Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

MRI Acquisition. The MRI protocol included sequences to measure brain structure and physiology and was performed at 7 centers using 3 Tesla scanners. The study used 3 Phillips Achieva scanners (University of Alabama at Birmingham, Boston University, Vanderbilt University), Siemens Skyra VD11B (Wake Forest University), Siemens TimTrio VB17 (University of Miami and University of Pennsylvania), Siemens Verio VB17 (Case Western Reserve University). Relevant to this study, the following imaging sequences were obtained: T1 (Repetition time=1900ms, Echo time=2.89ms, Field of view=250mm, slices=176, native resolution=1mm isotropic), T2 (Repetition time=200ms, Echo time=409ms, Field-of-view=250mm, slices=176, native resolution=1mm isotropic), FLAIR (Repetition time=6000ms, Inversion time=2200ms, Echo time=285ms, Field of view=258mm, thickness=1mm, slices=160, native resolution=1mm isotropic), 30-direction diffusion tensor imaging (Repetition time=7300ms, Echo time=82ms, Field-of-view=246mm, thickness=2.2mm, slices=64, native resolution=2.2mm isotropic), and pseudocontinuous arterial spin label (labeling time=1.5s, postlabeling delay=1.5s, repetition time=4000ms, echo time=11ms, field of view=220mm, voxel size=3.4x3.4x5mm^3, 20% distance factor, 40 label/control pairs). Scanner performance was monitored with quarterly Alzheimer's Disease Neuroimaging Initiative (ADNI) and Function Biomedical Informatics Research Network phantom acquisition, with all scanners showing stability of phantom measurements throughout the trial. Sixteen participants with scans showing structural brain lesions (large areas of encephalomalacia (n=10), tumors (n=3), subdural hematoma at the follow up scan (n=2), or prior brain resection (n=1)) were excluded from analyses.

SPatial Pattern for REcognition of Alzheimer's Disease (SPARE-AD). Neurodegenerative diseases have widespread effects on brain structure that are not well captured by typical region of interest (ROI) analyses. Machine learning methods are able to integrate changes throughout

the brain to classify a structural magnetic resonance imaging scan as coming from either a patient with Alzheimer disease or a healthy control with high accuracy, frequently above 85%.[1-4] We trained such a classifier using data from the Alzheimer's Disease Neuroimaging Initiative ADNI using the segmented ROI volumes derived for this study. A total of 476 training examples were included, comprised of 222 patients with Alzheimer disease and 254 healthy controls. For the classification algorithm, we used support vector machines with a linear kernel, and we implemented hyper-parameter tuning of the regularization penalty and class weights via cross-validated grid search (optimal parameters selected were C=0.135, class weight="balanced"). The algorithm achieved cross-validated accuracy of 90.1% for out-of-sample predictions in the training set.

Cognitive testing. For analyses of cognitive test results, we utilized composite cognitive domain scores that were derived from the raw cognitive test scores reflecting memory (Hopkins Verbal Learning Test-Revised delayed recall, the Modified Rey-Osterreith Complex Figure immediate recall, and Logical Memory I and II), processing speed (Trail Making Test-Parts A and B and Digit Symbol Coding), executive function (Trail Making Test – Part B minus Part A and Digit Span), language (Boston Naming Test-15 and Category Fluency – Animals), and global cognitive function (all tests included in the above domain scores).[5]

eReferences

1. Kloppel S, Stonnington CM, Chu C, et al. Automatic classification of MR scans in Alzheimer's disease. *Brain.* 2008;131(Pt 3):681-689.
2. Liu S, Liu S, Cai W, et al. Multimodal neuroimaging feature learning for multiclass diagnosis of Alzheimer's disease. *IEEE Trans Biomed Eng.* 2015;62(4):1132-1140.
3. Zhang Y, Dong Z, Phillips P, et al. Detection of subjects and brain regions related to Alzheimer's disease using 3D MRI scans based on eigenbrain and machine learning. *Front Comput Neurosci.* 2015;9:66.
4. Salvatore C, Cerasa A, Battista P, et al. Magnetic resonance imaging biomarkers for the early diagnosis of Alzheimer's disease: a machine learning approach. *Front Neurosci.* 2015;9:307.
5. Rapp SR, Gaussoin SA, Sachs BC, et al. Effects of intensive versus standard blood pressure control on domain-specific cognitive function: a substudy of the SPRINT randomised controlled trial. *Lancet Neurol.* 2020;19(11):899-907.

