

Supplementary Materials for “Hippocampal blood brain barrier permeability is related to the APOE4 mutation status of elderly individuals without dementia”

Supplementary Table 1. MR protocol details.

| | 3D MPRAGE | 3D FLAIR | 3D SWI | DCE-MRI |
|-----------------------------|------------------|-----------------|---------------|---------------------------------------|
| TR (ms) | 2300 | 5000 | 29 | 3.1 |
| TE (ms) | 2.98 | 393 | 20 | 1.04 |
| TI (ms) | 900 | 1800 | | |
| Flip Angle (°) | 9 | | 15 | 10 |
| FOV (mm) | 256×256 | 256×256 | 220 | 225×240 |
| Slice thickness (mm) | 1 | 1 | 2 | 3 |
| Matrix | 256×256 | 256×256 | 512×512 | 180×192 |
| Voxel size | 1×1×1 | 1×1×1 | 0.43×0.43×2 | 1.25×1.25×3 |
| NEX | 1 | 1 | 1 | |
| GRAPPA factor | 2 | 2 | 2 | |
| Other features | | | | 60 dynamics, 10 s temporal resolution |

3D MPRAGE: three-dimensional magnetization prepared-rapid gradient echo; 3D FLAIR: three-dimensional fluid attenuated inversion recovery; 3D SWI: three-dimensional susceptibility-weighted imaging; DCE: dynamic-contrast enhancement; TR: repetition time; TE: time to echo; TI: inversion time; FOV: field of view; NEX: number of excitation; GRAPPA: GeneRalized autocalibrating partial parallel acquisition.

Supplementary Tables and Figures

Supplementary Table 2. Regional comparison of the BBB permeability rate (K_{trans} , $\times 10^{-3}\text{min}^{-1}$) for the total population.

| | Region of Interest | Subjects with NC (n=33) | Subjects with MCI (n=33) | P value† |
|---------------------|---------------------------|------------------------------------|-------------------------------------|-----------------|
| CORTEX | Inferior Temporal | 0.595 ± 0.561 | 0.623 ± 0.474 | 0.232 |
| | right | 0.630 ± 0.666 | 0.653 ± 0.521 | 0.123 |
| | left | 0.560 ± 0.498 | 0.593 ± 1.418 | 0.510 |
| | Lateral Orbitofrontal | 0.703 ± 0.485 | 0.955 ± 1.008 | 0.126 |
| | right | 0.739 ± 0.550 | 1.028 ± 1.023 | 0.076 |
| | left | 0.667 ± 0.474 | 0.882 ± 1.109 | 0.260 |
| | Medial Orbitofrontal | 0.350 ± 0.354 | 0.487 ± 0.473 | 0.065 |
| | right | 0.374 ± 0.386 | 0.527 ± 0.548 | 0.068 |
| | left | 0.327 ± 0.328 | 0.447 ± 0.426 | 0.075 |
| DEEP GRAY | Caudate Nucleus | 0.482 ± 0.327 | 0.999 ± 1.070 | 0.055 |
| | right | 0.515 ± 0.489 | 1.029 ± 1.233 | 0.163 |
| | left | 0.449 ± 0.297 | 0.968 ± 0.959 | 0.016* |
| | Putamen | 0.442 ± 0.383 | 0.648 ± 0.681 | 0.085 |
| | right | 0.486 ± 0.457 | 0.686 ± 0.877 | 0.122 |
| | left | 0.397 ± 0.377 | 0.609 ± 0.603 | 0.098 |
| | Globus Pallidus | 0.578 ± 0.489 | 0.802 ± 0.853 | 0.291 |
| | right | 0.594 ± 0.535 | 0.755 ± 0.898 | 0.438 |
| | left | 0.562 ± 0.485 | 0.848 ± 0.935 | 0.231 |
| | Thalamus | 0.733 ± 0.596 | 0.936 ± 0.769 | 0.517 |
| | right | 0.709 ± 0.588 | 0.878 ± 0.733 | 0.539 |
| | left | 0.758 ± 0.618 | 0.994 ± 0.837 | 0.511 |
| | Hippocampus | 0.575 ± 0.740 | 0.570 ± 0.457 | 0.557 |
| | right | 0.559 ± 0.720 | 0.586 ± 0.564 | 0.400 |
| | left | 0.575 ± 0.788 | 0.555 ± 0.524 | 0.781 |
| WHITE MATTER | Frontoparietal WM | 0.812 ± 1.006 | 0.660 ± 1.001 | 0.621 |
| | right | 0.713 ± 0.923 | 0.510 ± 0.658 | 0.438 |

