REVIEW

Relationship between MRI perfusion and clinical severity in multiple sclerosis

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Abstract

Perfusion alterations within several brain regions have been shown in multiple sclerosis patients using different magnetic resonance imaging (MRI) techniques. Furthermore, MRI-derived brain perfusion metrics have been investigated in association with multiple sclerosis phenotypes, physical disability, and cognitive impairment. However, a review focused on these aspects is still missing. Our aim was to review all the studies investigating the relationship between perfusion MRI and clinical severity during the last fifteen years to understand the clinical relevance of these findings. Perfusion differences among phenotypes were observed both with 1.5T and 3T scanners, with progressive multiple sclerosis presenting with lower perfusion values than relapsing-remitting multiple sclerosis patients. However, only 3T scanners showed a statistically significant distinction. Controversial results about the association between MRI-derived perfusion metrics and physical disability scores were found. However, the majority of the studies showed that lower brain perfusion and longer transit time are associated with more severe physical disability and worse cognitive performances.

Key Words: *brain perfusion; cerebral blood flow; cognition; disability; magnetic resonance imaging; MRI; multiple sclerosis; phenotypes; progressive; relapsing remitting*

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Introduction

Multiple sclerosis (MS) is a chronic immune-mediated inflammatory demyelinating disease leading to neurodegeneration and disability. MS is characterized by the development of acute inflammatory white matter (WM) lesions (Thompson et al., 2018) that are visible on conventional T2-weighted magnetic resonance imaging (MRI) as focal hyperintensities (Datta et al., 2017). However, it is now well-recognized that focal lesions represent only an aspect of the disease (Tommasin et al., 2019). In the last few decades, emerging advanced quantitative MRI techniques have detected microstructural alterations even in the normal appearing WM (NAWM) of MS patients (Granberg et al., 2017). Furthermore, cortical lesions and gray matter (GM) atrophy have been defined as prominent additional features of the disease (Calabrese et al., 2012; Bergsland et al., 2018). A relationship between cortical and WM damages was recently shown (Bergsland et al., 2015).

Besides these findings, perfusion changes have been reported within both lesions and normal-appearing tissue in MS (Amann et al., 2012; Ota et al., 2013). It is still unclear if perfusion alterations in MS are a primary event or just an epiphenomenon due to Wallerian degeneration or atrophy (Amann et al., 2012; Ota et al., 2013; Debernard et al., 2015). However, accumulating evidence suggests that perfusion changes represent an important component of the disease process. In fact, hypoperfusion was reported even in non-atrophic regions (Debernard et al., 2014; Lagana et al., 2018; Mulholland et al., 2018) and it was shown to be not necessarily associated with lesion load (Inglese et al., 2008; Bester et al., 2015). Moreover, perfusion alterations have been suggested to precede atrophy (Debernard et al., 2014) and lesion formation (Wuerfel et al., 2004). A longitudinal MRI study reported local hyperperfusion in areas that developed gadolinium-enhancing plaques several weeks later (Wuerfel et al., 2004). In addition, a relationship between brain perfusion and WM lesion distribution was observed in a wide cohort of MS patients (Holland et al., 2012). Specifically, WM lesions of secondary progressive MS (SPMS) patients were detected in regions characterized by lower perfusion than NAWM (Holland et al., 2012). Conversely, relapsing-remitting MS (RRMS) patients, and especially early RRMS patients, predominantly presented lesions in hyperperfused regions (Holland et al., 2012). This finding indicates that remyelination, which is known to be more successful at the early stage of the disease, may be associated with the local perfusion extent. This result encouraged various research groups to seek brain perfusion biomarkers that might be used for MS monitoring and management.

Although brain perfusion has been investigated in MS with positron emission tomography and single photon emission tomography since the 1990s (Lycke et al., 1993; Sun et al., 1998), in the last 15 years, MRI sequences for the assessment of indices such as cerebral blood flow (CBF), cerebral blood volume (CBV) and transit time have been developed. Since MRI is a non-ionizing imaging technique, dynamic susceptibility contrast (DSC) MRI, dynamic contrast-enhanced (DCE) MRI and arterial spin labelling (ASL) MRI have been extensively used to assess brain perfusion in several neurological diseases, with (DSC and DCE) and without (ASL) an exogenous contrast agent (Eskildsen et al., 2017; Corno et al., 2018; Pelizzari et al., 2019; Xi et al., 2019). In MS, perfusion alterations have been observed with all these MRI techniques (Lapointe et al., 2018). Nonetheless, the relevance of these findings in the framework of pursuing

a better understanding of the mechanisms that drive the disease progression and disability development remains to be clarified. A potential link between brain perfusion, MS phenotypes, MS-induced physical disability, and cognition was hypothesized.

The aim of this review is to collect and synthesize the results from the studies that investigated the relationship between MRI perfusion and clinical severity of MS.

Search Strategy and Selection Criteria

An electronic search was conducted with PubMed and Web of Science, and it was limited to the papers published during the last 15 years (from January 1, 2004 to December 31, 2018). Two separate search strings were used as follows:

(1) ((multiple sclerosis) AND (((relapsing remitting) AND (benign)) OR ((relapsing remitting) AND (secondary progressive)) OR ((relapsing remitting) AND (primary progressive)) OR ((secondary progressive) AND (benign)) OR ((secondary progressive) AND (primary progressive)) OR ((benign) AND (primary progressive)))) AND (brain perfusion OR cerebral blood flow) AND (MRI OR magnetic resonance imaging), to identify the studies investigating the differences among MS phenotypes with brain perfusion MRI;

(2) (multiple sclerosis) AND ((brain perfusion) OR (cerebral blood flow) OR CBF OR CBV OR MTT) AND (MRI OR (magnetic resonance imaging)) AND (cognition OR (cognitive impairment) OR (cognitive assessment) OR (cognitive performance) OR (cognitive dysfunction) OR disability OR EDSS OR (motor disability) OR (physical disability) OR (Severity of Illness Index)OR (clinical outcome)OR (clinical measure)), to identify the studies investigating the relationship between brain perfusion MRI-derived metrics and MS-induced physical disability/cognitive dysfunctions.

The search results were screened by title and abstract, to exclude studies that met the following exclusion criteria: (1) studies not published in English; (2) animal studies; (3) studies conducted on neurological diseases other than MS; (4) reviews and trials; (5) studies assessing perfusion with techniques other than MRI; (6) studies performing either a clinical, physical or cognitive/neuropsychological assessment with self-reported scales; (7) studies not assessing the relationship between MRI-derived perfusion measures and either MS phenotypes or clinical performance scales.

The studies included in the current review are reported in **Additional Tables 1–3**.

MRI Perfusion Techniques

The common MRI techniques to assess brain perfusion are DSC, DCE and ASL MRI (Wintermark et al., 2005). All these techniques allow to quantify CBF [mL/min/100 g of tissue], CBV [mL/100 g of tissue] and transit time [s]. Both DSC and DCE work by imaging the dynamic passage of a gadolinium bolus. The former is based on T2*-weighted sequences, and the latter on T1-weighted sequences (Wintermark et al., 2005). Although DCE has the advantage of not suffering from estimation errors due to the attenuation of the signal in case of brain-blood barrier leakage, DSC is the MRI clinical standard for the assessment of cerebral perfusion (Wintermark et al., 2005). Unlike DSC and DCE, ASL relies on the use of an endogenous contrast agent. Water molecules of the blood are magnetically labelled with radiofrequency inversion pulses before they reach the brain. (Hernandez-Garcia et al., 2019) According to the specific labeling technique, ASL sequences can be classified in pulsed ASL (pASL), continuous ASL (CASL) and pseudo-continuous ASL (pCASL) (Hernandez-Garcia et al., 2019). As reported by the guidelines of the ISMRM Perfusion Study Group and the European 'ASL in Dementia' consortium, pCASL labeling is recommended among the ASL sequences, as it provides the best signal-to-noise ratio (Alsop et al., 2015).