eTable 1. Significantly different baseline characteristics between participants in the MRI substudy versus remaining trial participants

Characteristic	In MRI Substudy N = 673	Not in MRI Substudy N = 8688	Standardized Mean Difference	P Value
Age 75 years or older, No. (%)	150 (22.4)	2486 (28.6)	0.146	0.001
Sex, No. (%)			0.104	0.01
Male	402 (59.7)	5627 (64.8)		
Female	271 (40.3)	3061 (35.2)		
Race/Ethnicity, No. (%)			0.209	<0.001
White	409 (60.8)	4990 (57.4)		
Black	218 (32.4)	2584 (29.7)		
Hispanic[a]	36 (5.3)	948 (10.9)		
Other[b]	10 (1.5)	166 (1.9)		
History of CVD, No. (%)	93 (13.8)	1784 (20.5)	0.179	<0.001
Systolic Blood Pressure, mean (SD), mm Hg	138.1 (16.7)	139.8 (15.5)	0.105	0.007
Montreal Cognitive Assessment, median [IQR][c]	24 [21 to 26]	23 [20 to 26]	0.161	<0.001
Logical Memory form II, median [IQR][d]	9 [6 to 11]	8 [6 to 11]	0.101	0.02
Digit Symbol Coding test, median [IQR][e]	52 [42 to 62]	51 [41 to 61]	0.088	0.04
Total cholesterol, mean (SD), mg/dL	193.5 (40.6)	189.9 (41.2)	0.088	0.03
LDL cholesterol, mean (SD), mg/dL	115.4 (35.0)	112.2 (35.1)	0.094	0.02
Potassium, median [IQR], mmol/L	4.1 [3.9 to 4.4]	4.2 [3.9 to 4.5]	0.102	0.001

SD denotes standard deviation; CVD, cardiovascular disease; LDL, low density lipoprotein; IQR, interquartile range.
SI conversion factors: To convert LDL cholesterol to mmol/L, multiply by 0.0259.
[a]Hispanic race/ethnicity encompasses a self-report of being of Spanish, Hispanic, or Latino origin, independent of any other race/ethnicity designation. [b]Other race/ethnicity includes categories of Asian, American Indian/Alaskan Native, Native Hawaiian/Pacific Islander, or other. [c]Scores range from 0 to 30, with higher scores denoting better cognitive function. [d]Subtest of the Wechsler Memory Scale. Scores range from 0 to 14, with higher scores denoting a better performance. [e]Subtest of the Wechsler Memory Scale. Scores range from 0 to 135, with higher scores denoting better performance.

eTable 2. Change in magnetic resonance imaging outcomes by treatment group and stratified by sex