Supplementary Tables and Figures

| | | | |
|--------------|---------------|---------------|-------|
| left | 0.912 ± 1.167 | 0.809 ± 1.418 | 0.777 |
| Cingulate WM | 0.381 ± 0.491 | 0.384 ± 0.662 | 0.652 |
| right | 0.380 ± 0.545 | 0.362 ± 0.749 | 0.561 |
| left | 0.383 ± 0.490 | 0.385 ± 0.617 | 0.791 |
| Temporal WM | 0.803 ± 1.228 | 0.649 ± 1.116 | 0.982 |
| right | 0.625 ± 1.077 | 0.722 ± 1.468 | 0.626 |
| left | 0.983 ± 1.637 | 0.575 ± 0.999 | 0.622 |

* denotes significance; P value < 0.05. Data are presented as the mean ± standard deviation.

† denotes that a p-value was derived from an analysis of covariance adjusted for age, sex, education, vascular risk burden score, and normalized hippocampal volume.

NC: normal cognition; BBB: blood brain barrier; MCI: mild cognitive impairment; WM: white matter.

Supplementary Tables and Figures

Supplementary Table 3-1. Regional comparison of the BBB permeability rate (K_{trans} , $\times 10^{-3}\text{min}^{-1}$) according to APOE4 status (n=35).

| | Region of Interest | Non-carrier (n=18) | APOE4 carrier (n=17) | P value† |
|---------------------|-----------------------|-----------------------|-------------------------|----------|
| CORTEX | Inferior Temporal | 0.667 \pm 0.518 | 0.655 \pm 0.522 | 0.623 |
| | right | 0.703 \pm 0.582 | 0.697 \pm 0.673 | 0.716 |
| | left | 0.631 \pm 0.498 | 0.614 \pm 0.547 | 0.577 |
| | Lateral Orbitofrontal | 1.185 \pm 1.178 | 0.840 \pm 0.734 | 0.228 |
| | right | 1.204 \pm 1.108 | 0.955 \pm 0.962 | 0.357 |
| | left | 1.166 \pm 1.376 | 0.725 \pm 0.585 | 0.191 |
| | Medial Orbitofrontal | 0.513 \pm 0.528 | 0.478 \pm 0.494 | 0.904 |
| | right | 0.559 \pm 0.589 | 0.513 \pm 0.586 | 0.868 |
| | left | 0.467 \pm 0.481 | 0.444 \pm 0.416 | 0.955 |
| DEEP GRAY | Caudate Nucleus | 0.816 \pm 0.772 | 0.810 \pm 0.691 | 0.739 |
| | right | 0.795 \pm 0.824 | 0.815 \pm 0.827 | 0.852 |
| | left | 0.836 \pm 0.762 | 0.804 \pm 0.669 | 0.638 |
| | Putamen | 0.657 \pm 0.786 | 0.612 \pm 0.532 | 0.682 |
| | right | 0.700 \pm 1.112 | 0.695 \pm 0.586 | 0.621 |
| | left | 0.615 \pm 0.548 | 0.530 \pm 0.547 | 0.845 |
| | Globus Pallidus | 0.804 \pm 0.971 | 0.780 \pm 0.616 | 0.655 |
| | right | 0.780 \pm 1.117 | 0.788 \pm 0.643 | 0.549 |
| | left | 0.827 \pm 0.877 | 0.772 \pm 0.656 | 0.817 |
| | Thalamus | 0.983 \pm 0.797 | 0.978 \pm 0.772 | 0.906 |
| | right | 0.941 \pm 0.787 | 0.920 \pm 0.727 | 0.847 |
| | left | 1.025 \pm 0.836 | 1.036 \pm 0.848 | 0.963 |
| | Hippocampus | 0.406 \pm 0.339 | 0.790 \pm 0.512 | 0.007* |
| | right | 0.498 \pm 0.492 | 0.804 \pm 0.610 | 0.033* |
| | left | 0.320 \pm 0.324 | 0.776 \pm 0.584 | 0.010* |
| WHITE MATTER | Frontoparietal WM | 1.018 \pm 1.376 | 0.612 \pm 0.845 | 0.390 |
| | right | 0.848 \pm 1.014 | 0.441 \pm 0.659 | 0.353 |

