specific pain syndromes in MS. Methodologically higher-quality studies were however less likely to report positive associations of lesion location to the presence of headache, or of chronic central neuropathic pain (Kister et al., 2010; Svendsen et al., 2011).

Therefore, despite the prevalence and impact of pain in MS, the insight into pain mechanisms currently afforded by neuroimaging studies remains limited. There is considerable opportunity to advance our mechanistic understanding of MS-associated pain, and thus its therapy,

through future research. High quality hypothesis-driven studies, including those investigating the more common pain syndromes, comparison of lesion localisation in MS patients with and without pain, and perhaps using functional and advanced structural MRI techniques, could be well placed to advance this important field.

Conflicts of interest

None to declare.

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