Journal of the Neurological Sciences 400 (2019) 52–71

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Review article

Evaluation of MS related central fatigue using MR neuroimaging methods: Scoping review

Jameen ARM[a], Karen Ribbons[c], Jeannette Lechner-Scott[b,c,d], Saadallah Ramadan[a,d,*]

[a] School of Health Sciences, Faculty of Health and Medicine, University of Newcastle, Callaghan, NSW 2308, Australia
[b] School of Medicine and Public Health, Faculty of Health and Medicine, University of Newcastle, Callaghan, NSW 2308, Australia
[c] Department of Neurology, John Hunter Hospital, Lookout Road, New Lambton Heights, NSW 2305, Australia
[d] Hunter Medical Research Institute, Kookaburra Circuit, New Lambton Heights, NSW 2305, Australia

ARTICLE INFO

Keywords:
MS: Multiple Sclerosis
MRI: Magnetic Resonance Imaging
DTI: Diffusion Tensor Imaging
fMRI: Functional Magnetic Resonance Imaging
MRS: Magnetic Resonance Spectroscopy

ABSTRACT

Background: Fatigue is a common and debilitating symptom in multiple sclerosis (MS). Over the past decade, a growing body of research has focussed on the pathophysiological mechanisms underlying central (cognitive and physical) fatigue in MS. The precise mechanisms causing fatigue in MS patients are complex and poorly understood, and may differ between patients. Advanced quantitative magnetic resonance imaging (MRI) techniques allow for objective assessment of disease pathology and have been used to characterise the pathophysiology of central fatigue in MS.

Objective: To systematically review the existing literature of MRI-based studies assessing the pathophysiological mechanisms of MS-related central fatigue.

Methods: A systematic literature search of four major databases (PubMed, Medline, Embase, Scopus and Google Scholar) was conducted to identify MRI-based studies of MS-related fatigue published in the past 20 years. Studies using the following MRI-based methods were included: structural (lesion load/atrophy), T1 relaxation time/magnetisation transfer ratio (MTR), diffusion tensor imaging (DTI), functional MRI (fMRI) and magnetic resonance spectroscopy (MRS).

Results: A total of 92 studies were identified as meeting the search criteria and included for review. Structurally, regional gray/white matter atrophy, cortical thinning, decreased T1 relaxation times and reduced fractional anisotropy were associated with central fatigue in MS. Functionally, hyperactivity and reduced functional connectivity in several regional areas of frontal, parietal, occipital, temporal and cerebellum were suggested as causes of central fatigue. Biochemically, a reduction in N-acetyl aspartate/creatine and increased (glutamine + glutamate)/creatine ratios were correlated with fatigue severity in MS.

Conclusion: Several advanced quantitative MRI methods have been employed in the study of central fatigue in MS. Central fatigue in MS is associated with macro/microstructural and functional changes within specific brain regions (frontal, parietal, temporal and deep gray matter) and specific pathways/networks (cortico-cortical and cortico-subcortical). Alternations in the cortico-striatal-thalamocortical (CSTC) loop are correlated with the development of fatigue in MS patients.

Abbreviations: ACC, Anterior cingulate Cortex; AD, Axial diffusivity; BOLD, Blood oxygen dependant level; BPF, Brain parenchymal fraction; BVL, Brain volume loss; CIS, Clinically isolated syndrome; CNS, Central nervous system; Cho, Choline; Cr, Creatine; CSI, Chemical shift imaging; CSTC, Cortico-striato thalamo-cortical; DMN, Default motor network; DLPFC, Dorsi-lateral pre frontal cortex; DSI, Diffusion spectrum imaging; DTI, Diffusion tensor imaging; EDSS, Expanded disability severity score; FA, Fractional anisotropy; FC, Functional connectivity; fMRI, functional MRI; GABA, ɣ-aminobutyric acid; Gln, Glutamine; Glu, Glutamate; Glx, Glutamine + glutamate; GM, Gray matter; HARDI, High angular resolution diffusion imaging; IFN, Interferon; ITG, Inferior temporal gyrus; MD, Mean diffusivity; MFG, Middle frontal gyrus; MFIS, Modified fatigue impact scale; mIno, Myo inositol; mIno/Cr, Myo inositol/Creatine ratio; MRS, Magnetic resonance spectroscopy; MRSI, Magnetic resonance spectroscopic imaging; MS, Multiple sclerosis; MTI, Magnetisation transfer imaging; MTR, Magnetisation transfer ratio; NAA, N-acetyl aspartate; NAA/Cr, N-acetyl aspartate/Creatine ratio; NAAG, N-acetyl aspartate glutamate; NAWM, Normal Appearing White Matter; NAWM, Normal Appearing Gray Matter; NODDI, Neurite orientation dispersion and density imaging; PASAT, Paced auditory serial addition test; PCC, Posterior cingulate cortex; PET, Positron emission tomography; PMC, Pre motor cortex; PPMS, Primary progressive multiple sclerosis; PRISMA, Preferred reporting items for systematic reviews and meta-analyses; RD, Radial diffusivity; RRMS, Relapse remitting multiple sclerosis; rs-fMRI, resting state-fMRI; SFG, Superior frontal gyrus; SMA, Supplementary motor area; SMC, Sensory motor cortex; SMN, Sensory motor network; SII, Secondary somatosensory cortex; SPMS, Secondary progressive multiple sclerosis; SVS, Single voxel spectroscopy; TBM, Tensor based morphometry; VBM, Voxel based morphometry; WM, White matter

* Corresponding author at: School of Health Sciences, Faculty of Health and Medicine, University of Newcastle, Callaghan, NSW 2308, Australia.
E-mail address: Saadallah.ramadan@newcastle.edu.au (S. Ramadan).

https://doi.org/10.1016/j.jns.2019.03.007
Received 30 August 2018; Received in revised form 17 February 2019; Accepted 11 March 2019
Available online 14 March 2019

1. Introduction

Fatigue affects almost 80% of patients with multiple sclerosis (MS) and is one of the most common and disabling symptoms of the disease [1,2]. Patients describe fatigue as an overwhelming state of tiredness, lack of energy and feelings of exhaustion [1,3]. Compared to other MS-associated neurological deficits such as depression, pain and physical disability, MS patients indicate that fatigue is considered to be the most debilitating symptom with significant socio-economic impact and decreased work productivity [4]. Fatigue can be present in all stages of MS, regardless of disease severity. Fatigue tends to be more severe and frequent in patients with either primary or secondary progressive forms of MS (PPMS/SPMS), compared with relapse-remitting disease (RRMS) [5–8]. Fatigue can develop earlier in the disease course when patients present with the clinically isolated syndrome (CIS), and its severity is similar to that of RRMS patients [9]. From a symptom management perspective, differentiating different forms of fatigue is essential. Primary fatigue can be directly associated with disease mechanisms which include inflammation, demyelination and/or axonal loss [10]. The secondary form of fatigue may be related to sleep disorders, which are a common problem in MS patients due to spasms, pain, anxiety/depression and medications [11]. MS relapses quite typically are characterised by increased fatigue [12]. Although fatigue can manifest from alterations in either the central or peripheral nervous systems, MS-associated fatigue is primarily central with cognitive, physical and psychosocial elements [13,14].

2. Definition of fatigue

In 2000, Chaudhuri and Behan suggested the term “central fatigue’ which mainly refers to failure in performing/sustaining both mental (cognitive) and physical (motor) tasks requiring self-motivation [15]. This definition contrasts central fatigue with the fatigue experienced by healthy individuals after a period of sleep loss or viral infection. The central fatigue experienced by patients with neurological diseases such as MS can be chronic (persisting for up to six months or longer), differing from the short-lived physiological fatigue in healthy people. A more clinically relevant definition of fatigue with a physiological basis was proposed in 2008 by Mills and Young [16]. They defined MS fatigue as “*reversible, motor and cognitive impairment with reduced motivation and desire to rest, either appearing spontaneously or brought on by mental or physical activity, humidity, acute infection and food ingestion*” [16].

Neuroimaging techniques such as positron emission tomography (PET) and magnetic resonance imaging (MRI) have been used to study the factors related to cognitive [17–19] and physical domains [20–22] of MS fatigue. MRI is often the preferred choice owing to its versatility in providing both qualitative and quantitative measures of tissue characteristics using a wide range of MR metrics [23]. Qualitative or conventional structural MRI is used extensively in clinical settings to diagnose and manage MS. Recent advancements in quantitative MRI techniques have extended its use with a growing number of studies over the last two decades reporting the use of varied MRI approaches to characterise the pathophysiological mechanisms underlying MS-associated fatigue. The quantitative techniques include relaxometry, magnetisation transfer imaging (MTI), diffusion tensor imaging (DTI), functional MRI (fMRI), magnetic resonance spectroscopy (MRS). Despite significant research progress, an understanding of the pathophysiological mechanisms underpinning MS fatigue is still not completely understood. We proposed that a comprehensive, scoping review of novel MRI-based studies into the mechanisms underlying MS fatigue would be useful, to assess the current state-of-knowledge in the field and identify current gaps in knowledge. The primary objective of this scoping review is to identify and synthesise the MRI findings/features present in the current literature to understand MS-related central fatigue. The specific research questions are: (1) to identify the most common MRI methods that have been used to study MS-related fatigue and (2) to explore whether or not there is a cerebral imaging signature associated with fatigue in MS. MRI technology is sophisticated and technical, which can make the interpretation of MRI-based study findings difficult. Thus, we provide a brief overview of the principles underlying MRI techniques which have been used in studies of MS-related central fatigue to support the interpretation of published findings.

3. MRI methods used in MS fatigue evaluation

3.1. Conventional structural imaging

3.1.1. T1/T2 weighted imaging

Structural imaging, based on T2 weighted and contrast enhancing T1 images, is an essential aspect of the clinical diagnosis and further management of MS. Structural imaging provides information on localisation of tissue pathology in time and space, as well as alteration in cerebral and spinal lesions in response to treatment [24]. Both T1 and T2 weighted imaging provide information on focal areas of white matter (WM) and gray matter (GM) damage, inflammatory changes and presence of active lesions through its morphologic characteristics, signal intensity changes and degree of T1 enhancement with gadolinium [25]. T2 weighted imaging is the most widely used method for the evaluating of lesion load or burden due to its diagnostic sensitivity in providing information on disease progression/dissemination [26].

3.1.2. Volumetric imaging for brain atrophy and cortical thinning

Brain volume loss (BVL) or atrophy is a feature of MS disease progression and biomarker for irreversible neuronal tissue damage [27]. Average BVL in MS patients is 0.6-1%, substantially more than in healthy age-matched controls (0.5%) [28]. In MS, BLV starts at an early stage and progresses over the entire duration of the disease [29]. Diffuse global atrophy or total BVL occurs through the loss of both WM and GM tissues from demyelination and axonal damage [30]. GM atrophy typically occurs much earlier in the disease course than WM atrophy [31], and extensive research attention has focussed on the role of GM pathology (e.g. cortical thinning) in the progression of disability and cognitive impairment in MS [32]. GM structures are responsible for normal cognitive functioning, and cortical thickness and surface area are assessed as readouts of GM function [33]. Thus, evaluating cortical thickness provides insights into early pathologic changes associated with MS.

3.2. Quantitative imaging

3.2.1. Relaxometry and Magnetisation Transfer imaging

In contrast to qualitative structural imaging approaches, quantitative techniques, e.g. relaxometry and magnetisation transfer imaging (MTI) provide more detailed information about tissue characteristics, including disease-related tissue changes, developmental plasticity and biological processes. Relaxometry uses T1/T2 relaxation times as parameters to provide quantitative insights into tissue changes. T1 relaxation times quantify the number of free protons and organisation of molecules such as lipids and larger proteins such as macromolecules [34]. In contrast, T2 relaxation times quantify the dynamic nature of water and its interactions with macromolecules [35,36]. Measurement of T1/T2 relaxation times provides information on tissue structural integrity, amount of water content and the presence of paramagnetic ions (e.g. iron) [37].

MTI is based on the transfer of magnetisation between protons in free water and protons of water attached to macromolecules [38]. Quantification is based on the MT ratio, which is calculated based on the signal change before and after the application of the MT pulse. Altered MT ratio reflects the presence of demyelination and remyelination. In MS, it allows the quantification of indirect tissue damage, which precedes the appearance of lesions by several months

[39]. Decreased MT ratio in lesions, normal-appearing WM and GM (NAWM/NAGM) correlates with clinical disability [40]. Advantages of MT techniques over structural scan approaches include higher specificity for morphological and pathological changes, the assessment of WM lesion burden and the ability to create an MT histogram, which provides information on micro and macroscopic disease burden [41].

3.3. Advanced Quantitative imaging

3.3.1. Diffusion Tensor Imaging (DTI)

DTI examines the macroscopic and structural axonal organisation of neuronal tissue, in particular, WM tracts [42]. DTI is based on the measurement of the random motion of water molecules in the extracellular matrix, which is hindered or restricted in many pathological conditions. The significant diffusion properties used in neuroimaging research studies include fractional anisotropy (FA) axial diffusivity (AD), radial diffusivity (RD) and mean diffusivity (MD). FA, being the most sensitive index, provides information about the shape of diffusion ellipsoid in the form of scalar quantity between zero and one (zero represents perfect isotropic diffusivity, the value of 1 indicates diffusion along an ellipsoid). The FA value for healthy myelin ranges from 0.5 to 0.7, and a decrease in FA value is reflective of tissue damage such as demyelination. AD and MD are markers of the integrity of axons and myelin, respectively, while MD is a scalar quantity used to measure overall diffusion within a voxel, that is representative of vasogenic oedema, and axonal and myelin loss [43,44]. An increase in MD relates to the loss of physiological barriers to diffusion due to cell injury [39].

3.3.2. Functional MRI (fMRI)

Over the years, fMRI has become an essential tool in neuroscience research, which measures neuronal activity, or function, based on changes in haemodynamics based on blood oxygen dependent level (BOLD) signal changes [45]. Broadly, fMRI is used in two ways. The task-related experimental designs (Block & Event), commonly employed both in clinical and research, involve the performance of a task, or stimuli, presented to the subject with a period of rest (10seconds) in between [46]. Alternatively, resting state design (rs-fMRI) provides information on the functional connectivity (FC) of the brain at rest, allowing the exploration of the overall organisation of functional communication or the synchrony of neural activity among regions in the brain networks [47]. Areas of the brain which exhibit signal fluctuations that are correlated in time are interpreted as being functionally connected. The most commonly studied networks or BOLD signal active regions are the default mode network (DMN) and the sensory-motor network (SMN). The DMN consists (1) precuneus/posterior cingulate, (2) lateral parietal cortex, (3) medial prefrontal cortex while the SMN corresponds to the1) precentral gyrus, (2) postcentral gyrus (3) and supplementary motor area (SMA) [48].

3.3.3. Magnetic Resonance Spectroscopy (MRS)

While structural MRI techniques make use of high spatial resolution to provide physical characteristics of tissue anatomy, MRS provides data on chemical tissue properties (e.g. metabolite profiles) to provide information on biochemical processes [39]. MRS measures the interaction of an applied magnetic field with the local magnetic environment of atoms within molecules, through a phenomenon termed chemical shift [49]. The difference between the MRI and MRS lies in the timing of the applied gradient to localise signal. The former applies gradient during the acquisition period whereas MRS does not apply this gradient during the acquisition portion to preserve the chemical shift information [50]. Rather than providing images, MRS quantification generates a spectrum, where each spectral peak represents a particular metabolite based on that molecule's chemical shift properties (Fig. 1).

The area under the peak denotes the concentration of each metabolite [51]. Absolute quantification of metabolite concentrations involves complex computational steps and interpretation of quantified data requires expertise. Metabolite ratios (normalised to the concentration of a stable metabolite) are commonly used for simplified quantification based on the assumption that there are minimal changes to the reference metabolite in the pathological state being examined [52]. The most commonly reported metabolites in neuroscience are total N-Acetyl aspartic acid (NAA) (NAA + NAAG), creatine (Cr),

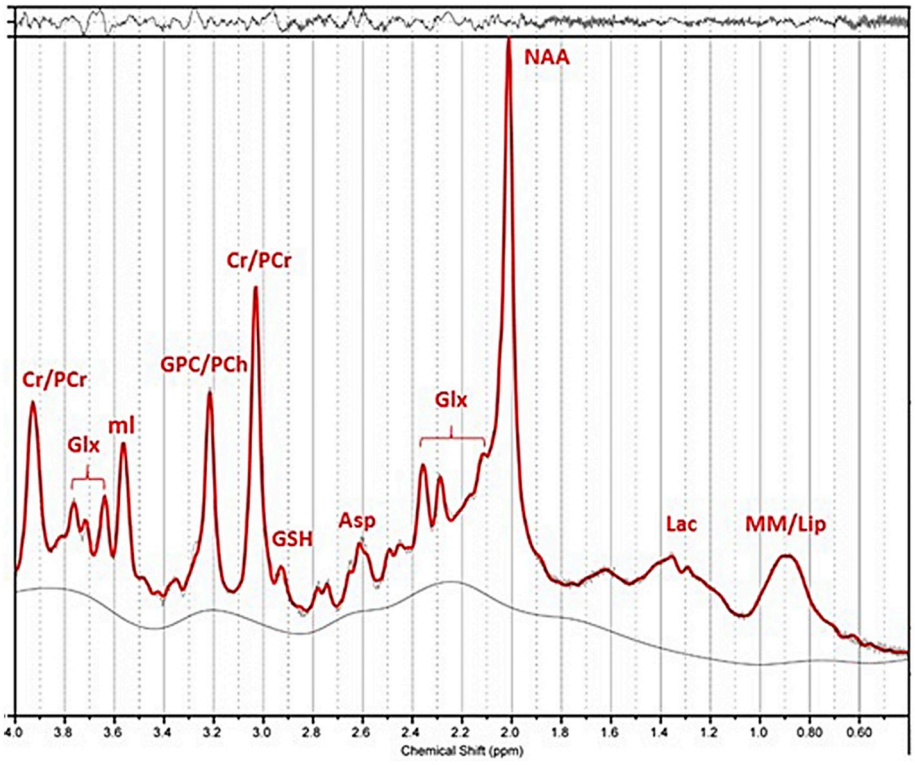

Fig. 1. A typical MRS spectrum acquired from posterior cingulate cortex in a healthy subject. **Cr/PCr**: Creatine/Phosphocreatine, **Glx**: Glutamine/Glutamate pool, **mI**: my-inositol, **GPC/PCh**: Glycerophosphocholine/Phosphoryl choline, **GSH**: Glutathione, **Asp**: Aspartate, **NAA**: N-Acetyl aspartic acid Lac: Lactate, **MM/Lip**: Macromolecules/Lipids

choline (Cho), myo-inositol (mI), Glx pool (glutamine (Gln), glutamate (Glu)), and lipids/lactate. Cr is commonly used as an internal reference metabolite in MRS in neurodegenerative disorders, including MS [53,54]. NAA/Cr ratio has been reported as a reliable metric for the assessment of changes in the integrity of axons and a surrogate imaging biomarker for neuronal integrity [55].

