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Neuroimaging differences between older adults with maintained versus declining cognition over a 10-year period

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Abstract

Background—Maintaining cognitive function protects older adults from developing functional decline. This study aims to identify the neuroimaging correlates of maintenance of higher global cognition as measured by the Modified Mini Mental State Test (3MS) score.

Methods—Repeated 3MS measures from 1997–98 through 2006–07 and magnetic resonance imaging with diffusion tensor in 2006–07 were obtained in a biracial cohort of 258 adults free from dementia (mean age 82.9 years, 56% women, 42% blacks). Participants were classified as having shown either maintenance (3MS slope>0) or decline (3MS slopeb1 SD below the mean) of cognition using linear mixed models. Measures of interest were white matter hyperintensity volume (WMHv) from total brain, volume of the gray matter (GMv) and microstructure (mean diffusivity, MD) for total brain and for brain areas known to be related to memory and executive control function: medial temporal area (hippocampus, parahippocampus and entorhinal cortex), cingulate cortex, dorsolateral prefrontal and posterior parietal cortex.

Results—Differences between cognitive maintainers (n=153) and non-maintainers (n=107) were significant for GMv of the medial temporal area (35.8%, p=0.004) and lower MD of the cingulate cortex (37.9%, p=0.008), but not for other neuroimaging markers. In multivariable regression models adjusted for age, race, WMHv and GMV from the total brain and vascular conditions, each standard deviation of GMv of the medial temporal area and each standard deviation of MD of the cingulate cortex were associated with a nearly 4 times greater probability (odds ratio [standard deviation]: 3.80 [1.16, 12.44]) and a 34% lower probability (0.66, [0.46, 0.97]) of maintaining

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Appendix A. Supplementary data Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2012.04.033.

cognitive function, respectively. In these models neither WMHv nor GMv from total brain were significantly associated with probability of maintaining cognitive function.

Conclusions—Preserving the volume of the medial temporal area and the microstructure of the cingulate cortex may contribute to maintaining cognitive function late in life.

Introduction

Maintaining cognitive function is critical for maintaining autonomy and optimal quality of life in later years. Although cognitive function is commonly thought to decline with age, recent studies suggest that some older adults maintain cognitive function late in life. We have recently shown that in a large cohort of community dwelling older adults 69–79 years old, about 30% maintain high scores on global cognition over a period of 8 years, indicating that maintaining cognition is not a rare phenomenon of aging (Barnes et al., 2007; Yaffe et al., 2009a). It is important to understand the physiology underlying maintaining cognitive function late in life, because higher cognitive function is associated with lower mortality and lower risk of developing disability (Depp and Jeste, 2006; Habib et al., 2007; Rosano et al., 2008; Rowe and Kahn, 1987). Our recent work indicates that maintenance of higher 3MS score is associated with lower risk of functional decline (Yaffe, Lindquist et al., 2010). Risk factors associated with maintenance of higher 3MS score in non-demented older adults include lower levels of plasma beta-amyloid (Yaffe et al., 2010, 2011b) and of advanced glycation end product levels (Yaffe et al., 2011a), longer telomere length (Yaffe et al., 2009b), lower levels of inflammatory factors (Yaffe et al., 2007), as well as modifiable factors including greater literacy, more exercise, less smoking, lower adiposity (Kanaya et al., 2009), continued working or volunteering and living with someone (Inzelberg et al., 2007; Middleton et al., 2010, 2011; Yaffe et al., 2009a).

However, reports on the neuroanatomical correlates of maintaining cognitive function are sparse. Specifically, it is not clear whether the brain characteristics associated with maintaining cognitive function simply consist of the absence of dementia-related brain changes or whether they represent an entity of their own right. Identifying the regions related to maintenance of cognitive function might be important to quantify the effects and underlying mechanisms of intervention studies to reduce functional decline.

This study aims to quantify the neuroimaging correlates associated with maintaining global cognitive function late in life by applying high resolution neuroimaging methods in a very well characterized cohort study of community-dwelling older adults participating in the Health, Aging, and Body Composition Study (Health ABC). This study applies diffusion tensor imaging measures of micro-structure because micro-structural abnormalities may accumulate in the aging brain before they can be visually detected as macro-structural abnormalities on a conventional brain MRI, for example as atrophy or hyperintensities. Specifically, lower fractional anisotropy and higher mean diffusivity from Diffusion Tensor Imaging (DTI) indicate loss of homogeneity of brain tissue and are observed in brain abnormalities that develop with aging (Benedetti et al., 2006). The primary hypothesis is that older adults who have maintained global cognition as measured with 3MS, will display greater tissue integrity (e.g. greater volume and lower mean diffusivity of the gray matter and higher fractional anisotropy of the white matter) of the medial temporal and prefronto-parietal areas. These areas were selected because of their known association with memory and with executive control function, two cognitive domains commonly impaired in older adults (Wen et al. 2011; Raz, 2004; Zola-Morgan and Squire, 1993). Furthermore, we hypothesize that the gray matter of the sensorimotor cortex, a region not expected to be associated with cognitive function, will not significantly differ between groups.