MRI Perfusion in Different Clinical Multiple Sclerosis Phenotypes

Only five studies (Rashid et al., 2004; Adhya et al., 2006; Inglese et al., 2007; Inglese et al., 2008; Amann et al., 2012) evaluated perfusion differences among MS phenotypes. Details about these studies are summarised in **Additional Table 1**.

Two out of five studies (Rashid et al., 2004; Amann et al., 2012) assessed perfusion with ASL MRI at 1.5T, while three out of five (Adhya et al., 2006; Inglese et al., 2007, 2008) used DSC MRI at 3T.

Although the two studies performed with 1.5T scanners did not report significant perfusion differences among MS phenotypes (Rashid et al., 2004; Amann et al., 2012), a trend for lower perfusion in case of higher physical disability was detected. Amann et al. (2012) showed cortical hypoperfusion in SPMS compared with RRMS, but significance was lost after correcting for T2 lesion volume, age, sex and disease duration. Rashid et al. (2004) did not find significant differences when comparing the various MS phenotypes in the whole WM. However, a different pattern of GM perfusion alterations was reported for each disease course (Rashid et al., 2004). Specifically, wide regions of hypoperfusion in PPMS compared to HC were shown. SPMS displayed both hypoperfusion and hyperperfusion in several brain areas. Conversely, RRMS perfusion was not significantly different from that of HC, while benign MS presented hypoperfusion in only small GM areas. These results suggest a trend for greater perfusion modification in the progressive phenotypes compared with RRMS. The trend reported by studies performed with ASL at 1.5T scanners was confirmed by DSC studies at 3T that consistently showed significant lower perfusion in PPMS than in RRMS (Adhya et al., 2006; Inglese et al., 2007, 2008). Specifically, significant CBF and CBV reduction in PPMS with respect to RRMS was reported in periventricular NAWM (Adhya et al., 2006), thalamus and caudate head (Inglese et al., 2007). PPMS showed lower CBV also in the frontal NAWM (Adhya et al., 2006). Conversely, comparable mean transit time (MTT) was reported among MS phenotypes (Adhya et al., 2006; Inglese et al., 2007, 2008). When compared with HC, both RRMS and PPMS presented reduced CBF (Adhya et al., 2006; Inglese et al., 2007, 2008). The regions for which PPMS displayed hypoperfusion with respect to HC were wider than the ones showing perfusion differences with RRMS patients. This finding consistently hints that perfusion alterations become greater as the disease progresses. However, the three 3T DSC studies investigat-

ing the impact of MS phenotype on perfusion changes were from the same research group. In order to generalize their conclusions, the results need to be confirmed in a wider and different cohort of subjects.

Although studies performed with both 1.5T scanner and 3T scanner involving different MS phenotypes suggested a trend of perfusion impairment in the PPMS and SPMS with respect to RRMS, all of them had a cross-sectional design. Longitudinal studies are warranted to confirm these results. A better understanding of brain perfusion differences among phenotypes may help to shed more light on the mechanisms that drive the disease progression.

Relationships between MRI Perfusion and Disability

Physical disability and brain perfusion in multiple sclerosis

Twelve studies investigating the correlation between MS physical disability and MRI-derived brain perfusion metrics were included in the current review. Characteristics of these studies are summarised in **Additional Table 2**.

In these works, clinical disability was assessed using the Expanded Disability Status Scale (EDSS), Multiple Sclerosis Severity Score (MSSS), and Multiple Sclerosis Functional Composite (MSFC) score. EDSS is the most commonly used global index to quantify physical disability in MS (Kurtzke, 1983). MSSS is obtained by normalising EDSS for disease duration (Roxburgh et al., 2005), and it was shown to predict disease severity over time (Pachner and Steiner, 2009). MSFC is a three-part, standardized, quantitative, assessment measure of leg, arm/hand, and cognitive functions (Whitaker et al., 1995; Rudick et al., 1996). The three MSFC domains are assessed with the timed 25-foot walking test, nine-hole peg test and Paced Auditory Serial Additions Test (PASAT) respectively. The obtained scores are combined into the MSFC score. Since MSFC assessment includes PASAT, both physical disability and cognitive dysfunction are evaluated. Disability worsening is mirrored by EDSS and MSSS increments, and by MSFC decrement.

Five out of 12 studies (42%) did not find any significant relationship between MRI-derived perfusion indices and physical disability scales, regardless of the magnetic field (1.5 T or 3 T), MRI sequence (DCE, DSC, ASL), and processing method (ROI-based or voxel-wise) (Rashid et al., 2004; Inglese et al., 2008; Amann et al., 2012; Debernard et al., 2014; Yin et al., 2018).

The remaining seven studies (58%) observed a relationship between neurological composite scores (assessed with EDSS or MSSS or MFSC) and MRI-derived perfusion measures (Adhya et al., 2006; Inglese et al., 2007; Garaci et al., 2012; Paling et al., 2014; Doche et al., 2017; Sowa et al., 2017; Zhang et al., 2018).

As detailed in **Additional Table 2**, four out of seven studies presented a relationship between MS physical assessment scores and CBF and/or CBV (Adhya et al., 2006; Inglese et al., 2007; Doche et al., 2017; Zhang et al., 2018); the other three with transit time (Garaci et al., 2012; Paling et al., 2014; Sowa et al., 2017).

Specifically, either a significant (Adhya et al., 2006; Doche et al., 2017; Zhang et al., 2018) or a trend for negative correlation (Inglese et al., 2007) between EDSS and CBF/CBV was reported. Doche et al. (2017) also showed a significant positive correlation between thalamic CBF and the global MSFC, as well as with the nine-hole peg test sub-score. Thus, symptoms worsening were associated with decreased CBF/CBV (Adhya et al., 2006; Inglese et al., 2007; Doche et al., 2017; Zhang et al., 2018). Nonetheless, one study reported both negative and positive correlation between EDSS and CBF in diffuse GM areas (Zhang et al., 2018). The discrepancies between Zhang's and other groups' findings may be ascribed to the differences in the methodological approach.

The three out of seven studies reporting an association between severity of physical disability and transit time (Garaci et al., 2012; Paling et al., 2014; Sowa et al., 2017) showed contrasting results. Prolonged transit time associated with higher EDSS was reported by (Paling et al., 2014) and (Garaci et al., 2012) in different regions of NAWM and DGM. This is in agreement with some cross-sectional studies finding prolonged transit time in MS subjects compared with healthy controls (HC) (Ge et al., 2005; Mancini et al., 2012; Monti et al., 2015). Conversely, Sowa et al. (2017) showed significantly lower normalised MTT in newly diagnosed RRMS patients that presented with MSSS > 3.79 one year after the scan with respect to the ones presenting with MSSS < 3.79, and their counterintuitive finding may be due to either a longer transit time in the lesions or lower transit time in the NAWM. Since no MTT alterations were previously observed in active lesions (Ge et al., 2005), the evidence of increased normalised mean transit time was probably due to the lower transit time in the NAWM. In this case, Sowa's result would be in line with Paling's and Garaci's ones (Garaci et al., 2012; Paling et al., 2014).

Firm conclusions about the brain structures where perfusion indices are associated to physical disability cannot be drawn, because the studies that reported a relationship between EDSS and CBF/CBV/MTT in MS investigated the correlation in different areas (*e.g.*, DGM, the NAWM, GM, voxel-level). Moreover, contrasting findings were reported for some regions commonly investigated across studies. For example, both positive and negative correlations between thalamic CBF and EDSS were reported (Doche et al., 2017; Zhang et al., 2018).