4. Methods

To identify research publications, we performed a systematic electronic literature search of PubMed, Ovid Medline, Embase, Scopus and Google Scholar. The following search terms were used: "fatigue", "multiple sclerosis", "magnetic resonance imaging", "brain atrophy", "brain volume", "structural MRI", "magnetisation transfer ratio", "diffusion tensor Imaging", "functional MRI" and "magnetic resonance spectroscopy". Only original research publications published in English from 1980 to 2018 were included. Publications were limited to those reporting data from human subjects, which included adult MS patients with fatigue who had undergone MRI. This search identified a total of 346 studies. Two authors (JA and SR) independently screened the abstracts before full-text extraction. After removing duplicate entries using Endnote software, the remaining studies (243 total) were transferred into Covidence software for screening and data extraction.

Articles were further categorised based on the reported MRI methods used. Fig. 2 provides a PRISMA flowchart overview of the search and screening strategy performed. Extracted data included magnetic field strength, data analysis method used, MRI metric applied, brain region studied, fatigue domain assessed (i.e. cognitive or physical), patient sample size, and significant findings.

5. Results

Our literature search and screening approach identified a total of 92 articles satisfying the inclusion criteria relevant to our research questions. The MRI methods used in the identified studies included structural, fMRI, DTI and MRS methods. Conventional MRI techniques were used to quantify atrophy/cortical thinning in 26 studies and only five studies utilised MRS techniques. Almost half of the studies carried out so far have adopted an integrated imaging approach, the common MRI methods used were structural imaging for lesion load, atrophy and DTI methods. Geographically, most of the identified studies were performed in European countries (> 60%), with more than 30 studies published by Italian groups using structural techniques and advanced methods including fMRI and DTI. Table 1 provides an overview of the MRI methods and features published in the identified studies of MS-associated fatigue. We have summarised the brain regions identified based on the type of MRI method applied, and their associations with different domains of fatigue assessed, including cognitive (mental), physical (motor), total fatigue score in the development of fatigue in MS.

6. Brain regions implicated in MS-associated fatigue

6.1. Lesion load

An overview of structural studies that assessed lesion load is presented in Table 2. The majority of earlier studies failed to identify an association between MS-related fatigue and either the total global extent of cerebral abnormalities or discrete T2/T1 lesions in regional areas [3,9,56–67]. Several theories have been suggested for the lack of correlation between anatomical feature and central fatigue. These

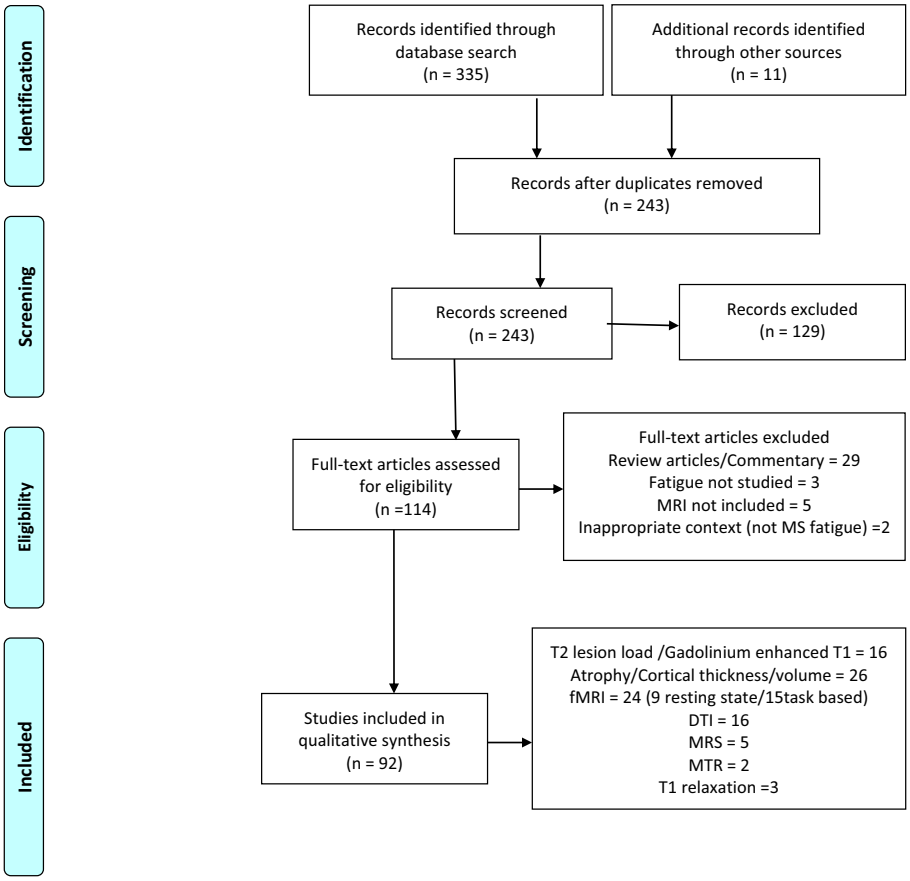

Fig. 2. PRISMA diagram of the search and screening strategy performed. **fMRI**: Functional MRI, **DTI**: Diffusion Tensor Imaging, **MRS**: Magnetic Resonance Spectroscopy, **MTR**: Magnetic Transfer Ratio.

Table 1
MRI measures used in the assessment of MS Fatigue.

Method	Technique	Outcome measures	Major MR features linked to Fatigue	Major Brain areas/network identified
Structural	3D T1w, 3D T2w, 3D FLAIR	Lesion load, Cortical thinning, Atrophy	+/- correlation with lesions load, +with atrophy/Dilated PVS	Frontal, parietal, temporal, occipital, thalamus, corpus callsoum and basal ganglia, SMA, brain stem, SCP
Tissue perfusion	DSC	CBF/CBV	Decreased CBF/CBV	Deep GM/WM (Thalamus, putamen and caudate)
Relaxometry	T1/T2/T2*	Relaxation time	Increased T1 values	Thalamus, Hypothalamus, Temporal lobe
MT	ON/OFF MT Pulse	Degree of myelination, axonal density	No change	No change observed
fMRI	Task based/resting state	Functional connectivity	Hyper/Hypo activation	***Hyper*** **:** Cerebellum, cingulate gyrus, STG, ITG, SPC, IPC, thalamus, basal ganglia, frontal (DLPFC), parietal, (precuneus/cuneus) occipital, contralateral SMA, PMC, ACC,SII, precuneus, OFC, left PPC, right substantia nigra, caudate nucleus ***Hypo:*** Frontal lobe, basal ganglia, contralateral thalamus, ipsilateral rolandic operculum
DTI	Movement of water	Structural connectivity	Reduced FA and increased MD/RD	Frontal, cingulum bundle, right ATR, Ulcinate fasciculus, forceps minor, SLF, cerebellar peduncle, temporal cortex, inferior fronto-occipital fasciculus, thalamus, basal ganglia
MRS	SVS, CSI	Metabolite concentrations	Low NAA/Cr ratio Glx/Cr	Corpus callosum/periventricular WM, tegmental pons/cerebellum, left parietal WM/hypothalamus, left frontal region/lentifrom nucleus, PCC

ACC: Anterior Cingulate Cortex, **ATR:** Anterior Thalamic Radiation, **CBF:** Cerebral Blood Flow, **CBV:** Cerebral Blood Volume, **3D:** Three Dimensional, **DLPFC:** Dorsi-Lateral Pre Frontal Cortex, **DSC:** Dynamic Susceptibility Contrast, **DTI:** Diffusion Tensor Imaging, **FA:** Fractional Anisotropy, **FLAIR:** Fluid Attenuated Inversion Recovery, **fMRI:** functional Magnetic Resonance Imaging, **Glx:** Glutamine/Glutamate pool, **GM:** Gray Matter, **IPC:** Inferior Parietal Cortex, **ITG:** Inferior Temporal Gyrus, **MD:** Mean Diffusivity, **MRS:** Magnetic Resonance Spectroscopy, **MRSI:** Magnetic Resonance Spectroscopic Imaging **MT:** Magnetisation Transfer, **NAA/Cr:** N-Acetyl Aspartate/Creatine, **PMC:** Primary Motor Cortex, **OFC:** Orbito Frontal Cortex, **PCC:** Posterior Cingulate Cortex, **PVS:** Peri Ventricular Space, **RD:** Radial Diffusivity, **SCP:** Superior Cerebral Peduncle, **SII:** Secondary somatosensory cortex, **SLF:** Superior Longitudinal Fasciculus, **SMA:** Sensori Motor Area, **SPC:** Superior Parietal Cortex, **STG:** Superior Temporal Gyrus, **SVS:** Single Voxel Spectroscopy, **WM:** White Matter.

include diffuse low-grade diffuse inflammation that is undetectable in MRI [56], peripheral inflammation rather than central inflammation [68], low sensitivity [61] and the discrepancies in patient selection, fatigue evaluation, and analysis methods applied. In contrast, recent studies reported significant correlations between T2 lesion load and both cognitive fatigue [63,69,70] and total fatigue score [21,71–75]. These studies included whole brain WM/GM lesion volume [75,76] as well as lesions in regional areas such as basal ganglia, parts of frontal, parietal lobes [74,77], periventricular/juxta cortical/basal ganglia/frontal lobe/deep WM [70], and cortical lesions [73].

6.2. Macrostructural changes (Brain volume loss and cortical thinning)

Studies (Table 3) using whole brain atrophy measurement found cognitive/motor fatigue in MS patients have an association with global brain atrophy (reduced brain parenchymal fraction and cortical volumes) [75,76,78–80]. Association between extensive atrophy predominantly in cortical and subcortical GM/WM [76,80–82], corpus callosum [83], and cognitive fatigue have been reported. Perhaps, the most compelling evidence that sheds lights to a clear link between fatigue and atrophy is from findings of the studies focussing on regional brain atrophy measurements using advanced analysis techniques such as voxel/tensor-based morphometry (VBM/TBM). VBM is a whole brain unbiased, objective method that compares different brains on a voxel by voxel basis which provides more sensitivity in evaluating small scale and regional differences in GM or WM [84]. Using VBM, several studies reported an association between fatigue and regional atrophy. Cognitive fatigue was associated with extensive WM/GM atrophy of occipital lobes (mainly right superior/inferior occipital gyrus [85], temporal lobes including right inferior temporal gyrus (ITG), frontal lobe, (dorsi lateral pre frontal cortex (DLPFC), left superior frontal gyrus (SFG), right inferior frontal gyrus (IFG), and forceps major) [63,86], parietal lobe, precuneus [86] primary sensorimotor area including precentral gyrus [67], supplementary motor area (SMA) such as paracentral gyrus, bilateral precentral motor cortex, and brain stem [18]. One study used TBM-based approach, which provides a more robust estimation of atrophy that improves statistical power over VBM [87], found significant regional cortical atrophy primarily in frontal (DLPFC, SFG and limbic lobe), parietal (posterior part of the parietal lobe) and basal ganglia [60]. Correlations between total fatigue score alterations in the lower thalamic [62,88], striatum [21], pallidal, superior cerebellar peduncle (SCP) also have been reported [88]. In a combined PET/MR study, total fatigue score was negatively correlated with GM atrophy in many areas of frontal, temporal, parieto-occipital as well as bilateral thalami along with resting cerebral metabolic rate of glucose [89]. Atrophy in other brain structures such as corpus callosum (especially anterior corpus callosal segment), caudate and accumbens are also associated with total fatigue [90–93]. Interestingly, these studies reveal the progression of corpus callosal atrophy over time as a potential independent risk factor of MS-related fatigue.

Cortical thinning along right inferior parietal, middle cingulate [94], and reduced cortical volumes along right rostral, middle frontal, pre/postcentral gyrus [79,95] posterior parietal cortex (PPC), middle cingulate gyrus (MCG), frontal lobe (middle frontal gyrus, MFG) [62,96] have also been correlated with cognitive fatigue scores. Physical fatigue was also associated with reduced striatal volume and cortical thickness along SFG [77]. In contrast, a few studies that report no associations between fatigue and global atrophy, deep GM structures and cortical GM volumes or thinning of the rolandic region [97–100] after correcting for disability score and including patients with early stage of MS.

Atrophy results mainly from neuroaxonal degeneration and cortical demyelination [31]. Atrophy measures reveal extensive WM/GM loss in frontal, parietal, temporal and deep gray matter structures with a close link on the pathogenesis of fatigue. Some of these areas are responsible for cognitive functions, attentional control, and reward functions

Table 2
Lesion load and fatigue.

Field strength/Analysis method	Region studied	Fatigue Domain	Depression status	N (MS phenotype)	Major findings linked to fatigue	Authors/Year/Ref
1T/semi quantitative	24 areas in both hemispheres (Global/ regional)	(Cognitive/ Physical)[a]	Not corrected	45 (26RR/19SP)	No correlation with WM/CL	Van der Werf et al. 1998 [56]
1.5T/Manual	Superior/Inferior frontal & parietal(Global and regional)	(Cognitive/ Physical)[a]	Excluded [+]	71 (50RR/21SP)	No correlation with WMLL	Bakshi et al. 1999 [61]
1.5T/Semi automated	Deep GM areas (thalamus, putamen, caudate nucleus)	(Cognitive/ Physical)[a]	Not mentioned	52 RRMS	No correlation with WMLL volume but T1 relaxation time.	Niepel et al. 2006 [64]
3T/Semi automated(LTT)	Thalamus/putamen/caudate nuclei	(Cognitive/ Physical)[a]	Accounted for	22 (11RR/11PP)	No correlation between MTT and fatigue score or lesion volume but significant correlation between CBF/CBV	Inglese et al. 2007 [65]
1.5T/3D slicer	Total brain T2 lesion	Overall Fatigue	Not mentioned	33 RRMS	No correlation between fatigue and T2 and BPF	Cavallari et al. 2016 [160]
3T/LPM	Right DLPFC, SFG, several regions within parietal and occipital lobes	Cognitive/Physical[a]	Excluded	123 (91RR/22SP/ 10PP)	No correlation with T2 lesion volume	Gobbi et al. 2014a) [3]
1.5T/Manual (LTT)	Brain stem/periventricular/juxtacortical	Cognitive	Excluded	24 RRMS	No correlation with T2 WMLL	Riccitelli et al. 2011 [67]
1.5T/not provided	T2/Gadolinium enhanced T1 lesions	Overall Fatigue	Included	42 RRMS	No correlation of T2/T1 lesions and fatigue	Putzki et al. 2009 [57]
3T/Manual	DLPFC, PPC, and basal ganglia	(Cognitive/ Physical)[a]	Not accounted for	34 RRMS	No correlation with WMLL	Andreasen et al. 2010 [60]
3T/Semi automated (LTT)	Frontal/Parietal	(Cognitive/ Physical)[a]	Excluded	24 RRMS	No correlation between WMLL/NAWM and fatigue	Pellicano et al. 2010 [62]
1.5T/not provided	Whole brain	Total FSS	Corrected	59 (CIS)	No association with either T2/T1 enhanced lesions	Runia et al. 2015 [9]
3T/LST	Thalamus	Cognitive/Motor	Not mentioned	79 (RRMS)	No correlation for cognitive but weak for motor	Wilting et al. 2016 [66]
3T/Semi-automatic	Total or regional	Overall fatigue	Corrected	49 RRMS	No correlation between fatigue and WMLL	Palotai et al. 2017 [58]
3T/Semi-quantitative	Whole brain	Cognitive/Physical	Not mentioned	150 (120RRMS/ 30CIS)	No relationship between T2LV and fatigue	Ntranos, et al. 2018 [93]
1.5T/Semi-automatic	Whole brain	Cognitive	Not mentioned	11 RRMS	No relationship between number/volume of T1 enhancing lesions.	Mainero et al. 1999 [59]
3T/Segmentation	Right accumbens, ITG, left STG, forceps major	Cognitive	Excluded	63 (56RR/7SP)	No correlation with global WMLL or CL but high occurrence of lesion in ATR	Rocca, Parisi et al. 2014 [63]
1.5T/Semi quantitative	Parietal/internal capsule/periventricular trigonum	Cognitive	Accounted for	42 RRMS	Positive correlation with WMLL	Colomboet al. 2000 [161]
1T/Semi quantification	GW/WM	(Cognitive/ Physical)[a]	Excluded	222 RRMS	Positive correlation T2 lesion load in patients with high fatigue.	Tedeschi et al. 2007 [75]
3T/In house software	Whole brain	(Cognitive/ Physical)[a]	Not corrected	507 (CIS/RR/SP/PP or PR)	Higher T2/T1 lesion load strongly associated with worse fatigue scores,	Mowry et al. 2009 [76]
1.5T/Semi-automatic	Periventricular/juxtacortical/Basal ganglia/frontal lobe/deep WM	Cognitive	Corrected	33 RRMS	Positive correlation of lesion in frontal areas with fatigue score/Frontal lobe impairment	Morgante et al. 2011 [70]
1.5T/Semi quantitative	Cortical/WM	Cognitive/Motor	Corrected	91 (CIS/RR/SP/PP)	Positive correlation of WMLL but not CL with motor fatigue and no correlation with cognitive fatigue.	Papadopoulou et al. 2013 [73]
3T/Semi-automatic	Basal ganglia, path of medullary perforating artery/midbrain	Total FSS score	Not mentioned	82 RRMS	Positive correlation of number of dPV with Fatigue	Conforti et al. 2016 [71]
1.5T/LPM	Left SFG, both MFG and cortical areas	Cognitive/Physical	Excluded	60 (22CIS/28RR/5SP/ 5PP)	Positively correlated with WMLL damage to deep WM pathways (parieto temporal and left frontal)	Sepulcre et al. 2009 [74]
1.5T/Semi automated (LTT)	PPC, SFG and MFG	Cognitive/Physical	Severe depression excluded	152 RRMS	Significant correlation between T2-WMLL and both cognitive and physical fatigue	Calabrese et al. 2010 [77]

[a] Reported as overall fatigue score, **BPF:** Brain Parenchymal Fraction, **CBF**: Cerebral Blood Flow, **CBV:** Cerebral Blood Volume, **CL:** Cortical Lesion, **CIS:** Clinically Isolated Syndrome, **DLPFC**: Dorsi-Lateral Pre Frontal Cortex, **dPV**: dilated Peri Ventricular Space, **FSS:** Fatigue Severity Scale, **GM/WM**: Grey Matter/White Matter, **MFG**: Middle Frontal Gyrus, **N**: Sample size, **PFG**: Posterior Frontal Gyrus, **PPC**: Posterior Parietal Cortex, **RRMS**: Relapse Remitting MS, **PP**: Primary Progressive, **SFG**: Superior Frontal gyrus, **SP**: Secondary Progressive, **PR**: Primary Relapsing, **LTT**: Lesion Thresholding Technique, **LPM**: Lesion Probability Map, **WMLL**: White Matter Lesion Load

Table 3
Atrophy/cortical thickness.

