Published in final edited form as:

Mult Scler. 2016 October ; 22(11): 1421–1428. doi:10.1177/1352458515622696.

Regional reduction in cortical blood flow among cognitively impaired adults with relapsing-remitting multiple sclerosis patients

Seyed-Parsa Hojjat, PhD, Charles Grady Cantrell, MSc, Rita Vitorino, BSc, Anthony Feinstein, MBChB, PhD, Zahra Shirzadi, MEd, Bradley J. MacIntosh, PhD, David E. Crane, MSc, Lying Zhang, PhD, Sarah A Morrow, MD, Liesly Lee, MD, Paul O'Connor, MD, Timothy J. Carroll, PhD, and Richard I. Aviv, MBChB

Sunnybrook Health Sciences Centre, Department of Psychiatry (AF), Neurology (LL), and Medical Imaging (SPH, RV, ZS, BJM, DC, RIA), 2075 Bayview Ave., Toronto, ON, M4N 3M5

University of Toronto (ZS, BJM, POC, LL, AF, RIA), 27 King's College Circle, Toronto, Ontario, M5S 1A1

Northwestern University, Chicago, IL, United States

Department of Clinical Neurological Sciences (SAM), 339 Windermere Rd, Western University, London, Ontario N6A 5A5

Abstract

Purpose—Detection of cortical abnormalities in relapsing-remitting multiple sclerosis (RRMS) remains elusive. Structural MRI measures of cortical integrity are limited, although functional techniques such as pseudocontinuous Arterial Spin Labeling (pCASL) show promise as a surrogate marker of disease severity. We sought to determine the utility of pCASL to assess cortical cerebral blood flow (CBF) in RRMS patients with (RRMS-I) and without (RRMS-NI) cognitive impairment.

Methods—19 age-matched healthy controls and 39 RRMS patients were prospectively recruited. Cognition was assessed using the MACFIMS battery. Cortical CBF was compared between groups using a mass univariate voxel-based morphometric analysis accounting for demographic and structural variable covariates.

Results—Cognitive impairment was present in 51.3% of patients. Significant CBF reduction was present in the RRMS-I compared to other groups in left frontal and right superior frontal cortex. Compared to healthy controls, RRMS-I displayed reduced CBF in the frontal, limbic, parietal and temporal cortex and putamen/thalamus. RRMS-I demonstrated reduced left superior frontal lobe cortical CBF compared to RRMS-NI. No significant cortical CBF differences were present between healthy controls and RRMS-NI.

Corresponding author: Seyed-Parsa Hojjat, Sunnybrook Health Sciences Centre, 2075 Bayview Ave., Room AB-204, Toronto, ON, M4N 3M5, Phone: 416-480-6100 x89617, Fax: 416-480-5218, parsa.hojjat@sunnybrook.ca.

Conflict of interest

The authors declare no conflict of interest.

Conclusion—Significant cortical CBF reduction occurs in RRMS-I compared to healthy controls and RRMS-NI in anatomically significant regions after controlling for structural and demographic differences.

Keywords

multiple sclerosis; cognitive disorders; magnetic resonance imaging; pCASL imaging; neurodegenerative disease

Introduction

Multiple Sclerosis (MS) is the most frequent cause of non-traumatic neurological disability in young and middle age adults and the most common inflammatory demyelinating disease of the central nervous system. 40–65% of MS patients experience cognitive dysfunction¹.

While MS is traditionally viewed as a predominantly white matter (WM) disease, only modest associations between T2-weighted hyperintense white matter lesions, T1 holes and cognitive test performance have been reported². An interdependent relationship is reported between normal appearing white matter (NAWM) axonal and grey matter (GM) damage in primary progressive MS patients³, yet a more recent study demonstrated cortical abnormality in the absence of white matter disease⁴. Cortical involvement is reported in 59–93% of MS cases significantly contributing to the progression of both physical and cognitive disability^{5, 6}. Cortical volume loss also demonstrates a stronger association for cognitive dysfunction than whole brain atrophy⁷.

Arterial spin labelling (ASL) is a non-invasive quantitative perfusion imaging technique utilizing inflowing cerebral blood as an endogenous tracer measuring cerebral blood flow (CBF)⁸. Pseudo-continuous ASL (pCASL) combines the advantages of both pulsed and continuous ASL yielding higher signal-to-noise ratio, higher tagging efficiency and reduced transit time sensitivity when compared to pulsed ASL⁹. pCASL is a robust clinical method to measure in vivo perfusion changes, used to detect perfusion abnormalities in patients with neurodegenerative disorders and MS¹⁰.