Longitudinal MRI studies in larger groups of patients, with a wider EDSS range and different phenotypes, might clarify the evolution of brain perfusion with disability progression. Moreover, since a trend for different perfusion pattern was shown among MS phenotypes, the relationship between physical disability and perfusion should be investigated in MS sub-groups. Conversely, when different phenotypes were contemporaneously investigated (Rashid et al., 2004; Adhya et al., 2006; Inglese et al., 2007, 2008; Amann et al., 2012; Garaci et al., 2012), correlations were tested merging all the MS subjects. A trend of negative correlation was found by one of them (Inglese et al., 2007), significant correlations were found by two studies (Adhya et al., 2006; Garaci et al., 2012), but no significant correlation was reported by the other three studies.

Finally, homogeneity of processing methods is warranted for future investigations, in order to make the results com-

parable among studies. Regions of interest could be a-priori selected similarly to previous studies but in larger groups of patients. Further, voxel-wise analyses would allow to differentiate hypo- and hyper-perfusion, that could be contemporaneously present in the same MS group compared to HC (Rashid et al., 2004; Zhang et al., 2018), and that would be averaged if a unique ROI is used.

Cognitive performance and brain perfusion in multiple sclerosis

Cognitive decline is a widely recognized symptom of MS that strongly impacts on daily activities and dramatically reduces patients' quality of life (Sumowski et al., 2018). Processing speed and episodic memory are the cognitive domains that are prevalently affected in MS patients, even though deficits in executive functions, verbal fluency and visuospatial analysis may also be present (Sumowski et al., 2018). The neuropsychological standard to assess these functions is the Minimal Assessment of Cognitive Functions in MS (MACFIMS) battery (Benedict et al., 2006). Understanding the pathophysiological bases of cognitive impairment in MS is important for prognostic prediction and for the definition of treatment strategies. Beside brain atrophy and WM lesion load, brain perfusion was suggested as a predictor for cognitive dysfunction in MS (Aviv et al., 2012; Hojjat et al., 2016b; Jakimovski et al., 2019).

Eleven studies investigated the relationship between cognition and MRI-derived brain perfusion measures in MS. Details about these studies are summarized in **Additional Table 3**. All these studies have consistently observed an association between these two aspects (Inglese et al., 2008; Aviv et al., 2012; D'Haeseleer et al., 2013a; Francis et al., 2013; Debernard et al., 2014; Papadaki et al., 2014; Hojjat et al., 2016a, b, c; Vitorino et al., 2016; Ma et al., 2017). However, the relatively limited number of studies were characterized by great methodological heterogeneity. This heterogeneity has to be ascribed to several factors. Firstly, some studies investigated a single MS phenotype (Aviv et al., 2012; Francis et al., 2013; Debernard et al., 2014; Papadaki et al., 2014; Hojjat et al., 2016a, b, c; Vitorino et al., 2016), while others included mixed cohorts of MS patients, regardless of the disease course (Inglese et al., 2008; D'Haeseleer et al., 2013a; Ma et al., 2017). Secondly, different neuropsychological batteries (e.g., MACFIMS, Wechsler Memory Scale –WMS, Rey Complex Figure Copy test-RCFT) and MRI techniques (i.e., DSC, ASL) were used. In addition, brain perfusion MRI indices were investigated with different spatial resolution, either performing a voxel-wise analysis (Francis et al., 2013; Debernard et al., 2014; Hojjat et al., 2016c; Vitorino et al., 2016) or focusing on regions of interest (Inglese et al., 2008; D'Haeseleer et al., 2013b; Papadaki et al., 2014; Hojjat et al., 2016a, b; Ma et al., 2017). Moreover, in some studies the association between cognitive performance and perfusion was assessed by computing the correlation between CBF/CBV and neuropsychological test scores (Inglese et al., 2008; D'Haeseleer et al., 2013a; Francis et al., 2013; Debernard et al., 2014; Papadaki et al., 2014; Ma et al., 2017), while in others CBF, CBV and MTT were compared between cognitively impaired and cognitively preserved MS patients (Aviv et al., 2012; Francis et al., 2013; Hojjat et al., 2016a, b, c; Vitorino et al., 2016). Given that cognitive impairment is defined according to an arbitrary threshold, the classification in either impaired or preserved may change across studies. Finally, MS patients categorized as impaired may present heterogeneous co-occurring cognitive deficits, because the classification is generally performed referring to the overall performance (Sumowski et al., 2018).

Despite all these sources of variability, some common observations can be derived from the studies that investigated the association between MRI-derived brain perfusion indices and cognition in MS so far. First, cognitive dysfunctions have unanimously been associated with hypoperfusion in MS (Inglese et al., 2008; Aviv et al., 2012; D'Haeseleer et al., 2013a; Francis et al., 2013; Debernard et al., 2014; Hojjat et al., 2016a, b, c; Vitorino et al., 2016; Ma et al., 2017) except for clinically isolated syncrome (CIS) patients (Papadaki et al., 2014), that were investigated in only one out of eleven studies (Papadaki et al., 2014). Papadaki and colleagues reported an inverse correlation between memory and CBV within several regions that are involved in memory functions (i.e. left frontal NAWM, bilateral thalami, right caudate and corpus callosum) (Papadaki et al., 2014). Inflammation-induced vasodilation and/or angiogenesis were suggested to produce increased CBV in CIS, leading to the disruption of mechanisms responsible for memory functions (Papadaki et al., 2014). Conversely, in all the other MS phenotypes, cognitive impairment was associated with GM or WM hypoperfusion. Notably, this association was observed at the global level, when considering GM and WM as a whole, suggesting that hypoperfusion is present in diffuse brain areas in both RRMS and SPMS cognitively impaired patients (Aviv et al., 2012; Hojjat et al., 2016b).

The association between MS cognitive dysfunctions and hypoperfusion was also detected at the local level. Decreased cognitive performances were consistently linked to hypoperfusion in the frontal lobes of RRMS and SPMS patients. Brain frontal regions are known to play a key role in high-level cognitive functions, such as working memory, executive functions and control (Badre and Nee, 2018). Cognitively impaired RRMS patients showed reduced DSC-derived perfusion indices in left middle frontal and left superior frontal gyri when compared to cognitively preserved RRMS patients and HC, even after correcting for regional volumes of focal atrophy (Vitorino et al., 2016). Likewise, Hojjat et al. (2016c) reported reduced ASL-derived CBF in left frontal and bilateral superior frontal lobes of cognitively impaired RRMS patients with respect to cognitively preserved RRMS patients and HC. Furthermore, Debernard's group showed a link between hypoperfusion in frontal and precentral gyri and memory, assessed with Brief Visuospatial Memory Test and California Verbal Leaning Test (CVLT) in RRMS (Debernard et al., 2014). Notably, the association between cognitive dysfunctions and hypoperfusion in the frontal lobe was observed also for SPMS. Aviv et al. (2012) showed that CBV in left inferior frontal, middle frontal, superior frontal regions, and bilateral medial superior frontal regions are significant predictors of overall cognitive impairment in SPMS. In addition, Francis et al. (2013) reported

reduced CBF in bilateral medial frontal gyrus and lower CBV in bilateral frontal gyrus of cognitively impaired SPMS compared with cognitively preserved SPMS patients. Perfusion indices in these areas were also correlated with the scores of all MACFIMS tests (apart from CVLT), presenting the strongest correlation with Symbol Digit Modalities Test (SDMT) (Francis et al., 2013). Given this evidence for RRMS and SPMS disease courses, the association between brain frontal hypoperfusion and cognitive decline could be expected also for PPMS. However, this relationship has not been investigated in PPMS cortex so far, therefore this hypothesis needs to be confirmed.