Field strength/analysis method	Region studied	Fatigue domain	Depression status	N (MS phenotype)	Major findings linked to fatigue	Authors/Year/Ref
3T/Freesurfer	Right Temporal Cortex and thalamus	Cognitive/ Physical	Excluded	43 RRMS	Positive correlation with fatigue and lower thalamic, pallidal, SCP	Bernitsas et al. 2017 [117]
NA/BPF[a]	GW/WM	Cognitive	Adjusted	134 RRMS	Brain atrophy with worsening fatigue	Marrie et al. 2005 [81]
3T/SIENAX	GW/WM	Cognitive	Included	507 (CIS/RR/SP/ PP)	Lower normalised GM/WM and BPF were associated with fatigue	Mowry et al. 2009 [76]
3T/Automated Segmentation	Frontal/Parietal	Cognitive/ Physical	Included	24 RRMS	Positive correlation between fatigue & cortical thinning in parietal lobe (first study showing CTh and fatigue)	Pellicano et al. 2010 [62]
3T/NeuroQLab	84 areas	Cognitive	Adjusted	95 RRMS	Reduced cortical thickness in right Inferior parietal lobe, middle cingulate gyrus,	Hanken et al. 2016 [116]
1T/Semi quantitative	GW/WM	Cognitive/ Physical	Controlled	222 RRMS	Positive correlation with brain atrophy. Fatigue is significantly related to a destructive pathological process in WM/GM	Tedeschi et al. 2007 [75]
1.5T/Freesurfer segmentation	Homologous sensorimotor region	Cognitive	Highly depressive patients excluded	27 RRMS	No association between both thalami volume/cortical thinning	Cogliati et al. 2015 [97]
3T/SIENAX	Cortical Brain Volume	Cognitive	Included	60 (52RR/8PP)	Reduced normalised cortical volume in highly depressed/fatigued patients	Nunnari, et al. 2015 [79]
1.5T/Linear measurement	Corpus callosum	Cognitive/ Motor	Included but controlled	113 (CIS/84RR/SP)	Correlation Anterior Corpus callosal segment atrophy with fatigue	Yaldizli et al. 2014 [162]
1.5T/Linear measurement	Corpus callosum	Cognitive	Excluded	70 RRMS	Progression of CC atrophy over time seems to be an independent risk factor of MS related fatigue	Yaldizli et al. 2011 [83]
1.5T/Semi automated (Freesurfer)	PPC, SFG and MFG	Cognitive/ Physical	Moderate/severe depression excluded	152 RRMS	Cognitive fatigue correlated with the volume of the striatum and CTh of PPC/MFG. Physical fatigue correlated with striatal volume and SFG CTh	Calabrese et al. 2010 [77]
3T/Segmentation	Accumbens/caudate nucleus	Cognitive/ Physical	Controlled	49 RRMS	Caudate and accumbens atrophy after correcting for physical disability and depression	Damasceno et al. 2016 [101]
3T/SIENAX/FSL[a]	Cerebellar cortical/Thalamic volume	Cognitive/ Physical	Corrected	43 CIS/RRMS	Global atrophy not associated with CIS patients but there is a trend in thalamic/cortical atrophy with physical fatigue	Nourbakhsh et al. 2016 [100]
3T/NeuroQlab[a]	TBV/BPF/ventricular volumes	Cognitive	Excluded	30 RRMS/12SPMS	Patients with fatigue developed more GM/WM atrophy than without fatigue and Healthy control	Sander et al. 2016 [80]
3T/CAT12	Total/cortical GM	Cognitive/ Physical	Included	34 CIS/199RRMS	No association between fatigue & whole/cortical GM volume after correcting for EDSS	Biberacher et al. 2017 [98]
1.5T/VBM	Frontal and central regions	Cognitive	Adjusted	60 RRMS	High fatigue levels were associated with smaller cortical volumes in the right rostral and caudal middle frontal, and in parts of the pre- and post-central	Nygaard et al. 2015 [95]
1.5T/VBM	Specific WM pathways (Left SFG, both MFG) and cortical areas	Cognitive/ Physical	Excluded	60 RRMS	Significant correlation with GM atrophy in frontal regions (left SFG and bilateral MFG)	Sepulcre et al. 2009 [74]
3T/VBM	Right DLPFC, SFG, parietal and occipital	Cognitive	Controlled	123 (80RR/18SP/ 17SP/8PP)	Atrophy of Right SOG and IOG related to fatigue, Atrophy of MFG and right IFG related to depression. Atrophy of the Right DLPFC, SFG and several regions of parietal/occipital lobes involved in both depression and fatigue	Gobbi et al. 2014a [85]
3T/SIENAX/VBM	Right accumbens, inferior temporal gyrus, left superior frontal gyrus, forceps major	Cognitive	Excluded	31 (26RR/5SP)	Fatigue correlated with Right ITG, Left SFG and forceps major. Atrophy of the right nucleus accumbens, dopaminergic circuitry that involves the PFC, amygdala, and ventral pallidum	Rocca et al. 2014a [63]
3T/TBM	DLPFC, PPC, and basal ganglia	Mental/Motor	Excluded	34 RRMS	Regional cortical atrophy in frontal, parietal lobes and basal ganglia leads to interruption of cortico-subcortical circuit.	Andreasen et al. 2010 [60]
1.5T/VBM	Ore central gyrus (GM atrophy)	Cognitive	Excluded	24 RRMS	Significant correlations were found between fatigue severity and GM atrophy in the left precentral gyrus	Riccitelli et al. 2011 [82]
1.5T/VBM (MR/PET)	Bilateral SFC, MFC, IFC and in left temporal and parietal cortex	Cognitive/ Physical	Excluded	17 RRMS	Reduced GM density within the frontal, parietal, temporal cortices and the thalami, functional cortico-subcortical circuitry alterations	Derache et al. 2013 [163]
3T/VBM	Basal ganglia and medial PFG, precuneus, PCC, caudate/motor cortex	Cognitive	Moderate/severe depression excluded	44 RRMS	No correlation of fatigue severity with grey matter density, white matter integrity and basal ganglia volumes.	Finke et al. 2015 [99]

(*continued on next page*)

Table 3 (*continued*)

Field strength/analysis method	Region studied	Fatigue domain	Depression status	N (MS phenotype)	Major findings linked to fatigue	Authors/Year/Ref
3T/VBM	Thalamus/basal ganglia/frontal cortex	Cognitive/ Physical	Excluded	79 RRMS	Morphological alterations in thalamus (higher CSF fraction, global GM fraction in fatigued groups). No Correlation with between BPF	Wilting et al. 2016 [66]
3T/Semi-quantitative	Whole brain	Cognitive/ Physical	Not mentioned	150(120 RRMS 30 CIS)	Fatigue associated with smaller caudate	Ntranos et al. 2018 [93]

AD: Axial Diffusivity, **AIC:** Anterior Internal Capsule, **ATR:** Anterior Thalamic Radiation, **ATT:** Anterior Thalamic Tract, **BMS:** Benign Multiple Sclerosis, **CC:** Corpus Callosum, **CCC:** Central Corpus Callosum, **CST:** Cortico Spinal Tract, **EC:** External Capsule, **FA:** Fractional Anisotropy, **Fm:** Forceps minor, **FM:** Forceps Major, **FSL: IC:** Internal Capsule, **ITG:** Inferior Temporal Gyrus, **JCF:** Juxta Cortical Fibres, **MS:** Multiple Sclerosis, **MD:** Mean Diffusivity, **N:** Sample size, **NABT:** Normal Appearing Brain Tissue, **NAWM:** Normal Appearing White Matter, **OR:** Optic Radiation, **PD:** Parallel Diffusivity, **PP:** Primary Progressive, **PTR:** Posterior Thalamic Radiation **RD:** Radial Diffusivity, **RR:** Relapse Remitting, **SFOF:** Superior Fronto-Occipital Fasciculus, **SFG:** Superior Frontal Gyrus, **SLF:** Superior Longitudinal Fasciculus, **SP:** Secondary Progressive, **TBSS:** Tract Based Spatial Statistics, **UF:** Ulcinate Fasciculus

[a] Longitudinal study, **BPF:** Brain Parenchymal Fraction, **CC:** Corpus Callosum, **CSF:** Cerebral Spinal Fluid, **CTh:** Cortical Thickness, **FSL:** FMRIB Software Library, **CIS:** Clinically Isolated Syndrome, **DLPFC:** Dorsi-Lateral Pre Frontal Cortex, **GM/WM:** Gray Matter/White Matter, **IFC:** Inferior Frontal Cortex, **IOG:** Inferior Occipital Gyrus, **MFC:** Middle Frontal Cortex, **MFG:** Middle Frontal Gyrus, **N:** Sample size, **PCC:** Posterior Cingulate Cortex, **PFG:** Posterior Frontal Gyrus, **PPC:** Posterior Parietal Cortex, **RRMS:** Relapse Remitting MS, **PP:** Primary Progressive,: Superior Frontal Cortex, SCP: Superior Cerebral Peduncle, **SFG:** Superior Frontal gyrus, **SIENAX:** Structural Image Evaluation using Normalisation of Atrophy-Cross-sectional, **SFC SP:** Secondary Progressive, **SOG:** Superior Occipital Gyrus, **TBM:** Tissue Based Morphometry, **TBV:** Total Brain Volume, **VBM:** Voxel Based Morphometry

[21,94,101,102]. Furthermore, atrophy was found to be a risk factor for the development of fatigue [75], serves as a disease biomarker [88], and determine fatigue severity over time [103]. However, studies that have failed to establish a correlation between atrophy changes and fatigue propose that atrophy has no bearing in fatigue development but rather other factors such as altered neuroplasticity in deep GM structures result from neurodegenerations may contribute to the development of fatigue, although the variability in disease type and method of analysis could explain the lack of association. This is plausible as neuroplasticity in MS contributes to altered strength of synaptic transmission, the formation of new synapses, cortical reorganisation, and the induction of neurogenesis [104]. The atrophy observed in these studies may also be caused by Wallerian degeneration with indirect primary damage, pseudo-atrophy from changes in brain water content due to drug treatment or even due to the natural ageing process [105].

Apart from lesion load and changes in atrophy, increased T1 relaxation times in deep GM, particularly in the thalamus and hypothalamus [106] decreased cerebral blood flow/volume in thalami/basal ganglia/hypothalamus and dilated periventricular space [71] have also been correlated with fatigue. However, studies using the MT technique failed to identify positive results. The first study assessed a small sample on two groups of MS patients (n = 28 patients, including a fatigued and non-fatigued group). The other study included a slightly larger cohort of patients (n = 34, 17 each). Assessed MT ratios did not differ between the groups [60,107]. The first study results appeared to be preliminary but robust because of the methodology used and avoidance of confounders. The second study, on the other hand, proposed that the lack of diffuse NAWM injury with primary fatigue is due to the homogeneity of RRMS patients. Regardless of the methodology applied or lack of diffuse disease, the lack of correlation in these studies could well be related to the smaller sample size.

Macrostructural characterisation studies suggest a potential correlation between lesion load and fatigue, although this correlation is rather modest and variable across studies. While the majority of reported studies failed to establish an association between lesion load and fatigue development, those that reported a link highlight the presence of damage or impairment to the deep WM pathways/cortical areas, including parts of frontal, temporal, parietal and diffuse disease involving the CNS. Atrophy assessment studies identify a positive correlation between cortical/subcortical atrophy and fatigue scores. Many neural pathways/network seems to have involved in the pathogenesis of fatigue, including attentional network, cortico-subcortical circuit, cortico-striatal network, Striato–thalamus–frontal cortex pathway, dopaminergic circuitry, thalamic microstructure as well as primary motor cortex.

6.3. Microstructural changes (DTI)

Early quantitative studies using DTI metrics did not find any difference between fatigued and non-fatigued MS patients [60,107] (summarised in Table 4). These studies measured DTI changes both in lesions as well as in NAWM, explicitly focussing on frontal, parietal and basal ganglia regions. The lack of identified association could be due to the smaller sample and variability in statistical analysis applied. In contrast, several studies assessing the relationship between fatigue perception and WM integrity reported a significant correlation between complex networks of affected WM regions [3,63,108–113].

In assessments of MS patients with cognitive fatigue, inverse correlations were identified between fatigue scores and decreased FA and increased MD/RD values in a range of brain regions. These include right anterior thalamic radiation [114] and right uncinate fasciculus, forceps minor [115], thalamus and basal ganglia [66,110] anterior internal capsule [22], inferior fronto-occipital fasciculus [63], corpus callosum [80], fibres between the posterior hypothalamus-mesencephalon [116] and fronto frontal-subcortical disconnections [117]. Of particular note, Genova et al. studied structural and functional interconnection in a

Table 4
DTI studies and fatigue.

Field strength/diffusion directions/analysis	Region studied	Fatigue domain	Depression status	N (MS phenotype)	Major findings	Authors/Year/Ref
1.5T/15/Voxel wise analysis	Left frontal WM Fronto-striatal, fronto-frontal, and fronto-limbic pathways	Cognitive/ Physical	Excluded	40 RRMS	Correlation with fatigue scores located in the deep left frontal white matter network such as fronto-frontal, fronto-striatal, fronto-occipital, and fronto-limbic network	Pardini et al. 2010 [108]
1.5T/15/Voxel wise analysis	Cingulate bundle and its projections	Cognitive/ Physical	Not mentioned	77 RRMS	Loss of structural connectivity in the anterior and medial cingulate cortices, dorsolateral prefrontal areas and in the left caudate.	Pardini et al. 2015 [109]
3T/NA/TBSS voxel wise analysis	Right ATR and UF	Cognitive	Corrected	147(24BMS/91RR/ 22SP/10PP)	Reduced FA of the right anterior thalamic radiation and right uncinate fasciculus, Forceps minor	Gobbi et al. 2014a [164]
3T/30/TBSS	Thalamus	Cognitive	Excluded	79 RRMS	Decreased FA and increased MD in thalamus and basal ganglia including the caudate nucleus, globus pallidus and putamen	Wilting et al. 2016 [110]
3T/30/TBSS	Posterior hypothalamus	Cognitive	Controlled	49 RRMS	Reduced FA and increased MD and AD for fibres posterior between posterior hypothalamus and mesencephalon	Hanken et al. 2015 [111]
3T/32/TBSS voxel wise analysis	Frontal/occipital, JCF, EC, UF, Fm, SLF, cingulum and pons.	Cognitive	Excluded	59 RRMS	Correlation between high fatigue score and decrease in FA along fronto frontal sub cortical disconnections and associated tracts might be main structural substrate in fatigue in MS	Bisecco et al. 2016
3T/64/Advection diffusion based algorithm[a]	Frontal corpus callosum to pyramidal	Cognitive	Excluded	42 (30RR/12SP)	Increased RD and MD along corpus callosum	Sander et al. 2016 [80]
3T/DTI studio	Right temporal cortex	Cognitive/ Physical	Excluded	43 RRMS	Higher RD and lower FA in right temporal cortex in high fatigue group	Bernitsas et al. 2017 [88]
3T/NA/Linear regression & TBSS	Right accumbens, ITG, left SFG,FM	Cognitive	Excluded	63 (56RR/7SP)	Reduced FA of the inferior fronto-occipital fasciculus	Rocca et al. 2014 [63]
3T/6/linear regression	ATT/CC	Cognitive	Included	26 BMS	Increased MD in AT tracts and reduced FA in body & genu of CC	Bester et al. 2013 [114]
3T/64/FSL tools	CCC, OR, Fm, FM	Cognitive	Excluded	44 RRMS	Decreased FA and increased MD, PD and RD in the regions studied compared to healthy. No association with fatigue severity	Finke et al. 2015 [99]
1.5T/8/Third party software	NABT and lesion	Cognitive/ Physical	Excluded	28 RRMS	Decreased average FA in MS, but no correlation with fatigue	Codella et al. 2002 [107]
3T/not provided	Bilateral thalamo frontal connections	Cognitive/ Physical	Excluded	30 RRMS	Significant increase in MD left thalamo-frontal pathway in fatigued patients as well correlation with fatigue score	Russo et al. 2017 [120]
3T/12/FSL tools	AIC	Cognitive	Included	23 RRMS	Reduced FA in anterior internal capsule with increased fatigue	Genova et al. 2013 [22]
3T/NeuroQlab	Interoceptive region (Amygdala)	Cognitive	Included	95 RRMS	The results show that MS patients without cognitive fatigue have lower FA values for the amygdala than MS patients with cognitive fatigue and healthy controls. MS patients without fatigue present reduced structural integrity of the amygdala.	Hanken et al. 2018 [119]
3T/not mentioned	Whole brain/Regional	Cognitive/ Physical	Not mentioned	60 RRMS	Significant correlations were found between global scores of MFIS and MD increase of the NAWM skeleton, including corona radiata, IC, EC, CST, cingulum, CC, fornix, SLF, SFOF, sagittal stratum, PTR, cerebral peduncle, UF	Novo et al. 2018 [165]

separate group of patients with state and trait forms of cognitive fatigue [22]. While the "state" form of cognitive fatigue is transient and change over time, the "trait" form is more stable. They found that patients with trait fatigue had decreased FA in the anterior internal capsule with increased fatigue score and hyperactivation in caudate. In stark contrast, Hanken et al. reported consistently lower FA values/increased AD and MD in the interoceptive region of the amygdala on non-fatigued MS patients compared to a fatigued group and healthy subjects [116,118,119]. Their studies concluded that fatigue is a symptom arising from inflammation-induced interoceptive information processing and that the absence of fatigue in MS patients could be due to disturbed information processing and peripheral inflammatory signals in these areas.