Recently, Debernard et al. showed differences in cortical CBF between healthy controls and early RRMS in the absence of cortical volume differences¹⁰. No significant cortical CBF differences were present between healthy controls and early RRMS for several cognitive tests although a trend to impairment in the visual memory domain (Brief Visual Memory Test) was present in the early RRMS group. A strong positive association was seen between cortical CBF and visual memory. Similarly, Aviv et al demonstrated significant cortical cerebral blood volume differences between cognitively unimpaired and impaired SPMS patients after controlling for confounding factors of atrophy and white matter disease¹¹. Cortical perfusion differences in both studies suggest a potential utility of CBF and CBV as surrogate markers of cortical disease activity and cognition. We sought to validate and extend upon these two prior studies and hypothesized that significant pCASL-derived cortical CBF differences exist between RRMS patients with and without cognitive impairment and healthy controls after controlling for clinical and structural confounders¹⁰.

Methods

Patients

Approval for this study was obtained from research ethics boards of Sunnybrook and St. Michael's hospitals. Thirty nine RRMS patients were prospectively recruited during a 1-year period from two tertiary referral MS clinics. Initially 20 patients demonstrating impairment with a MoCA screen were selected followed by 19 age- and gender-matched unimpaired RRMS patients. RRMS diagnosis was determined using the 2010 revised McDonald¹² criteria by a senior neurologist with specialist practice in MS (20 years' experience). Exclusion criteria were: history of drug/alcohol abuse, use of steroids within the past 3 months, premorbid (*i.e.* pre-MS) psychiatric history, head injury with loss of consciousness, concurrent medical diseases (*e.g.* cerebrovascular disease), and contraindication to magnetic resonance imaging (MRI). Clinical data included: age, gender, education level, and disease duration. MRI acquisition, neurocognitive examination, and EDSS assessment¹³ were completed on the same day. Nineteen age-matched healthy participants were also recruited as controls for the study.

Cognitive testing

The Minimal Assessment of Cognitive Function In Multiple Sclerosis (MACFIMS) was administered under the supervision of a senior neuropsychiatrist¹⁴. This standard MS cognitive battery is a comprehensive assessment tool consisting of seven neuropsychological tests as follows: Paced Auditory Serial Addition Test (PASAT) to assess working memory, Symbol Digit Modalities Test (SDMT) to assess processing speed, California Verbal Learning Test (CVLT) – 2nd Edition to assess verbal memory, revised Brief Visuospatial Memory Test (BVMT) to assess visuospatial memory, Delis-Kaplan Executive Function System (D-KEFS) to assess executive function, Controlled Word Association Test (COWAT) to assess verbal fluency, and Judgement of Line Orientation (JLO) to assess visuospatial perception. Raw test scores were converted to Z scores and impairment on an individual test was defined as scoring more than 1.5 standard deviations below normative data¹⁵. Z- scores are derived from population-representative or normalized data that corrects for educational level for three key neurocognitive constituents of the MACFIMS battery, namely PASAT, SDMT and COWAT. Patients with 2 or more test impairments were designated as having cognitive impairment¹⁵. Hospital Anxiety and Depression scores (HADS-A and HADS-D) were also obtained due to the association between depression/ anxiety and cognitive impairment in MS patients^{16, 17}.

MRI acquisition

MRI scanning was performed on a Philips 3T scanner (Philips Healthcare, Andover, MA, USA) with a 8-channel phased array coil. The following sequences were acquired: T1 3D (TR/TE: 9.5ms/2.3ms, resolution: 0.63×0.63×1.2mm³); PD/T2 (TR/TE: 2500ms/10.7ms, resolution: 0.63×0.63×1.2mm³); Phase-sensitive inversion recovery (PSIR) (TR/TE: 3374ms/15ms; FOV: 23cm; matrix: 400×255; resolution: 0.43×0.43×3mm³); pCASL acquisition for CBF signal [TR/TE: 4000/9.7ms, 64×64×18 matrix, resolution: 3×3×5mm³, label offset: 80mm, post label delay (PLD): 1600ms, label duration: 1650ms and scan duration of 248s (30 Tag control pair)]; reference ASL acquisition for absolute

quantification of CBF (TR/TE: 10000/9.7ms, 64×64×18 matrix, resolution: 3×3×5mm³ and scan duration of 40s).

