ACCSCIENCE PUBLISHING

Brain & Heart

ORIGINAL RESEARCH ARTICLE

Design and methodology of a multidimensional investigation of brain structure and function in women with suspected ischemia with no coronary artery disease

Supplementary Files

S1. Imaging acquisition and processing details

To streamline the main manuscript, scanner- and sequence-specific acquisition parameters, quality-control criteria, and software/version details are summarized below. Core acquisition elements were harmonized across sites when feasible; site- and vendor-specific parameters were maintained in local acquisition manuals and are available upon reasonable request.

Table S1. Brain, heart, and retinal imaging protocol

Body part	Imaging category	Image type	Scan time	Sequence details	Voxel size
Brain	Structural MRI	T1-weighted MPRAGE	5 min 12 s	Three-dimensional (3D), sagittal	1 mm iso
		T2-weighted FLAIR	6 min 11 s	3D, sagittal	1 mm iso
		T2*-weighted 3D EPI	6 min 25 s	3D, sagittal	0.65 mm iso
		T2*-weighted mGRE	4 min 11 s	3D, axial, 3TE	0.9 mm × 0.9 mm × 4 mm
		pASL	8 min 34 s	3D, axial	1.9 mm × 1.9 mm × 4.5 mm
		Diffusion tensor imaging (DTI)	10 min 54 s	Single shell, 64 directions, b = 1000 s/mm^2	2 mm iso
		T1-weighted space intracranial vessel wall	5 min 44 s	3D, sagittal	0.5 mm × 0.5 mm × 0.6 mm
	Functional MRI	T2*-weighted BOLD-sensitized resting state fMRI	10 min	Two-dimensional (2D), axial, 976 measurements	2.5 mm iso
		Cerebral vascular reactivity - BOLD	9min 33 s	2D, axial, 369 measurements	3.4 mm × 3.4 mm × 3.8 mm
Heart	Pre-contrast	Tissue tagging	5 min	FLASH, 3 SAX slices	1.5 ×1 .5 × 8mm
		T1 mapping	10 min	MOLLI, 3 SAX slices	1.4 × 1.4 ×8 mm
		T2 mapping	1 min	FLASH, midventricular SAX slice	1.9 × 1.9 × 8 mm
	Perfusion	First pass perfusion	5 min	Cartesian FLASH, 3 SAX slices	1.7 × 1.7 mm
		Multi-view cardiac cines	25 min	SSFP cine (full-stack SAX, VLA, and LVOT)	1.3 × 1.3 × 8 mm
	Post-contrast	Multi-view late gadolinium enhancement	5 min	Single-shot TRUFI (full-stack SAX, HLA, and VLA)	1.8 × 1.8 × 8mm
		Tissue tagging	5 min	FLASH, 3 SAX slices	1.5 × 1 .5 × 8mm

(*Cont'd...*)

Table S1. ***(Continued)***

Body part	Imaging category	Image type	Scan time	Sequence details	Voxel size
Retina	Fundus photography	Non-mydriatic color fundus photography	5 min	Stereo images, optic-disc centered and macula-centered	3 × 3mm
	OCT	Macular cube; optic nerve			
	OCT-A	Macular cube; optic nerve head			

Abbreviations: TE: Echo times; BOLD: Blood oxygen level–dependent; EPI: Echo-planar imaging; FLAIR: Fluid-attenuated inversion recovery; FLASH: Fast low-angle shot; fMRI: Functional magnetic resonance imaging; HLA: Horizontal long-axis; iso: Isotropic; LVOT: Left ventricular outflow tract; mGRE: Multi-echo gradient-recalled echo; MPRAGE: Magnetization-prepared rapid gradient echo; OCT: Optical coherence tomography; OCT-A: Optical coherence tomography angiography; pASL: Pseudo-continuous arterial spin labeling; SAX: Short-axis; SSFP: Steady-state free precession; TRUFI: True fast imaging with steady-state precession; VLA: Vertical long-axis.

Table S2. Summary of imaging acquisitions, derived endpoints, and primary software tools