Studies that included overall fatigue score (both cognitive/physical) have identified correlations with reduced FA and increased MD/AD values in deep left frontal WM [108], cingulum bundle (anterior/medial cingulate cortices, DLPFC, left caudate) [109], right temporal cortex [117] [99], left thalamo-frontal pathway [120] and many parts of NAWM skeleton [80,99,114,121]. Fig. 3 shows the neural tracts that have been associated with fatigue.

Collectively, studies assessing microstructural changes using DTI found reported a significant reduction in FA and increased AD/MD values in several WM regions particularly the fronto-striatal and parieto-striatal networks among highly fatigued MS patients, compared to non-fatigued and healthy control participants. Almost two-thirds of these studies noted a robust negative correlation between FA values and fatigue scores, indicating FA is a useful objective marker for microstructural changes in MS patients with fatigue. These changes may result in the alteration and disruption of pathways/circuits within the frontal lobes and between frontal lobes and other brain structures including striatal, limbic, pyramidal, thalamic and occipital regions. These complex WM pathways/circuits are fronto striatal fibres, fronto-frontal connections, fibres between posterior hypothalamus and mesencephalon, and cortical-subcortical loops. Mounting evidence suggests a link between deep GM substrates and fatigue, in particular in the thalamus and basal ganglia. The fronto thalamic pathways are of great importance as they are one of the major loops (association loop) that connects basal ganglia to the entire frontal lobe [15]. These structures are closely associated with functions such as processing, attention and cognition and impairment within these regions is reported to have profound effects on information speed processing and cognitive decline [122].

6.4. Functional correlates

Cognitive and physical domains of fatigue assessed using task-based and rs-fMRI techniques have been reported (Table 5). DeLuca et al used a task-based paradigm to describe increased cerebral activation within the basal ganglia and frontal lobes including superior, medial, middle and inferior regions, parietal regions (precuneus and cuneus), thalamus, occipital lobe, orbital frontal, and inferior parietal cortex during cognitive performance or cognitive fatigue over time [17]. Similarly, another study showed increased cerebral activation in the contralateral SMA and premotor cortices (PMC) when fatigued patients were subject to a challenging mental task [123]. Their observations suggest functional reorganisation or unmasking of existing motor pathways in MS patients, with the additional effort required to perform a task adequately and that these adaptations make use of more brain areas.

Engstrom et al. (2013) used fMRI to assess whether axonal loss and demyelination contribute central fatigue in MS, due to the disruption of the thalamo striato cortical network. They found altered brain activity in this network in a complex working memory task that challenged fatigue and that brain activation in certain cortical and subcortical areas of the network (the left posterior parietal cortex and the right substantia nigra) were positively correlated with perceived fatigue ratings. Their findings also revealed that fatigued patients had stronger functional intercortical and subcortical connections, but weaker cortical to subcortical connections. Genova et al. (2013) studied "state and

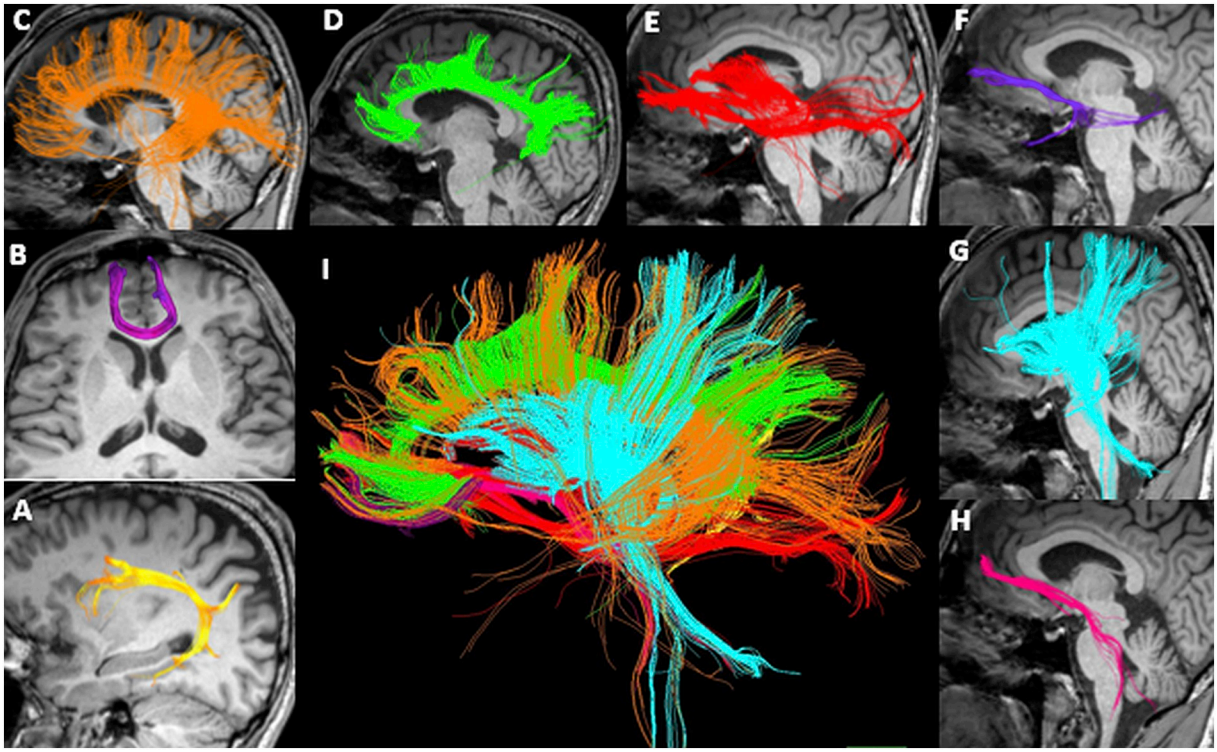

Fig. 3. Author's sketch of DTI fibre tracking of the neural tracts identified in fatigued patients. A: Arcuate Fasciculus, B: Forceps minor, C: Corpus callosal tracts, D: Cingular bundle: Fronto striatal and Inferior fronto occipital tracts, E: Inferior fronto occipital fasciculus, F: Ulcinate fasciculus, G: Thalamic: Fibres between posterior hypothalamus and mesencephalon. H: Anterior Internal Capsule, I: the entire fibre tracts.

Table 5
Studies showing the functional correlates of MS related fatigue.

Field strength/Paradigm	Region studied	Fatigue Domain	Depression status	N (MS phenotype)	Major findings	Authors/Year/Ref
1.5T/Motor task (finger tapping)	Fronto-striatal network (premotor area)	Physical	Excluded	24 RRMS	MS-f group showed DLPFC, Putamen, bilateral activation of the SMA and ipsilateral activation of the PMC and cerebellum and primary left SMC	Specogna et al. 2012 [166]
1.5T/Motor task (PASAT)	Sensory & motor areas	Cognitive	Excluded	10 RRMS	Hyper activation of bilateral cingulate gyri, left post-central gyrus, right SFG and MFG and left primary sensory cortex, while activating less of the left premotor and supplementary motor area	Tartaglia et al. 2008 [123]
1.5T/visual stimuli with PASAT	Bilateral SFG and MFG	Cognitive	Included	15 RRMS	Widespread stronger bilateral frontal activation after 15mins cognitive effort, but showed further bilateral frontal activation and modest improvement in processing speed after rivastigmine	Huolman et al. 2011 [124]
1.5T/simple motor task, (before and after IFN injection)/	Basal ganglia, thalami, Primary SMC, SMA, SII, and several frontal regions	Physical	Excluded	22 RRMS	progressive reduction of the activation of the primary SMC during follow-up and increased activation of basal ganglia, thalami, and frontal lobes	Rocca et al. 2007 [132]
3T/Visual mSDMT	Fronto-parietal regions, basal ganglia, and thalamus	Cognitive	Included	15 (12RR/2PP)	Increased activation over time in basal ganglia, frontal areas including superior, medial, middle and inferior regions, parietal regions (precuneus and cuneus), thalamus and the occipital lobes, orbital frontal, inferior parietal cortex	DeLuca et al. 2008 [17]
1.5T/complex cognitive task	Left PPC right substantia nigra	Cognitive	Included	15 (11RR/3SP/1PP)	Positive correlation with brain activation in certain cortical and subcortical areas of the network (the left PPC and the right substantia nigra) but less activation in the thalamus, basal ganglia and right DLPFC.	Engstrom et al. 2013 [125]
3T/Sustained cognitive task	Fronto-parietal regions including the left IFG and left postcentral gyrus	Physical	Excluded	24 RRMS	Decreased activation of the precentral gyrus, the postcentral gyrus and the basal ganglia and an increased activation of the SII, the precuneus and the cerebellum in fatigued MS patients. Significant interaction in the left postcentral gyrus, SII, lingual gyrus, the right precentral gyrus, precuneus, basal ganglia, and the cerebellum, bilaterally.	Rocca et al. 2009 [167]
3T/motor task/	Left MTG, SMA, bilateral SFG, left post central gyrus and basal	Physical	Excluded	79 RRMS	F-MS patients experienced reduced activations of the left MTG, left SMA, bilateral SFG, left postcentral gyrus and basal ganglia. Increased activation of the right MFG is related to global fatigue score and reduced recruitment of left MTG, right thalamus and SMA with physical fatigue score.	Rocca et al. 2016 [168]
3T/RS and PASAT	SFG and occipital, frontal and temporal areas on RS and task	Cognitive	Excluded	22 RRMS	Increased connectivity in regions studied, Development of cortico-cortical and cortico -subcortical connections involving the L-SFG,	Pravata et al. 2016 [169]
3T/RS/Brain Voyager	DMN/SMN	Cognitive/ Motor	Excluded	59 RRMS	DMN-FC increased in PCC and decreased in ACC in fatigued group, SMN-FC increased FC in left PMC and SMC	Bisecco et al. 2016 [170]
3T/RS	62 regions in Harvard-Oxford brain atlas	Cognitive	Not mentioned	21 MS-F	Positive association with characteristic path length network with fatigue	Welton et al. 2016 [171]
3T/RS	5 Thalamic subregions	Cognitive/ Physical	Excluded	36 RRMS	Higher FC with precuneus and lower FC with posterior cerebellum correlated with cognitive fatigue. Higher thalamic RS FC with sensorimotor network in frontal-, motor-, and temporal thalamic sub-regions correlated with physical and psychosocial fatigue.	Hidalgo de la Cruz et al. 2017 [129]
3T/RS	5 regions of Striatum and dlPFC	Cognitive/ Physical	Excluded	77 RRMS	Fatigue was correlated negatively with functional connectivity of the caudate nucleus and ventral striatum with the SMC. Fatigue was correlated negatively with functional connectivity of the caudate nucleus and ventral striatum with the SMC	Jaeger et al. 2018 [127]
3T/RS	Basal ganglia and medial PFG, precuneus, PCC	Cognitive	Excluded	44 RRMS	Fatigue severity was negatively correlated with functional connectivity of basal ganglia nuclei with medial prefrontal cortex, precuneus and posterior cingulate cortex in patients. Positive correlation with functional connectivity between caudate nucleus (reduction caudate volume) and motor cortex.	Finke et al. 2015) [172]
3T/RS	FC between 116 cortical/subcortical regions	Cognitive/ Motor		124 RRMS	F- and NF-MS patients lost hubs in the bilateral anterior cingulate cortex and cerebellar regions (lobule VII-VIII, crus II). F-MS patients also lost hubs in the thalami and middle cingulate cortex. Compared to HC, F- and NF-MS patients had a decreased degree in the bilateral caudate nucleus. F-MS patients also experienced a decreased degree in the bilateral thalamus.	Filippi et al. 2014 [20]
1.5T/RS	Left supplementary motor area	Motor	Corrected	60 RRMS	Patients with high FSS scores were associated with decreased rs-FC between the SMA and associative somatosensory cortex. Fatigue scores were also associated with rs-FC levels in the pathways connecting these brain areas involved in processing sensory and motor information	Gomez et al. 2013 [18]

(*continued on next page*)

Table 5 (*continued*)

Field strength/Paradigm	Region studied	Fatigue Domain	Depression status	N (MS phenotype)	Major findings	Authors/Year/Ref
3T/RS	ReHo and FC whole brain	Cognitive	Included	22 RRMS	Increased FC between right caudate and right DLPFC and positive correlation with fatigue score.	Wu et al. 2016 [173]
1.5T/External stimulus	Cervical cord function	Physical	Excluded	35 RRMS-F	Patients with fatigue showed a reduced recruitment compared with NF patients and negative correlation was found between the severity of fatigue and cervical cord recruitment	Rocca et al. 2012 [174]
3T/External stimulus (VAS)	PFC, temporal/cerebellum	Cognitive	Included	12 (9RR/1PP/ 1SP)	Brain activity positively associated with "state" fatigue in prefrontal regions and cerebellum and negatively associated with "state" fatigue in temporal regions	Genova et al. 2013 [22]
1.5T/motor task (finger tapping)	Thalamus (contralateral) and rolandic operculum (ipsilateral)	Physical	Excluded	29 RRMS	Decreased recruitment of several regions of the frontal lobes, basal ganglia, and thalamus in fatigued MS patients, areas responsible for motor planning and execution. Large and significant activation of ACC in fatigue patients, the area responsible for attentional tasks and subserves several executive functions	Filippi et al. 2002 [20]
3T/Fatigue inducing N-back task	Fronto-striatal-subcortical networks	Cognitive/ Motor	Corrected	40 (25RR/13SP/ 2PP)	High fatigue scores were associated with higher activity in the anterior, middle cingulum region involved in cognitive functions, including error detection, performance monitoring, response selection, and attention control. Also, higher fatigue scores are left paracentral lobule, a region involved in sensory-motor processing as well as in the regulation of physiologic functions such as micturition	Spiteri et al. 2017 [131]
1.5T/Hand-grip task	Motor regions	Motor	Included	10 (8RR/2SP)	Increased activity (pre task) in precentral gyrus, the insula and the cingulate gyrus in MS patients. After fatigue inducing task, MS group did not show further activation compared to controls.	White et al. 2009 [134]
1.5T/Finger thumb motor task	Orbitofrontal cortex and cerebellum	Physical	Excluded	14 RRMS	Correlation between motor performance during a brief and simple motor task and persistent subjective fatigue, suggesting a potential adaptive role for fatigue.	Pardini et al. 2013 [175]

ACC: Anterior Cingulate Cortex, **DMN:** Default Motor Network, **DLPFC**: Dorsi-Lateral Pre Frontal Cortex, **FC**: Functional Connectivity, **GM/WM**: Gray Matter/White Matter, **IFN**: Interferons, **IFG:** Inferior Frontal Gyrus, **IOG**: Inferior Occipital Gyrus, **MS:** Multiple Sclerosis, **F-MS:** MS fatigued, **MFC**: Middle Frontal Cortex, **MFG**: Middle Frontal Gyrus, **MTG**: Middle Temporal Gyrus, **N**: Sample size, **NF**: Non Fatigued, **mSDMT**: modified Symbol Digit Modalities Test, **PASAT**: Paced Auditory Serial Addition Test, **PMC:** Primary Motor Cortex, **PFC**: Posterior Frontal Cortex, **PCC**: Posterior Cingulate Cortex, **PFG**: Posterior Frontal Gyrus, **PPC**: Posterior Parietal Cortex, **ReHO**: Regional Homogeneity, **RRMS**: Relapse Remitting MS, **RS**: Resting State, **PP**: Primary Progressive, **SFG**: Superior Frontal Gyrus, **SCP**: Superior Cerebral Peduncle, **SFG**: Superior Frontal gyrus, **SMA**: Sensori Motor Area, **SMN**: Sensori Motor Network, **SMC**: Sensori Motor Cortex, **SII:** Secondary somatosensory cortex **VAS:** Visual Analogue Scale

trait" forms of cognitive fatigue and showed hyper-activation in the caudate nucleus, prefrontal regions and cerebellum with increased trait fatigue score and a negative association with "state" fatigue in temporal regions [22]. They concluded that the disruption of the pathways through the basal ganglia via the associated loop of the striato-thalamocortical fibres might be primarily responsible for central fatigue. The increased activation identified may result as fatigued patients require more effort to perform simple tasks, due to functional adaptive changes in response to demyelination. Further support for this finding was provided by an additional study investigating the effect of a single dose of rivastigmine, a cholinergic agent used to modify neuronal activity [124]. A stronger bilateral frontal activation was demonstrated after a sustained cognitive effort, which further increased after rivastigmine treatment. [125]. Similar to Genova et al, Spiteri and colleagues observed increased activation of the bilateral ACC, right middle cingulum and left paracentral lobule in effort independent fatigue (trait), while reduced activation was noted in effort dependent fatigue (state) in brain regions responsible for frontal attention control and sensory motor regions such as left anterior insula, precuneus, basal ganglia and right SMA during the performance of cyclic and coordinated fatigue-inducing N-back task [126]. They concluded fatigue in MS is caused by complex interactions of both increased activity in control networks and drop in haemodynamic activity in executive networks such as attention.

Using the rs-fMRI technique, several studies demonstrated interesting findings involving resting state connection between different brain regions. Fatigue severity was positively correlated with increased between caudate nucleus with the motor cortex [99], rostral inferior parietal gyrus and SMC [127], DLPFC and right caudate [127,128], increased DMN in posterior cingulate cortex (PCC), SMN-FC in left PMC and SMC [121] and several regions within thalamus with MFG, SMN, precuneus, insula, and cerebellum [129]. On the other hand, fatigue was negatively correlated with reduced FC of basal ganglia with structures within DMN network [99], caudate nucleus and ventral striatum with the SMC [127], decreased DMN-FC in anterior cingulate cortex (ACC) [121], SMA and associative somatosensory cortex (SII) [130]. Following the Paced Auditory Serial Addition Test (PASAT), Pravata et al. found cognitively fatigued patients had hyper-connectivity in cortico-cortical (left SFG and occipital, temporal) and cortico-subcortical areas (left SFG with the left caudate nucleus) immediately after completion of the mentally challenging task. Several theories have been proposed for the changes of FC network and development of fatigue in these studies. These include development of new cortico-cortical and cortico-subcortical connections, reorganisation of DMN/remodelling of SMN, maladaptive/compensatory mechanisms and disruptions of motor/non motor basal ganglia functions.

