SUPPLEMENTARY METHODS

S1. Exclusion criteria

Patients were excluded if they were < 50 years old, had a history of symptomatic cerebrovascular disease (e.g., prior stroke) with residual deficits, alcoholism (>2 drinks/day), anxiety disorder requiring therapy, or renal insufficiency failure (GFR < 60 ml/min/1.73 sq. m). Pregnant or premenopausal women and patients who were unable to read and thus complete the cognitive testing or who scored <24 on a baseline Mini Mental State examination (MMSE) or >27 on the baseline Center for Epidemiological Studies Depression (CES-D) scale or were unsafe for 3 Tesla (3T) MRI were similarly excluded.

S2. Surgical Patient Management

Cardiac Surgery: Anesthesia was induced with propofol, midazolam, fentanyl, and neuromuscular blocking agents, and isoflurane or sevoflurane was used for maintenance. All patients underwent nonpulsatile, hypothermic (30°C - 32°C) CPB with a membrane oxygenator and arterial line filter by a pump primed with crystalloid. Serial hematocrit levels were maintained at ≥ 21%. Before initiating CPB, heparinization (300 - 400 U/kg) was performed to a target activated coagulation time of >480 s. Perfusion was maintained at flow rates of 2 – 2.4 L/min/m2 throughout CPB to maintain a mean arterial pressure of 50 – 80 mmHg. Arterial blood gases were measured every 15 – 30 min to maintain the PaCO2 at 35 – 40 mmHg, unadjusted for temperature (α-stat) and the PaO2 at 150 – 250 mmHg.

Noncardiac Surgery: All patients underwent general anesthesia in the prone position. Anesthesia was induced with propofol, midazolam, fentanyl or sufentanil, and neuromuscular blocking agents and maintained with a combination of isoflurane or sevoflurane, propofol, ketamine, lidocaine, fentanyl and/or sufentanil.

S3. Cognitive Testing

Cognitive testing was performed at baseline (preoperatively) and at 6 weeks after surgery. In accordance with the consensus statement on assessment of neurobehavioral outcomes after cardiac surgery[1], the following tests were included in the assessment battery: 1) *Hopkins Verbal Learning Test – Revised[2]*, assesses verbal list-learning and memory 2) *The Short Story module* of the Randt Memory Test[3], assesses both verbatim and gist recall 3) *WAIS-III Digit Span*[4], tests short-term auditory attention and working memory 4) *Modified Visual Reproduction Test* from the Wechsler Memory Scale[4], assesses short- and long-term figural memory 5) *WAIS-III Digit Symbol*[4], measures psychomotor processing speed and visual attention 6) *Trail Making Test*, Part A and B[5], assesses visual sequencing and cognitive/executive flexibility 7) *Grooved Pegboard*[6], measures perceptual motor speed and manual coordination.

S4. Magnetic Resonance Imaging

MRI was performed post-operatively (on days 1-5, based on clinical stability) on a single 3T Siemens Magnetom Trio Trim scanner. After standard localizer, a T_1- EPI sequence using a fixed flip angle and two alternating TRs (60_ 120 and 120_240) was acquired for generation of a fast B_1 field map for minimizing spatial variations in flip angle[7]. RF field inhomogeneities were also minimized using non-selective pulses. DWI sequences were obtained using an EPI-based sequence (TR/TE 4400/93) with 4 b-values (50/100/200/1200 s/mm^2) to assess for the presence of infarction. The following sequences were then performed prior to contrast material administration: axial T_2-weighted FLAIR (TR/TE/TI 9000/99/2500 ms), sagittal T_1-weighted MPRAGE (TR/TE/TI 2100/2.52/900 ms), 9^O flip angle; sagittal T_1-weighted 3D FLASH (TR/TE 20.0/4.92), 6^O flip angle; sagittal T_1-weighted 3D FLASH (TR/TE 20.0/4.92) 34^O flip angle. Data were acquired at a matrix size of 256 x 256 and FOV 25 x 25 cm. Following administration of Gadobutrol, 0.1 mmol/kg, injected at 4 cc/sec, three additional sagittal T_1-weighted FLASH (TR/TE 20.0/4.92) 34^O flip angle acquisitions were acquired at 5 min intervals.