		Intensive Treatment	Standard Treatment		
Outcome	Sex	Change (SE)	Change (SE)	Difference (95% CI)	Interaction P value
Hippocampal volume, cm^3	Male	-0.06 (0.02)	-0.05 (0.02)	-0.006 (-0.055, 0.042)	0.19
	Female	-0.06 (0.01)	-0.01 (0.01)	-0.047 (-0.084, -0.010)	
Frontal gray matter volume, cm^3	Male	-6.99 (0.49)	-6.88 (0.57)	-0.11 (-1.58, 1.36)	0.10
	Female	-8.23 (0.39)	-6.57 (0.42)	-1.67 (-2.79, -0.54)	
SPARE-AD	Male	0.33 (0.04)	0.30 (0.04)	0.033 (-0.080, 0.146)	0.95
	Female	0.30 (0.03)	0.26 (0.03)	0.038 (-0.049, 0.124)	
Meta-ROI mean cortical thickness, mm	Male	-0.10 (0.01)	-0.14 (0.02)	0.035 (-0.007, 0.076)	0.03
	Female	-0.11 (0.01)	-0.09 (0.01)	-0.022 (-0.054, 0.010)	
Mean FA in the cingulum bundle	Male	0.001 (0.003)	-0.002 (0.003)	0.003 (-0.005, 0.010)	0.10
	Female	-0.003 (0.002)	0.002 (0.002)	-0.005 (-0.011, 0.001)	
Mean FA in the corpus callosum genu	Male	-0.018 (0.004)	-0.023 (0.004)	0.005 (-0.006, 0.016)	0.05
	Female	-0.025 (0.003)	-0.016 (0.003)	-0.009 (-0.017, -0.0004)	
CBF posterior cingulate gyrus, mL/100 mg/min	Male	-1.85 (1.76)	-0.66 (1.99)	-1.20 (-6.41, 4.01)	0.20
	Female	1.35 (1.46)	-1.77 (1.56)	3.13 (-1.07, 7.32)	
rCBF posterior cingulate gyrus relative to Putamen	Male	-0.15 (0.03)	-0.04 (0.04)	-0.11 (-0.21, -0.01)	0.03
	Female	-0.06 (0.03)	-0.09 (0.03)	0.03 (-0.05, 0.11)	
Frontal gray matter CBF, mL/100 mg/min	Male	1.09 (1.41)	-1.48 (1.57)	2.58 (-1.57, 6.72)	0.82
	Female	1.49 (1.18)	-0.48 (1.23)	1.97 (-1.38, 5.32)	