It is worthy of note that the association between cognitive dysfunction and perfusion alterations was observed also within deep GM, and prominently in the thalamus. As part of the cortico-basal ganglia-thalamocortical loop, basal ganglia and thalamus act as important hubs to integrate and modulate information during the execution of complex attention and executive function tasks (Batista et al., 2012). In particular, structural and functional changes in the thalamus are known to be informative regarding the overall cognitive dysfunction of MS patients (Schoonheim et al., 2015). Interestingly, a significant correlation between deep GM hypoperfusion and Rey Complex Figure Copy test (RCFT) score was reported in PPMS patients and in a mixed group of RRMS and PPMS patients (Inglese et al., 2008). Also, memory assessed with Brief Visuospatial Memory Test and CVLT was observed to be correlated with thalamus hypoperfusion in RRMS (Debernard et al., 2014). In addition, compared to cognitively preserved RRMS and SPMS, cognitively impaired patients presented with lower perfusion in the thalamic medial dorsal nuclei (Vitorino et al., 2016) or in the thalamic pulvinar nuclei (Francis et al., 2013; Hojjat et al., 2016c). Beside thalamus, also caudate nucleus displayed altered perfusion in cognitively impaired RRMS and SPMS patients (Francis et al., 2013; Hojjat et al., 2016c), in line with the hypothesis that cortico-striatal-thalamic circuit may be central in supporting the network interaction required for hierarchical control (Badre and Nee, 2018).

Cognitive impairment in MS may depend on the extent and location of WM lesions, that lead to disconnection syndrome (Manca et al., 2018). Interestingly, cognitive performance was suggested to be associated also to WM lesion perfusion. A significant correlation between perfusion within WM lesions and SDMT score was reported in a mixed group of MS patients (RRMS and SPMS) (Ma et al., 2017). Moreover, there is evidence of an association between MS cognitive dysfunction and hypoperfusion both in WM lesions and NAWM (Hojjat et al., 2016a). D'Haeseleer and colleagues observed a significant correlation between PASAT score and hypoperfusion in normal appearing semioval center in MS (D'Haeseleer et al., 2013b). In addition, cognitively impaired SPMS patients showed reduced perfusion in the corpus callosum splenium compared with cognitively preserved patients (Francis et al., 2013). The corpus callosum has great importance in complex cognitive tasks, because it is the major WM bundle that provides both inter- and intra-hemispheric connections.

Finally, changes in terms of MTT were less consistently associated with cognitive dysfunctions with respect to CBF and CBV alterations. Only three studies among the ones included in this review assessed the relationship between cognitive performance in MS and MTT, with contrasting results. Although one of them did not show any significant MTT alteration between cognitively impaired and cognitively preserved patients (Aviv et al., 2012), prolonged MTT was observed in normal-appearing GM (Hojjat et al., 2016a), cortical GM and whole WM of cognitively impaired MS patients (Hojjat et al., 2016b).

In conclusion, the association between MS cognitive dysfunction and brain hypoperfusion is suggested by all the MRI studies that have been performed so far. However, only a few heterogeneous studies have been published about this topic. Therefore, the current knowledge of how MS-related cognitive impairment is affected by brain perfusion alterations has to be considered only preliminary. Longitudinal studies taking into account MS phenotype, atrophy, and lesion distribution are warranted to draw final conclusions.

Conclusion

In this review, the studies investigating the relationship between MRI-derived brain perfusion parameters and MS clinical characterization indices were collected and summarized. The literature reviewed here does not allow to draw final conclusions due to the limited number of studies that are currently available. However, some preliminary observations can be made.

(1) Brain perfusion assessed with 3T MRI scanner proved to be a biomarker that highlights differences between MS phenotypes (Adhya et al., 2006; Inglese et al., 2007; Inglese et al., 2008). The lower signal to noise ratio of 1.5T scanners presumably impacted on the ability to detect MS phenotype-related perfusion differences in the published studies (Rashid et al., 2004; Amann et al., 2012).

(2) Controversial results about the relationship between MRI perfusion-derived metrics and physical disability scores were reported (Adhya et al., 2006; Inglese et al., 2007; Garaci et al., 2012; Paling et al., 2014; Doche et al., 2017; Zhang et al., 2018). Although Zhang and colleagues observed both a positive and negative correlation between EDSS and CBF in various GM regions (Zhang et al., 2018), the majority of the studies agreed that the severity of physical disability is associated with brain hypoperfusion. Specifically, higher EDSS (Adhya et al., 2006; Inglese et al., 2007; Garaci et al., 2012; Paling et al., 2014; Doche et al., 2017; Zhang et al., 2018) or lower nine-hole score (Doche et al., 2017) were associated with brain hypoperfusion and prolonged transit time in several brain areas.

(3) Cognitive dysfunctions were found to be associated with reduced CBF and CBV in diffuse GM regions, predominantly within frontal lobe and deep GM, in all MS phenotypes except for CIS (Inglese et al., 2008; Aviv et al., 2012; Francis et al., 2013; Debernard et al., 2014; Hojjat et al., 2016a, b, c; Vitorino et al., 2016). Inflammation-induced vasodilation, angiogenesis or compensatory mechanism have been suggested as plausible causes of the patterns of increased perfusion reported in CIS patients (Papadaki et al., 2014). Assessing molecular markers of inflammation

together with brain perfusion may help in disentangling the pathophysiological origin of hyperperfusion in the various MS phenotypes.

(4) Transit time increment was significantly correlated with both physical (Garaci et al., 2012; Paling et al., 2014) and cognitive worsening (Hojjat et al., 2016a, b).

(5) It is worthy of note that the relationship between perfusion metrics and either physical disability scores or cognitive performance was observed in several GM and WM areas. However, in the studies reviewed here, the thalamus perfusion was recurrently identified as a region showing associations with both physical disability (Doche et al., 2017; Zhang et al., 2018) and cognitive dysfunction (Francis et al., 2013; Debernard et al., 2014; Papadaki et al., 2014; Hojjat et al., 2016c; Vitorino et al., 2016). This observation is in line with the well-recognized role that thalamic alterations play in MS (Schoonheim et al., 2015; Motl et al., 2016).

Although the presence of an association between the perfusion alteration and MS is evident, the kind of relationship between them is still unclear. The studies included in this review are characterized by great methodological and inherent heterogeneity (various MRI acquisition techniques, magnetic field strength, processing pipelines, and clinical assessment criteria). This probably prevented from identifying a clear perfusion-related hallmark in MS so far. A better understanding of the relationship between perfusion alterations, MS and clinical/neuropsychological outcomes may be important to provide new potential biomarkers for the assessment of pharmacological and rehabilitation intervention effects. Indeed, besides an epiphenomenon due to atrophy, hypoperfusion may be involved in MS pathogenetic mechanisms. CBF is not directly modulated by neuronal metabolic needs: both endothelial (i.e., endothelin) and vascular factors (e.g., vascular endothelial growth factor, nitric oxide) mediate the complex biochemical communication among neurons, astrocytes, pericytes, and endothelial cells. This mechanism may be altered in MS (Monti et al. 2018). Micro- and macro-circulation changes are known to enhance brain-blood-barrier permeability that precede lesion formation (Monti et al., 2018), while WM plasticity was suggested to involve local changes even in capillaries (Steele and Zatorre, 2018). Furthermore, cardiovascular pathology was reported to significantly contribute to worse clinical and MRI-derived disease outcomes in MS (Jakimovski et al., 2019). To clarify the relationship between MRI-derived perfusion parameters, MS and MS-related clinical measures, studies characterized by a more homogeneous methodological design are warranted. Therefore, adopting a longitudinal multimodal approach, assessing atrophy, microstructural alterations, iron deposits together with CBF and inflammatory markers might help in interpreting the mechanisms underlying brain perfusion changes in MS.