Image processing

We used an image processing pipeline developed by Shirzadi et al to derive CBF maps. Briefly, GM voxels were automatically segmented on the T1-weighted image (FMRIB's Automated Segmentation Tool (FAST))^{18, 19}. T1-weighted images with the overlaid tissue masks were then coregistered to the ASL coordinate space. GM detectability metric was iteratively calculated using an aligning/sorting/discarding/refining pipeline¹⁸. The point of maximum GM detectability was then identified and only intermediate perfusion images contributing to this peak level were used in the calculation of the optimized CBF estimate¹⁸.

The reference pCASL scans were transformed to MNI 152 space (Montreal Neurological Institute, McGill University) using the normalize function in SPM 8 (SPM 8, Wellcome Department of Imaging Neuroscience, London, UK). The scans in MNI 152 space were then averaged to form a study specific MNI template. Individual CBF maps were coregistered to the study specific MNI template using a linear registration (FSL-FLIRT) followed by non-linear intensity modulation and multi-resolution non-linear registration (FSL-FNIRT) with 4 subsampling levels. The CBF maps were smoothed at each respective resolution level using full width half max Gaussian kernels of 6, 4, 2, 2 mm. The perfusion measures at each voxel were then statistically analyzed using the analyses described below.

Statistical analysis

Clinical and demographic measures—To compare each demographic, clinical, and volume data among 3 groups, univariate general linear regression was performed on all continuous outcomes such as age, educational years, and all brain volume data. For categorical variables such as gender, logistic regression was conducted. Statistical Analysis Software (SAS version 9.4 for windows) was used for analysis.

Voxel-based analysis—Mass univariate methodology of SPM8 was used to perform a voxel-by-voxel two-sample t-test between the study groups to assess the regional GM CBF differences measured in mL/100g/min (i.e. the test comparisons include (1) healthy controls vs. RRMS-I, (2) healthy controls vs. RRMS-NI and (3) RRMS-NI vs RRMS-I)²⁰. Significance was defined as a voxel-wise p-value threshold (Bonferroni adjusted $p < 0.01$) and an extent threshold of 20 contiguous voxels. The clinical and demographics measures that were significantly different ($p < 0.05$) between the test groups were considered as confounders to be added in the respective mass univariate analysis. Xjview software 8.12 (<http://www.alivelearn.net/xjview>) was used to extract the brain regions where focal differences were found. Similar voxel-wise analyses were performed to assess voxel-wise structural differences between study groups based on T1 structural images segmented using both unified space segmentation and DARTEL functions in SPM8. This was achieved by registering each participant's native space segmentation to a group-specific template created using the DARTEL space segmentations. The registered segmentations were then affine transformed into MNI space and smoothed with an 8 mm full width half maximum (FWHM) isotropic Gaussian kernel.

Results

Clinical and demographic characteristics

Of 39 RRMS prospectively recruited patients, 20 (51.3%) were cognitively impaired. Compared to healthy controls RRMS-NI ($p=0.0117$) and RRMS-I ($p=0.0004$) demonstrated higher HADS-A scores. A higher HADS-D scores was present in RRMS-I patients ($p<0.0001$) compared to both RRMS-NI and healthy controls. RRMS-I patients demonstrated reduced years of education ($p=0.0038$), lower normalized global brain parenchymal fraction (BPF) ($p=0.0149$), lower global WM volume ($p=0.0079$) and increased global cerebrospinal fluid (CSF) volume ($p=0.0065$) compared to healthy controls. No significant difference in normalized global cortical volume was found in either of the RRMS subgroups compared to healthy controls (Table 1).

Voxel-based analysis

Voxel based analysis demonstrated reduced cortical CBF in RRMS-I group compared to RRMS-NI and healthy controls in the left frontal (pre- and postcentral gyrus: Brodmann area (BA) 6 including supplementary motor area and BA4 respectively) and right superior frontal lobes (BA 10 and BA 6 including supplementary motor area). Compared to healthy controls, RRMS-I also displayed reduced GM CBF in the left middle frontal (BA 9 and 10), bilateral inferior frontal (BA 11, 46 and 47), bilateral limbic (cingulate gyrus, BA 32), bilateral parietal (postcentral gyrus, supramarginal gyrus, BA 2, 3 and 40), bilateral temporal (right middle temporal gyrus, BA 20 and 21) lobes, right putamen and left thalamus/pulvinar (Table 2). Compared with RRMS-NI, RRMS-I demonstrated reduced cortical grey matter CBF in the left superior frontal (supplementary motor area, BA 6) lobe (Table 3, Figure1). No cortical grey matter CBF differences were observed between healthy controls and RRMS-NI. No regional voxel-wise structural differences were present between RRMS subgroups to account for perfusion abnormality.