Supplementary Tables and Figures

| | | | |
|--------------|---------------|---------------|-------|
| left | 1.189 ± 1.830 | 0.783 ± 1.150 | 0.443 |
| Cingulate WM | 0.212 ± 0.327 | 0.407 ± 0.581 | 0.240 |
| right | 0.213 ± 0.338 | 0.308 ± 0.562 | 0.565 |
| left | 0.211 ± 0.384 | 0.505 ± 0.637 | 0.112 |
| Temporal WM | 0.862 ± 1.559 | 0.702 ± 1.100 | 0.911 |
| right | 0.739 ± 1.297 | 0.799 ± 1.767 | 0.698 |
| left | 0.986 ± 1.192 | 0.606 ± 0.719 | 0.846 |

* denotes significance at a P value < 0.05. Data are presented as the mean ± standard deviation.

† denotes that p values were derived from an analysis of covariance adjusted for age, sex, education, vascular risk burden score, and normalized hippocampal volume.

APOE: apolipoprotein E; WM: white matter.

Supplementary Tables and Figures

Supplementary Table 3-2. Regional comparison of the plasma fractional volume (Vp) (%) according to APOE4 status (n=35) .

| | Region of Interest | Non-carrier (n=18) | APOE4 carrier (n=17) | P value |
|---------------------|---------------------------|-------------------------------|---------------------------------|----------------|
| CORTEX | Inferior Temporal | 3.523 ± 1.443 | 2.669 ± 0.913 | 0.003* |
| | right | 3.224 ± 1.257 | 2.438 ± 0.964 | 0.005* |
| | left | 3.821 ± 1.704 | 2.902 ± 0.993 | 0.004* |
| | Lateral Orbitofrontal | 2.073 ± 1.131 | 1.568 ± 0.522 | 0.056 |
| | right | 2.086 ± 1.069 | 1.734 ± 0.603 | 0.143 |
| | left | 2.070 ± 1.287 | 1.403 ± 0.567 | 0.038 |
| | Medial Orbitofrontal | 1.269 ± 0.402 | 1.242 ± 0.389 | 0.668 |
| | right | 1.222 ± 0.329 | 1.156 ± 0.372 | 0.451 |
| | left | 1.316 ± 0.503 | 1.328 ± 0.439 | 0.894 |
| | DEEP GRAY | Caudate Nucleus | 1.056 ± 0.529 | 1.285 ± 0.447 |
| right | | 1.523 ± 0.592 | 1.303 ± 0.461 | 0.187 |
| left | | 1.489 ± 0.604 | 1.267 ± 0.492 | 0.152 |
| Putamen | | 2.394 ± 1.077 | 1.888 ± 0.630 | 0.023* |
| right | | 2.353 ± 1.028 | 1.776 ± 0.517 | 0.003* |
| left | | 2.436 ± 1.233 | 1.999 ± 0.856 | 0.120 |
| Globus Pallidus | | 1.796 ± 1.021 | 1.251 ± 0.676 | 0.005* |
| right | | 1.784 ± 1.037 | 1.209 ± 0.665 | 0.004* |
| left | | 1.807 ± 1.062 | 1.294 ± 0.746 | 0.011* |
| Thalamus | | 1.706 ± 0.840 | 1.595 ± 0.979 | 0.369 |
| right | | 1.601 ± 0.769 | 1.542 ± 1.068 | 0.435 |
| left | | 1.811 ± 0.931 | 1.647 ± 1.051 | 0.356 |
| Hippocampus | | 2.716 ± 1.989 | 3.327 ± 3.712 | 0.951 |
| right | | 2.294 ± 1.272 | 3.219 ± 2.914 | 0.683 |
| left | 3.138 ± 2.901 | 3.434 ± 4.683 | 0.760 | |
| WHITE MATTER | Frontoparietal WM | 1.506 ± 1.009 | 1.356 ± 0.632 | 0.223 |
| | right | 1.186 ± 0.924 | 1.016 ± 0.724 | 0.278 |