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Additional files:
Additional Table 1: *Characteristics of studies on MRI perfusion in different MS phenotypes.*
Additional Table 2: *Characteristics of studies on the relationship between MRI perfusion and MS physical disability.*
Additional Table 3: *Characteristics of studies on the relationship between MRI perfusion and MS cognitive performance.*

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Table 1 Characteristics of studies on MRI perfusion in different MS phenotypes

Study	Group	Demographics	Clinical variables	MRI	Perfusion assessment approach	Brain perfusion differences between phenotypes	
						Assessed comparison	Regions
Amann et al., 2012	RRMS (n = 123)	Age: 42.7±10.6 98 females (80%)	EDSS: 2.6±1.3 dd: 12.7±8.2	pCASL (1.5T)	ROI-based	CBF: ○SPMS < RRMS (significant only without correcting for T2 lesion volume, age, sex and disease duration)	Cortical GM
	SPMS (n = 42)	Age: 54.3±8.3 24 females (57%)	EDSS: 4.6±1.3 dd: 12.7±8.2				
Inglese et al., 2008	RRMS (n = 18)	Age: 48 (31–71) 12 females (66.7%)	EDSS: 1 (0–6.5)[b] dd: 7.6 (1–34)[c]	DSC (3T)	ROI-based	CBF: ○ RRMS < HC ○ PPMS < HC ○ PPMS < RRMS	NAWM, DGM NAWM, DGM NAWM, DGM
	PPMS (n = 14)	Age: 55 (29–75) 7 females (50.0%)	EDSS: 4 (3–7)[b] dd: 5 (1–19)[c]			CBV: ○ RRMS < HC ○ PPMS < HC ○ PPMS < RRMS	NAWM NAWM, DGM NAWM, DGM
	HC (n = 11)	Age: 51 (29–65) 7 females (63.6%)				MTT: No differences	All the ROIs
Inglese et al., 2007	RRMS (n = 11)	Age: 46.2 (31–71) 8 females (73%)	EDSS: 1 (0.0–6.5) dd: 5.0 (1–13)	DSC (3T)	ROI-based	CBF: ○ RRMS < HC ○ PPMS < HC ○ PPMS < RRMS	Head of caudate, DGM DGM Thalamus, caudate, DGM (trend)
	PPMS (n = 11)	Age: 53.6 (29–71) 4 females (36%)	EDSS: 4 (3.0–7.0) dd: 4.0 (1–19)			CBV: ○ No RRMS-vs-HC differences ○ SPMS < HC ○ PPMS < RRMS	All ROIs DGM Thalamus, caudate, DGM (trend)
	HC (n = 11)	Age: 50.8 (29–65) 7 females (64%)				MTT: No differences	All the ROIs
Adhja et al., 2006	RRMS (n = 11)	Age: 46.2 (31–71) 8 females (73%)	EDSS: 1.0 (0.0 –6.5) dd: 5 (1–13)	DSC (3T)	ROI-based	CBF: ○ RRMS < HC ○ PPMS < HC ○ PPMS < RRMS	All WM ROIs All WM ROIs NAWM (periventricular)
	PPMS (n = 11)	Age: 53.6 (29–71) 4 females (36%)	EDSS: 4.0 (3.0 –7.0) dd: 4 (1—-19)			CBV: ○ RRMS < HC ○ SPMS < HC ○ PPMS < RRMS	NAWM (periventricular, frontal, occipital) All WM ROIs NAWM (periventricular, frontal)
	HC (n = 11)	Age: 50.8 (29–65) 7 females (64%)				MTT: No differences	All ROIs
Rashid et al., 2004	RRMS (n = 21)	Age: 38.9 (17–59) 13 females (62%)	EDSS: 2.5 (0–6.5) dd: 10 (1–31)	CASL (1.5T)	○ ROI-based	CBF: ○ All MS > HC ○ RRMS+SPMS > HC ○ RRMS without therapy > HC ○ RRMS > HC ○ No PPMS-vs-HC differences ○ Benign MS > HC (trend)	WM WM WM WM WM WM
	SPMS (n =14)	Age: 51.2 (30–65) 11 females (79%)	EDSS: 6.0 (2–8) dd: 18 (7–40)				
	PPMS (n =12)	Age: 55.7 (40–69) 7 females (58%)	EDSS: 6.5 (3.5–8.5) dd: 16 (8–34)				
	Benign MS (n =13)	Age: 52.6 (40–60) 8 females (62%)	EDSS: 2.5 (1–3) dd: 24 (20–36)		○ Voxel-wise	CBF: ○ No RRMS *vs.*others differences ○ RRMS without therapy > HC ○ SPMS > HC ○ SPMS < HC ○ PPMS < HC ○ Benign MS < HC	Whole brain WM region adjacent to the L precentral and superior temporal gyrus R frontal subcortical WM thalami, caudate, middle frontal and precentral and postcentral gyri, inferior parietal areas, superior frontal and medial gyrus, precuneus, cingulate gyri, paracentral lobule L superior parietal lobule, subgyral areas thalami, caudate, middle frontal, precentral and postcentral gyri, inferior parietal areas, superior frontal and medial gyrus Thalami, caudate, middle frontal, precentral and postcentral gyri, inferior parietal areas
	HC (n = 34)	Age: 40.7 (20–67) 19 females (56%)					

Age and dd are expressed in years. Values are provided as mean ± standard deviation or median (range). The percentage of females out of the total number of subjects is reported in parenthesis after the female number. CBF: Cerebral blood flow; CBV: cerebral blood volume; dd: disease duration; DGM: deep gray matter; DSC: dynamic susceptibility contrast; EDSS: Expanded Disability Status Scale; HC: healthy controls; GM: gray matter; L: left; MS: multiple sclerosis; MSFC: Multiple Sclerosis Functional Composite Measure (including leg function evaluated by the timed 25-foot walk (25FTW), nine-hole peg test (9HPT), and three-second paced auditory serial addition test (PASAT3)); MTT: mean transit time; NAGM: normal appearing gray matter; n: number; NAWM: normal-appearing white matter; PASAT: Paced Auditory Serial Addition Test; PPMS: primary progressive multiple sclerosis; pCASL: pseudo Continuous Arterial Spin Labeling; R: right; ROI: region of interest; RRMS: relapsing-remitting multiple sclerosis; WML: white matter lesions; SPMS: secondary progressive multiple sclerosis.

Table 2 Characteristics of studies on the relationship between MRI perfusion and MS physical disability