Discussion

After controlling for structural and/or demographic group confounders, we observed significant cortical CBF reductions in the left frontal and right superior frontal lobes in cognitively impaired RRMS patients compared to unimpaired RRMS patients and healthy controls. RRMS-I also demonstrated significantly reduced CBF in bilateral inferior and middle frontal and medial frontal, bilateral parietal, bilateral limbic, left temporal and right middle temporal cortices, basal ganglia and thalamus in comparison to healthy controls. Reduced left superior frontal gyrus cortical CBF was present compared to RRMS-NI.

Reduced CBF in the temporal, frontal and postcentral gyri as well as deep GM (left thalamus, and right putamen) were similarly reported by Debernard et al¹⁰. In contrast, we did not find any CBF differences in the lingual gyrus, intracalcarine, insular and operculum cortex, temporal fusiform cortex, superior parietal lobule, precuneus cortex, frontal orbital cortex, right thalamus, left hippocampus or right caudate. Further, no cortical CBF differences were observed in our study between healthy controls and RRMS-NI. These discrepancies could be explained by important differences in the patient populations in each

study. Unlike Debernard who reported borderline significant BVMT reduction in their 'early' RRMS-NI cohort compared to healthy controls, we observed no significant difference in cognitive test scores between RRMS-NI and healthy control groups. This suggests a higher disease burden in their unimpaired RRMS patients; an assumption supported by a higher EDSS upper range of 4.5 compared to 3.5 in our study despite similar median EDSS values of 1.5.

Significant CBF reduction in Brodmann 6 was seen in RRMS-I patients compared to both healthy controls and RRMS-NI. This region is functionally important for numerical and verbal mental-operation tasks²¹, as well as encoding and recognition within the context of working memory and long-term memory tasks²². Abnormalities in these regions are consistent with the finding of significant impairments related to working (PASAT and SDMT) and long-term memory (BVMT and CVLT) observed in the RRMS-I group compared to both RRMS-NI and healthy controls (Table 1).

The parietal lobe (especially superior parietal lobe) plays an important role in spatial cognition and constitutes a part of the dorsal visual processing system which is responsible for encoding of the spatial location of stimuli²³. Sack et al utilized fMRI to demonstrated bilateral parietal activity during the execution of spatial cognition tasks and observed significant spatial cognition deficits after inducing right parietal neural activity disruptions with transcranial magnetic stimulation²³. In another fMRI study, participants performed auditory and visual tasks alone and simultaneously with working memory tasks. Analysis revealed that while the majority of activation identified during individual tasks was also activated in the dual task condition, several neural substrates such as left middle frontal gyrus, left superior parietal lobule, posterior region of right inferior temporal gyrus and bilateral parahippocampal gyri were selectively activated during the dual tasks²⁴. The authors concluded that new neural networks are activated to assist with the greater load placed on working memory²⁴. The distribution of activations associated with working memory correspond with the CBF reductions we demonstrated in RRMS-I patients of the present cohort.

Grey matter CBF reduction in MS could be explained through primary and secondary pathogenic mechanisms, which cumulatively cause GM demyelination and axonal degeneration²⁵. Magliozzi et al showed a spatial relation between ectopic meningeal B-cell follicles and a superficial to deep gradient of cortical pathology suggesting that cortical subpial demyelination results from primary meningeal, rather than cortical lesion inflammation possibly mediated through a soluble cytotoxic/myelinotoxic factor²⁶. Secondary grey matter neuroaxonal degeneration occurs in association with amyloid precursor protein positive active white matter lesions, with abnormal sodium channel distribution resulting in higher ATP production causing "virtual hypoxia"^{27, 28}. Other secondary mechanisms of GM demyelination include variable firing patterns in different repertoires of sodium channels, glutamate imbalance leading to excitotoxicity and axonal damage and selective response to acetylcholinesterase inhibitor invastigmine²⁹⁻³¹. We, and others have previously demonstrated the presence of perfusion differences in the absence of structural abnormality in RRMS patients without and with cognitive impairment and in healthy controls compared to early RRMS respectively^{10, 32}. Cortical perfusion reduction

was also independent of white matter volume suggesting a primary vascular or mitochondrial disturbance as the most likely etiology.