Methods

Study population

We studied a subset of participants enrolled in the Health, Aging, and Body Composition Study (Health ABC). The Health ABC began in 1997–1998 as a longitudinal, observational cohort study of 3075 well-functioning older white and black men and women, 70–79 years old, from Pittsburgh, PA and Memphis, TN (Simonsick et al., 2001), who reported no difficulty walking a quarter of a mile (400 m), climbing 10 steps, or performing activities of daily living. Participants were enrolled if they were free of life-threatening cancers with no active treatment within the prior 3 years and had planned to remain within the study area for at least 3 years.

In 2006–2007, 314 Health ABC participants from the Pittsburgh site who were interested and eligible for a brain 3 T MRI and who were able to walk 20 m, participated in the ancillary study called the Healthy Brain Project. Participants received a brain MRI in addition to Health ABC assessments. Among the 314 participants, 280 had complete DTI data. Of these, 258 had a Modified Mini-Mental State Examination (3MS) score of at least 80 in 1997–98 (without clinical impairment (Teng and Chui, 1987)) and at least one additional cognitive assessment during the 10 years between 1997 and 1998 and the time of MRI. This study was approved by the institutional review boards of the clinical site (University of Pittsburgh) and the coordinating center (University of California, San Francisco).

Magnetic resonance image acquisition

MRI scanning used a Siemens 12-channel head coil and was performed on a 3 T Siemens Tim Trio MR scanner at the MR Research Center of the University of Pittsburgh. Four series of MRI images were acquired on the MR scanner. Magnetization-prepared rapid gradient echo (MPRAGE) T1-weighted images were acquired in the axial plane: TR=2300 ms; TE=3.43 ms; TI=900 ms; flip angle=9; slice thickness=1 mm; FOV=256*224 mm; voxel size=1 mm*1 mm; matrix size=256*224; and number of slices=176. Fluid-attenuated inversion recovery (FLAIR) images were acquired in the axial plane: TR=9160 ms; TE=89 ms; TI=2500 ms; FA=150; FOV=256*212 mm; slice thickness=3 mm; matrix size=256*240; number of slices=48 slices; and voxel size=1 mm*1 mm. Diffusion Weighted Images (DTI) were acquired using single-short spin-echo sequence with the following parameters: TR=5300 ms; TE=88 ms; TI=2500 ms; flip angle=90; FOV=256*256 mm; two diffusion values of b=0 and 1000 s/mm; 12 diffusion directions; four repeats; 40 slices; matrix size=128*128; voxel size=2 mm*2 mm; slice thickness=3 mm; and GRAPPA=2. A radiologist verified that the MR images for this study did not have unexpected findings.

Image processing and analysis

White matter hyperintensity volume was obtained from T2-weighted FLAIR image using an automated method for quantification and localization of WMH. The WMH quantification was done using a fuzzy connected algorithm with automated seed selection (Wu et al., 2006). Total WMH volume was estimated by summing all the voxels classified as WMH and normalized for brain volume. Volumes of the gray matter, white matter, and cerebrospinal fluid, were calculated by segmenting the skull-stripped T1-weighted image in native anatomical space using the FAST — FMRIB's Automated Segmentation Tool (Zhang et al., 2001). The total gray matter volume, white matter volume, and CSF volume were estimated in cubic millimeters by summing all voxels classified as these tissue types. Total intracranial volume was computed as the volume contained within the 'inner skull' using the brain extraction tool (BET) (Jenkinson et al., 2005). Atrophy index was computed by

subtracting brain parenchyma volume (gray and white matter volume from the total brain) from the intracranial volume.