Study	Group	Demographics	Clinical variables	MRI	Perfusion assessment approach	Relationship between perfusion metrics and motor assessment	
						Assessed relationship	Regions
Yin et al., 2018	RRMS (*n* = 30)	Age: 13.6 (19–78) 20 females (67%)	EDSS: 1.0 (0.0–5.0) dd: 3.4 (0.2–16.5)	DCE (3T)	ROI-based	Correlation between DCE-derived parameters and EDSS: ○ Non-significant	Enhancing/non-enhancing WML, NAWM
Zhang et al., 2018	RRMS (*n* =39)	Age: 38.7±12.6 23 females (59%)	EDSS: 2.0 (0.0–6.0) dd: 4.2 ±4.9	pCASL (3T)	Voxel-wise	Correlation between CBF and EDSS: ○ Positive, significant ○ Negative, significant	Frontal, temporal, partial parietal, limbic lobes, bilateral putamen, thalamus Occipital, partial frontal, parietal lobes, temporal poles
	HC (*n* = 73)	Age: 47.7±13.9 55 females (75%)					
Doche et al., 2017	RRMS (*n* = 23)	Age: 34.2±9.3 19 females (83%)	EDSS: 1.5±1.2 MSFC z-score –0.7±1.04 dd: 4.5±4.6	pCASL (3T)	ROI-based	Correlation between CBF and EDSS: ○ Negative, trend	Bilateral thalami
	HC (*n* = 16)	Age: 37.1±10.2 12 females (75%)				Correlation between CBF and MSFC: ○ Positive, significant Correlation between CBF and 9HPT sub-score: ○ Positive, significant	Bilateral thalami Bilateral thalami
Sowa et al., 2017	RRMS (early: < 3 years since MS diagnosis) (*n* = 65)	Age: 34.9±7.2 44 females (66%)	EDSS at follow-up: 2 (1.5–2.5) MSSS at follow-up: 4.2±2.0	DSC (1.5T)	ROI-based	nCBF: ○ No differences between lower and higher disease severity groups nCBV: ○ No differences between lower and higher disease severity groups nMTT: ○ Lower disease severity group > higher disease severity group	WML, NAWM WML, NAWM WML, NAWM
	Groups divided based on MSSS at follow-up:						
	Lower disease severity group MSSS≤3.79	Age: 32.6±6.5 23 females (79%)	dd: 1.9 (1.2–4.0)				
	Higher disease severity group MSSS>3.79 (*n* = 36)	Age: 36.6±6.9 22 females (61%)	dd: 1.4 (0.8–2.6)				
Debernard et al., 2014	RRMS patients (early) (*n* = 25)	N:25 Age: 37.2±8.6 22 females (88%)	EDSS: 1.5 (0–4.5) MSSS: 3.5±1.8 MSFC: 0.7±0.4 dd: 2.4±1.5	pCASL (3T)	○ROI-based ○ Voxel-wise	Correlation between CBF and EDSS: ○ Non-significant Correlation between CBF and MSFC: ○ Non-significant	GM GM
	HC (*n* = 25)	Age: 35.2±10.3 17 females (68%)				Correlation between CBF and MSSS: ○ Non-significant	GM
Pailing et al., 2014	RRMS (*n* = 35)	Age: 38.1±8.0 23 females (66%)	EDSS: 2.5 (0.0–6.5) dd: 8.2±6.5	pASL (3T)	ROI-based	Correlation between CBF and EDSS: ○ Non-significant	NAWM (frontal, occipital, parietal), DGM (thalamus, caudate)
	HC (*n* = 33)	Age: 40.0±11.1 19 females (58%)				Correlation between BAT and EDSS: ○ Positive, significant (partial, covariates: age, gender, atrophy, WML volume)	NAWM (frontal, occipital, parietal), DGM (thalamus, caudate)
Amann et al., 2012	RRMS (*n* = 123)	Age: 42.7±10.6 98 females (80%)	EDSS: 2.6±1.3 dd:12.7±8.2	pCASL (1.5T)	ROI-based	Correlation between CBF and EDSS: ○ Non-significant	Cortical GM
	SPMS (*n* = 42)	Age: 54.3±8.3 24 females (57%)	EDSS: 4.6±1.3 dd:12.7±8.2				

Table 2 Continued

Study	Group	Demographics	Clinical variables	MRI	Perfusion assessment approach	Relationship between perfusion metrics and motor assessment	
						Assessed relationship	Regions
Garaci et al., 2012	RRMS (n = 33) and SPMS (n = 6) (n = 39)	26 females (67%), age: 43.1±9.5 13 males (33%), age: 44.9±8.5	14 CCSVI-, EDSS: 2.2±1.4	DSC (3T)	ROI-based	Correlation between CBF and EDSS/ MSSS: ○ Non-significant	NAWM (semioval center, periventricular, frontal, occipital)
	HC (n = 26)	15 females (58%), age: 40.9±7.2 11 males (42%), age: 40.0±8.2	25 CCSVI+, EDSS: 3.0±2.3			Correlation between CBV and EDSS/ MSSS: ○ Non-significant	NAWM (semioval center, periventricular, frontal, occipital)
						Correlation between MTT and EDSS/ MSSS: ○ Positive, significant	NAWM (semioval center, periventricular, frontal, occipital)
Inglese et al., 2008	RRMS (n = 18)	Age: 48 (31–71) 12 females (66.7%)	EDSS: 1 (0–6.5)[b] dd: 7.6 (1–34)[c]	DSC (3T)	ROI-based	Correlation between CBF and EDSS: ○ Non-significant.	DGM (thalamus, putamen, caudate head), NAWM (frontal, periventricular, splenium)
	PPMS (n = 14)	Age: 55 (29–75) 7 females (50.0%)	EDSS: 4 (3–7)[b] dd: 5 (1–19)[c]			Correlation between CBV and EDSS: ○ Non-significant	DGM (thalamus, putamen, caudate head), NAWM (frontal, periventricular, splenium)
	HC (n = 11)	Age: 51 (29–65) 7 females (63.6%)				Correlation between MTT and EDSS: ○ Non-significant	DGM (thalamus, putamen, caudate head), NAWM (frontal, periventricular, splenium)
Inglese et al., 2007	RRMS (n = 11)	Age: 46.2 (31–71) 8 females (73%)	EDSS: 1.0 (0.0–6.5) dd: 5.0 (1–13)	DSC (3T)	ROI-based	Correlation between CBF and EDSS: ○ Negative, trend	DGM (thalamus, putamen, caudate head)
	PPMS (n = 11)	Age: 53.6 (29–71) 4 females (36%)	EDSS: 4.0 (3.0–7.0) dd: 4.0 (1–19)			Correlation between CBV and EDSS: ○ Negative, trend	DGM (thalamus, putamen, caudate head)
	HC (n = 11)	Age: 50.8 (29-65) 7 females (64%)				Correlation between MTT and EDSS: ○ Non-significant	DGM (thalamus, putamen, caudate head)
Adhja et al. 2006	RRMS (n = 11)	Age: 46.2 (31–71) 8 females (73%)	EDSS: 1.0 (0.0– 6.5) dd: 5 (1–13)	DSC (3T)	ROI-based	Correlation between CBF and EDSS: ○ Negative, significant	NAWM (periventrivular)
	PPMS (n = 11)	Age: 53.6 (29–71) 4 females (36%)	EDSS: 4.0 (3.0–7.0) dd: 4 (1–19)			Correlation between CBV and EDSS: ○ Negative, significant	NAWM (frontal, periventrivular)
	HC (n = 11)	Age: 50.8 (29–65) 7 females (64%)				Correlation between MTT and EDSS: ○ Non-significant	NAWM (frontal, periventrivular, splenium, occipital)
Rashid et al., 2004	RRMS (n = 21)	Age: 38.9 (17–59) 13 females (62%)	EDSS: 2.5 (0–6.5) dd: 10 (1–31)	CASL (1.5T)	ROI-based Voxel-wise	Correlation between CBF and EDSS: ○ Non-significant	WM, whole brain
	SPMS (n = 14)	Age: 51.2 (30–65) 11 females (79%)	EDSS: 6.0 (2–8) dd: 18 (7–40)			Correlation between CBF and MSFC: ○ Non-significant	WM, whole brain
	PPMS (n = 12)	Age: 55.7 (40–69) 7 females (58%)	EDSS: 6.5 (3.5–8.5) dd: 16 (8–34)				
	Benign MS (n = 13)	Age: 52.6 (40–60) 8 females (62%)	EDSS: 2.5 (1–3) dd: 24 (20–36)				
	HC (n = 34)	Age: 40.7 (20–67) 19 females (56%)					

Age and dd are reported in years. Values are provided as mean ± standard deviation or median (range). The percentage of females out of the total number of subjects is expressed in parenthesis after the female number. CCSVI: Chromic cerabrospinal venous insufficiency; ASL: arterial spin labeling; CBF: cerebral blood flow; BAT: Bolus Arrival Time; CBV: cerebral blood volume; dd: disease duration; CASL: Continuous Arterial Spin Labeling; DGM: deep gray matter; DCE: Dynamic Contrast-Enhanced; DSC: Dynamic Susceptibility Contrast; EDSS: Expanded Disability Status Scale; HC: healthy controls; GM: gray matter; L: left; MS: multiple sclerosis; MSFC: Multiple Sclerosis Functional Composite Measure (including leg function evaluated by the timed 25-foot walk (25FTW), nine-hole peg test (9HPT), and three-second paced auditory serial addition test (PASAT3)); MSSS: Multiple Sclerosis Severity Score; MTT: mean transit time; NAGM–normal appearing gray matter; NAWM: normal-appearing white matter; nCBF: average CBF in the whole WML divided by CBF in NAWM; nCBV: average CBV in the whole WML divided by CBF in NAWM; nMTT: average MTT in the whole WML divided by CBF in NAWM; PASAT: Paced Auditory Serial Addition Test; PPMS: primary progressive multiple sclerosis; pCASL: pseudo Continuous Arterial Spin Labeling; R: right; ROI: region of interest; RRMS: relapsing-remitting multiple sclerosis; WM: white matter; WML: white matter lesions; SPMS: secondary progressive multiple sclerosis.