A limitation of pCASL is its intrinsically low signal to noise ratio (SNR) and unexpected variations of control and tag images resulting from head motion, physiological noise and hardware instabilities³³. To circumvent these issues we utilized a pipeline to discard ASL pairs that do not pass “detectability criteria”. This approach is shown to improve detection of CBF in GM¹⁸. The effect of disease modifying drugs on perfusion is unknown and therefore we initially tested for differences of drug class usage between the RRMS subgroups. In the absence of differences a confounding effect was considered unlikely and this variable was not included in our VBM analysis. Depression is shown to have an effect on cognition and cerebral perfusion although is seldom considered a confounding covariate in the literature. Hypoperfusion was observed in right inferior prefrontal cortex and anterior cingulate cortices in middle-age adults with major depressive disorder and in frontal, limbic, paralimbic, and cingulate in adolescent population suffering from depression^{16, 34, 35}. Given the demonstrated differences between groups for HADS performance we accounted for its effect on perfusion and cognition by including the HADS-D scores as covariates in the voxel based analysis. Finally, despite a small group sample size, we showed significant group differences, however these results should be validated in larger series.

In conclusion, significant grey matter CBF reduction in anatomically significant regions associated with cognition after controlling for structural and demographic differences suggests that pCASL-derived CBF may provide surrogate measures of RRMS disease severity; however this requires validation in larger studies.

Acknowledgments

Sources of support

This study was supported by Canadian institute of Health Research operating grant #130366, National Institute of Healthy (NIH) /EB017928, American Heart Association grants 20380798 and 14PRE20380810 as well as a Biogen fellowship funding award.

Abbreviation key

MS	Multiple Sclerosis
RRMS	Relapsing Remitting Multiple Sclerosis
ASL	Arterial spin labelling
pCASL	Pseudo-continuous ASL
MACFIMS	Minimal Assessment of Cognitive Function In Multiple Sclerosis
CBF	cerebral blood flow
EDSS	Expanded Disability Status Scale
FSL	FMRIB Software Library

MNI Montreal Neurological Institute

References

1. Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. *Lancet Neurol.* 2008; 7:1139–1151. [PubMed: 19007738]
2. Filippi M, Rocca MA, Benedict RH, DeLuca J, Geurts JJ, Rombouts SA, et al. The contribution of mri in assessing cognitive impairment in multiple sclerosis. *Neurology.* 2010; 75:2121–2128. [PubMed: 21135387]
3. Bodini B, Khaleeli Z, Cercignani M, Miller DH, Thompson AJ, Ciccarelli O. Exploring the relationship between white matter and gray matter damage in early primary progressive multiple sclerosis: An in vivo study with tbss and vbm. *Hum Brain Mapp.* 2009; 30:2852–2861. [PubMed: 19172648]
4. Calabrese M, Poretto V, Favaretto A, Alessio S, Bernardi V, Romualdi C, et al. Cortical lesion load associates with progression of disability in multiple sclerosis. *Brain.* 2012; 135:2952–2961. [PubMed: 23065788]
5. Calabrese M, De Stefano N, Atzori M, Bernardi V, Mattisi I, Barachino L, et al. Detection of cortical inflammatory lesions by double inversion recovery magnetic resonance imaging in patients with multiple sclerosis. *Arch Neurol.* 2007; 64:1416–1422. [PubMed: 17923625]
6. Calabrese M, Rocca MA, Atzori M, Mattisi I, Favaretto A, Perini P, et al. A 3-year magnetic resonance imaging study of cortical lesions in relapse-onset multiple sclerosis. *Annals of neurology.* 2010; 67:376–383. [PubMed: 20373349]
7. Amato MP, Portaccio E, Goretti B, Zipoli V, Battaglini M, Bartolozzi ML, et al. Association of neocortical volume changes with cognitive deterioration in relapsing-remitting multiple sclerosis. *Arch Neurol.* 2007; 64:1157–1161. [PubMed: 17698706]
8. Detre JA, Leigh JS, Williams DS, Koretsky AP. Perfusion imaging. *Magn Reson Med.* 1992; 23:37–45. [PubMed: 1734182]
9. Tan, H.; Burdette, JH. *Functional neuroradiology.* Springer; 2012. Non-gadolinium perfusion technique (arterial spin labeling); p. 61-69.
10. Debernard L, Melzer TR, Van Stockum S, Graham C, Wheeler-Kingshott CA, Dalrymple-Alford JC, et al. Reduced grey matter perfusion without volume loss in early relapsing-remitting multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 2014; 85:544–551. [PubMed: 24039024]
11. Francis PL, Jakubovic R, O'Connor P, Zhang L, Eilaghi A, Lee L, et al. Robust perfusion deficits in cognitively impaired patients with secondary-progressive multiple sclerosis. *AJNR Am J Neuroradiol.* 2013; 34:62–67. [PubMed: 22700746]
12. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the mcdonald criteria. *Annals of neurology.* 2011; 69:292–302. [PubMed: 21387374]
13. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (edss). *Neurology.* 1983; 33:1444–1452. [PubMed: 6685237]
14. Benedict RH, Fischer JS, Archibald CJ, Arnett PA, Beatty WW, Bobholz J, et al. Minimal neuropsychological assessment of ms patients: A consensus approach. *Clin Neuropsychol.* 2002; 16:381–397. [PubMed: 12607150]
15. Benedict RH, Bruce JM, Dwyer MG, Abdelrahman N, Hussein S, Weinstock-Guttman B, et al. Neocortical atrophy, third ventricular width, and cognitive dysfunction in multiple sclerosis. *Arch Neurol.* 2006; 63:1301–1306. [PubMed: 16966509]
16. Benedict RH, Weinstock-Guttman B, Fishman I, Sharma J, Tjoa CW, Bakshi R. Prediction of neuropsychological impairment in multiple sclerosis: Comparison of conventional magnetic resonance imaging measures of atrophy and lesion burden. *Arch Neurol.* 2004; 61:226–230. [PubMed: 14967771]
17. Goretti B, Viterbo RG, Portaccio E, Niccolai C, Hakiki B, Piscolla E, et al. Anxiety state affects information processing speed in patients with multiple sclerosis. *Neurol Sci.* 2014; 35:559–563. [PubMed: 24072658]