Two parameters were obtained from the diffusion weighted images: mean diffusivity (MD) — an average magnitude of molecular motion or measure of cell structure damage (Bhagat and Beaulieu, 2004), and fractional anisotropy (FA) — a marker of white matter tract integrity (Pierpaoli and Basser, 1996). The diffusion-weighted images were pre-processed using the FMRIB's Diffusion Toolbox (Smith et al., 2004) to remove unwanted distortions due to eddy current, the tensor were computed (Basser et al., 1994), and diagonalized to determine the eigenvalues from which the FA and MD maps were computed (Pierpaoli et al., 1996).

The FA and MD maps were registered to the FMRIB58-FA template (Smith et al., 2004) using the FMRIB's Non-linear Image Registration Tool (FNIRT) (Andersson et al., 2007), similar to the Tract-based Spatial Statistics (Smith et al., 2006). Using the segmentation of white matter, gray matter, and white matter hyperintensities that were obtained from the T1-weighted and T2-weighted FLAIR images, the FA and MD maps were restricted to normal appearing white matter and normal appearing gray matter (Barrick et al., 2010, Epub ahead of print; Budde et al., 2007; Spilt et al., 2005). Masking the aligned images with the gray matter (segmented with FAST from the T1 image as described above) was done to minimize partial volume effects of the MD.

Neuroanatomical boundaries for the brain areas of interest

Neuroanatomical boundaries of the gray matter regions for the mean diffusivity and the volumetric analyses were identified using a previously published atlas (Tzourio-Mazoyer et al., 2002) separately for the right and left hemispheres. The medial temporal lobe comprises the hippocampus, entorhinal cortex and parahippocampus, regions known to be related to memory (Dickerson et al., 2001; Rusinek et al., 2003; Zola-Morgan and Squire, 1993). The entorhinal cortex was defined using the boundaries of Brodmann area 28. Regions known to be related to executive control function included the dorsolateral prefrontal, posterior parietal and cingulate cortex (Eckert, 2011; Raz, 2004; Rosano et al., 2011). The dorsolateral prefrontal cortex was identified using the boundaries of the middle frontal gyrus. The posterior parietal cortex comprises the precuneus medially, and the superior and inferior lobule dorsally. The cingulate cortex was defined using the boundaries of Brodmann areas 24 and 32. The sensorimotor area includes the pre and post-central gyri. White matter tracts were identified using the Johns Hopkins University (JHU) White Matter Atlas (Smith et al., 2006) and included tracts related to memory (uncinate fasciculus (Fujie et al., 2008; Metzler-Baddeley et al., 2011) and cingulum) and (Kantarci et al., 2011 to executive control function (superior longitudinal fasciculus (Turken et al., 2008; Sasson et al., 2011)).

Cognitive function

The 3MS was administered to participants at study baseline and after 2, 4, 7 and 10 years of follow-up. The 3MS is a brief, general cognitive battery with components for orientation, concentration, language, praxis, and immediate and delayed memory (Teng and Chui, 1987). Possible scores range from 0 to 100, with higher scores indicating better cognitive function. The method to obtain the slope over time in cognitive function has been previously published (Yaffe et al., 2009a). Briefly, the participant-specific slopes of 3MS scores were estimated by best liner unbiased predictions using a linear mixed model with random intercepts and slopes. Participants with predicted slopes of 0 or greater (indicating no change or improvement in cognitive scores over time) were classified as having maintained function. Those with predicted slopes less than 0 (decline in cognitive score over time) were classified as having 'cognitive decline'. In this group, we also identified those with a slope

more than 1 SD below the mean, because they might have had a more severe decline as compared to those with decline below 0 and above 1 SD. Analyses were repeated after exclusion of these participants with a more severe decline.

Other measures of interest

Other variables of interest were selected based on our prior work that identified predictors of maintaining cognitive function in this cohort (Yaffe et al., 2009a). In addition to participant's gender, age, race, and whether or not they achieved a high-school level of education, health characteristics were collected since study entry and included self-rated health (categorized as good, very good, or excellent vs fair or poor) and weekly moderate/vigorous exercise. Weekly moderate/vigorous exercise was defined as engagement in moderate to vigorous exercise and activity (e.g., aerobics, weight training, or brisk walking) at least once a week. At the time of MRI, information was obtained on: current smoking, body mass index (BMI) (kg/m^2), systolic blood pressure (average of two measurements), history of myocardial infarction, prevalence of cardiovascular disease and presence of diabetes mellitus. These were determined using prevalent disease algorithms based on self-report of physician diagnoses and recorded medications along with measurements from the clinic examination used for selected conditions (eg. fasting blood glucose for diabetes). Depressive symptoms were assessed with the 20-item Center for Epidemiologic Studies-Depression Scale (CES-D), with a score ≥16 consistent with possible depression (Radloff, 1977). Apolipoprotein E (APOE) genotype was analyzed using standard techniques and coded as having one or more APOE e4 or no e4.