Studies have also assessed the physical domain of fatigue. An earlier study, pioneering work by Filippi et al. reported decreased level of movement-related brain activity in fatigued patients in several cortical and subcortical areas (related to motor planning and execution) including frontal lobes (contralateral MFG), ipsilateral precuneus/cerebellum, and contra lateral thalamus [20]. Areas that significantly correlated with fatigue scores included the contralateral thalamus and ipsilateral rolandic operculum. These findings reveal the involvement of thalamic circuit (primarily functional disruption of cortical to subcortical pathways) in the development of fatigue. The thalamus seems to be an important structure in the study of fatigue, as it is thought to be a relay station that connects prefrontal cortices to basal ganglia, which are part of a feedback loop within the limbic system that controls the cortical motor output [15].

On the other hand, significantly higher activation in the cingulate motor area, primarily in ACC and right cingulum, was also reported in the fatigue group when compared with the non-fatigued group [20,131]. Increased activation of basal ganglia, thalami, and frontal lobes after interferon (IFN) injection following a simple motor task was also reported in a group of 22 fatigued patients [132]. This increased activity was interpreted as compensatory mechanism due to the increased effort needed to accomplish the task. Using Graph theory (a mathematical representation of structural and functional brain architecture) with rs-fMRI, Filippi et al. suggest that disruption of the thalamic connector may contribute to fatigue [126]. In a recent study, Rocca et al. reported increased activation of the right MFG is related to global fatigue score, while reduced recruitment of the left MTG, right thalamus and SMA was associated with physical fatigue [133]. The findings of this study suggest that functional inefficiency within the motor network may be responsible for fatigue in MS.

In another study designed to determine activation patterns during a simple motor task and after fatiguing hand grip, greater activation on contralateral PMC, (M1) insula and cingulate gyrus were noted when compared with controls, even before commencing the fatiguing task and no change in activation observed after the task [134]. This findings indicate that functionally adaptive changes in response to demyelination and patients with fatigue require more effort to perform a simple task. Orbitofrontal cortex and cerebellum activation were also found to correlate with motor performance during a brief and straightforward motor task and development of persistent subjective fatigue [108]. Outside the brain, cervical cord recruitment and severity of fatigue were also found to have a link especially inter neuronal dysfunction including an abnormal function of local circuits and altered modulation from supratentorial pathways [135]. Fig. 4 highlights some of the functional brain regions implicated in the pathogenesis of fatigue.

fMRI has proven to play a significant role in our understanding of MS fatigue. Increased and decreased activities within several

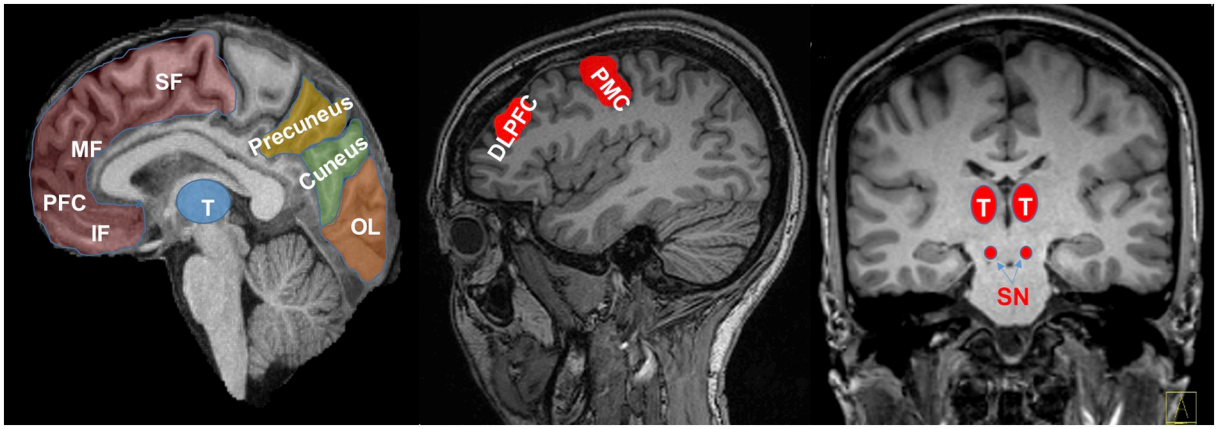

Fig. 4. Authors' illustrations of hyper-activation of brain areas in patients with fatigue. (Left) Midsagittal image shows activation in **IF**: Inferior Frontal, **PFC**: Pre Frontal Cortex, **MF**: Middle Frontal, **SF**: Superior Frontal, **OL**: Occipital Lobe, Precuneus, Cuneus, (Middle) Sagittal image shows increased activation in Dorsolateral PFC and **PMC**: Pre Motor Cortex and (Right) mid coronal image shows activation in **T**: Thalamus and SN: Substantia Nigra.

functionally connected (both ipsilateral and contralateral regions) brain regions were observed in patients with cognitive and physical domain of fatigue. The increased activity is interpreted as a result of functional cortical reorganisation (maladaptive) within functional circuits mainly striato-thalamo-frontal circuit, thalamo-striato cortical network, striato-thalamo-frontal cortical system, recruitment of new cortico-cortical and cortico-subcortical connections, reorganisation of DMN/remodelling of SMN while reduced activity is a consequence of dysfunction along cortico-cortical and cortico-subcortical connections and disruptions of motor/non motor basal ganglia functions.

6.5. Biochemical (metabolic) correlates

Table 6 shows the MRS studies on MS-related fatigue. MRSI identified reduced levels of N-Acetyl Aspartate/Creatine (NAA/Cr) ratios in a high fatigue group of MS patients compared to those with low fatigue suggesting fatigue may be a consequence of diffuse axonal dysfunction [136]. This study assessed metabolic ratios from the corpus callosum, corticospinal tracts, frontal, parietal, and occipital lobe WM as regions of interest. Similarly, a lower NAA/Cr ratio in the lentiform nucleus region in fatigued RRMS patients suggests focal dysfunction of the basal ganglia may contribute to fatigue [137]. Another study found no association between decreased NAA/Cr or increased Myo-inositol/Creatine and fatigue [138]. Increased glutamate in the hypothalamus was also correlated with fatigue scores in patients [139].

Brainstem structures such as the ascending reticular activating system and the monoaminergic nuclei are also thought to have a role in the perception of fatigue [140]. Along with this line, a recent study investigating the involvement of ascending reticular activation system originating from upper pontine brain stem in a high fatigue group of patients compared with healthy subjects showed similar metabolite changes [141]. The authors suggest the changes in NAA/Cr were driven by an increase in total creatine, rather than a decrease in NAA levels [141]. However, the authors collected metabolic concentrations from PCC and parietal WM. Variations in regional metabolic concentrations have been previously observed [142], and this may partially explain the lack of correlation.

In summary, MRS data shows decreased NAA/Cr ratio levels in corticospinal tracts, frontal, parietal, and occipital lobe WM and hypothalamus of fatigued patients compared to healthy participants. The reduced NAA/Cr can be ascribed to neuronal damage from the axonal loss in otherwise NAWM. Biochemically, there is a paucity in MRS studies in the evaluation of MS fatigue, in order to provide insights into biochemical changes underlying this symptom. Reduced NAA/Cr ratio has been highlighted in most MRS studies although these studies collected metabolites from regional areas. Understanding the metabolic behaviour of a symptom like fatigue is complex but important and requires mapping of whole brain metabolic profiles. There are several challenges to overcome, and these include the availability of hardware, standardisation of acquisition/analysis of spectral data and clinically meaningful interpretation of this complex data.

7. Summary

We performed this scoping review to summarise findings from published neuro MRI imaging studies to determine whether a common cerebral imaging signature exists for the pathophysiology underlying MS-related fatigue. Collectively, studies using a range of advanced MRI techniques and analysis methods (including atrophy using VBM, DTI, fMRI and MRS) have identified macro/microstructural, functional and metabolic changes in MS patients with fatigue. Unlike any other, these imaging techniques have great potential in expanding our understanding of fatigue owing to their quantitative and objective measurement approach.

Many neuronal factors have been proposed for the possible pathophysiological mechanism in MS fatigue. These include dysfunction in

Table 6
Magnetic resonance spectroscopic studies and fatigue.

Field strength/MRS technique	Region studied	Fatigue domain	Depression status	N (MS phenotype)	Major findings	Authors/year/ref
1.5T/MRSI	Corticospinal tracts, frontal, parietal and occipital lobe WM (NAWM and lesion)	Cognitive/ Physical	Corrected	76(46RRMS/ 14SPMS)	Lower NAA/Cr ratio; diffuse axonal dysfunction	Tartaglia et al. 2004 [136]
1.5T/SVS	Bilateral frontal WM and Lentifrom nuclei (NAWM)	Cognitive/ Physical	Excluded	41 RRMS	Reduction in NAA/Cr ratio in lentifrom nuclei, The main reason for a decrease in the NAA/Cr ratio in the lentifrom nucleus could be a focal dysfunction of the basal ganglia, that contributes to fatigue	Tellez et al. 2008 [137]
3T/SVS	Parietal WM/Posterior cingulate gyrus (NAWM)	Cognitive	Excluded	32 RRMS	No correlation of decreased NAA or increased my inositol with fatigue	Pokryszko-Dragan et al. 2014 [176]
1.5T/MRSI	Pons (NAWM)	Cognitive/ Physical	Excluded	17 RRMS	Ascending reticular activating system, imbalance of total creatine suggest involvement of the tegmental pons in RRMS patients with higher levels of fatigue.	Zaini et al. 2016 [141]
1.5T/MRSI	Hypothalamus (NAWM)	Cognitive	Included	33 RRMS	Reduced NAA/Cr, Ch/Cr and increased Glx/Cr. Glx/NAA & Glx/Cr positively correlated with fatigue	Kantorova et al. 2017 [177]

Cr: Creatine, **Ch:** Choline, **Glx:** Glutamine/Glutamate, **MRSI:** Magnetic Resonance Spectroscopic Imaging, **NAA:** N-Acetyl Aspartate, **NAWM:** Normal Appearing White Matter, **SVS:** Single Voxel Spectroscopy, WM: White Matter

premotor [143], limbic, basal ganglia [19,137] or hypothalamic region [111,139,144]; disruption of the neuro-endocrine axis leading to low arousal [145]; alteration in dopamine serotoninergic pathways [146]; changes in neurotransmitter levels [147]; mitochondrial dysfunction and altered CNS functioning caused by a disruption of the immune response [68]. The highlight of this review is that although we could not identify a single cerebral signature responsible for fatigue in MS, the findings from advanced quantitative MRI studies suggest that the cortico-striato-thalamo-cortical (CSTC) loop has close connections with the development of central fatigue in MS.

CSTC is a functionally connected network that modulates executive functioning, problem-solving and high order cognitive tasks such as maintaining goals and allocating attentional resources. CSTC has important projections (Fig. 5) that provide biases for recurrent excitatory operations of the local canonical circuits [148]. Demyelination and axonal damage along the long-distance projections of this network can cause a significant effect on the synchronisation of brain activity such as diminished signal transmission. In patients with fatigue, these inefficient operations are compensated through adaptive/maladaptive mechanisms including compensatory reorganisation, cortical deafferentiation, diaschisis effect and recruitment of new circuits.

However, there is mounting evidence from published studies to suggest that the pathophysiological mechanism of central fatigue in MS patients is not a focal event. Rather, fatigue likely results from the complex interplay of global changes involving significant structural alterations and changes in functional connectivity in cortical/subcortical areas and pathways within the frontal, parietal, temporal and basal ganglial structures. MS is a chronic neurodegenerative disease with intricate etiology and multiple pathophysiological underpinnings. The heterogeneous disease course coupled with simultaneous occurrence of several independent processes (i.e. neurodegeneration and compensatory mechanisms) has huge impact on many cognitive functions such as attention, information processing, learning, planning, and motor/sensory functions. A symptom like fatigue in MS can therefore be viewed as a malfunction of well co-ordinated events and at the same time a consequence of a balancing act of sustaining normality.

While published findings have reported a number of associations, it is prudent to highlight the methodological limitations of the current approaches and studies. There is moderate to substantial heterogeneity within each MRI method in terms of study design, sample size, disease subtype, fatigue assessment, scan protocol, data acquisition/analysis, and statistical analysis. Most studies were performed using cross sectional designs while only four studies followed longitudinal designs [54–57]. Longitudinal designs not only provide the nature of accumulative changes especially when MS patients undergoing disease modifying therapies but importantly predict potential future changes [149]. Slightly over half of the studies (54%) included healthy subjects as a control group, while many studies compared results with low/no fatigue groups of MS patients. Sample size varies considerably between studies (ranging from 10 to 500 patients). The low sample sizes used in task-based fMRI in particular likely reflects the difficulty in patient recruitment and study logistics. The largest single cohort of patients reported (n = 507) included all MS phenotypes from CIS to PRMS [76]. Of the 5327 patients included in the published studies, almost two-thirds of the patients had RRMS subtype (> 4000), although fatigue levels in CIS, SPMS and PPMS were also included in the remaining studies. It is important to mention that there is considerable variability in the fatigue assessments performed in the identified studies. Most studies reported a combined overall fatigue score rather than individual scores while 38 studies focussed on cognitive and nine studies on physical fatigue only. It was, therefore, challenging to separate findings related to cognitive versus physical fatigue from studies that reported overall fatigue score.

The majority of identified studies did not report power analyses. The average patient sample size across all studies was 59, suggesting studies may be underpowered to identify small differences. This may be particularly relevant for task-based fMRI studies where seven studies included 15 patients or less. This is concerning as underpowered studies can introduce type II errors [150]. The choice of statistical analysis also varied across studies. Many studies performed regression and corrected for some variables such as age, gender disability and disease duration. However, some failed to include a multivariate analysis to address potential confounders. Identification of correlations (or lack thereof) may be affected by patient inclusion criteria, varying degrees of disability, disease subtypes from clinically isolated syndromes to primary progressive form of the disease and differing cognitive status.

From a technical perspective, these advanced MRI methods are far from perfect. Considerable variability exists in the field strength used, scan protocol, the method of data collection/analysis, clinical evaluation of fatigue and interpretation of MR features. 3Tesla (T) systems were predominantly used although earlier studies were performed on low field scanners (1T and 1.5T). Further, there was considerable variability between studies in terms of paradigm design, data acquisition and interpretation of results. Many pitfalls associated with each MRI method as well as the data analysis should be highlighted. There are different analyses methods used to measure changes in brain volumes, from semi-automated atlas based approaches, to fully automated VBM, TBM techniques that may be impacting on the accuracy of

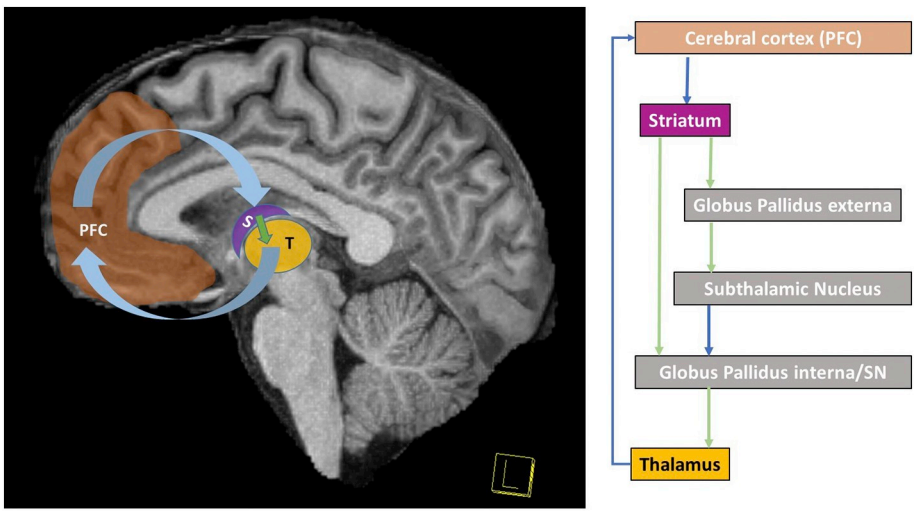

Fig. 5. Left: Midline Sagittal T1 image shows illustration of CSTC circuit. **PFC**: Prefrontal cortex **S**: Striatum, **T**: Thalamus. Right: Diagrammatic representation of CSTC. Blue lines indicate inhibitory GABAergic connections; green lines display excitatory pathways regulated by glutamate. **SN**: Substantia Nigra

atrophy estimates [29]. A cut-off value for annual brain loss must be identified that enables a distinction between normal physiological processes and disease pathology [31]. Almost two-thirds of the identified fMRI studies assessed localised activation in fatigued MS patients. As fatigue is a perception, drawing inferences based purely on a localised T2* sensitive haemodynamic response can be a misrepresentation of functional changes at the network level. Going forward, an understanding of the interconnection between both functional and structural connectivity is necessary, as demonstrated by Genova et al. [22]. fMRI is a powerful and non-invasive advanced technique that enables us to understand functional neuronal changes, which will undoubtedly provide further insights into MS-associated fatigue pathology in the future.

Technical limitations also exist with current DTI methods. It cannot be assumed that each voxel (region of interest) provides information on a coherently oriented bundle of white matter tracts. Approaches such as high angular resolution diffusion-weighted imaging (HARDI) and diffusion spectrum imaging (DSI) may be useful to resolve crossing fibres within a voxel [151]. Moreover, the current DTI model does not entirely describe the diffusion properties of WM but instead assumes a single pool of water [152]. One way to address this issue is by incorporating multiple diffusion sensitising gradients (b values) to separate diffusion properties of brain tissue from the surrounding water. However, this would be at the cost of increased scan time [153]. Application of newer novel DTI models such as neurite orientation dispersion and density imaging (NODDI) may be beneficial in future studies.