Domain	Acquisition/measure	Key derived endpoints	Primary software/notes
Brain MRI	T1-weighted structural (MPRAGE) + T2-FLAIR	Brain volumes; WMH segmentation; CSVD markers	FreeSurfer; LesionBrain; visual adjudication
Brain MRI	Diffusion MRI	DTI metrics (FA/MD); structural connectivity	MRtrix3; ANTs/registration
Brain MRI	Susceptibility / QSM (T2*/EPI-based)	Deep gray matter susceptibility; microbleeds/ lacunes/perivascular space	QSM reconstruction; ITK-SNAP adjudication
Brain MRI	Perfusion (pASL)	Global and regional cerebral blood flow (CBF)	Standard ASL pipelines; QC for motion
Brain MRI	Resting-state fMRI	Functional connectivity; network metrics	Standard rs-fMRI preprocessing; nuisance regression
Brain MRI	Cerebrovascular reactivity (CVR) paradigm	CVR maps; vascular responsiveness	Model-based CVR estimation
Cardiac MRI/ coronary physiology	Stress perfusion + cine + tissue characterization	MPRI; structure/function indices; fibrosis markers	Protocols per parent study; harmonized analysis
Retinal imaging	Fundus photography + OCT + OCT-A	CRAE/CRVE; RNFL/macular thickness; OCT-A vessel density	Standardized acquisition; centralized grading

Abbreviations: ANTs: Advanced normalization tools; ASL: Arterial spin labeling; CRAE/CRVE: Central retinal arteriolar equivalent/central retinal venular equivalent; CSVD: Cerebral small vessel disease; DTI: Diffusion tensor imaging; EPI: Echo-planar imaging; FA: Fractional anisotropy; FLAIR: Fluid-attenuated inversion recovery; fMRI: Functional magnetic resonance imaging; ITK-SNAP: Insight toolkit–based segmentation and navigation platform; MD: Mean diffusivity; MPRAGE: Magnetization-prepared rapid acquisition gradient echo; MPRI: Myocardial perfusion reserve index; OCT: Optical coherence tomography; OCT-A: Optical coherence tomography angiography; pASL: Pseudo-continuous arterial spin labeling; QC: Quality control; QSM: Quantitative susceptibility mapping; RNFL: Retinal nerve fiber layer; rs-fMRI: Resting-state functional magnetic resonance imaging; WMH: White matter hyperintensities.

S1.1. Structural magnetic resonance imaging-derived biomarkers

S1.1.1. Brain volumes (T1-weighted magnetization-prepared rapid acquisition gradient echo)

Whole-brain T1-weighted images were segmented and labeled using FreeSurfer.[1] Regional volumes were normalized to intracranial volume to account for head-size differences. We prioritized regions commonly implicated in cerebral small vessel disease (CSVD)-related injury and cognitive vulnerability, including total gray and white matter, cerebrospinal fluid and ventricular volumes, thalamus, hippocampus, amygdala, caudate, and putamen. These measures provide complementary indices of brain atrophy, ventricular enlargement, and subcortical vulnerability, hypothesized to relate to microvascular dysfunction and downstream cognitive outcomes.

S1.1.2. White matter hyperintensities (T2-fluid-attenuated inversion recovery)

White matter hyperintensities (WMH) were segmented using the automated LesionBrain pipeline.[2] Total WMH volume was quantified and further partitioned by location (periventricular, deep, and juxtacortical). WMH burden is a core marker of CSVD and a primary structural endpoint for testing whether coronary microvascular dysfunction is associated with greater brain small-vessel injury.

*S1.1.3. Brain iron deposition (T2*W three-dimensional echo-planar imaging to quantitative susceptibility mapping)*

Submillimeter T2*W three-dimensional echo-planar imaging images were post-processed to generate quantitative susceptibility mapping (QSM) using the total generalized variation approach,[3] including phase unwrapping and dipole inversion. Regions of interest derived from T1-weighted parcellation were registered to QSM space using advanced normalization tools,[4] and regional susceptibility values were extracted as an index of iron accumulation. Because abnormal iron deposition in deep gray matter has been linked to vascular injury and neurodegeneration, QSM-derived measures provide an additional structural marker relevant to the hypothesized heart-brain microvascular pathway.

*S.1.1.4. Cerebral microbleeds (*W three-dimensional echo-planar imaging)*

The presence and number of cerebral microbleeds (CMBs), defined as round or ovoid hypointense lesions 10 mm or smaller according to Standards for Reporting Vascular changes on nEuroimaging (STRIVE) criteria,[5] were rated on T2*W images using the microbleed anatomical rating scale.[6] Where feasible, CMB volume was estimated using semi-automated contouring and thresholding in an insight toolkit–based segmentation and navigation platform (ITK-SNAP).[7] CMB burden is a key CSVD marker that may reflect microhemorrhagic consequences of small-vessel fragility and impaired microvascular integrity.

S1.1.5. Lacunes (T2-fluid-attenuated inversion recovery with T1 reference as needed)

Lacunes were identified according to STRIVE criteria and adjudicated on T2-fluid-attenuated inversion recovery images, with reference to T1-weighted images when needed. Lacune volume was quantified using ITK-SNAP. Lacunes capture focal ischemic injury and represent a central CSVD feature hypothesized to be associated with impaired microvascular perfusion and reduced vascular reserve.