Statistical analysis

Population characteristics at time of the MRI were compared between groups using analyses of variance for continuous variable and chi-square for categorical variable (Table 1). Characteristics that significantly differed between groups ($p<0.1$) were entered as covariates in subsequent analyses.

MRI measures were compared across groups using *t*-tests and the MRI measures that differed at $p<0.05$ between groups in these univariate analyses were further adjusted for age, race and for intracranial volume to address potential atrophy issues. MRI measures that remained significantly associated with the outcome entered logistic regression models further adjusted for other contributors of cognitive function, including population characteristics that differed between groups. Secondary analyses also examined interhemispheric between-group differences, corrected for multiple comparisons using the Sidak correction factor of $p<0.0020$ for 26 comparisons (13 areas of interest, for two hemispheres). All analyses were conducted using IBM SPSS version 17.0 (SPSS Inc., Chicago, IL). The IRB at the University of Pittsburgh has approved the use of human subjects for this study.

Results

Among the participants with brain MRI and longitudinal prior cognitive assessment (n=258), 59% maintained a slope of decline in 3MS score of >0 from study entry through the time of brain MRI and 41% showed decline (Table 1). Among these, 14 participants (5% of the study population) had 3MS decline greater than 1 standard deviation below the mean. Differences in number of follow-ups between the cognitive decliners and the non-decliners were not statistically significant.

Compared to those with cognitive decline, those who maintained cognitive function had similar 3MS score at study entry, higher 3MS score at time of MRI, and were less likely to

be black, men, to have had prior myocardial infarction, to consider their health “fair/poor” and to have depressive symptoms (Table 1). The maintainers also had lower systolic blood pressure at time of brain MRI, larger gray matter volume and smaller white matter hyperintensity volume (Table 1). At the time of MRI, 18 participants (15% of those who declined) had a 3MS score of <80, indicating presence of overt cognitive impairment.

At time of MRI, higher 3MS score was associated with larger gray matter volume and lower mean diffusivity of the medial temporal area independently of total brain atrophy (adjusted correlation coefficients: 0.34, $p<0.0001$ and −0.23, $p<0.0001$, respectively). Higher DSST score was associated with larger gray matter volume and lower mean diffusivity of the middle frontal gyrus (adjusted correlation coefficients: 0.24, $p<0.0001$ and −0.19, $p=0.003$, respectively) and with larger gray matter volume of the posterior parietal cortex but not with mean diffusivity (adjusted correlation coefficients: 0.27, $p<0.0001$ and −0.72, $p=0.26$, respectively).

Compared to those with decline, participants who maintained cognitive function had larger volumes, lower mean diffusivity from normal appearing gray matter and higher fractional anisotropy from normal appearing white matter in the brain areas and tracts examined (Table 2). However, between-group differences reached statistical significance at $p<0.05$ only for the gray matter volume and mean diffusivity of the medial temporal lobe, for the mean diffusivity of the cingulate cortex and for the fractional anisotropy of the cingulum. Further inspection of these areas and tracts separately for the left and right hemispheres indicated that differences were stronger and above the threshold for multiple comparisons only for gray matter volume of the left medial temporal lobe and for mean diffusivity of the right cingulate cortex (Supplementary Tables 1 and 2). Among these MRI measures (gray matter volume and mean diffusivity of the medial temporal lobe, mean diffusivity of the cingulate cortex and fractional anisotropy of the cingulum), only gray matter volume of the medial temporal area and mean diffusivity of the cingulate cortex remained significantly different between groups after adjustment for age, race and intracranial volume. Therefore, these variables entered multivariable logistic models with maintenance of function as outcome (Table 3). In these models, gray matter volume of the medial temporal area and mean diffusivity of the cingulate cortex were associated with the outcome independently of each other and of intracranial volume (Table 3). Each standard deviation of gray matter volume was associated with a 3.8 greater probability of maintaining cognitive function (Table 3, Model 1). Each standard deviation of mean diffusivity was associated with a nearly 30% lower probability of maintaining cognitive function (Table 3, Model 1). Associations remained significant after adjustment for age, race and gray matter volume from the total brain (Table 3, Model 2) or after adjustment for white matter hyperintensity volume (Table 3, Model 3). In these models, neither volume of white matter hyperintensities nor of gray matter from the total brain was associated with maintenance of function (Table 3, Models 2 and 3). Associations of gray matter volume of the medial temporal area and mean diffusivity of the cingulate cortex with maintenance of function were only marginally attenuated after further adjustment for systolic blood pressure, myocardial infarction, self-reported health, age and race (Table 3, Model 4).