Table 3 Characteristics of the studies on the relationship between MRI perfusion and MS cognitive performance.

study	Group	Demographics	Clinical variables	NPS tests	MRI	Perfusion assessment approach	Relationship between perfusion metrics and cognitive assessment	
							Assessed relationship/comparison	Regions
Ma et al., 2018	CI-RRMS (n = 20)	Age: 48.1±4.7[a] 12 females (60.0%) Edu: 14.6±1.9[a]	EDSS: 2.5 (2–3)[b] dd: 11.6±4.9[a]	MACFIMS	DSC (3T)	ROI-based	Association between DSC-derived parameters and SDMT score: ○ Positive, significant (in the whole MS group, n = 84)	WML
	CP-RRMS (n = 19)	Age: 46.4±7.2[a] 15 females (79.0%) Edu: 16.1±1.3[a]	EDSS: 1.5 (1–2)[b] dd: 11.8±5.4[a]					
	CI-SPMS (n = 25)	Age: 55.8±10.7[a] 16 females (68.0%) Edu: 14.6±3.1[a]	EDSS: 6.5 (6–6.5)[b] dd: 21.6±11.7[a]					
	CP-SPMS (n = 20)	Age: 55.2±6.5[a] 11 females (55.0%) Edu: 15.1±2.6[a]	EDSS: 6 (6–6.5)[b] dd: 16.7±6.5[a]					
	HC (n = 19)	Age: 49±7.1[a] 14 females (73.7%) Edu: 16.9±2.9[a]						
Vitorino et al., 2016	CI-RRMS (n = 20)	Age: 48.1±4.7[a] 12 females (60.0%) Edu: 14.6±1.9[a]	EDSS: 2.5 (2–3)[b] dd: 11.6±4.9[a]	MACFIMS	DSC (3T)	Voxel-wise	CBF: ○ CI-RRMS<CP-RRMS ○ CI-RRMS<HC ○ CP-RRMS<HC CBV: ○ CI-RRMS<CP-RRMS ○ CI-RRMS<HC ○ CP-RRMS<HC	 L middle frontal gyrus (BA 10, 11, 46), L superior frontal gyrus (BA 6, 10), caudate head, thalamus, R caudate body L middle frontal gyrus (BA 10, 11, 46), L superior frontal gyrus (BA 6, 10), R middle frontal gyrus L middle frontal gyrus, superior temporal lobe L middle frontal gyrus (BA 10, 11, 46), L superior frontal gyrus (BA 6, 10), R lingual gyrus, R inferior parietal lobule, L fusiform gyrus, L inferior frontal gyrus L middle frontal gyrus (BA 10, 11, 46), L superior frontal gyrus (BA 6, 10), L parahippocampal gyrus L middle frontal gyrus
	CP-RRMS (n = 19)	Age: 46.4±7.2[a] 15 females (79.0%) Edu: 16.1±1.3[a]	EDSS: 1.5 (1–2)[b] dd: 11.8±5.4[a]				MTT: NA	
	HC (n = 19)	Age: 49±7.1[a] 14 females (73.7%) Edu: 16.9±2.9[a]						
Hojjat et al., 2016c	CI-RRMS (n = 20)	Age: 48.1±4.7[a] 12 females (60.0%) Edu: 14.6±1.9[a]	EDSS: 2.58±0.67[a] dd: 11.6±4.9[a]	MACFIMS	pCASL (3T)	Voxel-wise	CBF: ○ CI-RRMS < CP-RRMS ○ CI-RRMS < HC	 L frontal lobe (BA 4, BA 6), L/R superior frontal lobe (BA 6, BA 10) L frontal lobe (BA 4, BA 6), R superior frontal lobe (BA 6, BA 10), L middle frontal lobe (BA 9, BA 10), L/R inferior frontal lobe (BA 11, BA46, BA 47), L/R limbic lobe, L/R parietal lobe, L/R temporal lobe, R putamen, L thalamus/pulvinar
	CP-RRMS (n = 19)	Age: 46.4±7.2[a] 15 females (79.0%) Edu: 16.1±1.3[a]	EDSS: 1.79±0.71[a] dd: 11.8±5.4[a]				○ No CP-RRMS-vs-HC differences	Whole brain
	HC (n = 19)	Age: 49±7.1[a] 14 females (73.7%) Edu: 16.9±2.9[a]						

Table 3 Continued

Study	Group	Demographics	Clinical variables	NPS tests	MRI	Perfusion assessment approach	Relationship between perfusion metrics and cognitive assessment	
							Assessed relationship/comparison	Regions
Hojjat et al., 2016a	CI-RRMS (n = 20)	Age: 48.1±4.7[a] 12 females (60.0%) Edu: 14.6±1.9[a]	EDSS: 2.5 (2–3)[b] dd: 11.6±4.9[a]	MACFIMS	DSC (3T)	ROI-based	CBF: ○ CI-RRMS < CP-RRMS ○ CI-RRMS < HC ○ CP-RRMS < HC	 NAGM, NAWM, WML NAGM, NAWM NAGM
	CP-RRMS (n = 19)	Age: 46.4±7.2[a] 15 females (79.0%) Edu: 16.1±1.3[a]	EDSS: 1.5 (1–2)[b] dd: 11.8±5.4[a]				CBV: ○ CI-RRMS < CP-RRMS ○ CI-RRMS < HC	 NAGM, NAWM, WML NAGM, NAWM
	HC (n = 19)	Age: 49±7.1 a 14 females (73.7%) Edu: 16.9±2.9 a					MTT: ○ CI-RRMS > CP-RRMS ○ CI-RRMS > HC	 NAGM NAGM, NAWM
Hojjat et al., 2016b	CI-RRMS (n = 20)	Age: 48.1±4.7[a] 12 females (60.0%) Edu: 14.6±1.9[a]	EDSS: 2.5 (2–3)[b] dd: 11.6±4.9[a]	MACFIMS	DSC (3T)	ROI-based	CBF: ○ CI-RRMS < HC ○ CI-RRMS < CP-RRMS	 Cortical GM, WM Cortical GM, WM
	CP-RRMS (n = 19)	Age: 46.4±7.2[a] 15 females (79.0%) Edu: 16.1±1.3[a]	EDSS: 1.5 (1–2)[b] dd: 11.8±5.4[a]				CBV: ○ CI-RRMS < HC ○ CI-RRMS < CP-RRMS	 Cortical GM, WM Cortical GM, WM
	HC (n = 19)	Age: 49±7.1[a] 14 females (73.7%) Edu: 16.9±2.9[a]					MTT: ○ CI-RRMS > HC ○ CI-RRMS > CP-RRMS ○ CP-RRMS > HC	 Cortical GM,WM Cortical GM, WM Cortical GM, WM
							Association between CBF and overall cognitive impairment: ○ Inverse, significant	 All brain lobes
							Association between CBV and overall cognitive impairment: ○ Inverse, significant	 All brain lobes
							Association between MTT and overall cognitive impairment: ○ Inverse, significant	 All brain lobes
Debernard et al., 2014	RRMS (n = 25)	Age: 37.2±8.6[a] 22 females (88.0%) Edu: 13.5±2.7[a]	EDSS: 1.5 (0–4.5)[c] dd: 2.4±1.5[a]	MoCA Letter fluency	pCASL (3T)	Voxel-wise	Association between CBF and memory: ○ Positive, significant	 Precentral gyrus, postcentral gyrus, cingulate gyrus, lingual gyrus, frontal gyrus, intracalcarine cortex, supracalcarine cortex, parietal areas, occipital areas, L/R accumbens, L/R putamen, L/R caudate, R thalamus
	HC (n = 25)	Age: 35.2±10.3[a] 17 females (68.0%) Edu: 13.8±2.1[a]		Category fluency BVMT CVLT SCWT SDMT PASAT BJLO RCFT			Association between CBF andPASAT, SDMT, MSFC, MoCA, executive function, attention, working memory, visuospatial function: ○ Non-significant	 Whole GM