S1.1.6. Cerebral blood flow (pseudo-continuous arterial spin labeling)

Whole-brain cerebral blood flow maps were generated from pseudo-arterial spin labeling (pASL) data using nonlocal estimation of multispectral magnitude noise filtering to improve precision.[8] T1-derived regions of interest were registered and down-sampled to pASL space to extract cerebral blood flow values for the whole brain, total gray matter, total white matter, and selected subcortical regions. These perfusion metrics provide a functional complement to structural CSVD markers and will be used to test whether coronary microvascular dysfunction is associated with altered baseline cerebral perfusion.

S1.1.7. White matter microstructural integrity and structural connectivity (diffusion tensor imaging)

Diffusion data underwent denoising, Gibbs-ringing correction, and eddy-current and motion correction. Tensor fitting yielded fractional anisotropy, mean diffusivity, radial diffusivity, and axial diffusivity maps. FA maps were registered to T1 space and parcellated using the Destrieux atlas.[9] Structural connectivity was estimated using MRtrix3 (fiber orientation distribution estimation and tractography) to generate connectivity matrices across atlas nodes, consistent with prior work.[10] These measures capture diffuse microstructural injury and network disruption that may represent downstream consequences of chronic microvascular dysfunction.

S1.1.8. Intracranial vessel wall imaging biomarkers

Intracranial vessel wall images were analyzed using established methods.[11] Lumen and outer wall boundaries were delineated using a digital imaging and communications in medicine viewer workstation (Horos; Nimble Co LLC d/b/a Purview, USA) to quantify lumen area, outer wall area, wall area, normalized wall index, and mean and maximum wall thickness across major proximal intracranial segments (middle cerebral artery M1, anterior cerebral artery A1, internal carotid artery cavernous segment, posterior cerebral artery P1, basilar artery, and vertebral artery V4). Two independent readers performed measurements. These macrovascular measures complement CSVD biomarkers by characterizing large-artery remodeling that may influence cerebral hemodynamics and interact with microvascular injury.

S1.2. Functional magnetic resonance imaging-derived biomarkers

Functional brain magnetic resonance imaging (MRI): After standard data preprocessing,[12] a seed-based approach was used[13] and the assessment was performed using the default-mode network,[14,15] salience network,[16] dorsal attention network,[17] and executive control network.[16] Both within- and between-network connectivity were quantified based on the group-level significance maps of different functional networks. The middle cerebral artery cross-sectional area (CSA) was analyzed blinded as previously published.[18]

Cerebral vascular reactivity: CO_2-blood oxygen level–dependent (BOLD) images were analyzed using published protocols (with units of % blood oxygenation signal change per mmHg of end-tidal CO_2 change or % BOLD/

mmHg CO_2).[18–22] To assess macrovascular cerebrovascular reactivity, the middle cerebral artery CSA will be measured at baseline (room air) and again after 3 min of continuous hypercapnia. Analysis of volume and function was performed.

S2. Retinal imaging and cognitive assessment procedures

Detailed acquisition and grading procedures are provided below to support reproducibility while keeping the main manuscript focused on hypothesis-linked measurement domains and endpoints.

S2.1. Retinal imaging acquisition and analysis (expanded)

Retinal imaging was performed without dilation (non-mydriatic) as follows:

S2.1.1. Non-mydriatic retinal color fundus photography

Forty-five-degree digital color fundus images were obtained from one eye. A pair of stereo optic disc-centered images and a pair of stereo macula-centered images were obtained. The following parameters of retinal microvascular dysfunction were quantified by the core laboratory, after grading for imaging quality: central retinal arteriolar equivalent, central retinal vein equivalent, and arteriolar-venular ratio.[23] Additionally, other markers of retinopathy will be identified and graded (if applicable): age-related macular degeneration, diabetic retinopathy, diabetic macular edema, microaneurysm, retinal hemorrhage, soft exudate, hard exudate, focal arteriolar narrowing, arterio-venous nicking, hypertensive retinopathy, retinal vein occlusion, optic nerve changes, and other abnormalities.[24]

S2.1.2. Optical coherence tomography

Optical coherence tomography (OCT) images were obtained using a spectral-domain Cirrus HD-OCT device (model 5000; Carl Zeiss Meditec, USA). Peripapillary and macular scans were obtained using the optic disc cube 200 × 200 and macular cube 512 × 128 protocols, respectively. The following parameters were quantified using automated software provided by the manufacturer: (i) OCT optic nerve: average and sectoral retinal nerve fiber layer thickness (superior, temporal, nasal, inferior); (ii) OCT macular cube: average ganglion cell complex (ganglion cell- internal plexiform layer) thickness, average macular cube thickness, macular cube volume, and central subfield thickness.[25,26] Macular OCT segmentation was performed using an automated open-source system to compute thicknesses of the ganglion cell–inner plexiform layer, inner nuclear and outer plexiform layers, outer nuclear, inner and outer segments as described in detail previously.[27]