Supplementary Tables and Figures

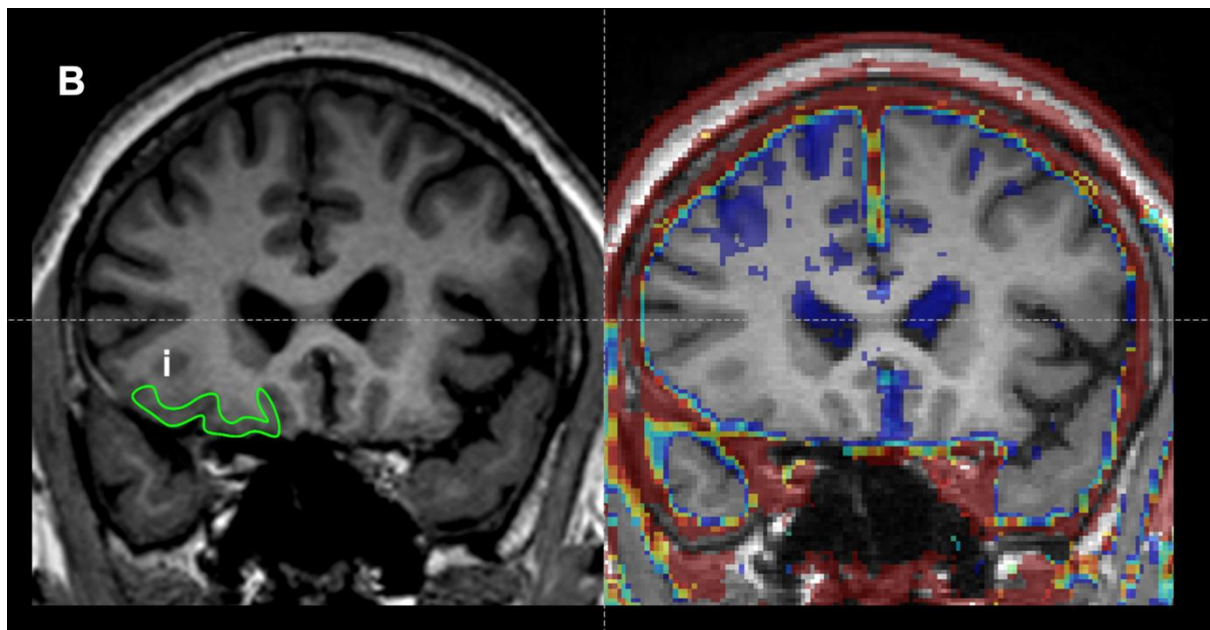
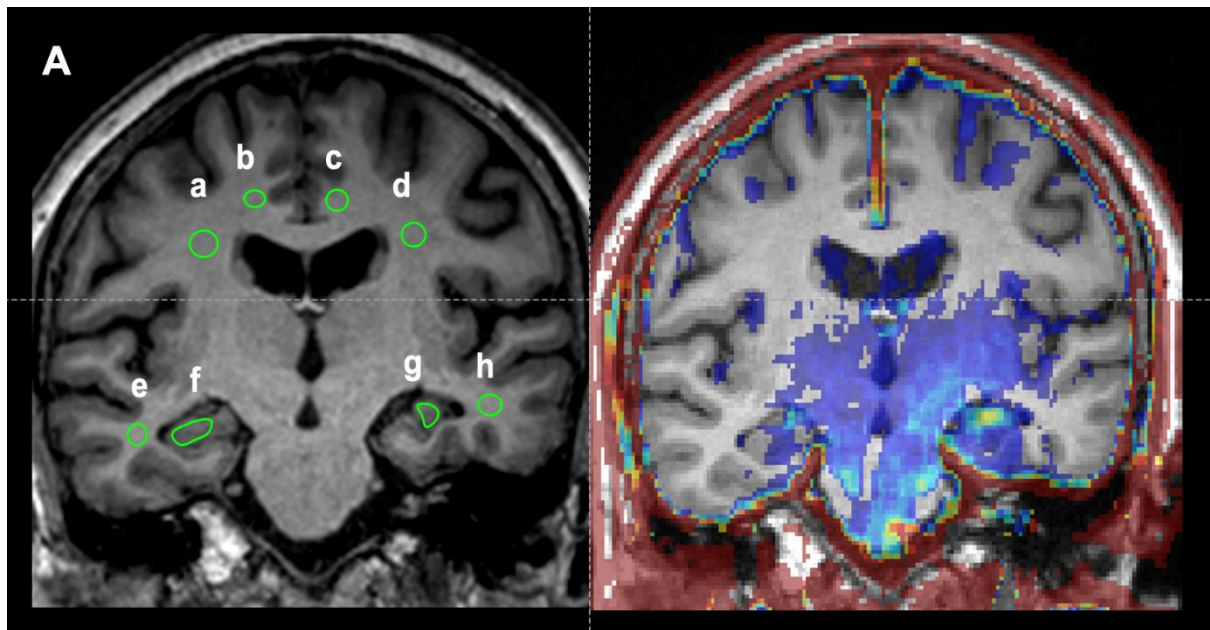
| | | | |
|--------------|---------------|---------------|--------|
| left | 1.826 ± 1.268 | 1.696 ± 0.700 | 0.268 |
| Cingulate WM | 0.542 ± 0.550 | 0.528 ± 0.532 | 0.836 |
| right | 0.463 ± 0.514 | 0.464 ± 0.479 | 0.928 |
| left | 0.622 ± 0.656 | 0.592 ± 0.610 | 0.776 |
| Temporal WM | 3.590 ± 2.639 | 2.951 ± 2.249 | 0.021* |
| right | 2.859 ± 2.303 | 2.288 ± 1.960 | 0.042* |
| left | 4.321 ± 3.167 | 3.615 ± 3.057 | 0.032* |