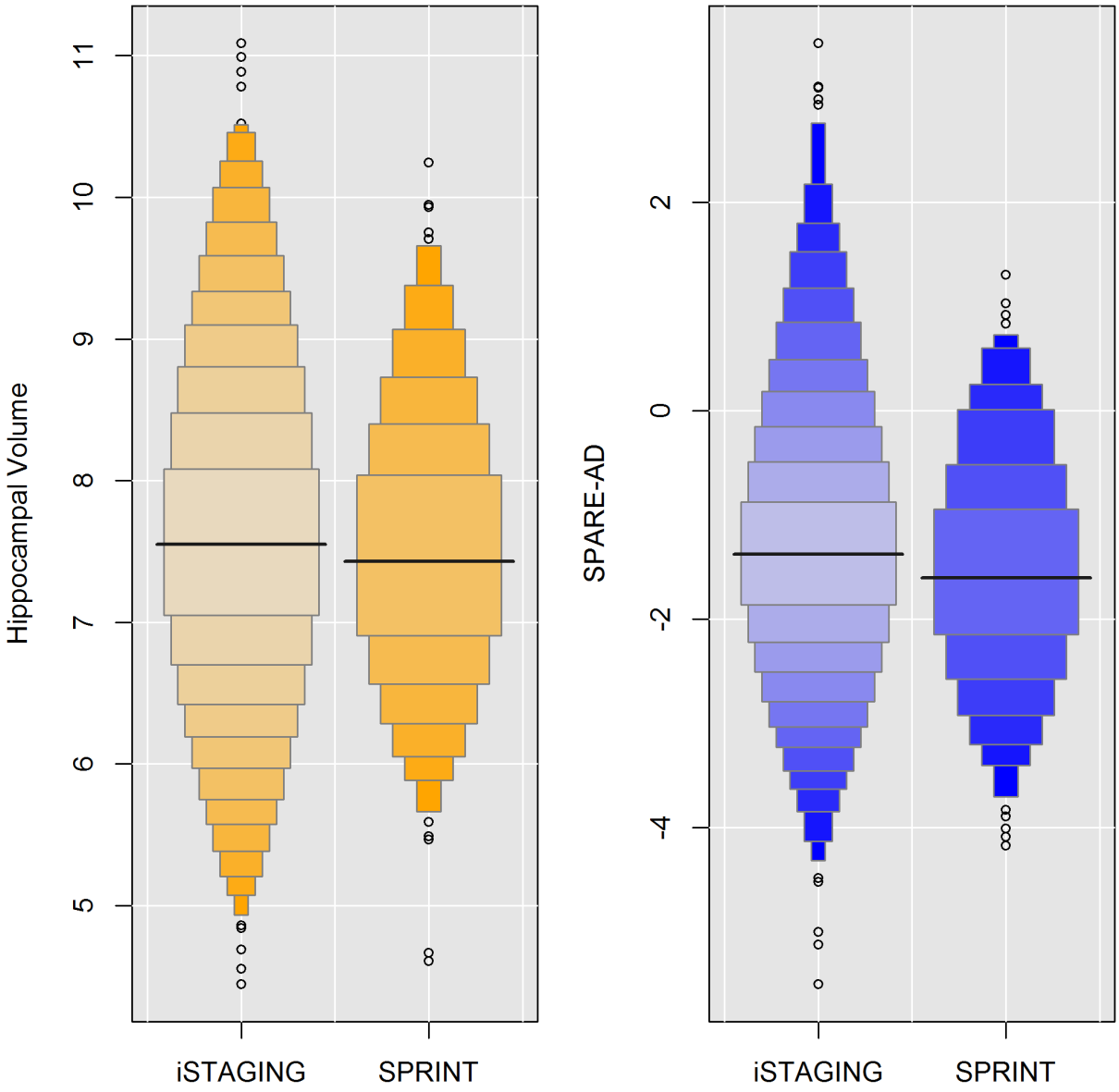
CBF denotes cerebral blood flow, CI confidence interval, FA fractional anisotropy, rCBF regional CBF, ROI region of interest, SE standard error, SPARE-AD SPatial Pattern for REcognition of Alzheimer Disease. Estimates based on a linear mixed model adjusting for age, intracranial volume (for hippocampal volume, frontal gray matter volume, and SPARE-AD), and days since randomization, with random effects for participant and MRI facility. Change denotes estimated least square mean comparing follow-up (estimated at 3.98 years post-randomization); negative values denote decreases from baseline, while positive values indicate increases from baseline. Difference in change reflects intensive treatment group minus standard treatment group.

eTable 3. Annual Change in Cognitive Domain Scores by Treatment Group for Participants in the Magnetic Resonance Imaging Sub-study

	Intensive Treatment		**Standard Treatment**			