Given the breadth and width of the topic, we must acknowledge the shortcomings in our search and analysis of this review. Firstly, we limited our search to adults, journals published in the English language, and major databases. Age or gender characteristics affecting fatigue and their associations with imaging features were also not assessed. It is also worth mentioning that this review only identified studies using subjective fatigue questionnaire and hence the fatigue scores might be biased by individual perception. Finally, although there is a debate on whether fatigue is caused by dopamine imbalance or inflammation and elevated levels of various cytokines or excessive and lengthy cognitive load that leads to mental exhaustion [154], fatigue is a subjective perception and most imaging studies used cross-sectional study design which captured fatigue at a one-time point. Longitudinal trials incorporating an integrated imaging approach are needed to understand fatigue in its entirety over multiple time points so better treatments options can be derived.

It is also important to consider the overlap of other neurological deficits such as pain, sleep disorder and depression in MS patients with fatigue. Although fatigue and depression are different conditions, it is often difficult to separate them as fatigue can manifest as a symptom of depression and depression can be seen as a consequence of fatigue [155] [89]. It is possible that these symptoms also share a similar neurobiological pathway [156]. Further, depression is a predictor of chronic factor for secondary fatigue [7,157,158].Some of the identified studies considered depression as a potential co-founder and have either excluded or corrected for depression during statistical analysis (see Tables). However, it is worth noting that there was substantial variation in the assessment methods used to evaluate depression and the inclusion/exclusion criteria used. Some studies screened patients based on antidepressants prescriptions rather than assessing depression symptoms at the time of the study and others included patients with mild depression. Furthermore, the inclusion criteria used to screen for depression varied. For example, the cut-off score used in the commonly used Beck Depression Inventory scale varied (while a cut-off value of 19 is recommended when evaluating depression in MS patients [159].

The objective evaluation of a symptom like fatigue in MS warrants multiple MR metrics to understand the changes that occur not just at the micro/macro-structural level but also in functional and metabolic outcomes. Imaging research in MS is always complicated and requires support from a multidisciplinary team including radiology, neurology, physics and biomedical engineering input. Factors such as cost, availability of equipment, and patient compliance for lengthy data collection must be considered for the successful and timely completion of studies. However, MRI technology is going through a paradigm shift at the moment with remarkable improvements in hardware/software allowing for rapid data acquisition, delineation of brain anatomy with exquisite details, improved signal/spatial resolution with higher field scanners and the introduction of deep machine learning to improve analysis. With these new developments, MRI-based approaches hold considerable promise in improving understanding of this debilitating symptom. Mounting evidence suggests that fatigue in MS is caused by structural alterations, functional abnormalities and biochemical imbalances. However, further work is required, and it is imperative that future studies involve large multicentre trials with standardised imaging protocols, data analysis method and inclusion of a well-controlled patient cohort perhaps in longitudinal study design to enhance our understanding the pathophysiological of MS fatigue.

8. Conclusions

A number of MRI methods ranging from conventional structural techniques to advanced quantitative MRI metrics such as atrophy measurements, DTI, fMRI, MRS have been used in the study of central fatigue in MS. Although structural MRI (lesion load) failed to link changes with the development of fatigue, advanced methods have consistently established correlations between disruptions in several brain regions with cognitive and physical fatigue. The evidence suggests that central fatigue is associated with alterations in structural as well as functional pathways and the major neural network that has close correlations is the cortico-striato-thalamo-cortical (CSTC) loop.

The MR features identified have improved our understanding of the development of fatigue in MS, yet the exact pathophysiological mechanisms remain unclear. With the continued development of MRI technology, advanced techniques have the great potential to provide new insight into the exact nature of this symptom. Future studies should include a large cohort of well-designed prospective longitudinal trials with an integrated multiparametric approach.

Competing interests

JA, KR and SR declare that they have no competing interests. JLS has accepted travel compensation from Novartis, Biogen and Merck Serono. Her institution receives the honoraria for speaking and advisory board commitment as well as research grants from Biogen, Sanofi Genzyme, Merck, Novartis, Roche and TEVA.

Funding

SR received research funding from Hunter Medical Research Institute.

Author's contributions

JA has been involved in writing, compiling and revising the manuscript critically to suit publication standards. KR, JLS, and SR contributed significantly on revising, literature and critical suggestions to reshape the manuscript. All authors read and approved the final version of manuscript.

Acknowledgements

This research was supported by the Imaging Centre of the University of Newcastle and Hunter Medical Research Institute, Australia. The authors wish to thank Mr Stephen Mears and Dr Steven Maltby for their assistance in database search and proof reading.

References

[1] L.B. Krupp, L.A. Alvarez, N.G. LaRocca, L.C. Scheinberg, Fatigue in multiple sclerosis, Arch. Neurol. 45 (4) (1988) 435–437.
[2] R. Bakshi, Z.A. Shaikh, R.S. Miletich, D. Czarnecki, J. Dmochowski, K. Henschel, V. Janardhan, N. Dubey, P.R. Kinkel, Fatigue in multiple sclerosis and its relationship to depression and neurologic disability, Mult. Scler. 6 (3) (2000) 181–185.
[3] C. Gobbi, M.A. Rocca, G. Riccitelli, E. Pagani, R. Messina, P. Preziosa, B. Colombo, M. Rodegher, A. Falini, G. Comi, M. Filippi, Influence of the topography of brain damage on depression and fatigue in patients with multiple sclerosis, Mult. Scler. 20 (2) (2014) 192–201.
[4] O. Hadjimichael, T. Vollmer, M. Oleen-Burkey, S. North American Research Committee on Multiple, Fatigue characteristics in multiple sclerosis: the North American Research Committee on Multiple Sclerosis (NARCOMS) survey, Health Qual. Life Outcomes 6 (2008) (100).
[5] L. Leocani, B. Colombo, G. Comi, Physiopathology of fatigue in multiple sclerosis, Neurol. Sci. 29 (Suppl. 2) (2008) S241–S243.
[6] G. Comi, L. Leocani, P. Rossi, B. Colombo, Physiopathology and treatment of fatigue in multiple sclerosis, J. Neurol. 248 (3) (2001) 174–179.
[7] D.C. Kroencke, S.G. Lynch, D.R. Denney, Fatigue in multiple sclerosis: relationship to depression, disability, and disease pattern, Mult. Scler. 6 (2) (2000) 131–136.
[8] R.J. Mills, C.A. Young, The relationship between fatigue and other clinical features of multiple sclerosis, Mult. Scler. 17 (5) (2011) 604–612.
[9] T.F. Runia, N. Jafari, D.A.M. Siepman, R.Q. Hintzen, Fatigue at time of CIS is an independent predictor of a subsequent diagnosis of multiple sclerosis, J. Neurol.Neurosurg Psychiatry 86 (5) (2015) 543–546.
[10] D. Kos, E. Kerckhofs, G. Nagels, B. D'Hooghe, M.S. Ilsbroukx, Origin of fatigue in multiple sclerosis: review of the literature, Neurorehabil. Neural Repair 22 (1) (2008) 91–100.
[11] L.B. Strober, P.A. Arnett, J.M. Bruce, The relationship between fatigue, depression, and sleep disturbance in MS, Arch. Clin. Neuropsychol. 16 (8) (2001) 713.
[12] M. Mäurer, G. Comi, M.S. Freedman, L. Kappos, T.P. Olsson, J.S. Wolinsky, A.E. Miller, C. Dive-Pouletty, S. Bozzi, P.W. O'Connor, Multiple sclerosis relapses are associated with increased fatigue and reduced health-related quality of life – a post hoc analysis of the TEMSO and TOWER studies, Mult. Scler. Relat. Dis. 7 (2016) 33–40.
[13] L.B. Krupp, Fatigue in multiple sclerosis: definition, pathophysiology and treatment, CNS Drugs 17 (4) (2003) 225–234.
[14] L.B. Krupp, D.J. Serafin, C. Christodoulou, Multiple sclerosis-associated fatigue, Expert. Rev. Neurother. 10 (9) (2010) 1437–1447.
[15] A. Chaudhuri, P.O. Behan, Fatigue and basal ganglia, J. Neurol. Sci. 179 (1-2) (2000) 34–42.
[16] R.J. Mills, C.A. Young, A medical definition of fatigue in multiple sclerosis, QJM 101 (1) (2008) 49–60.
[17] J. DeLuca, H.M. Genova, F.G. Hillary, G. Wylie, Neural correlates of cognitive fatigue in multiple sclerosis using functional MRI, J. Neurol. Sci. 270 (1-2) (2008) 28–39.
[18] A.J.C. Gomez, N.V. Campos, A. Belenguer, C. Avila, C. Forn, Regional brain atrophy and functional connectivity changes related to fatigue in multiple sclerosis, PLoS ONE 8 (10) (2013).
[19] U. Roelcke, L. Kappos, J. Lechner-Scott, H. Brunnschweiler, S. Huber, W. Ammann, A. Plohmann, S. Dellas, R.P. Maguire, J. Missimer, E.W. Radu, A. Steck, K.L. Leenders, Reduced glucose metabolism in the frontal cortex and basal ganglia of multiple sclerosis patients with fatigue: a 18F-fluorodeoxyglucose positron emission tomography study, Neurology 48 (6) (1997) 1566–1571.
[20] M. Filippi, M.A. Rocca, B. Colombo, A. Falini, M. Codella, G. Scotti, G. Comi, Functional magnetic resonance imaging correlates of fatigue in multiple sclerosis, NeuroImage 15 (3) (2002) 559–567.
[21] M. Calabrese, F. Rinaldi, P. Grossi, I. Mattisi, V. Bernardi, A. Favaretto, P. Perini, P. Gallo, Basal ganglia and frontal/parietal cortical atrophy is associated with fatigue in relapsing-remitting multiple sclerosis, Mult. Scler. 16 (10) (2010) 1220–1228.
[22] H.M. Genova, V. Rajagopalan, J. Deluca, A. Das, A. Binder, A. Arjunan, N. Chiaravalloti, G. Wylie, Examination of cognitive fatigue in multiple sclerosis using functional magnetic resonance imaging and diffusion tensor imaging, PLoS ONE 8 (11) (2013) e78811.
[23] C.L. Tardif, C.J. Gauthier, C.J. Steele, P.L. Bazin, A. Schafer, A. Schaefer, R. Turner, A. Villringer, Advanced MRI techniques to improve our understanding of experience-induced neuroplasticity, Neuroimage 131 (2016) 55–72.
[24] M. Rovaris, M.A. Rocca, M. Filippi, Magnetic resonance-based techniques for the study and management of multiple sclerosis. [Review] [67 refs], Br. Med. Bull. 65 (2003) 133–144.
[25] M. Rovaris, M.A. Rocca, M. Filippi, Magnetic resonance-based techniques for the study and management of multiple sclerosis, Br. Med. Bull. 65 (2003) 133–144.
[26] K.O. Lovblad, N. Anzalone, A. Dorfler, M. Essig, B. Hurwitz, L. Kappos, S.K. Lee, M. Filippi, MR imaging in multiple sclerosis: review and recommendations for current practice, AJNR Am. J. Neuroradiol. 31 (6) (2010) 983–989.
[27] D.H. Miller, F. Barkhof, J.A. Frank, G.J. Parker, A.J. Thompson, Measurement of atrophy in multiple sclerosis: pathological basis, methodological aspects and clinical relevance, Brain 125 (Pt 8) (2002) 1676–1695.
[28] E. Pagani, M.A. Rocca, A. Gallo, M. Rovaris, V. Martinelli, G. Comi, M. Filippi, Regional brain atrophy evolves differently in patients with multiple sclerosis according to clinical phenotype, AJNR Am. J. Neuroradiol. 26 (2) (2005) 341–346.
[29] R. Alroughani, D. Deleu, K. El Salem, J. Al-Hashel, K.J. Alexander, M.A. Abdelrazek, A. Aljishi, J. Alkhaboori, F. Al Azri, N. Al Zadjali, M. Hbahbih, T.E. Sokrab, M. Said, A. Rovira, A regional consensus recommendation on brain atrophy as an outcome measure in multiple sclerosis, BMC Neurol. 16 (1) (2016) 240.
[30] M. Sailer, B. Fischl, D. Salat, C. Tempelmann, M.A. Schonfeld, E. Busa, N. Bodammer, H.J. Heinze, A. Dale, Focal thinning of the cerebral cortex in multiple sclerosis, Brain 126 (Pt 8) (2003) 1734–1744.
[31] J.I. Rojas, L. Patrucco, J. Miguez, E. Cristiano, Brain atrophy in multiple sclerosis: therapeutic, cognitive and clinical impact, Arq. Neuropsiquiatr. 74 (3) (2016) 235–243.
[32] D. Pareto, J. Sastre-Garriga, C. Auger, Y. Vives-Gilabert, J. Delgado, M. Tintore, X. Montalban, A. Rovira, Juxtacortical Lesions and Cortical Thinning in Multiple Sclerosis, AJNR Am. J. Neuroradiol. 36 (12) (2015) 2270–2276.
[33] A.E. Lyall, F. Shi, X. Geng, S. Woolson, G. Li, L. Wang, R.M. Hamer, D. Shen, J.H. Gilmore, Dynamic development of regional cortical thickness and surface area in early childhood, Cereb. Cortex 25 (8) (2015) 2204–2212.
[34] S.C. Deoni, Quantitative relaxometry of the brain, Top. Magn. Reson. Imaging 21 (2) (2010) 101–113.
[35] C. Laule, I.M. Vavasour, G.R. Moore, J. Oger, D.K. Li, D.W. Paty, A.L. MacKay, Water content and myelin water fraction in multiple sclerosis. A T2 relaxation study, J. Neurol. 251 (3) (2004) 284–293.
[36] D. Lacomis, M. Osbakken, G. Gross, Spin-lattice relaxation (T1) times of cerebral white matter in multiple sclerosis, Magn. Reson. Med. 3 (2) (1986) 194–202.
[37] G. Bonnier, A. Roche, D. Romascano, S. Simioni, D. Meskaldji, D. Rotzinger, Y.C. Lin, G. Menegaz, M. Schluep, R. Du Pasquier, T.J. Sumpf, J. Frahm, J.P. Thiran, G. Krueger, C. Granziera, Advanced MRI unravels the nature of tissue alterations in early multiple sclerosis, Ann. Clin. Transl. Neurol. 1 (6) (2014) 423–432.
[38] R.I. Grossman, J.M. Gomori, K.N. Ramer, F.J. Lexa, M.D. Schnall, Magnetization transfer: theory and clinical applications in neuroradiology, Radiographics 14 (2) (1994) 279–290.
[39] R.J. Fox, E. Beall, P. Bhattacharyya, J.T. Chen, K. Sakaie, Advanced MRI in multiple sclerosis: current status and future challenges, Neurol. Clin. 29 (2) (2011) 357–380.
[40] M. Filippi, M. Rovaris, Magnetisation transfer imaging in multiple sclerosis, J. Neuro-Oncol. 6 (Suppl. 2) (2000) S115–S120.
[41] M.A. Horsfield, G.J. Barker, F. Barkhof, D.H. Miller, A.J. Thompson, M. Filippi, Guidelines for using quantitative magnetization transfer magnetic resonance imaging for monitoring treatment of multiple sclerosis, J. Magn. Reson. Imaging 17 (4) (2003) 389–397.
[42] S. Mori, J.Y. Zhang, Principles of diffusion tensor imaging and its applications to basic neuroscience research, Neuron 51 (5) (2006) 527–539.
[43] M. Filippi, G. Iannucci, M. Cercignani, M.A. Rocca, A. Pratesi, G. Comi, A quantitative study of water diffusion in multiple sclerosis lesions and normal-appearing white matter using echo-planar imaging, Arch. Neurol-Chicago 57 (7) (2000) 1017–1021.
[44] E. Sbardella, F. Tona, N. Petsas, P. Pantano, DTI measurements in multiple sclerosis: evaluation of brain damage and clinical implications, Mult. Scler. Int. 2013 (2013) 671730.
[45] M.A. Rocca, M. Filippi, Functional MRI in multiple sclerosis, J. Neuroimaging 17 (Suppl. 1) (2007) 36S–41S.
[46] E. Amaro Jr., G.J. Barker, Study design in fMRI: basic principles, Brain Cogn. 60 (3) (2006) 220–232.
[47] M.P. van den Heuvel, H.E. Hulshoff Pol, Exploring the brain network: a review on resting-state fMRI functional connectivity, Eur. Neuropsychopharmacol. 20 (8) (2010) 519–534.
[48] C. Rosazza, L. Minati, Resting-state brain networks: literature review and clinical applications, Neurol. Sci. 32 (5) (2011) 773–785.
[49] D. Bertholdo, A. Watcharakorn, M. Castillo, Brain proton magnetic resonance spectroscopy: introduction and overview, Neuroimaging Clin. N. Am. 23 (3) (2013) 359–380.
[50] J.P. Cousins Clinical MR spectroscopy: Fundamentals, Current applications and Future potentials, AJR Am. J. Roentgenol. 164 (1337-1347) (1995).
[51] D.P. Soares, M. Law, Magnetic resonance spectroscopy of the brain: review of metabolites and clinical applications, Clin. Radiol. 64 (1) (2009) 12–21.
[52] B.R. Sajja, J.S. Wolinsky, P.A. Narayana, Proton Magnetic Resonance Spectroscopy in Multiple Sclerosis, Neuroimaging Clin. N. Am. 19 (1) (2009) 45–58.
[53] P. Sarchielli, O. Presciutti, G.P. Pelliccioli, R. Tarducci, G. Gobbi, P. Chiarini, A. Alberti, F. Vicinanza, V. Gallai, Absolute quantification of brain metabolites by proton magnetic resonance spectroscopy in normal-appearing white matter of multiple sclerosis patients, Brain 122 (Pt 3) (1999) 513–521.
[54] V. Rackayova, C. Cudalbu, P.J.W. Pouwels, O. Braissant, Creatine in the central nervous system: From magnetic resonance spectroscopy to creatine deficiencies, Anal. Biochem. 529 (2017) 144–157.
[55] C.A. Davie, C.P. Hawkins, G.J. Barker, A. Brennan, et al., Serial proton magnetic resonance spectroscopy in acute multiple sclerosis lesions, Brain 117 (1) (1994) 49.
[56] S.P. van der Werf, P.J. Jongen, G.J. Lycklama, F.A. Nijeholt, O.R. Barkhof, G. Hommes, Bleijenberg, Fatigue in multiple sclerosis: interrelations between fatigue complaints, cerebral MRI abnormalities and neurological disability, J. Neurol. Sci. 160 (2) (1998) 164–170.
[57] N. Putzki, O. Yaldizli, B. Tettenborn, H.C. Diener, Multiple sclerosis associated fatigue during natalizumab treatment, J. Neurol. Sci. 285 (1-2) (2009) 109–113.
[58] M. Palotai, A. Mike, M. Cavallari, E. Strammer, G. Orsi, B.C. Healy, K. Schregel, Z. Illes, C.R. Guttmann, Changes to the septo-fornical area might play a role in the pathogenesis of anxiety in multiple sclerosis, Mult. Scler. 24 (8) (2018 Jul)

