Version 2 – update has been highlighted.

Supplementary Material 1: Detailed Brain MRI Protocol

The detailed MRI protocol is provided below:

The MRI protocol includes a number of standardized MRI sequences for analyzing brain morphometry, microstructure and function including:

1. T1-weighted MPRAGE (1mm contiguous, matrix size 256x240x192, FOV 256x240x192, TE = 2.13ms, TR, = 2300ms, TI = 900ms, bandwidth=230Hz/pixel) acquisition for grey and white matter morphometry as well as an anatomical reference;

2. Fluid attenuated inversion recovery (FLAIR) (1.2 mm contiguous, matrix size 256x240x160, FOV 256x240x192, TE = 395ms, TR, = 5000ms, TI = 1800ms, bandwidth=781Hz/pixel) acquisition to highlight gross white matter abnormalities and detect WMH;

3. Susceptibility weighted imaging (SWI) acquisition to identify CMB and venous vasculature (1.8 mm contiguous, matrix size 256x232x72, FOV 230x208x130, TE = 20ms, TR, = 30ms, bandwidth=120Hz/pixel);

4. Diffusion weighted imaging (2.0 mm contiguous, matrix size 110x100x60, FOV 256x240x192, TE = 95ms, TR, = 8200ms, 33 diffusion directions with b=1500 mm2/s and 3 b=0, bandwidth=781Hz/pixel) to examine white matter micro-structure using both tensor based and tractography analyses using higher angular resolution techniques;

5. Resting state functional MRI (rs-fMRI) scan (3 mm contiguous, matrix size 64x64x42, FOV 190x190x129, TE = 21ms, TR, = 754ms , bandwidth=1474Hz/pixel) using a simultaneous multi-slice imaging technique to provide temporal resolution of 0.75 seconds);

6. A multiple inversion arterial spin-labelling scan (4.8 mm contiguous, matrix size 64x52x23, FOV 220x220x116, TE = 19.6ms, TR, = 2600ms, bandwidth=1002Hz/pixel) to assess cerebral blood flow; and

7. A gradient echo based field map to correct for distortions in the diffusion and rs-fMRI scans.

Image analyses are being conducted and stored at Monash Biomedical Imaging, utilising the Multi-modal Australian ScienceS Imaging and Visualisation Environment (MASSIVE) high performance computer facility [1].

Image analysis pipelines are using best practice for large MRI studies.
The T1-weighted MP-RAGE scans are segmented into grey matter (GM), white matter (WM) and cerebrospinal fluid, as well as cortical and sub-cortical regions, with the Freesurfer structural MRI pipeline [2].

The T2-weighted FLAIR scans are segmented with the Wisconsin White Matter Hyperintensities Segmentation Toolbox (W2MHS) [3] to identify WMH as defined by accepted criteria [4]. Prior brain infarcts, including lacunes (as defined by the STRIVE consortium) and cortical lesions are also identified. WMH volumes will be measured from the segmentation, and stratified between periventricular and deep white matter [4].

Cerebral blood flow (CBF) and blood arrival time maps are automatically generated from the ASL data. The ASL images are corrected for head movement and CBF and blood arrival time maps are calculated using an established subtraction algorithm[5] and in-house customized software, based on techniques originally developed by Wang and co-workers[6].

Measures of functional connectivity are computed from the resting state functional MRI data. The resting-state fMRI (rsfMRI) data pre-processing is implemented using tools from FSL[7]. Briefly, a first level MELODIC (including steps of field map distortion correction, motion correction, brain extraction and high-pass filtering (75 s)) is applied to each subject's data with automatic Independent Components Analysis (ICA) estimation of the number of components. These results are processed by FSL-FIX in order to automatically detect and remove noisy components, after initial manual training of the algorithm using 25 random subjects. Finally, each image is smoothed (FWHM=5mm) and registered to the Montreal Neurological Institute (MNI) template (with 2mm isotropic voxels). The rsfMRI data second level group ICA analysis (data for all subjects) is processed using MELODIC to extract the first 15 ICA components that are the resting state functional connectivity maps.

Other measures including regional cortical thickness, regional perfusion, regional white matter microstructure integrity and ventricular volumes will be computed from the dataset using well-validated automatic techniques[8].

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