We used a variant of the delayed contrast extravasation subtraction method for determining BBB permeability by comparing variant flip angle 3D FLASH T_1-maps rather than T_1-weighted signal intensity images over time following contrast administration. Pre and post contrast raw FLASH images at different flip angles used for map generation were co-registered for each subject using conventional anatomic landmarks (e.g., corpus callosum, internal capsule). A board-certified neuroradiologist manually segmented different brain regions (cortex, deep gray, and cerebellum) for regional T_1-relaxivity calculations. T_1 maps were generated using a standard linear equation system as described by Bluml[8] after B_1 field correction, performed offline in Osirix[9].

The threshold for BBB disruption was defined as a positive difference in T_1 relaxivity over the acquisition time within a region of interest (ROI), reflecting progressive accumulation of contrast material in brain tissue (positive value relative ratio (RR) = $T_{1\ map3} - T_{1\ map1} / T_{1\ map1}$ of retained contrast material in one or more brain regions (cortex, deep gray matter, or cerebellum). Brain ROIs with negative relaxivity differences, consistent with 'wash out' of contrast material between initial and final T_1 maps, were defined as having an intact BBB. T_1 maps from extracranial tissues (e.g. paraspinal musculature) served as internal control for wash out dynamics over time. To allow for inter-subject comparisons, time-relaxivity changes were normalized to the T_1 relaxivity change measured in the first post-contrast T_1 map for each subject.

S5. Statistical Analyses

To characterize cognitive function over time while minimizing potential redundancy in the cognitive measures, a factor analysis with orthogonal rotation (a linear transformation of the data, creating uncorrelated factors) was performed on the 14 cognitive test scores. Scoring coefficients (weights) of each test on each factor were determined using the rotated factor solution from the factor analysis conducted on baseline scores among 409 cardiac patients participating in one of our larger concurrent prospective studies (NCT00938964). Factor scores of each subject in our cohort were computed for all time points using the same scoring coefficients, so that the cognitive

domain structure remained consistent and comparable over time. Factor analysis suggested a five-factor solution representing five cognitive domains: (1) structured verbal memory (*i.e.*, the ability to recall from a list); (2) unstructured verbal memory (*i.e.*, the ability to remember from a narrative); (3) visual memory; (4) executive function; and (5) attention and concentration. We defined continuous cognitive outcome measures for each cognitive domain as the change in cognitive score calculated by subtracting the baseline from the follow-up domain score (a change score of 0 indicates no change from baseline, while a negative score indicates cognitive decline, and a positive score indicates cognitive improvement). We also defined a composite cognitive score outcome (the cognitive index) as the average of the five domain change scores. Permeability was analyzed as a continuous measure or binary indicator of any positive value by region, and globally as the average RR value across regions and as a cumulative number of regions with increased permeability.

We described the demographic and clinical characteristics of the cardiac and non-cardiac patient cohorts via mean (SD) or median (Q1, Q3) for numeric factors, and N (%) for categorical factors. Since this was a pilot study, only the strength of association between cognitive score change (both composite and by domain) at 6 weeks and the quantitative measures of BBB disruption (globally and by region) was measured using Pearson or Spearman correlations, as appropriate. Differences in cognitive change for patients with and without BBB disruption were assessed using t-tests or Wilcoxon rank sum tests. $P < 0.05$ was considered significant, and analyses were conducted in SAS v 9.4 (SAS Inc., Cary, NC).

Supplementary Table 1. Characteristics of the cardiac and non-cardiac patient cohorts. CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; POD, postoperative day

Variable	Cardiac (n=10)	Non-Cardiac (n=8)	P-value
Age (yr)	62.7 (3.7)	63.5 (7.0)	0.759[1]
Sex (Male)	6 (60.0)	3 (37.5)	0.637[3]
Race (White)	8 (80.0)	5 (62.5)	0.608[3]
Weight (Kg)	88.5 (16.4)	86.0 (7.1)	0.680[1]
History of Hypertension	7 (70.0)	7 (87.5)	0.588[3]
Diabetes Mellitus	5 (50.0)	4 (50.0)	>0.999[3]
Previous MI	2 (22.2)	0 (0.0)	0.471[3]
Ejection Fraction (%)	55.0 (50.0, 60.0)	--	
Years Education	15.0 (14.0, 17.0)	15.5 (12.0, 16.5)	0.650[2]
Preoperative Statins	6 (60.0)	4 (50.0)	>0.999[3]
Preoperative Platelet inhibitors	6 (60.0)	4 (50.0)	>0.999[3]
Surgical Procedure			
CABG	4 (40.0)	0 (0.0)	
CABG + Valve	1 (10.0)	0 (0.0)	
Valve	5 (50.0)	0 (0.0)	
Lumbar Fusion	0 (0.0)	4 (50)	
Lumbar Laminectomy	0 (0.0)	3 (37.5)	