1105–1114 (1352458517711273).
[59] C. Mainero, J. Faroni, C. Gasperini, M. Filippi, E. Giugni, O. Ciccarelli, M. Rovaris, S. Bastianello, G. Comi, C. Pozzilli, Fatigue and magnetic resonance imaging activity in multiple sclerosis, J. Neurol. Neurosurg. 246 (6) (1999) 454–458.
[60] A.K. Andreasen, J. Jakobsen, L. Soerensen, H. Andersen, T. Petersen, C.R. Bjarkam, J. Ahdidan, Regional brain atrophy in primary fatigued patients with multiple sclerosis, Neuroimage 50 (2) (2010) 608–615.
[61] R. Bakshi, R.S. Miletich, K. Henschel, Z.A. Shaikh, V. Janardhan, M. Wasay, L.M. Stengel, R. Ekes, P.R. Kinkel, Fatigue in multiple sclerosis: cross-sectional correlation with brain MRI findings in 71 patients, Neurology 53 (5) (1999) 1151–1153.
[62] C. Pellicano, A. Gallo, X. Li, V.N. Ikonomidou, I.E. Evangelou, J.M. Ohayon, S.K. Stern, M. Ehrmantraut, F. Cantor, H.F. McFarland, F. Bagnato, Relationship of cortical atrophy to fatigue in patients with multiple sclerosis, Arch. Neurol. 67 (4) (2010) 447–453.
[63] M.A. Rocca, L. Parisi, E. Pagani, M. Copetti, M. Rodegher, B. Colombo, G. Comi, A. Falini, M. Filippi, Regional but not global brain damage contributes to fatigue in multiple sclerosis, Radiology 273 (2) (2014) 511–520.
[64] G. Niepel, R. Tench Ch, P.S. Morgan, N. Evangelou, D.P. Auer, C.S. Constantinescu, Deep gray matter and fatigue in MS: A T1 relaxation time study, J. Neurol. Neurosurg. 253 (7) (2006) 896–902.
[65] M. Inglese, S.J. Park, G. Johnson, J.S. Babb, L. Miles, H. Jaggi, J. Herbert, R.I. Grossman, Deep gray matter perfusion in multiple sclerosis: dynamic susceptibility contrast perfusion magnetic resonance imaging at 3 T, Arch. Neurol. 64 (2) (2007) 196–202.
[66] J. Wilting, H.O. Rolfsnes, H. Zimmermann, M. Behrens, V. Fleischer, F. Zipp, A. Groger, Structural correlates for fatigue in early relapsing remitting multiple sclerosis, Eur. Radiol. 26 (2) (2016) 515–523.
[67] G. Riccitelli, M.A. Rocca, C. Forn, B. Colombo, G. Comi, M. Filippi, Voxelwise assessment of the regional distribution of damage in the brains of patients with multiple sclerosis and fatigue, AJNR Am. J. Neuroradiol. 32 (5) (2011) 874–879.
[68] K. Hanken, P. Eling, H. Hildebrandt, The representation of inflammatory signals in the brain - a model for subjective fatigue in multiple sclerosis, Front. Neurol. 5 (2014) 264.
[69] B. Colombo, F. Martinelli Boneschi, P. Rossi, M. Rovaris, L. Maderna, M. Filippi, G. Comi, MRI and motor evoked potential findings in nondisabled multiple sclerosis patients with and without symptoms of fatigue, J. Neurol. Neurosurg. 247 (7) (2000) 506–509.
[70] F. Morgante, V. Dattola, D. Crupi, M. Russo, V. Rizzo, M.F. Ghilardi, C. Terranova, P. Girlanda, A. Quartarone, Is central fatigue in multiple sclerosis a disorder of movement preparation? J. Neurol. Neurosurg. 258 (2) (2011) 263–272.
[71] R. Conforti, M. Cirillo, A. Sardaro, G. Caiazzo, A. Negro, A. Paccone, R. Sacco, M. Sparaco, A. Gallo, L. Lavorgna, G. Tedeschi, S. Cirillo, Dilated perivascular spaces and fatigue: is there a link? Magnetic resonance retrospective 3Tesla study, Neuroradiology 58 (9) (2016) 859–866.
[72] E.M. Mowry, A. Beheshtian, E. Waubant, D.S. Goodin, B.A. Cree, P. Qualley, R. Lincoln, M.F. George, R. Gomez, S.L. Hauser, D.T. Okuda, D. Pelletier, Quality of life in multiple sclerosis is associated with lesion burden and brain volume measures, Neurology 72 (20) (2009) 1760–1765.
[73] A. Papadopoulou, N. Muller-Lenke, Y. Naegelin, G. Kalt, K. Bendfeldt, P. Kuster, M. Stoecklin, A. Gass, T. Sprenger, E.W. Radue, L. Kappos, I.-K. Penner, Contribution of cortical and white matter lesions to cognitive impairment in multiple sclerosis, Mult. Scler. 19 (10) (2013) 1290–1296 Houndmills, Basingstoke, England.
[74] J. Sepulcre, J.C. Masdeu, J. Goni, G. Arrondo, N. Velez de Mendizabal, B. Bejarano, P. Villoslada, Fatigue in multiple sclerosis is associated with the disruption of frontal and parietal pathways, Mult. Scler. 15 (3) (2009) 337–344 Houndmills, Basingstoke, England.
[75] G. Tedeschi, D. Dinacci, L. Lavorgna, A. Prinster, G. Savettieri, A. Quattrone, P. Livrea, C. Messina, A. Reggio, G. Servillo, V. Bresciamorra, G. Orefice, M. Paciello, A. Brunetti, A. Paolillo, G. Coniglio, S. Bonavita, A. Di Costanzo, A. Bellacosa, P. Valentino, M. Quarantelli, F. Patti, G. Salemi, E. Cammarata, I. Simone, M. Salvatore, V. Bonavita, B. Alfano, Correlation between fatigue and brain atrophy and lesion load in multiple sclerosis patients independent of disability, J. Neurol. Sci. 263 (1-2) (2007) 15–19.
[76] E.M. Mowry, A. Beheshtian, E. Waubant, D.S. Goodin, B.A. Cree, P. Qualley, R. Lincoln, M.F. George, R. Gomez, S.L. Hauser, D.T. Okuda, D. Pelletier, Quality of life in multiple sclerosis is associated with lesion burden and brain volume measures, Neurology 72 (20) (2009) 1760–1765.
[77] M. Calabrese, F. Rinaldi, P. Grossi, I. Mattisi, V. Bernardi, A. Favaretto, P. Perini, P. Gallo, Basal ganglia and frontal/parietal cortical atrophy is associated with fatigue in relapsing-remitting multiple sclerosis, Mult. Scler. 16 (10) (2010) 1220–1228 Houndmills, Basingstoke, England.
[78] R.A. Marrie, E. Fisher, D.M. Miller, J.C. Lee, R.A. Rudick, Association of fatigue and brain atrophy in multiple sclerosis, J. Neurol. Sci. 228 (2) (2005) 161–166.
[79] D. Nunnari, M.C. De Cola, G. D'Aleo, C. Rifici, M. Russo, E. Sessa, P. Bramanti, S. Marino, Impact of depression, fatigue, and global measure of cortical volume on cognitive impairment in multiple sclerosis, Biomed. Res. Int. 2015 (2015) 519785.
[80] C. Sander, P. Eling, K. Hanken, J. Klein, A. Kastrup, H. Hildebrandt, The impact of MS-related cognitive fatigue on future brain parenchymal loss and relapse: a 17-month follow-up study, Front. Neurol. 7 (2016) 155.
[81] R.A. Marrie, E. Fisher, D.M. Miller, J.C. Lee, R.A. Rudick, Association of fatigue and brain atrophy in multiple sclerosis, J. Neurol. Sci. 228 (2) (2005) 161–166.
[82] G. Riccitelli, M.A. Rocca, C. Forn, B. Colombo, G. Comi, M. Filippi, Voxelwise assessment of the regional distribution of damage in the brains of patients with multiple sclerosis and fatigue, AJNR Am. J. Neuroradiol. 32 (5) (2011) 874–879.
[83] O. Yaldizli, S. Glassl, D. Sturm, A. Papadopoulou, A. Gass, B. Tettenborn, N. Putzki, Fatigue and progression of corpus callosum atrophy in multiple sclerosis, J. Neurol. Neurosurg. 258 (12) (2011) 2199–2205.
[84] A. Mechelli, C.J. Price, K.J. Friston, J. Ashburner, Voxel-based morphometry of the human brain: methods and applications, Curr. Med. Imaging Rev. 1 (2) (2005) 105–113.
[85] C. Gobbi, M.A. Rocca, G. Riccitelli, E. Pagani, R. Messina, P. Preziosa, B. Colombo, M. Rodegher, A. Falini, G. Comi, M. Filippi, Influence of the topography of brain damage on depression and fatigue in patients with multiple sclerosis, Mult. Scler. 20 (2) (2014) 192–201 Houndmills, Basingstoke, England.
[86] C. Gobbi, M.A. Rocca, G. Riccitelli, E. Pagani, R. Messina, P. Preziosa, B. Colombo, M. Rodegher, A. Falini, G. Comi, M. Filippi, Influence of the topography of brain damage on depression and fatigue in patients with multiple sclerosis, Mult. Scler. 20 (2) (2014) 192–201.
[87] G. Tao, S. Datta, R. He, F. Nelson, J.S. Wolinsky, P.A. Narayana, Deep gray matter atrophy in multiple sclerosis: a tensor based morphometry, J. Neurol. Sci. 282 (1-2) (2009) 39–46.
[88] E. Bernitsas, K. Yarraguntla, F. Bao, R. Sood, C. Santiago-Martinez, R. Govindan, O. Khan, N. Seraji-Bozorgzad, Structural and neuronal integrity measures of fatigue severity in multiple sclerosis, Brain Sci. 7 (8) (2017).
[89] N. Derache, B. Grassiot, F. Mezenge, A. Emmanuelle Dugue, B. Desgranges, J.M. Constans, G.L. Defer, Fatigue is associated with metabolic and density alterations of cortical and deep gray matter in relapsing-remitting-multiple sclerosis patients at the earlier stage of the disease: A PET/MR study, Mult. Scler. Relat. Disord. 2 (4) (2013) 362–369.
[90] O. Yaldizli, S. Glassl, D. Sturm, A. Papadopoulou, A. Gass, B. Tettenborn, N. Putzki, Fatigue and progression of corpus callosum atrophy in multiple sclerosis, J. Neurol. 258 (12) (2011) 2199–2205.
[91] O. Yaldizli, I.K. Penner, K. Frontzek, Y. Naegelin, M. Amann, A. Papadopoulou, T. Sprenger, J. Kuhle, P. Calabrese, E.W. Radu, L. Kappos, A. Gass, The relationship between total and regional corpus callosum atrophy, cognitive impairment and fatigue in multiple sclerosis patients, Mult. Scler. 20 (3) (2014) 356–364.
[92] A. Damasceno, B.P. Damasceno, F. Cendes, Atrophy of reward-related striatal structures in fatigued MS patients is independent of physical disability, Mult. Scler. J. 22 (6) (2016) 822–829.
[93] A. Ntranos, S. Krieger, M. Fabian, V. Leavitt, C. Lewis, G. Pelle, M. El Mendili, A. Droby, M. Inglese, J. Sumowski, Fatigue in early multiple sclerosis and the role of the caudate nucleus. (P4.412), Neurology 90 (15 Supplement) (2018) (4.412).
[94] K. Hanken, P. Eling, J. Klein, E. Klaene, H. Hildebrandt, Different cortical underpinnings for fatigue and depression in MS? Mult. scler. Relat. Disord. 6 (2016) 81–86.
[95] G.O. Nygaard, K.B. Walhovd, P. Sowa, J.-L. Chepkoech, A. Bjornerud, P. Due-Tonnessen, N.I. Landro, S. Damangir, G. Spulber, A.B. Storsve, M.K. Beyer, A.M. Fjell, E.G. Celius, H.F. Harbo, Cortical thickness and surface area relate to specific symptoms in early relapsing-remitting multiple sclerosis, Mult. Scler. 21 (4) (2015) 402–414 Houndmills, Basingstoke, England.
[96] K. Hanken, P. Eling, J. Klein, E. Klaene, H. Hildebrandt, Different cortical underpinnings for fatigue and depression in MS? Mult. Scler. Relat. Dis. 6 (2016) 81–86.
[97] I. Cogliati Dezza, G. Zito, L. Tomasevic, M.M. Filippi, A. Ghazaryan, C. Porcaro, R. Squitti, M. Ventriglia, D. Lupoi, F. Tecchio, Functional and structural balances of homologous sensorimotor regions in multiple sclerosis fatigue, J. Neurol. Neurosurg. 262 (3) (2015) 614–622.
[98] V. Biberacher, P. Schmidt, R.C. Selter, V. Pernpeinter, M.C. Kowarik, B. Knier, D. Buck, M.M. Hoshi, T. Korn, A. Berthele, J.S. Kirschke, C. Zimmer, B. Hemmer, M. Muhlau, Fatigue in multiple sclerosis: Associations with clinical, MRI and CSF parameters, Mult Scler, 2017 (1352458517712078).
[99] C. Finke, J. Schlichting, S. Papazoglou, M. Scheel, A. Freing, C. Soemmer, L.M. Pech, A. Pajkert, C. Pfuller, J.T. Wuerfel, C.J. Ploner, F. Paul, A.U. Brandt, Altered basal ganglia functional connectivity in multiple sclerosis patients with fatigue, Mult. Scler. 21 (7) (2015) 925–934 Houndmills, Basingstoke, England.
[100] B. Nourbakhsh, C. Azevedo, J. Nunan-Saah, A.-H. Maghzi, R. Spain, D. Pelletier, E. Waubant, Longitudinal associations between brain structural changes and fatigue in early MS, Mult. scler. Relat. Disord. 5 (2016) 29–33.
[101] A. Damasceno, B.P. Damasceno, F. Cendes, Atrophy of reward-related striatal structures in fatigued MS patients is independent of physical disability, Mult. Scler. 22 (6) (2016) 822–829.
[102] J. Sepulcre, J.C. Masdeu, J. Goni, G. Arrondo, N. Velez de Mendizabal, B. Bejarano, P. Villoslada, Fatigue in multiple sclerosis is associated with the disruption of frontal and parietal pathways, Mult. Scler. 15 (3) (2009) 337–344.
[103] B. Nourbakhsh, C. Azevedo, J. Nunan-Saah, A.H. Maghzi, R. Spain, D. Pelletier, E. Waubant, Longitudinal associations between brain structural changes and fatigue in early MS, Mult. Scler. Relat. Disord. 5 (2016) 29–33.
[104] D.J. Ksiazek-Winiarek, P. Szpakowski, A. Glabinski, Neural Plasticity in Multiple Sclerosis: The Functional and Molecular Background, Neural plast. 2015 (2015) 307175.
[105] Y. Ge, Seeing is believing: In vivo evolution of multiple sclerosis pathology with magnetic resonance, Top. Magn. Reson. Imaging 17 (4) (2006) 295–306.
[106] F. Zellini, G. Niepel, C.R. Tench, C.S. Constantinescu, Hypothalamic involvement assessed by T1 relaxation time in patients with relapsing-remitting multiple sclerosis, Mult. Scler. 15 (12) (2009) 1442–1449.
[107] M. Codella, M.A. Rocca, B. Colombo, P. Rossi, G. Comi, M. Filippi, A preliminary study of magnetization transfer and diffusion tensor MRI of multiple sclerosis patients with fatigue, J. Neurol. Neurosurg. 249 (5) (2002) 535–537.
[108] M. Pardini, L. Bonzano, G.L. Mancardi, L. Roccatagliata, Frontal networks play a role in fatigue perception in multiple sclerosis, Behav. Neurosci. 124 (3) (2010)