Cognitive Domain Or Test	Baseline Mean (95 %CI)	Estimated Change Per Year (95% CI)	Baseline Mean (95 %CI)	Estimated Change Per Year (95% CI)	Difference (95% CI)	P value
Memory	-0.006 (-0.124, 0.113)	-0.011 (-0.024, 0.002)	-0.008 (-0.13, 0.113)	0.001 (-0.013, 0.015)	-0.012 (-0.031, 0.007)	0.20
Processing Speed	-0.062 (-0.176, 0.053)	-0.004 (-0.016, 0.007)	-0.031 (-0.15, 0.087)	0.002 (-0.01, 0.014)	-0.006 (-0.023, 0.011)	0.47
Language	-0.116 (-0.239, 0.006)	-0.007 (-0.018, 0.005)	-0.061 (-0.187, 0.065)	-0.008 (-0.02, 0.005)	0.001 (-0.016, 0.018)	0.91
Executive Function	0.001 (-0.106, 0.108)	-0.019 (-0.034, -0.005)	0.012 (-0.098, 0.123)	0.005 (-0.011, 0.02)	-0.024 (-0.045, -0.003)	0.02
Global Cognitive Function	-0.079 (-0.213, 0.055)	-0.009 (-0.018, 0)	-0.052 (-0.189, 0.086)	-0.001 (-0.011, 0.009)	-0.008 (-0.021, 0.006)	0.25
Montreal Cognitive Assessment	23.616 (23.081, 24.152)	-0.039 (-0.116, 0.039)	23.846 (23.29, 24.402)	-0.103 (-0.187, -0.019)	0.064 (-0.051, 0.178)	0.27