Thoracolumbar	0 (0.0)	1 (12.5)	
Laminectomy			
No. of Grafts*			
1	0 (0.0)	--	
2	1 (20.0)	--	
3	3 (60.0)	--	
>3	1 (20.0)	--	
Cross-Clamp time (min)	161.5 (115.0, 182.0)	--	
CPB time (min)	116.0 (82.0, 120.0)	--	
Baseline Cognitive Score	0.2 (0.5)	0.2 (0.6)	0.908[1]
6-Week Cognitive Score	0.4 (0.5)	0.2 (0.7)	0.542[1]
Scan POD	3.0 (3.0, 4.0)	2.0 (1.0, 2.0)	<0.001[2]

Numeric variables described by mean (SD) or median (Q1, Q3). Categorical variables described by N (%). MI – myocardial infarction; CABG – coronary artery bypass grafting; CPB – cardiopulmonary bypass; POD postoperative day

*Among Patients undergoing CABG or CABG + Valve procedures.

P-value key: [1]t-test, [2]Wilcoxon Rank Sum, [3]Fisher Exact

Table 2. Relative relaxivity (RR) values, and global cognitive (CCI) and domain change scores for all 18 study subjects. CX = cortex, DG = deep gray, CERE =cerebellum, C = cardiac surgery, NC = non-cardiac surgery

Patient	Group	RR CX	RR DG	RR CERE	RR Global	Regions with RR>0	CCI	Unstructured Verbal Memory	Executive Function	Structured Verbal Memory	Visual Memory	Attention/ Concentration
1	NC	-0.33	-0.42	-0.64	-0.46	0	0.001	0.119	1.356	0.146	-0.900	-0.716
2	NC	-0.23	-0.20	-0.50	-0.31	0	0.081	-0.580	0.780	0.452	-0.316	0.067
3	C	-0.25	-0.33	-0.31	-0.30	0	0.360	-0.966	1.938	0.747	-1.262	1.341
4	NC	-0.20	-0.28	-0.39	-0.29	0	-0.201	-0.171	1.051	0.484	-2.211	-0.160
5	NC	-0.14	-0.20	-0.27	-0.20	0	0.152	0.966	0.454	-0.296	-0.747	0.384
6	C	-0.11	-0.14	-0.35	-0.20	0	0.429	-0.741	0.504	1.078	1.256	0.048
7	C	0.00	-0.33	-0.22	-0.18	0	0.494	1.445	0.292	-0.101	0.668	0.166

8	C	-0.12	-0.11	-0.16	-0.13	0	0.119	0.951	0.315	-1.001	0.858	-0.526
9	C	-0.20	0.00	-0.11	-0.10	0	0.370	1.430	0.308	-1.194	0.533	0.773
10	C	0.14	-0.18	-0.08	-0.04	1	0.214	-2.384	0.057	1.837	0.908	0.653
11	NC	0.00	0.08	-0.13	-0.02	1	0.058	-0.066	0.932	0.486	-1.338	0.278
12	NC	0.00	0.00	0.00	0.00	0	0.238	-0.565	1.161	0.798	0.063	-0.269
13	NC	0.13	0.07	-0.11	0.03	2	0.048	0.282	0.828	-0.158	-0.164	-0.547
14	C	0.00	0.10	0.00	0.03	1	0.137	0.062	0.302	-0.277	0.957	-0.361
15	C	0.25	0.36	-0.28	0.11	2	0.020	0.577	0.347	-0.306	-0.092	-0.427
16	C	0.00	0.25	0.10	0.12	2	-0.005	0.486	1.681	-1.445	-0.245	-0.502
17	NC	0.27	0.19	-0.04	0.14	2	-0.008	-1.226	0.218	2.405	-1.440	0.000
18	C	-0.28	0.50	0.20	0.14	2	0.365	0.180	-0.248	0.286	1.044	0.563

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