S2.1.3. Optical coherence tomography angiography

Macular OCT-A 3 × 3mm scans centered at the fovea were obtained and analyzed with the AngioPlex software (Zeiss Inc, USA) for quantification of the superficial retinal capillary plexus density and foveal avascular zone area.[28,29]

S2.2. Cognitive assessments (expanded)

The Montreal cognitive assessment (MoCA) and NIH toolbox cognition battery (NIHTB-CB) were administered to all participants. The MoCA consists of 30 items (30 points) that take 10–15 minutes to administer, and assesses core cognitive domains, including attention, executive functions, language, memory, and visuospatial skills.[30,31] The MoCA is an established screening tool that has been utilized to differentiate specific cardiovascular disease profiles across the stages of the continuum.[32]

The NIHTB-CB is increasingly being used in research studies across diagnostic cohorts and clinical settings.[33] Core NIHTB-CB subtests measure attention, processing speed, executive function, memory, and language.[34,35] Specific subtests include dimensional change card sort and flanker inhibitory control and attention tests, measuring executive functions and attention; pattern comparison processing speed test and oral symbol digit test, measuring information processing speed and attention; list sorting working memory test, measuring working memory; picture sequence memory test, measuring episodic memory; Rey auditory verbal learning test, measuring learning and immediate memory; and picture vocabulary and oral reading recognition tests, measuring language functions and crystalized abilities. The NIHTB-CB test administration took approximately 45 minutes.

To examine both "relative changes" in the participant and "absolute levels" of functioning relative to the community-based comparison using NIHTB-CB data, analyses included both demographically corrected and uncorrected scores, for relative changes versus absolute functional levels, respectively.[35] Moreover, demographically corrected scores substantially reduce premorbid influences in cognitive scores, which increases sensitivity to acquired neurocognitive dysfunction. This increased sensitivity will enable greater accuracy and precision in distinguishing the severity of dysfunction. Cognitive data were examined in the demographically matched NIHTB standardized sample (i.e., age, education), comprising 1,038 English-speaking adults. In contrast, application of uncorrected neurocognitive scores will provide context for absolute levels of functioning relevant to completing real-world

tasks that the average adult in society should be able to perform

Analysis of MoCA subdomains continues to aid in elucidating cognitive profiles. Subdomain make-up includes: (i) visuospatial/executive skills, assessed by a modified trail making test (1 point), copy of a three-dimensional object (1 point), a clock-drawing task (3 points), and abstraction: two-item similarity task (2 points); total visuospatial/executive skills points: 7; (ii) language: confrontation naming of three low-familiarity animal figures (3 points); repetition of two complex sentences (2 points) and list generation phonemic fluency task (1 point awarded if ≥ 11 words are produced in 1 min starting with a particular letter); total language points: 6; (iii) attention: forward and backward digit span task (2 points), a letter tapping task (1 point) and a serial 7-subtraction task (3 points); total attention points: 6; (iv) memory: 5 item registration with 5 min delayed recall: total memory points: 5; (v) time and place orientation (6 points). The total score on the MoCA is obtained by summing all items, with a maximum of 30 points.

Table S3. Retinal and cognitive endpoints and scoring components

Component	Primary endpoints	Operational/scoring notes
Fundus photography	CRAE/CRVE; vessel tortuosity; qualitative microvascular lesions	Non-mydriatic; disc- and macula-centered fields; centralized grading
OCT	RNFL thickness; macular thickness/volume	Spectral-domain OCT; standard scan patterns; QC for signal strength
OCT-A	Vessel density; perfusion metrics (3 × 3 mm macular scans)	Standard AngioPlex/analogous metrics; segmentation QC
MoCA	Total score; domain subscores (executive/visuospatial, attention, language, memory, orientation)	30-point screening tool; prespecified domains used in primary models
NIH toolbox cognition battery	Domain and composite cognition scores	Standardized age-adjusted scores; administered per NIH toolbox manual

Abbreviations: CRAE/CRVE: Central retinal arteriolar equivalent/central retinal venular equivalent; MoCA: Montreal cognitive assessment; NIH: National Institutes of Health; OCT: Optical coherence tomography; OCT-A: Optical coherence tomography angiography; QC: Quality control; RNFL: Retinal nerve fiber layer.

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