Supplementary material:

1) MRI parameters:

MPRAGE images were acquired with the following parameters: repetition time (TR) = 8.1ms, echo time (TE) = 3.7ms, resolution= 1mm^3 isotropic, flip angle = 12°, field of view (FOV) = 256mm x 204mm x 160mm, matrix size = 256 x 204 x 160, sagittal slice orientation.

T_2-FLAIR data were acquired with the following scan parameters: TR = 4800ms TE = 344ms, inversion time (TI) = 1600ms, slice gap = 0, FOV = 250mm x 250mm x 179 mm, matrix size = 228 x 227 x 163, resolution = 1.1mm^3 isotropic, sagittal slice orientation.

2) Hypercapnia inhalation data processing:

Echo 1 and Echo 2 data were pre-processed using Analysis of Functional Neuroimages software (AFNI).[1] Data were despiked and registered to the fifth functional volume of each dataset's Echo 2 sequence using a heptic polynomial interpolation method to correct for motion. There were no significant group-differences in motion parameters (all *p*s>0.05), x-translation (p=0.1154), y-translation (p=0.1258), z-translation (p=0.3673), yaw (p=0.0594), pitch (p=0.5541), and roll (p=0.0740) between the groups. Cerebral blood flow (CBF) was estimated from Echo 1 images (control and label) using surround subtraction.[2] Echo 2 data were neighbor-averaged to mitigate the effects of labelling on BOLD signal. Echo 2 data were registered to each participant's anatomical data. The transformation matrix from this registration was then applied to Echo 1 data. Data were then visually inspected and corrected for alignment errors. Echoes 1 and 2 data were then spatially smoothed and high-pass filtered.

Echo 1 data (CBF) were then converted to physiologic units in ml/100g/min using Buxton's General Kinetic Model for Perfusion Quantification.[3,4] Control images from echo 1 were used to calculate the equilibrium magnetization of arterial blood (M_0) using asl_calib program. Ventricular cerebrospinal fluid (CSF) mask was used as a reference to calculate M_0 due to minimal partial volume effects.[5] The CSF ROI was obtained in native space based on a Freesurfer surface-based atlas following cortical reconstruction.[6] Estimated CBF values were masked within range [0-200] ml/100g/min to exclude implausible physiologic values.[7] CBF and BOLD values during room air inhalation (i.e., normocapnia) and carbogen inhalation (i.e., hypercapnia) were then averaged across time to reduce variability and maximize statistical power. Hypercapnia-evoked CBF and BOLD changes were then calculated by subtracting CBF and BOLD during hypercapnia from CBF and BOLD during normocapnia.

Whole brain CBF- and BOLD-based CVR maps were calculated as the hypercapnia-evoked positive changes in CBF and BOLD per unit change in $etCO_2$ (see equation 1,2 in main manuscript). CBF-based CVR distribution across the brain was right-skewed as a result of removing physiologically implausible (i.e., below zero) CBF values. The distribution was log-transformed to convert the right-skewed CBF distribution to a Gaussian distribution. Average CBF- and BOLD-based CVR were obtained in all ROIs (i.e., layers 1-4; see section 4.1) from the log-transformed whole brain maps. There were no significant group-differences in voxel numbers across the layers (p=0.0929). As expected, voxel numbers significantly changed moving from layer 1 to layer 4 (p=0.0005) and such changes were not significantly different between the three groups (p=0.1744). The mean voxel numbers across our study sample for each layer are: Layer 1 = 74175.1 voxels, Layer 2 = 70192.3 voxels, Layer 3 = 66506.8 voxels and Layer 4 = 54746.9 voxels. Subsequent antilog of the average log CBF- and log BOLD-based CVR values reflected the true mean of CBF- and BOLD-based CVR in respective ROIs (i.e., layers 1-4).

3) *Statistical analyses*

All analyses were performed in R (version 3.4.3) and SPSS (version 24.0). Two-way mixed ANOVA models were performed to test the effects of between- and within-subject factors on physiologic variables, arterial CVR and venous CVR. The between-subjects factor was that of group (i.e., healthy controls, cognitively normal, and, slow MS patients as defined by in-scanner simple RT [see results]), and the within-subjects factors were regions namely layers 1-4. For all models, there were no outliers, as assessed by boxplot.[8] The data were normally distributed, as assessed by Shapiro-Wilk's test of normality. The variance between the groups was homogenous, as assessed by Levene's test. Mauchly's test of sphericity indicated that the assumption of sphericity was violated for the two-way interaction. Therefore, we used Greenhouse-Geisser corrections to assess the two-way interaction.[9] Post-hoc tests were performed using one-way ANOVA, Bonferroni-corrected for multiple comparisons.

Linear regression was performed to test the association between simple RT and arterial compliance index (see results). Data were inspected and tests were performed to assure that assumptions of linearity, normality and independence of residuals were met. Linearity was assessed by visually inspecting the scatterplot of arterial compliance index against simple RT. There were no outliers. The residuals were homoscedastic and normal. Multiple regression and hierarchical multiple regression were performed to determine the predictors of simple RT in MS patients. Plots of partial regression and studentized residuals against the predicted values indicated linearity of the predictors. Residuals were independent as assessed by a Durbin-Watson statistic.[10] There was homoscedasticity, as assessed by visual inspection of a plot of studentized residuals versus unstandardized predicted values. There was no evidence of multicollinearity, as assessed by tolerance values greater than 0.1.[10] There were no outliers as assessed by studentized residuals and Cook's distance. The assumption of normality was met, as assessed by Q-Q plots.

4) Cognitively slow MS patients have reduced processing speed, working memory, and verbal fluency compared to cognitively normal MS patients.

To assess whether the simple RT performance differences were reflected in broader cognitive abilities, we calculated the differences between each MS patient group and HCs. In Fig. 2B, it is apparent that the cognitively slower group had greater differences from HCs than the cognitively normal group on processing speed ($t(28)=2.794$, $p=0.0092$), working memory (($t(28)=2.942$, $p=0.0064$) and verbal fluency ($t(28)=2.637$, $p=0.0134$), when accounting for multiple comparisons using Holm-Bonferroni correction. There were no differences between the groups on verbal memory ($p=0.29$) and visuospatial memory ($p=0.99$).

5) *ACI affects RT independent of disease duration.*

We performed a principal component reduction analysis on the RT predictors. Based on the scree plot [11], two components were retained. Component 1 and 2 explained 37.95% and 18.69% of the total variance, respectively. The correlation angle between the arterial compliance index and disease duration ($\theta=104.39^{o}$) was close to 90^{o} confirming the independent nature of the two variables ($\cos 104.39^{o}=-0.75$).

References:

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