329–336.
[109] M. Pardini, L. Bonzano, M. Bergamino, G. Bommarito, P. Feraco, A. Murugavel, M. Bove, G. Brichetto, A. Uccelli, G. Mancardi, L. Roccatagliata, Cingulum bundle alterations underlie subjective fatigue in multiple sclerosis, Mult. Scler. 21 (4) (2015) 442–447.
[110] J. Wilting, H.O. Rolfsnes, H. Zimmermann, M. Behrens, V. Fleischer, F. Zipp, A. Groger, Structural correlates for fatigue in early relapsing remitting multiple sclerosis, Eur. Radiol. 26 (2) (2016) 515–523.
[111] K. Hanken, P. Eling, A. Kastrup, J. Klein, H. Hildebrandt, Integrity of hypothalamic fibers and cognitive fatigue in multiple sclerosis, Mult. Scler. Relat. Disord. 4 (1) (2015) 39–46.
[112] A. Bisecco, G. Caiazzo, A. d'Ambrosio, R. Sacco, S. Bonavita, R. Docimo, M. Cirillo, E. Pagani, M. Filippi, F. Esposito, G. Tedeschi, A. Gallo, Fatigue in multiple sclerosis: The contribution of occult white matter damage, Mult. Scler. 22 (13) (2016 Nov) 1676–1684.
[113] M. Bester, M. Lazar, M. Petracca, J.S. Babb, J. Herbert, R.I. Grossman, M. Inglese, Tract-specific white matter correlates of fatigue and cognitive impairment in benign multiple sclerosis, J. Neurol. Sci. 330 (1-2) (2013) 61–66.
[114] M. Bester, M. Lazar, M. Petracca, J.S. Babb, J. Herbert, R.I. Grossman, M. Inglese, Tract-specific white matter correlates of fatigue and cognitive impairment in benign multiple sclerosis, J. Neurol. Sci. 330 (1-2) (2013) 61–66.
[115] C. Gobbi, M.A. Rocca, E. Pagani, G.C. Riccitelli, E. Pravata, M. Radaelli, F. Martinelli-Boneschi, A. Falini, M. Copetti, G. Comi, M. Filippi, Forceps minor damage and co-occurrence of depression and fatigue in multiple sclerosis, Mult. Scler. 20 (12) (2014) 1633–1640.
[116] K. Hanken, A. Manousi, J. Klein, A. Kastrup, P. Eling, H. Hildebrandt, On the relation between self-reported cognitive fatigue and the posterior hypothalamic-brainstem network, Eur. J. Neurol. Neurosurg. 23 (1) (2016) 101–109.
[117] E. Bernitsas, K. Yarraguntla, F. Bao, R. Sood, C. Santiago-Martinez, R. Govindan, O. Khan, N. Seraji-Bozorgzad, Structural and neuronal integrity measures of fatigue severity in multiple sclerosis, Brain sci. 7 (8) (2017).
[118] K. Hanken, P. Eling, A. Kastrup, J. Klein, H. Hildebrandt, Integrity of hypothalamic fibers and cognitive fatigue in multiple sclerosis, Mult. scler. Relat. Disord. 4 (1) (2015) 39–46.
[119] K. Hanken, Y. Francis, A. Kastrup, P. Eling, J. Klein, H. Hildebrandt, On the role of the amygdala for experiencing fatigue in patients with multiple sclerosis, Mult. Scler. Relat. Disord. 20 (2018) 67–72.
[120] M. Russo, A. Calamuneri, A. Cacciola, L. Bonanno, A. Naro, V. Dattola, E. Sessa, M. Buccafusca, D. Milardi, P. Bramanti, R.S. Calabro, A. Quartarone, Neural correlates of fatigue in multiple sclerosis: a combined neurophysiological and neuroimaging approach (R1), Arch. Ital. Biol. 155 (3) (2017) 142–151.
[121] A. Bisecco, F.D. Nardo, R. Docimo, G. Caiazzo, A. d'Ambrosio, S. Bonavita, R. Capuano, L. Sinisi, M. Cirillo, F. Esposito, G. Tedeschi, A. Gallo, Fatigue in multiple sclerosis: The contribution of resting-state functional connectivity reorganization, Mult. Scler. 24 (13) (2018 Nov) 1696–1705 Houndmills, Basingstoke, England. (1352458517730932).
[122] S.L. Costa, H.M. Genova, J. DeLuca, N.D. Chiaravalloti, Information processing speed in multiple sclerosis: Past, present, and future, Mult. Scler. J. 23 (6) (2017) 772–789.
[123] M.C. Tartaglia, S. Narayanan, D.L. Arnold, Mental fatigue alters the pattern and increases the volume of cerebral activation required for a motor task in multiple sclerosis patients with fatigue, Eur. J. Neurol. Neurosurg. 15 (4) (2008) 413–419.
[124] S. Huolman, P. Hamalainen, V. Vorobyev, J. Ruutiainen, R. Parkkola, T. Laine, H. Hamalainen, The effects of rivastigmine on processing speed and brain activation in patients with multiple sclerosis and subjective cognitive fatigue, Mult. Scler. 17 (11) (2011) 1351–1361.
[125] M. Engstrom, G. Flensner, A.M. Landtblom, A.C. Ek, T. Karlsson, Thalamo-striato-cortical determinants to fatigue in multiple sclerosis, Brain Behav 3 (6) (2013) 715–728.
[126] M.A. Rocca, R. Gatti, F. Agosta, P. Broglia, P. Rossi, E. Riboldi, M. Corti, G. Comi, M. Filippi, Influence of task complexity during coordinated hand and foot movements in MS patients with and without fatigue : AA kinematic and functional MRI study, J. Neurol. Neurosurg. 256 (3) (2009) 470–482.
[127] S. Jaeger, F. Paul, M. Scheel, A. Brandt, J. Heine, D. Pach, C.M. Witt, J. Bellmann-Strobl, C. Finke, Multiple sclerosis-related fatigue: Altered resting-state functional connectivity of the ventral striatum and dorsolateral prefrontal cortex, Mult. Scler. (2018 Feb 1) (1352458518758911).
[128] L. Wu, Y. Zhang, F. Zhou, L. Gao, L. He, X. Zeng, H. Gong, Altered intra- and interregional synchronization in relapsing-remitting multiple sclerosis: a resting-state fMRI study, Neuropsychiatr. Dis. Treat. 12 (2016) 853–862.
[129] M. Hidalgo de la Cruz, A. d'Ambrosio, P. Valsasina, E. Pagani, B. Colombo, M. Rodegher, A. Falini, G. Comi, M. Filippi, M.A. Rocca, Abnormal functional connectivity of thalamic sub-regions contributes to fatigue in multiple sclerosis, Mult. Scler. 24 (9) (2018 Aug) 1183–1195 Houndmills, Basingstoke, England. (1352458517717807).
[130] A.J. Cruz Gomez, N. Ventura Campos, A. Belenguer, C. Avila, C. Forn, Regional brain atrophy and functional connectivity changes related to fatigue in multiple sclerosis, PLoS ONE 8 (10) (2013) e77914.
[131] S. Spiteri, T. Hassa, D. Claros-Salinas, C. Dettmers, M.A. Schoenfeld, Neural correlates of effort-dependent and effort-independent cognitive fatigue components in patients with multiple sclerosis, Mult. Scler. 25 (2) (2019 Feb) 256–266 Houndmills, Basingstoke, England. (1352458517743090).
[132] M.A. Rocca, F. Agosta, B. Colombo, D.M. Mezzapesa, A. Falini, G. Comi, M. Filippi, fMRI changes in relapsing-remitting multiple sclerosis patients complaining of fatigue after IFNbeta-1a injection, Hum. Brain Mapp. 28 (5) (2007) 373–382.
[133] M.A. Rocca, A. Meani, G.C. Riccitelli, B. Colombo, M. Rodegher, A. Falini, G. Comi, M. Filippi, Abnormal adaptation over time of motor network recruitment in multiple sclerosis patients with fatigue, Mult. Scler. 22 (9) (2016) 1144–1153 Houndmills, Basingstoke, England.
[134] A.T. White, J.N. Lee, A.R. Light, K.C. Light, Brain activation in multiple sclerosis: a BOLD fMRI study of the effects of fatiguing hand exercise, Mult. Scler. 15 (5) (2009) 580–586 Houndmills, Basingstoke, England.
[135] M.A. Rocca, M. Absinta, P. Valsasina, M. Copetti, D. Caputo, G. Comi, M. Filippi, Abnormal cervical cord function contributes to fatigue in multiple sclerosis, Mult. Scler. 18 (11) (2012) 1552–1559 Houndmills, Basingstoke, England.
[136] M.C. Tartaglia, S. Narayanan, S.J. Francis, A.C. Santos, N. De Stefano, Y. Lapierre, D.L. Arnold, The relationship between diffuse axonal damage and fatigue in multiple sclerosis, Arch Neurol-Chicago 61 (2) (2004) 201–207.
[137] N. Tellez, J. Alonso, J. Rio, M. Tintore, C. Nos, X. Montalban, A. Rovira, The basal ganglia: a substrate for fatigue in multiple sclerosis, Neuroradiology 50 (1) (2008) 17–23.
[138] A. Pokryszko-Dragan, J. Bladowska, A. Zimny, K. Slotwinski, M. Zagrajek, E. Gruszka, M. Bilinska, M. Sasiadek, R. Podemski, Magnetic resonance spectroscopy findings as related to fatigue and cognitive performance in multiple sclerosis patients with mild disability, J. Neurol. Sci. 339 (1-2) (2014) 35–40.
[139] E. Kantorova, H. Polacek, M. Bittsansky, E. Baranovicova, P. Hnilicova, D. Cierny, S. Sivak, V. Nosal, K. Zelenak, E. Kurca, Hypothalamic damage in multiple sclerosis correlates with disease activity, disability, depression, and fatigue, Neurol. Res. 39 (4) (2017) 323–330.
[140] E. Blomstrand, D. Perrett, M. Parry-Billings, E.A. Newsholme, Effect of sustained exercise on plasma amino acid concentrations and on 5-hydroxytryptamine metabolism in six different brain regions in the rat, Acta Physiol. Scand. 136 (3) (1989) 473–481.
[141] W.H. Zaini, F. Giuliani, C. Beaulieu, S. Kalra, C. Hanstock, Fatigue in multiple sclerosis: assessing pontine involvement using proton mr spectroscopic imaging, PLoS ONE 11 (2) (2016) e0149622.
[142] E. Angelie, A. Bonmartin, A. Boudraa, P.-M. Gonnaud, J.-J. Mallet, D. Sappey-Marinier, Regional differences and metabolic changes in normal aging of the human brain: proton mr spectroscopic imaging study, Am. J. Neuroradiol. 22 (1) (2001) 119–127.
[143] J. Liepert, D. Mingers, C. Heesen, T. Baumer, C. Weiller, Motor cortex excitability and fatigue in multiple sclerosis: a transcranial magnetic stimulation study, Mult. Scler. 11 (3) (2005) 316–321.
[144] M. Gottschalk, T. Kumpfel, P. Flachenecker, M. Uhr, C. Trenkwalder, F. Holsboer, F. Weber, Fatigue and regulation of the hypothalamo-pituitary-adrenal axis in multiple sclerosis, Arch. Neurol. 62 (2) (2005) 277–280.
[145] M.P. Davis, D. Walsh, Mechanisms of fatigue, J. Support. Oncol. 8 (4) (2010) 164–174.
[146] E. Dobryakova, H.M. Genova, J. DeLuca, G.R. Wylie, The dopamine imbalance hypothesis of fatigue in multiple sclerosis and other neurological disorders, Front. Neurol. 6 (2015) 52.
[147] W.S. MacAllister, L.B. Krupp, Multiple sclerosis-related fatigue, Phys. Med. Rehabil. Clin. N. Am. 16 (2) (2005) 483–502.
[148] R.J. Douglas, K.A. Martin, Mapping the matrix: the ways of neocortex, Neuron 56 (2) (2007) 226–238.
[149] M. Goni, N. Basu, A.D. Murray, G.D. Waiter, Neural indicators of fatigue in chronic diseases: a systematic review of MRI studies, Diagnostics (Basel) 8 (3) (2018).
[150] K.J. Psoter, B.S. Roudsari, M.K. Dighe, M.L. Richardson, D.S. Katz, P. Bhargava, Biostatistics primer for the radiologist, AJR Am. J. Roentgenol. 202 (4) (2014) W365–w375.
[151] V.J. Wedeen, R.P. Wang, J.D. Schmahmann, T. Benner, W.Y. Tseng, G. Dai, D.N. Pandya, P. Hagmann, H. D'Arceuil, A.J. de Crespigny, Diffusion spectrum magnetic resonance imaging (DSI) tractography of crossing fibers, Neuroimage 41 (4) (2008) 1267–1277.
[152] A.L. Wheeler, A.N. Voineskos, A review of structural neuroimaging in schizophrenia: from connectivity to connectomics, Front. Hum. Neurosci. 8 (2014) 653.
[153] P. Kochunov, J. Chiappelli, L.E. Hong, Permeability-diffusivity modeling vs. fractional anisotropy on white matter integrity assessment and application in schizophrenia, Neuroimage Clin. 3 (2013) 18–26.
[154] C. Dettmers, J. DeLuca, Editorial: fatigue in multiple sclerosis, Front. Neurol. 6 (2015) 266.
[155] S.L. Johnson, The concept of fatigue in multiple sclerosis, J. Neurosci. Nurs. 40 (2) (2008) 72–77.
[156] S.M. Gold, M.R. Irwin, Depression and immunity: inflammation and depressive symptoms in multiple sclerosis, Immunol. Allergy Clin. N. Am. 29 (2) (2009) 309–320.
[157] R. Bakshi, Fatigue associated with multiple sclerosis: diagnosis, impact and management, Mult. Scler. 9 (3) (2003) 219–227.
[158] G. Comi, Pathophysiology of central fatigue in MS, Eur. J. Neurol. Neurosurg. 14 (2007) 308.
[159] L.B. Strober, P.A. Arnett, Depression in multiple sclerosis: The utility of common self-report instruments and development of a disease-specific measure, J. Clin. Exp. Neuropsychol. 37 (7) (2015) 722–732.
[160] M. Cavallari, M. Palotai, B.I. Glanz, S. Egorova, J.C. Prieto, B.C. Healy, T. Chitnis, C.R. Guttmann, Fatigue predicts disease worsening in relapsing-remitting multiple sclerosis patients, Mult. Scler. 22 (14) (2016) 1841–1849.
[161] B. Colombo, F.M. Boneschi, P. Rossi, M. Rovaris, L. Maderna, M. Filippi, G. Comi, MRI and motor evoked potential findings in nondisabled multiple sclerosis patients with and without symptoms of fatigue, J. Neurol. Neurosurg. 247 (7) (2000) 506–509.
[162] O. Yaldizli, I.K. Penner, K. Frontzek, Y. Naegelin, M. Amann, A. Papadopoulou, T. Sprenger, J. Kuhle, P. Calabrese, E.W. Radu, L. Kappos, A. Gass, The

relationship between total and regional corpus callosum atrophy, cognitive impairment and fatigue in multiple sclerosis patients, Mult. Scler. J. 20 (3) (2014) 356–364.
[163] N. Derache, B. Grassiot, F. Mezenge, A. Emmanuelle Dugue, B. Desgranges, J.-M. Constans, G.-L. Defer, Fatigue is associated with metabolic and density alterations of cortical and deep gray matter in relapsing-remitting-multiple sclerosis patients at the earlier stage of the disease: a PET/MR study, Mult. scler. Relat. Disord. 2 (4) (2013) 362–369.
[164] C. Gobbi, M.A. Rocca, E. Pagani, G.C. Riccitelli, E. Pravata, M. Radaelli, F. Martinelli-Boneschi, A. Falini, M. Copetti, G. Comi, M. Filippi, Forceps minor damage and co-occurrence of depression and fatigue in multiple sclerosis, Mult. Scler. 20 (12) (2014) 1633–1640.
[165] A.M. Novo, S. Batista, C. Alves, O.C. d'Almeida, I.B. Marques, C. Macário, I. Santana, L. Sousa, M. Castelo-Branco, L. Cunha, Neural basis fatigue mult. Scler. Multimodal MRI Approach (2018), https://doi.org/10.1212/CPJ.0000000000000545.
[166] I. Specogna, F. Casagrande, A. Lorusso, M. Catalan, A. Gorian, L. Zugna, R. Longo, M. Zorzon, M. Naccarato, G. Pizzolato, M. Ukmar, M.A. Cova, Functional MRI during the execution of a motor task in patients with multiple sclerosis and fatigue, Radiol. Med. 117 (8) (2012) 1398–1407.
[167] M.A. Rocca, R. Gatti, F. Agosta, P. Broglia, P. Rossi, E. Riboldi, M. Corti, G. Comi, M. Filippi, Influence of task complexity during coordinated hand and foot movements in MS patients with and without fatigue. A kinematic and functional MRI study, J. Neurol. Neurosurg 256 (3) (2009) 470–482.
[168] M.A. Rocca, A. Meani, G.C. Riccitelli, B. Colombo, M. Rodegher, A. Falini, G. Comi, M. Filippi, Abnormal adaptation over time of motor network recruitment in multiple sclerosis patients with fatigue, Mult. Scler. 22 (9) (2016) 1144–1153.
[169] E. Pravata, C. Zecca, C. Sestieri, M. Caulo, G.C. Riccitelli, M.A. Rocca, M. Filippi, A. Cianfoni, C. Gobbi, Hyperconnectivity of the dorsolateral prefrontal cortex following mental effort in multiple sclerosis patients with cognitive fatigue, Mult. Scler. 22 (13) (2016 Nov) 1665–1675.
[170] A. Bisecco, F. DiNardo, R. Docimo, C. Giuseppina, A. d'Ambrosio, R. Sacco, S. Bonavita, M. Cirillo, F. Esposito, G. Tedeschi, A. Gallo, Fatigue in Multiple Sclerosis: The Contribution of Resting-State Functional Connectivity Reorganization, AAN Anual Meeting, Vancouver, 2016.
[171] T. Welton, C.S. Constantinescu, D.P. Auer, R.A. Dineen, Functional brain network organisation is related to cognition and fatigue in MS, Mult. Scler. J. 22 (2016) 553–554.
[172] C. Finke, J. Schlichting, S. Papazoglou, M. Scheel, A. Freing, C. Soemmer, L.M. Pech, A. Pajkert, C. Pfuller, J.T. Wuerfel, C.J. Ploner, F. Paul, A.U. Brandt, Altered basal ganglia functional connectivity in multiple sclerosis patients with fatigue, Mult. Scler. 21 (7) (2015) 925–934.
[173] L. Wu, Y. Zhang, F. Zhou, L. Gao, L. He, X. Zeng, H. Gong, Altered intra- and interregional synchronization in relapsing-remitting multiple sclerosis: a resting-state fMRI study, Neuropsychiatr. Dis. Treat. 12 (2016) 853–862.
[174] M.A. Rocca, M. Absinta, P. Valsasina, M. Copetti, D. Caputo, G. Comi, M. Filippi, Abnormal cervical cord function contributes to fatigue in multiple sclerosis, Mult. Scler. 18 (11) (2012) 1552–1559.
[175] M. Pardini, L. Bonzano, L. Roccatagliata, G.L. Mancardi, M. Bove, The fatigue-motor performance paradox in multiple sclerosis, Sci. Rep. 3 (2013) 2001.
[176] A. Pokryszko-Dragan, J. Bladowska, A. Zimny, K. Slotwinski, M. Zagrajek, E. Gruszka, M. Bilinska, M. Sasiadek, R. Podemski, Magnetic resonance spectroscopy findings as related to fatigue and cognitive performance in multiple sclerosis patients with mild disability, J. Neurol. Sci. 339 (1-2) (2014) 35–40.
[177] E. Kantorova, H. Polacek, M. Bittsansky, E. Baranovicova, P. Hnilicova, D. Cierny, S. Sivak, V. Nosal, K. Zelenak, E. Kurca, Hypothalamic damage in multiple sclerosis correlates with disease activity, disability, depression, and fatigue, Neurol. Res. 39 (4) (2017) 323–330.