

## Quasar arterial spin labelled MRI shows increase in white matter arterial transit time and perfusion in MS

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**Introduction:** Cerebral metabolism requires high delivery of oxygen and glucose by cerebral blood flow in the face of limited space within the skull. This is achieved by high capillary density, low cerebral blood volume and perfusion regulation that anticipates changes in metabolic demand. Alteration in perfusion has been previously seen in patients with MS.<sup>1,2</sup> These changes could be secondary to alteration in cerebral metabolism, or represent pathophysiological alteration in perfusion regulation. To further understand these changes it is helpful to study other aspects of cerebral haemodynamics including the arterial transit time (ATT), the time taken for labelled blood to traverse from feeding arteries to capillaries, and the arterial blood volume (ABV), the percentage of the voxel containing arterial blood. Arterial spin labelling (ASL) is a non-invasive method of assessing perfusion, and when performed using a pulsed sequence with multiple inversion times can also assess ATT. Here, we used the QUASAR (ASL) sequence,<sup>3,4</sup> to simultaneously quantify cerebral blood flow (CBF), ATT and ABV in a clinical study in patients with relapsing remitting MS and controls.

**Method:** MRI scans were performed using a 3 T Philips Achieva scanner with 32 channel receive coil in 16 patients with relapsing remitting MS (4M, 12F, mean age 39.2, median EDSS 4.75) and 19 controls (8M, 11F, mean age 35.6). Patients had a clinical assessment which included EDSS<sup>5</sup> and 9 hole peg test, timed 25 ft walk and PASAT B 3s test from which the MS functional composite was calculated.<sup>6</sup> The study was approved by the local research ethics committee.

**MRI protocol:** A 7-slice multiple time point ASL perfusion sequence was used (QUASAR<sup>3,4</sup>). Labelled and control experiments were preceded by a saturation pulse and Look-Locker sampling was used to capture of train of images at 13 inversion times (40-3640ms following labelling). Control-label pairs were performed with and without arterial crusher gradients. The scan parameters were TR 4000ms, TE 23ms,  $\Delta T_1$  300ms, T11 40ms, 13 inversion times (40-3640ms), 64 x 64 matrix, field of view 240 x 240, voxel size 3.75x3.75x6mm3, slice number 7, slice thickness 6mm, slice gap 2mm, flip angle = 35/11.7°, SENSE=2.5, 84 averages (48 with vascular crusher gradients of 4cm/s, 24 with no vascular crusher gradients, 12 with the lower flip angle), acquisition time 6mins.

**Post processing:** Images were exported to a windows PC running IDL 6.1 (ITT Visual Information Solutions, Boulder, Co). In house software (EasyMRI) was used to calculate CBF, ATT, ABV and tissue R<sub>1</sub> maps automatically as previously described.<sup>3</sup> R<sub>1</sub> maps were lesion filled and then segmented into white and grey matter and CSF probability maps using SPM 8 update 4010 (Wellcome Trust Centre for Neuroimaging, University College London), and tissue masks were created from the probability maps using an 80% threshold. Masks were applied to CBF, ABV and ATT maps to produce average values for segmented white and grey matter. Statistical analysis was performed using SPSS version 19. Multivariate regression was used to explore differences between age and gender in controls. General linear model was used to compare ATT and CBF in controls vs patients with covariate of age and sex in view of previously reported associations.<sup>4,7</sup>

**Results:** In controls we found that ATT increased with age in white ( $\beta=0.67$ ,  $p=0.010$ ), and grey matter ( $\beta=0.73$ ,  $P=0.004$ ). In the white matter in patients with MS we found significant increase in ATT (1.1 vs 0.94s,  $p=0.05$ ) and CBF (20.4 vs 17.1 mls min<sup>-1</sup> 100mls<sup>-1</sup>,  $p=0.019$ ) as compared to controls. In grey matter in patients with MS we found significant increase in ATT (0.99 vs 0.85s,  $p=0.017$ ) and a non-significant trend towards reduction in CBF (33.8 vs 39.2 mls min<sup>-1</sup> 100mls<sup>-1</sup>,  $p=0.08$ ) compared to controls. Increase in white matter perfusion was associated with worse score in the PASAT B 3s test ( $\beta=0.64$ ,  $p=0.015$ ).

**Discussion:** We found an increase in white matter CBF in MS. This contrasts to previous studies showing a reduction in perfusion in the normal appearing white matter.<sup>1,2</sup> The difference may be due to the fact that we used segmented whole white matter including lesions which tend to have higher perfusion than the surrounding normal appearing white matter.<sup>1</sup> Increase in perfusion may be secondary to increased metabolic demand from infiltrating inflammatory cells and following electrophysiological changes in demyelinated axons. However the joint finding of increase in CBF and ATT suggests dysregulation of perfusion control. Widespread arteriolar dilatation would lead to an increase in CBF, however since 70% of vascular resistance is at capillary rather than arterial level this increase may be small. In addition, since flow velocity is inversely proportional to cross sectional area, arteriolar dilatation would lead to an increase in ATT as seen in our study. Glutamate, lactate and nitric oxide all have arteriolar dilatatory effects and are elevated in multiple sclerosis,<sup>8</sup> and studies using other MRI modalities including R<sub>2</sub><sup>3</sup> and susceptibility weighted imaging have suggested that perfusion may be increased relative to demand.<sup>9,10</sup> Further studies using MRI modalities in combination are planned to investigate the pathophysiological mechanism of these changes.

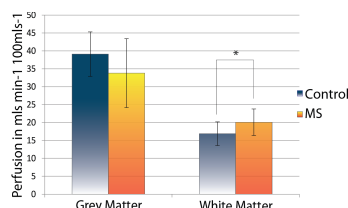


Figure 1: Graph of perfusion in MS and controls. \* =  $p < 0.05$

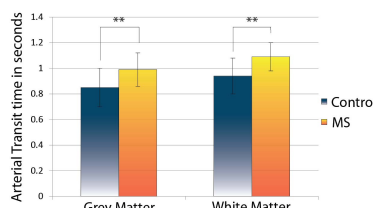


Figure 2: Graph of ATT in MS and controls. \*\*  $p < 0.001$

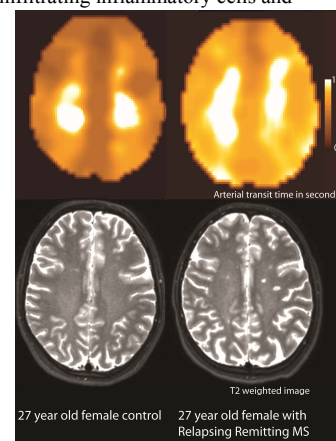


Figure 3: ATT maps and T<sub>2</sub> weighted images. Note increased white and grey matter ATT in the patient with MS (right)

### References:

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