18. Shirzadi Z, Crane DE, Robertson AD, Maralani PJ, Aviv RI, Chappell MA, et al. Automated removal of spurious intermediate cerebral blood flow volumes improves image quality among older patients: A clinical arterial spin labeling investigation. *J Magn Reson Imaging*. 2015
19. Zhang Y, Brady M, Smith S. Segmentation of brain mr images through a hidden markov random field model and the expectation-maximization algorithm. *IEEE Trans Med Imaging*. 2001; 20:45–57. [PubMed: 11293691]
20. Friston KJ, Holmes AP, Worsley KJ, Poline J, Frith CD, Frackowiak RS. Statistical parametric maps in functional imaging: A general linear approach. *Human brain mapping*. 1994; 2:189–210.
21. Hanakawa T, Honda M, Sawamoto N, Okada T, Yonekura Y, Fukuyama H, et al. The role of rostral brodmann area 6 in mental-operation tasks: An integrative neuroimaging approach. *Cereb Cortex*. 2002; 12:1157–1170. [PubMed: 12379604]
22. Ranganath C, Johnson MK, D'Esposito M. Prefrontal activity associated with working memory and episodic long-term memory. *Neuropsychologia*. 2003; 41:378–389. [PubMed: 12457762]
23. Sack AT. Parietal cortex and spatial cognition. *Behav Brain Res*. 2009; 202:153–161. [PubMed: 19463696]
24. Yoo SS, Paralkar G, Panych LP. Neural substrates associated with the concurrent performance of dual working memory tasks. *Int J Neurosci*. 2004; 114:613–631. [PubMed: 15204056]
25. Geurts JJ, Barkhof F. Grey matter pathology in multiple sclerosis. *Lancet Neurol*. 2008; 7:841–851. [PubMed: 18703006]
26. Magliozzi R, Howell O, Vora A, Serafini B, Nicholas R, Puopolo M, et al. Meningeal b-cell follicles in secondary progressive multiple sclerosis associate with early onset of disease and severe cortical pathology. *Brain*. 2007; 130:1089–1104. [PubMed: 17438020]
27. Craner MJ, Newcombe J, Black JA, Hartle C, Cuzner ML, Waxman SG. Molecular changes in neurons in multiple sclerosis: Altered axonal expression of nav1.2 and nav1.6 sodium channels and na⁺/ca²⁺ exchanger. *Proc Natl Acad Sci U S A*. 2004; 101:8168–8173. [PubMed: 15148385]
28. Stys PK. Axonal degeneration in multiple sclerosis: Is it time for neuroprotective strategies? *Annals of neurology*. 2004; 55:601–603. [PubMed: 15122698]
29. Waxman SG. The neuron as a dynamic electrogenic machine: Modulation of sodium-channel expression as a basis for functional plasticity in neurons. *Philos Trans R Soc Lond B Biol Sci*. 2000; 355:199–213. [PubMed: 10724456]
30. Geurts JJ, Wolswijk G, Bo L, van der Valk P, Polman CH, Troost D, et al. Altered expression patterns of group i and ii metabotropic glutamate receptors in multiple sclerosis. *Brain*. 2003; 126:1755–1766. [PubMed: 12805104]
31. Parry AM, Scott RB, Palace J, Smith S, Matthews PM. Potentially adaptive functional changes in cognitive processing for patients with multiple sclerosis and their acute modulation by rivastigmine. *Brain*. 2003; 126:2750–2760. [PubMed: 12958082]
32. Hojjat SP, Cantrell CG, Carroll TJ, Vitorino RC, Feinstein A, Zhang L, Symons SP, Morrow S, Lee L, O'Connor P, Aviv RI. Bookend perfusion reduction in the absence of structural differences in cognitively impaired versus unimpaired RRMS patients. *Multiple Sclerosis Journal*. 2015 (submitted).
33. Ferre JC, Bannier E, Raoult H, Mineur G, Carsin-Nicol B, Gauvrit JY. Arterial spin labeling (asl) perfusion: Techniques and clinical use. *Diagn Interv Imaging*. 2013; 94:1211–1223. [PubMed: 23850321]
34. Ota M, Noda T, Sato N, Hattori K, Teraishi T, Hori H, et al. Characteristic distributions of regional cerebral blood flow changes in major depressive disorder patients: A pseudo-continuous arterial spin labeling (pcasl) study. *Journal of affective disorders*. 2014; 165:59–63. [PubMed: 24882178]
35. Ho TC, Wu J, Shin DD, Liu TT, Tapert SF, Yang G, et al. Altered cerebral perfusion in executive, affective, and motor networks during adolescent depression. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2013; 52:1076–1091 e1072. [PubMed: 24074474]

