Supplement 1

Image Acquisition Parameters

All patients underwent the following MRI protocol with whole-brain coverage:

Structural Imaging

T1-weighted 3D spoiled gradient echo (FAST-SPGR) sequence [slice thickness = 1 mm; no interslice gap; field of view = 22 x 22 cm; matrix size = 256 x 256; flip angle = 12°; TE = 3.1 ms; TR = 7.8 ms; TI = 450 ms; 146 slices per volume]

Axial Single-Shot BOLD CVR Acquisition

T2*-weighted echoplanar imaging gradient echo (EPI-GRE) sequence [slice thickness = 3.5 mm; field of view = 24 x 24 cm; matrix size = 64 x 64; flip angle = 70°; echo time = 30 ms; repetition time = 2400 ms; number of frames = 338]

2D FLAIR Image

Standard T2-weighted FLAIR image [slice thickness = 3 mm; 36 slices per volume; matrix size = 256 x 256; field of view = 22 x 22 cm; flip angle = 90°; TE = 138 ms; TR = 9002 ms; TI = 2250 ms]

Proton Density/T2-weighted Sequence (acquired for skull stripping)

Fast spin echo-XL [slice thickness = 3 mm; matrix size = 256 x 256; field of view = 24 x 24 cm; flip angle = 90º; TE = 10.5/90 ms; TR = 3000 ms]

BOLD Processing

The BOLD acquisitions were analyzed using AFNI software[1] and Matlab (2014b, The MathWorks, Inc., Natick, Massachusetts, US). Using AFNI, the raw BOLD dataset was first corrected for slice timing and volume re-registered to the first frame. In addition, scans were evaluated for extent of motion, and those with greater than 2mm of motion in any direction were discarded. Finally, the BOLD time series were scaled to percent change, then aligned to the T1-weighted anatomical images.

Calculating CVR

Each patient's $P_{ET}CO_2$ time series was first time-shifted to the point of maximum correlation with the whole brain average BOLD signal using Matlab to align the onset time of stimulus with the BOLD response. CVR was then calculated as the regression coefficient of a linear, least-squares fit of the BOLD signal to the shifted $P_{ET}CO_2$ time series on a per voxel basis.[2] CVR is expressed as the percent change in BOLD signal per mmHg change in $P_{ET}CO_2$. For visualization purposes, the CVR value in each voxel can be assigned a color and superimposed on the corresponding voxel of the anatomical images (using real-time linear interpolation) to produce a color-coded CVR map (Figure 1).

Calculating speed of cerebrovascular response

Calculating the speed of the cerebrovascular response has been previously described.[3] Using the time-shifted $P_{ET}CO_2$ trace, the BOLD response to the hypercapnic step portion of the inspired CO_2 stimulus was modeled by convolving the $P_{ET}CO_2$ time series, $P_{ET}CO_2(t)$, with a hemodynamic response function (HRF) in the form of an exponential decay function, $\exp(-t/\tau)$,

where t is time and τ is the time constant of the cerebrovascular response. This results in the following function:

$$\boldsymbol{S(t) = A\,x\,\{P_{ET}CO_2(t)\ \otimes \mathbf{HRF}(t/\tau)\}\ +\ B\ +\ \varepsilon(t)}$$

where S is the BOLD signal response, A is the scaling factor of the function, B is the baseline BOLD signal, and ε is the residual time series error. Also note that $HRF(t,\tau) = e^{-t/\tau}/C(\tau)$, where $C(\tau)$ is also a scaling factor equal to the area under the curve from t=0 to t=5τ. Using this function, a set of 50 convolved $P_{ET}CO_2$ curves was generated for τ values ranging from 2 to 100 seconds, in 2-second increments. A Pearson correlation was then carried out between the BOLD response in each voxel and each convolved $P_{ET}CO_2$ curve to determine the curve of best fit. The τ value associated with the curve of best fit defines the speed of cerebrovascular response to the vasodilatory stimulus, expressed in seconds. Therefore, smaller τ values reflect a faster cerebrovascular response, while larger τ values reflect a slower response. The τ value in each voxel is then assigned a color and superimposed on the corresponding voxel of the anatomical images (using real-time linear interpolation) to produce a color-coded τ map (Figure 2).

Partial volume correction

Progressive cortical atrophy is a cardinal feature of AD and may cause a partial volume effect in imaging data. To address this potential confound, the analysis was confined to cortical GM and the following correction was applied to both the CVR and τ values in each voxel:

$$\boldsymbol{S_{uncorr} = (S_{GM}\,x\,P_{GM}) + (S_{WM}\,x\,P_{WM})}$$

$$\boldsymbol{\therefore S_{GM} = \frac{\left(S_{uncorr}\ -(S_{WM}\,x\,P_{WM})\right)}{P_{GM}}}$$

S_{uncorr} refers to the uncorrected signal of interest (CVR or τ), S_{GM} and S_{WM} are the components of the signal contributed by the GM and WM in the voxel, and P_{GM} and P_{WM} are the proportions of GM and WM in that voxel, respectively. Simply put, the signal measured can be resolved in components arising from the GM and WM individually, assuming the contribution of the CSF to the signal is negligible. Therefore, by estimating the intrinsic signal of WM as well as the proportion of GM and WM in a given voxel, a correction can be applied that accounts for variable levels of cortical atrophy across subjects. This correction is similar to that used arterial spin-labelling MRI studies in AD.[4,5] To generate an estimate of S_{WM}, a cerebral WM mask was generated using the FreeSurfer image analysis suite (https://surfer.nmr.mgh.harvard.edu, reviewed at Fischl, 2012), then eroded to produce a cerebral WM volume with minimal GM contamination. Mean CVR and τ were then calculated across the eroded mask for each patient, yielding estimates of S_{WM}. To calculate P_{GM} and P_{WM}, T1-weighted anatomical images were segmented using SPM8 (Wellcome Trust Centre for Neuroimaging, University College London, London, UK). The resultant GM and WM probability maps were used to produce estimates of P_{GM} and P_{WM} for each voxel, respectively.

REFERENCES

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