SUPPLEMENTAL MATERIAL

Effects Of Arterial Stiffness On Brain Integrity In Young Adults From The Framingham Heart Study

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Supplemental Methods

Noninvasive Hemodynamic Data Acquisition

Participants were studied in the supine position after resting for ≈5 minutes. Supine brachial systolic and diastolic blood pressures were obtained with the use of a semiautomatic auscultatory device. Arterial tonometry with simultaneous ECG was obtained from brachial, radial, femoral, and carotid arteries with the use of a custom tonometer (Cardiovascular Engineering, Inc., Norwood, MA). All of the recordings were performed on the right side of the body. Transit distances were assessed by body surface measurements from the suprasternal notch to each pulse-recording site; a caliper was used for the femoral site. Tonometry and ECG data were digitized (1000 Hz) during the primary acquisition and transferred to the core laboratory (Cardiovascular Engineering, Inc, Norwood, MA) for analyses that were performed blinded to clinical data. Tonometry waveforms were signal averaged with the ECG R wave used as a fiducial point. Systolic and diastolic cuff BP obtained at the time of the tonometry acquisition were used to calibrate the peak and trough of the signal-averaged brachial pressure waveform. Diastolic and integrated mean brachial pressures were used to calibrate carotid pressure tracings.[1] Calibrated carotid pressure was used as a surrogate for central pressure.[1]

Brain MRI analysis

MRIs were performed on a 1.5T Siemens Avanto scanner (version syngo MR B15). Three sequences were used: a 3-dimensional T1-weighted coronal spoiled gradient-recalled echo (SPGR) acquisition, a fluid attenuated inversion recovery (FLAIR) sequence, and a diffusion tensor imaging (DTI) sequence. DTI was performed using the following parameters: repetition time (TR)=3600 ms, echo time (TE)=94 ms, 25 slices total, FOV=25 cm, acquisition matrix = 128 × 128, slice thickness = 5 mm with 5 mm gap. Diffusion weighted images were generated using 30 gradients directions with total gradient diffusion sensitivity of b=1000 s/mm2, and one image with b =0 s/mm2. Centralized reading of all images was performed using in-house designed imaging, visualization and analysis software (Quanta 2). The segmentation and quantification of WMH was performed using a semi-automated procedure that has been previously described[2, 3] and which demonstrates high inter-rater reliability[4]. Segmentation of GM was performed on native T1-weighted images using an in-house implementation of a Bayesian maximum-likelihood expectation-maximization algorithm method[5]. FA maps were calculated from DTI[6] and linearly aligned to the corresponding T1-weighted scan, which in turn was deformed to a minimal deformation template[6, 7] (MDT) with voxel dimensions of 0.98 x 1.5 x 0.98 mm^3. This allowed transfer of GM and FA maps to the MDT space. A map of mean FA in the MDT space was created by averaging individual FA images across the population. Thresholding this mean FA map provided a binary WM mask in the MDT space. An FA threshold of 0.3 was chosen to select voxels in highly organized tracts, while minimizing inclusion of voxels with a higher degree of partial volume contamination.

Total cranial volume based on FLAIR was quantified using the Quanta 2 package of software routines according to a previously reported analysis protocol[2] and was used to correct for differences in head size. WMH volumes were log-transformed to normalize population variance.

Threshold free cluster enhancement

The T-maps obtained were evaluated for statistical significance using threshold free cluster enhancement (TFCE)[8]. In short, this methodology combines cluster size and significance

into a single parameter, the TCFE-score, by integrating the cluster size over a range of significance thresholds. A TFCE image was computed for each T map. The distribution of maximum TFCE scores under the null hypothesis was investigated for each independent variable using random permutation analysis, with 1000 iterations. Once the 95th percentile in the null distribution was found then the TFCE images were thresholded at this level to allow inference at the $p < 0.05$ level[8].

Supplemental Tables

Table I: Associations between decreasing fractional anisotropy and gray matter density with carotid-femoral pulse wave velocity