Figure 1.
Representative slices displaying regional reduction of cortical cerebral blood flow in the RRMS-I compared to RRMS-NI ($p<0.01$) after controlling for the confounding factor.

Table 1

Clinical and radiological characteristics of the study groups

Variable	Healthy Controls (n=19)	RRMS-NI (n=19)	RRMS-I (n=20)
Demographics			
Age (yrs)	49.0 ± 7.1	46.4 ± 7.2	48.1 ± 4.7
Female gender (%)	73.68	78.95	60
Disease duration (yrs)	0.0 ± 0.0	11.8 ± 5.4	11.6 ± 4.9
Education (yrs)	16.9 ± 2.9 [‡]	16.1 ± 1.3	14.6 ± 1.9 [‡]
MOCA	27.5 ± 1.7 [‡]	26.9 ± 2.1 [*]	23.9 ± 4.1 ^{‡*}
HADS-A (log)	4.4 ± 4.3 [‡]	6.4 ± 3.1	8.5 ± 3.7 [‡]
HADS-D (log)	2.3 ± 2.3 [‡]	3.5 ± 3.2 [*]	7.6 ± 2.9 ^{‡*}
EDSS	NA	1.79 ± 0.71	2.58 ± 0.67
Treatment Regimen			
Interferon	n = 0	n = 4	n = 3
Immunosuppressant	n = 0	n = 11	n = 12
Brain Volume			
BPF (%)	79.0 ± 9.0 [‡]	75.0 ± 6.0	72.0 ± 8.0 [‡]
fGM (%)	45.151 ± 5.118	43.430 ± 3.909	41.874 ± 5.499
fWM (%)	31.661 ± 4.074 [‡]	29.612 ± 2.825	28.352 ± 3.510 [‡]
fCL (%)	0.000 ± 0.000	0.008 ± 0.007	0.014 ± 0.024
fBG (%)	1.345 ± 0.194	1.313 ± 0.184	1.245 ± 0.218
fTh (%)	0.679 ± 0.118	0.642 ± 0.141	0.546 ± 0.136
fWML (%)	0.000 ± 0.000 [‡]	0.665 ± 0.740	0.919 ± 0.900 [‡]
fT1hole (%)	0.000 ± 0.000 [‡]	0.226 ± 0.216	0.410 ± 0.506 [‡]
fCSF (%)	21.164 ± 8.776 [‡]	24.104 ± 6.239	26.640 ± 7.322 [‡]
Z-score Cog Test			
COWAT_FAS	-0.671 ± 0.825	-0.262 ± 1.061 [*]	-1.159 ± 0.887 [*]
COWAT_Animals	-0.125 ± 1.135	0.410 ± 0.954 [*]	-0.593 ± 1.175 [*]
BVMT-R_IR	0.373 ± 1.149 [‡]	-0.068 ± 1.036 [*]	-1.677 ± 1.340 ^{‡*}
BVMT-R_DR	0.404 ± 1.140 [‡]	0.423 ± 0.772 [*]	-1.618 ± 1.479 ^{‡*}
PASAT-2	-0.205 ± 0.882 [‡]	-0.257 ± 0.662 [*]	-1.799 ± 0.571 ^{‡*}
JLO	0.981 ± 0.197	0.828 ± 0.588	0.403 ± 0.668
SDMT	-0.135 ± 0.921 [‡]	0.024 ± 0.747 [*]	-1.802 ± 1.172 ^{‡*}
CVLT-II_IR	-0.251 ± 1.048 [‡]	-0.228 ± 1.039 [*]	-1.937 ± 1.364 ^{‡*}
CVLT-II_DR	-0.105 ± 0.658 [‡]	0.211 ± 0.918 [*]	-2.200 ± 1.609 ^{‡*}
DKEFS	0.507 ± 0.730	0.263 ± 0.606	-0.202 ± 1.248