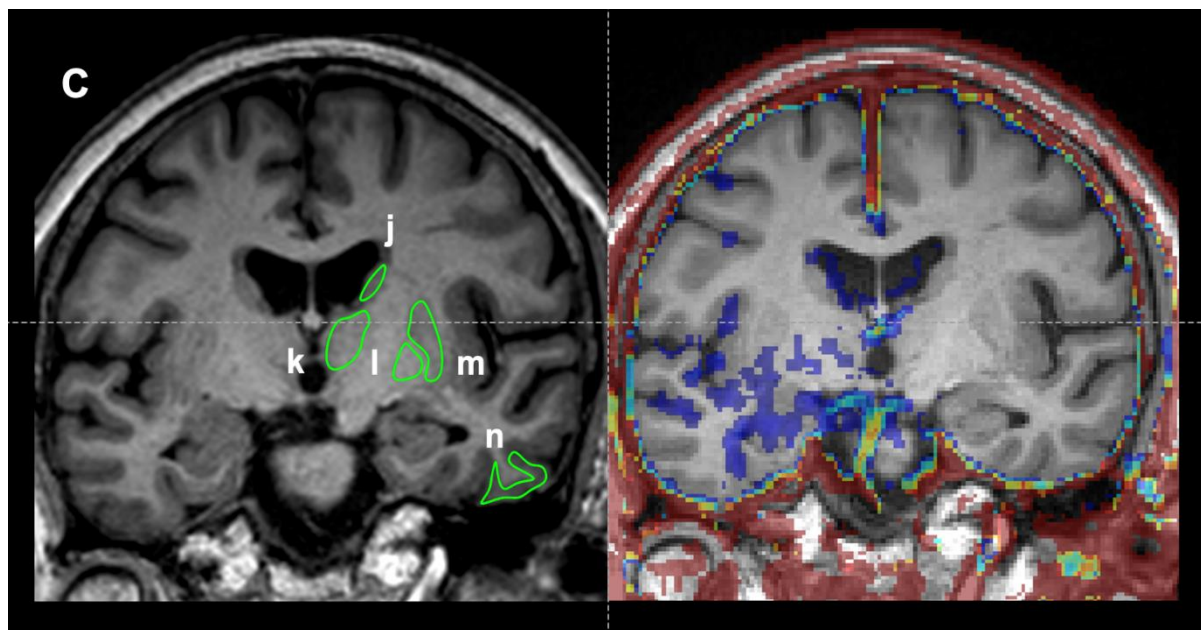
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APOE: apolipoprotein E; WM: white matter.

Supplementary Figures





Supplementary Figure 1. Region of interest (ROI) placement onto T1 volumetric images. A. a, right frontoparietal white matter (WM); b, right cingulate WM; c, left cingulate WM; d, left frontoparietal WM; e, right temporal WM; f, right hippocampus; g, left hippocampus; h, left temporal WM. B. The level of corpus callosal genu; i, lateral orbitofrontal cortex. C. The level of mammillary body; j, caudate nucleus; k, thalamus; l, globus pallidus; m, putamen; n, inferior temporal gyrus. ROIs drawn on T1 volumetric images were transferred to the co-registered K_{trans} map for analysis.