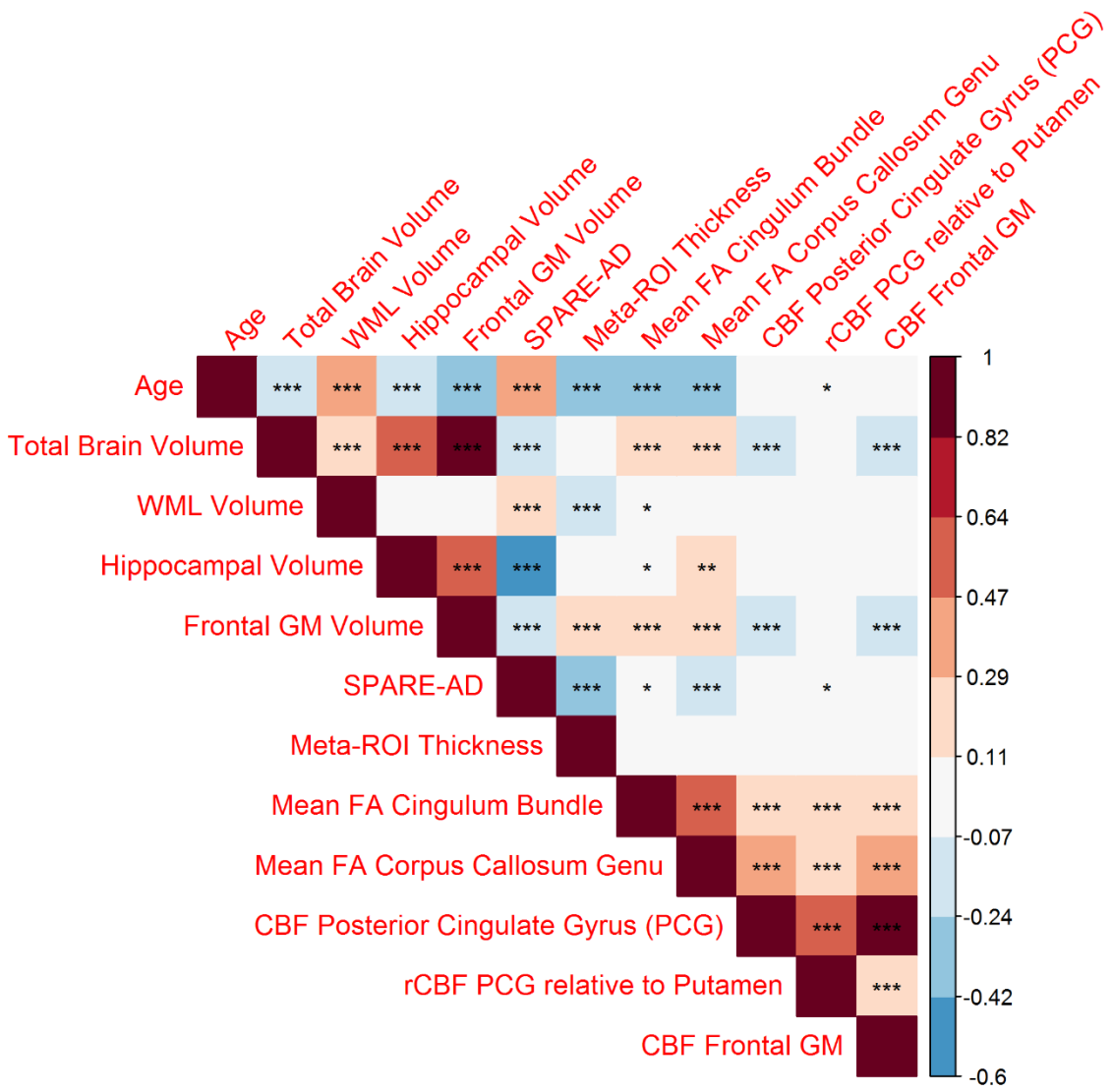
Estimates represent baseline mean and annual slope (estimated change per year) assuming linear change over time based on a robust linear mixed model. CI denotes Confidence Interval. The memory composite outcome includes the Logical Memory I and II, Modified Rey-Osterreith Complex Figure Immediate Recall, and the Hopkins Verbal Learning Test-Revised Delayed Recall. The processing speed composite includes Trail Making Test Parts A and B and the Digit Symbol Coding. The language composite includes the Boston Naming Test and Category Fluency – Animals. The executive function composite includes the Trail Making Test Part B minus Part A and the Digit Span. The global cognitive function composite includes all of the above tests, but not the Montreal Cognitive Assessment.