Table 3 Continued

Study	Group	Demographics	Clinical variables	NPS tests	MRI	Perfusion assessment approach	Relationship between perfusion metrics and cognitive assessment	
							Assessed relationship/comparison	Regions
Francis et al., 2013	CI-SPMS (n = 25)	Age: 55 (47.5–61.5)[b] 16 females (64.0%) Edu: 14 (13–17)[b]	EDSS: 6.5 (6–6.5)[b] dd: 19 (12–28.5)[b]	MACFIMS	DSC (3T)	Voxel-wise	CBF: ○ CI-SPMS<CP-SPMS CBV: ○ CI-SPMS<CP-SPMS	L/R thalamus (pulvinar), L/R caudate body, R caudate tail, L/R medial frontal gyrus (BA 9), R cingulate gyrus (BA 31) L/R thalamus (pulvinar), L/R caudate body, L caudate tail, L/R superior frontal gyrus (BA 6, BA9), corpus callosum
	CP-SPMS (n = 20)	Age: 54.5 (49.3–62.3)[b] 11 females (55.0%) Edu: 15.5 (13–17.8)[b]	EDSS: 6 (6–6.5)[b] dd: 18.5 (10.5–20.8)[b]				MTT: NA Association between CBF and all the neuropsychological test scores, except for CVLT ○ Significant (SDMT showed the strongest association) Association between CBV and all the neuropsychological test scores, except for CVLT ○ Significant (SDMT showed the strongest association)	 Areas of reduced perfusion Areas of reduced perfusion
Papadaki et al., 2014	CIS (n = 40)	Age: 33.9±10[a] NA females Edu: 13.4±2.7[a]	EDSS: 1.2±0.65[a] dd: 2.3±2.7[a]	WASI WMS-MD WMS-LM MTCF	DSC (1.5T)	ROI-based	Correlation between CBV and WMS-MD (digit reverse): ○ Negative, significant	 L/R thalamus, L frontal NAWM, L/R periventricular NAWM, splenium
	HC (n = 30)	NA					Correlation between CBV and immediate free recall scores of WMS-LM: ○ Negative, significant	 R thalamus, L/R caudate, L frontal NAWM, L/R periventricular NAWM, splenium
D'haeseleer et al., 2013	MS (n = 18)	Age: 50.2±5.7[a] 9 females (50.0%) Edu: NA	EDSS: 3.3 (1.5–6)[b] dd: 18±9[a]	PASAT	pCASL (3T)	ROI-based	Association between CBF and PASAT: ○ Positive, significant ○ Non-significant	 L centrum semiovale (in MS group) R centrum semiovale (NAWM) , L/R frontoparietal cortex, L/R cerebellar hemisphere
	HC (n = 10)	Age: 50.2±5.5[a] 5 females (50.0) Edu: NA						

Table 3 Continued

Study	Group	Demographics	Clinical variables	NPS tests	MRI	Perfusion assessment approach	Relationship between perfusion metrics and cognitive assessment	
							Assessed relationship/comparison	Regions
Aviv et al., 2012	CI-SPMS (n = 18)	Age: 58±10[a] 12 females (66.6%) Edu: 15.5 (13-17.5)[b]	EDSS: 6.5 (6.13–6.5)[b] dd: 23±12[a]	MACFIMS	DSC (3T)	ROI-based	CBF: ○ CI-SPMS < CP-SPMS	GM, WM
							CBV: ○ CI-SPMS < CP-SPMS	GM, WM
	CP-SPMS (n = 17)	Age: 55±6[a] 11 females (64.7) Edu: 16 (13-17.5)[b]	EDSS: 6 (6–6.5)[b] dd: 17±6[a]				MTT: ○ No CI-SPMS-vs-CP-SPMS differences	GM, WM
							Association between CBF and overall cognitive impairment: ○ Non-significant	Any lobes and sub-ROIs
							Association between CBV and overall cognitive impairment: ○ Inverse, significant	All L/R lobes, L inferior frontal ROI, L middle frontal ROI, L/R medial superior frontal, L superior frontal ROI
Inglese et al., 2008	RRMS [n = 18]	Age: 48 (31–71)[d] 12 females (66.7%) Edu: 18 (16–21)[d]	EDSS: 1 (0–6.5)[c] dd: 7.6 (1–34)[d]	RCFT D-KEFSVF CVLT-II DB WAIS-III SDMT	DSC (3T)	ROI-based	Correlation between CBF and RCFT-Copy: ○ Positive, significant (in PPMS) ○Positive, significant (in all MS)	DGM DGM
	PPMS [n = 14]	Age: 55 (29–75)[d] 7 females (50.0%) Edu: 17 (12–21)[d]	EDSS: 4 (3–7)[c] dd: 5 (1–19)[d]	PASAT-3secs D-KEFSI D-KEFSIS			Correlation between CBV and D-KEFSI: ○ Positive, significant (in all MS)	DGM
	HC [n = 11]	Age: 51 (29–65)[d] 7 females (63.6%) Edu: NA						

BA: Brodmann area; BJLO: Benton Judgment of line orientation test; BVMT-R: Brief Visuo-Spatial Memory Test-Revised; CBF: cerebral blood flow; CBV: cerebral blood volume; CI: cognitively impaired; CL: cortical lesions; COWAT: Controlled Oral Word Association Test; CP: cognitively preserved; CVLT-II: California Verbal Learning Test-II; DGM: deep gray matter; D-KEFS: Delis-Kaplan Executive Function System Sorting Test; D-KEFSI: D-KEFS Color Word Interference Test inhibition; D-KEFSIS: D-KEFS Color Word Interference Test inhibition Switching; D-KEFSVF: D-KEFS Verbal fluency; DB: Digit Backward portion of Digit Span subset of Wechsler Adult Intelligence Scale; dd: disease duration; DMN: Default Mode Network; DSC: Dynamic Susceptibility Contrast; EDSS: Expanded Disability Status Scale; ECN: Executive Control Network; Edu: education level; HC: healthy controls; GM: gray matter; L: left; MoCA: Montreal Cognitive Assessment; MS: multiple sclerosis; MTCF: Modified Taylor Complex Figure; MTT: mean transit time; NAGM: normal appearing gray matter; NA: not available; NAWM: normal appearing white matter; NPS: neuropsychological; PASAT: Paced Auditory Serial Addition Test; PPMS: primary progressive multiple sclerosis; pCASL: pseudo Continuous Arterial Spin Labeling; R: right; RCFT: Rey Complex Figure copy; ROI: region of interest; RRMS: relapsing remitting multiple sclerosis; SCWT: Stroop Color and Word Test; SDMT: Symbol Digit Modalities Test; WM: white matter; WML: white matter lesions; SN: Salience Network; SPMS- secondary progressive multiple sclerosis; WASI: Wechsler Abbreviated Scale of Intelligence; WMS-LM: Wechsler Memory Scale Logical memory subscale; WMS-MD: Memory for digit subset of Wechsler Memory Scale. [a]Mean±SD; [b]median (IQR); [c]median (range); [d]mean (range). Age, dd, edu are expressed in years. MACFISM includes PASAT, SDMT, CVLT-II, BVMT-R, D-KEFS, BJLO, COWAT. Subjects tested with MACFISM were classified as CI according to (Benedict J NeurolSci 2006).