, ‡ and * demonstrate measures that were significantly different ($p < 0.05$) between 1) healthy controls vs. RRMS-NI, 2) healthy controls vs RRMS-I, 3) RRMS-NI vs RRMS-I respectively

BPF: Brain parenchymal fraction, fGM: fractional grey matter, fWM: fractional white matter, fCL: fractional cortical lesion, fBG: fractional basal ganglia, fTh: fractional thalamus, fWML: fractional white matter lesion, fT1hole: fractional T1 hole, fCSF: fractional cerebrospinal fluid

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2

Areas of significantly reduced GM perfusion in the RRMS-I compared to healthy controls ($p < 0.01$)

MNI coordinate	Region	K _E	T-score
24,64,-4	Right Superior Frontal Gyrus // BA 10	678	5.12
56,24,-6	Right Inferior Frontal Gyrus // BA 47	55	4.90
-32,58,8	Left Middle Frontal Gyrus // BA 10	217	4.37
14,28,-24	Right Inferior Frontal Gyrus // BA 11	61	3.95
-52,40,-14	Left Inferior Frontal Gyrus // BA 47	75	4.59
4,10,46	Right Limbic Lobe // Cingulate Gyrus // BA 32 // supplementary motor area	30	4.41
-4,16,52	Left Medial Frontal Gyrus // BA 8 // supplementary motor area		3.20
-62,-50,38	Left Parietal Lobe // Supramarginal Gyrus // BA 40	68	2.84
58,-22,44	Right Parietal Lobe // Postcentral Gyrus // BA 3	49	4.18
56,-16,-20	Right Middle Temporal Gyrus // BA 21	16	3.24
-64,-24,42	Left Temporal Lobe/ BA 20	185	4.14
-66,-22,30	Left Parietal Lobe // Postcentral Gyrus // BA 2		3.69
-52,-22,58	Left Parietal Lobe // BA 3		2.92
-56,-20,42	Left Frontal Lobe // Postcentral Gyrus // BA 4		3.13
26,-4,14	Right Sub-lobar // Lentiform Nucleus // Putamen	25	2.89
-8,-30,2	Left Sub-lobar // Thalamus // Pulvinar	15	3.10
60,30,20	Right Inferior Frontal Gyrus // BA 46	61	3.88
54,16,30	Right Middle Frontal Gyrus // BA 9	45	3.76
-36,-4,60	Left Middle Frontal Gyrus // BA 6	47	3.75
-26,34,-22	Left Inferior Frontal Gyrus // BA 11	20	3.66
-46,-18,42	Left Frontal Lobe // Precentral Gyrus // BA 4	17	3.23
-4,22,46	Left Limbic Lobe // Cingulate Gyrus // BA 32	31	3.18
54,-6,36	Right Frontal Lobe // Precentral Gyrus // BA 6	24	3.11

Table 3

Areas of significantly reduced GM perfusion in the RRMS-I compared to RRMS-NI ($p < 0.01$)

MNI coordinate	Region	K _E	T-score
-38,-20,70	Left Frontal Lobe// Precentral Gyrus	78	3.82
-30,-16,70	Left Frontal Lobe // Precentral Gyrus // BA 6		3.40
0,22,64	Left Superior Frontal Gyrus // BA 6 // supplementary motor area	250	3.32
8,20,64	Right Superior Frontal Gyrus // BA 6 // supplementary motor area		3.11