eFigure 1. Baseline comparison of SPRINT MRI cohort to participants in the iSTAGING cohort without mild cognitive impairment or dementia



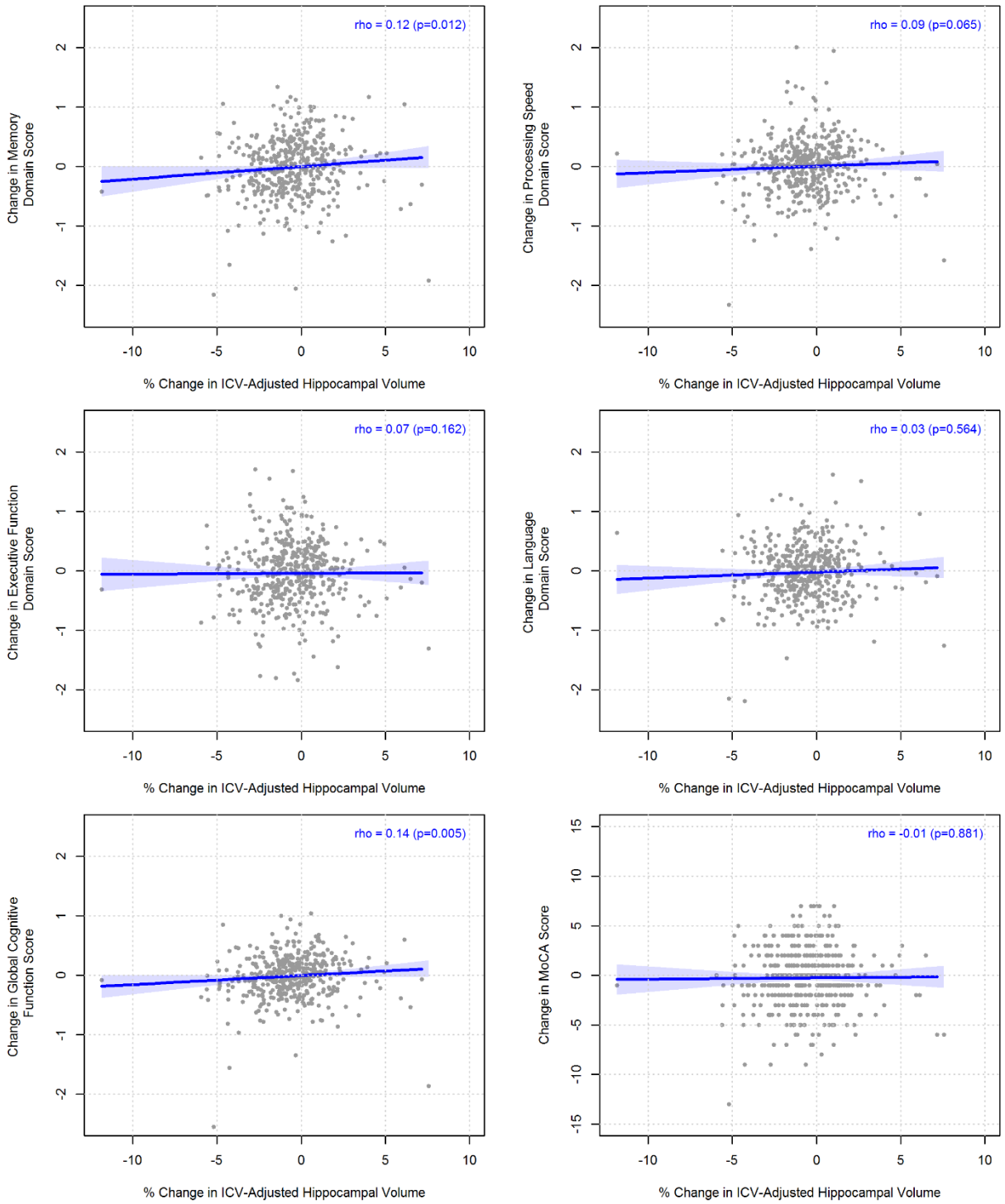
Participants in the iSTAGING cohort were between 50 and 90 years of age, with a mean age of 66.1 ± 6.4 years, with 8.7% ≥75 years of age. The iSTAGING cohort used for this analysis includes cognitively normal participants from the following studies: the Alzheimer's Disease Neuroimaging Initiative, the Baltimore Longitudinal Study of Aging, the Coronary Artery Risk Development in Young Adults study, and the UK BioBank. Data from these studies was processed with the same analysis methods used in SPRINT.

