GREY MATTER PERFUSION ABNORMALITIES ARE MORE EXTENSIVE THAN GREY MATTER ATROPHY IN EARLY RELAPSING-REMITTING MULTIPLE SCLEROSIS PATIENTS

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Target Audience: Clinicians interested in multiple sclerosis

Introduction: Magnetic resonance imaging (MRI) assists the diagnosis of multiple sclerosis (MS) by detecting demyelinating white matter lesions on T2-weighted MR images. While grey matter (GM) demyelination and neuronal loss is often extensive in histopathology studies, they are less detectable in vivo using conventional MRI. Some GM abnormalities in MS, including atrophy, correlate with disability and lesion load [1], but evidence is limited. Perfusion MRI has also identified reduced GM blood flow, which would be consistent with reduced metabolism due to either neuronal loss or dysfunction [2, 3]. One question is whether perfusion MRI in early relapsing remitting MS (RRMS) might detect abnormalities in the absence of GM atrophy, thus indicating a potentially reversible state of neuronal dysfunction. The objective of this study is to 1) investigate grey matter (GM) atrophy and perfusion abnormalities in early RRMS patients (≤ 5 years from symptom onset), and 2) to correlate these findings with clinical and cognitive impairments. The coupling of both imaging modalities in the same patient sample will provide a more complete description of early GM perfusion abnormalities in MS.

Methods: Fifteen healthy controls (C) and 15 RRMS patients with disease duration of ≤ 5 years were investigated. All subjects underwent neurological and neuropsychological assessments, which generated an Expanded Disability Status Scale (EDSS), a MS Severity Score (MSSS), a MS Functional Composite (MSFC) and a composite cognitive test scores (Z scores). MRI assessments including T2 FLAIR (SE, TE/TR=11/500ms, T1=2250ms, acquisition matrix=512x512x160, FOV=220mm, voxel size=0.43x0.43x3.0mm^3), T2 PROPELLER (SE, TE/TR=91/3700ms, acquisition matrix=512x512x160, FOV=220mm), T1 weighted SPGR (TE/TR=2.8/6.6ms, T1=400ms, flip angle=15°, acquisition matrix=256x256x170, FOV=250mm, voxel size=0.98x0.98x1.0mm^3) and perfusion images using pseudo-continuous arterial spin labeling [4] (5 NEX, 512x8 spiral acquisition, 2 phases, post-labeling delay=1525ms, FOV=240mm, voxel size=3.75x3.75x5 mm^3) were acquired on a 3T General Electric HDx scanner with an eight channel head coil. MS lesions were manually outlined on T2 FLAIR images using Jim software (Jim 4.0 Xinapse System Leicester, UK) to measure T2 lesion loads. The presence of lesions was confirmed by reference to T2 PROPELLER scan. In addition, lesions were manually outlined on T1 SPGR, and were automatically filled with a lesion filling program (UCL, London) [5] in order to avoid GM misclassifications during structural segmentation. Data preprocessing and analysis were performed using VBM8, a toolbox of SPM8. GM volume and GM perfusion differences were assessed using voxel based morphometry (VBM) [6]. After normalizing, modulating and smoothing images, differences in GM volume and GM perfusion were assessed using ANCOVA, with age, gender and years of education as covariates. Multiple linear regressions were used to assess the relationship between clinical and cognitive impairments, and GM volume and perfusion measurements, with age, gender and years of education as covariates. Results were corrected for multiple comparisons using false discovery rate ($p < 0.05$).

Results: Demographic, clinical and cognitive scores are summarized in the table below (Table 1). While relatively intact cognitive scores were evident in the MS group, their performance was below that of controls. VBM analysis identified no significant difference in global and regional GM volume changes between controls and MS patients. Compared to controls, the MS group showed a significant decrease in global perfusion (Figure 1). VBM analysis showed decreased perfusion in parietal and occipital cortex with more limited frontal and temporal reductions (Figure 2). There was also decreased GM perfusion in subcortical structures (thalamus, hippocampus, caudate, putamen and accumbens). Higher lesion loads in cortical GM were associated with decreased perfusion.

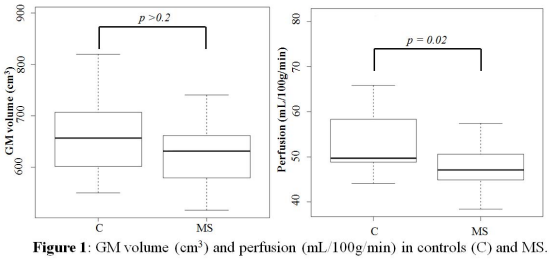

Figure 1: GM volume (cm^3) and perfusion (mL/100g/min) in controls (C) and MS.

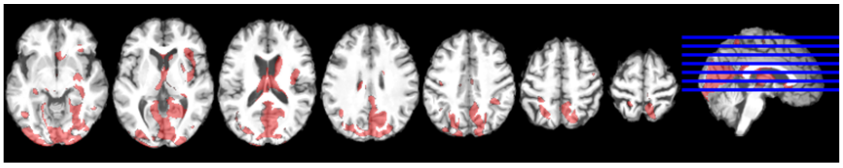

Figure 2: Voxelwise SPM map showing significantly reduced perfusion in MS relative to controls (FDR, p<0.05)

Discussion: This group of early RRMS patients showed no global GM atrophy. However, the same patients showed a widespread decrease in perfusion in cortical and deep GM. Reduced perfusion, in the absence of atrophy, may reflect neuronal dysfunction rather than structural loss in early RRMS. Further longitudinal studies of the evolution of these early GM perfusion abnormalities are required to determine whether they predict future GM atrophy and clinical evolution. Serial perfusion MRI could also be used as an outcome measure in proof-of-concept trials to investigate experimental therapies aimed at reversing neuronal metabolic dysfunction - and restoring normal GM perfusion - in early MS.

References

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	C	MS
N (Female : male)	15 (11 : 4)	15 (13 : 2)
Mean age, years (SD)	34.5(12.2)	38(9.6)
Mean education years, years (SD)	13.2(1.9)	13.3(2.9)
Mean disease duration, years (SD)	-	2.1(1.2)
Mean Lesion loads, mL (range)	-	23.1(0-69.8)
Mean EDSS (SD)	-	1.8(1)
Mean MSSS (SD)	-	3.8(1.7)
Mean MSFC (SD)*	0.7(0.4)	0.2(0.6)
Z scores (SD)*	0.8(0.4)	0.5(0.5)

Table 1: Descriptive table for demographic, clinical and cognitive data for controls (C) and MS. SD: standard deviation, *p<0.05