			Model 1		Model 3	
Tissue	Region	Volume (cc)	Beta ($\times 10^3$)	P value	Beta ($\times 10^3$)	P value
White matter	Anterior corona radiata	4.13	-0.15	<0.001	-0.19	<0.001
	Body of corpus callosum	3.78	-0.19	<0.001	-0.21	<0.001
	Splenium of corpus callosum	2.77	-0.11	<0.001	-0.14	<0.001
	Superior corona radiata	2.55	-0.13	<0.001	-0.16	<0.001
	Genu of corpus callosum	2.05	-0.15	<0.001	-0.18	<0.001
	Posterior corona radiata	1.86	-0.13	<0.001	-0.15	<0.001
	Posterior thalamic radiation	1.84	-0.15	<0.001	-0.15	<0.001
	Posterior limb of internal capsule	1.74	-0.08	<0.001	-0.10	<0.001
	Anterior limb of internal capsule	1.06	-0.09	<0.001	-0.09	<0.001
	Cerebral peduncle	0.95	-0.09	<0.001	-0.11	<0.001
	External capsule	0.62	-0.09	<0.001	-0.09	<0.001
	Superior longitudinal fasciculus	0.60	-0.11	<0.001	-0.12	<0.001
	Superior fronto-occipital fasciculus	0.43	-0.12	<0.001	-0.11	0.0028
	Fornix (cres) / Stria terminalis	0.30	-0.12	<0.001	-0.15	<0.001
	Fornix (column and body of fornix)	0.26	-0.19	0.0046	-0.19	0.0155
	Cingulum (cingulate gyrus)	0.25	-0.11	<0.001	-0.12	<0.001
	Sagittal stratum	0.14	-0.11	0.0056	-0.14	0.0021
	Retrolenticular part of internal capsule	0.11	-0.10	<0.001	-0.11	<0.001
	Cingulum (hippocampus)	0.01	-0.08	0.0197	-0.10	0.0122
	Tapetum	0.01	-0.11	0.041	-0.15	0.0172
Gray matter	Thalamus	0.93	-0.81	<0.001	-0.88	<0.001

Model 1 refers to the linear regression including fractional anisotropy or gray matter density as the dependent variable and carotid-femoral pulse wave velocity as the independent variable, adjusting for age, gender, use of antihypertensive therapy, total cholesterol, current smoking status and presence of diabetes mellitus, ICV and time between clinical and MRI exams. Model 3 corresponds to Model 1 with central pulse pressure mean arterial pressure and augmentation index included as additional adjusting variables.

Table II Interaction between Age and Hypertension with carotid-femoral pulse wave velocity on fractional anisotropy

Covariate	White matter tract	Volume (cc)	Beta (×103)	P value	Interaction (×103)	P value
Age	Anterior corona radiata	3.44	-0.05	0.062	-0.01	<0.001
	External capsule	1.20	-0.04	0.042	-0.01	<0.001
	Superior corona radiata	0.89	-0.05	<0.001	-0.01	<0.001
	Superior longitudinal fasciculus	0.82	0.00	0.99	-0.01	<0.001
	Posterior limb of internal capsule	0.55	-0.06	0.043	-0.01	<0.001
	Cerebral peduncle	0.43	-0.05	0.011	-0.01	<0.001
	Anterior limb of internal capsule	0.29	-0.02	0.088	-0.01	<0.001
	Posterior corona radiata	0.19	-0.05	0.0040	-0.01	<0.001
	Superior cerebellar peduncle	0.19	-0.03	0.018	-0.01	<0.001
	Fornix (cres) / Stria terminalis	0.13	-0.07	0.005	-0.01	<0.001
	Fornix (column and body of fornix)	0.13	-0.11	0.017	-0.02	0.0013
	Retrolenticular part of internal capsule	0.08	-0.04	0.029	-0.01	0.0030
	Inferior cerebellar peduncle	0.08	-0.09	0.004	-0.02	<0.001
	Superior fronto-occipital fasciculus	0.02	-0.06	0.003	-0.01	0.0046
	Splenium of corpus callosum	0.01	-0.02	0.19	-0.01	<0.001
	Genu of corpus callosum	0.00	0.03	0.99	-0.01	0.0053
	Posterior corona radiata	0.77	-0.07	0.50	0.29	<0.001
Antihypertensive treatment	Superior corona radiata	0.53	-0.09	0.15	0.34	<0.001
	Posterior thalamic radiation	0.12	-0.07	0.93	0.33	<0.001
	Retrolenticular part of internal capsule	0.07	-0.04	0.73	0.28	<0.001
	Superior longitudinal fasciculus	0.04	-0.12	0.63	0.38	0.0021
	Tapetum	0.04	-0.04	0.77	0.26	0.0012
	Body of corpus callosum	0.03	-0.19	0.015	0.34	0.0073
	Splenium of corpus callosum	0.02	-0.14	0.029	0.27	0.0032
	Posterior limb of internal capsule	0.01	-0.04	0.26	0.27	0.0021

Analysis refers to the linear regression including fractional anisotropy as the dependent variable and carotid-femoral pulse wave velocity (CFPWV) as the independent variable including the interaction of CFPWV with age, gender and use of antihypertensive therapy and adjusting for age, gender, use of antihypertensive therapy, total cholesterol, current smoking status and presence of diabetes mellitus, ICV and time between clinical and MRI exams.

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