eFigure 2. Spearman rank correlations between baseline measurements of total brain volume, white matter lesion volume, and other magnetic resonance imaging biomarkers



Values are Spearman's rank correlation for correlations with age, all other values are a partial Spearman's correlation adjusting for age. CBF denotes cerebral blood flow, FA denotes fractional anisotropy, GM gray matter, rCBF regional CBF, ROI region of interest, SPARE-AD SPatial Pattern for REcognition of Alzheimer Disease, and WML white matter lesion. *P value<0.05, **P value<0.01, ***P value<0.001.

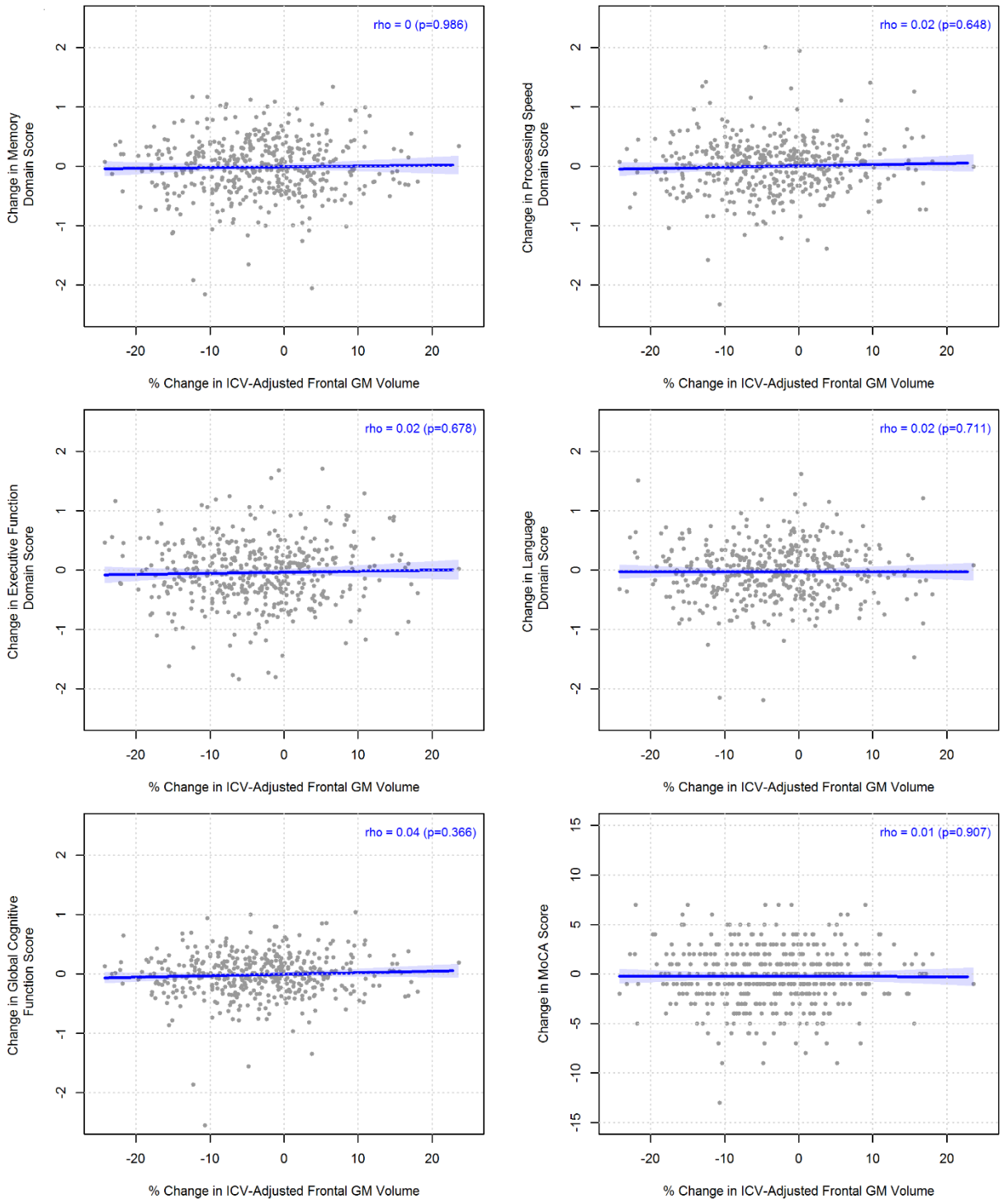
eFigure 3. Correlation between change in cognitive domain scores and scores on the Montreal Cognitive Assessment with change in hippocampal volume



ICV denotes intracranial volume. Blue lines represent least squares regression line with associated 95% confidence intervals. The memory composite outcome includes the Logical

Memory I and II, Modified Rey-Osterreith Complex Figure Immediate Recall, and the Hopkins Verbal Learning Test-Revised Delayed Recall. The processing speed composite includes Trail Making Test Parts A and B and the Digit Symbol Coding. The language composite includes the Boston Naming Test and Category Fluency – Animals. The executive function composite includes the Trail Making Test Part B minus Part A and the Digit Span. The global cognitive function composite includes all of the above tests, but not the Montreal Cognitive Assessment.

eFigure 4. Correlation between change in cognitive domain scores and scores on the Montreal Cognitive Assessment with change in frontal gray matter volume



GM denotes gray matter and ICV intracranial volume. Blue lines represent least squares regression line with associated 95% confidence intervals. The memory composite outcome includes the Logical Memory I and II, Modified Rey-Osterreith Complex Figure Immediate Recall, and the Hopkins Verbal Learning Test-Revised Delayed Recall. The processing speed composite includes Trail Making Test Parts A and B and the Digit Symbol Coding. The language composite includes the Boston Naming Test and Category Fluency – Animals. The executive function composite includes the Trail Making Test Part B minus Part A and the Digit Span. The global cognitive function composite includes all of the above tests, but not the Montreal Cognitive Assessment.