Discussion

In this cohort of older adults, maintenance of cognitive function was associated with a more favorable neuroimaging profile of two specific brain areas, the medial temporal area and the cingulate cortex. These associations were independent of other contributors of cognitive maintenance, including neuroimaging markers from the total brain.

Associations within 'traditional' memory-related regions, for example the hippocampus, parahippocampus or entorhinal cortex, were significant for the gray matter volume and not for the micro-structural markers derived from diffusion tensor imaging. The medial temporal lobe is known to be affected early on in the degeneration associated with dementia (Markesbery, 2010). Numerous independent works, including our prior study, have shown that volume and function of the medial temporal lobe areas are related to cognitive impairment and dementia in older adults (Daulatzai, 2010; Markesbery, 2010; Rosano et al., 2007). While these regions might be a target of dementia-related degenerative processes, they may be spared in the earlier stages and play a less important role in maintaining cognitive function.

Differences in integrity of the cingulate cortex were significant for the diffusion tensor imaging measures and not for the volumetric measures of the gray matter. The cingulate cortex is associated with higher memory performance (Elgh et al., 2003; Encinas et al., 2003; Piert et al., 1996), faster information processing and greater mobility control (Cabeza, 2000; MacDonald et al., 2000; Rosano et al., 2005a, 2005b) in non-demented older adults. These functional domains are all important components of overall functioning and maintenance of independence. Recently, cross-sectional neuroimaging reports using diffusion tensor in older adults have shown an association between the cingulate cortex and memory and mood (Kantarci et al., 2011; Kieseppä et al., 2010).

With the exception of a few studies, most of the evidence relating to brain structural integrity with cognition is derived from studies using disease-related approaches, e.g. comparing dementia cases with controls. Our findings indicate that maintaining cognitive function may not be the same as 'absence of cognitive decline'. It is important to note that our neuroimaging methodologies detected between-group differences even in the presence of only a mild decline. In fact, even the participants classified as having "cognitive decline", were nonetheless well functioning older adults: among these participants, the large majority had shown decline by no more than 1 SD below the mean over the prior decade, and with 15% displaying overt cognitive impairment (3MS score below 80) at the time of the MRI. This is lower than the rates observed in cohort of adults of similar age, for whom the rate of conversion to dementia is about 5% per year, or 50% over 10 years (Rosano et al., 2007). Eligibility for the brain MRI and having remained in the study for over a decade could have inserted a selection bias toward healthier participants and it may explain why the prevalence of maintaining cognitive function was higher in this study as compared to what was previously observed in the parent population (60% in this study as compared to 30% in Yaffe et al.'s prior reports) (Barnes et al., 2007; Yaffe et al., 2009a). While this selection bias hampers the ability to generalize our results to the general population, it is also intrinsic to our study design. Our goal was to examine neuroanatomical correlates of preserved maintained function in late life. A study to answer this question has to target 'healthier' populations. However, the inclusion of well-functioning older adults is expected to bias the results toward the null and could lead to an underestimation of between-group differences. We should also note that the definition of cognitive maintainers in this study was based on the 3MS score. It is likely that neuroimaging patterns would be different if maintenance was based on other cognitive domains. Nevertheless, there is robust consistent evidence that the 3MS is a strong correlate of conversion to dementia and recent work indicates that lower 3MS values predict risk of death and disability even among well-functioning populations (Yaffe et al., 2010).

There are also limitations in the imaging methods, including that the registration of the MD to the template for regional gray matter assessments was based on the standard TBSS pathway, and was therefore optimized for registration of the FA maps and not necessarily optimized for registration of the MD maps. Since there are FA value differences between

cerebrospinal fluid and gray and white matter, the FA registration should be accurate for registration of gray matter boundaries. This was confirmed by the visual inspection of the registered images. There is also the possibility of partial volume effects in the calculation of the MD values; that is, the surrounding CSF could have affected boundary voxels in the gray matter regions of interest. These effects were minimized through the use of gray matter masks. Strengths of this study include a detailed sample characterization with retrospective and extensive measures of health and high resolution neuroimaging measures. Notwithstanding the higher precision of the neuroimaging methods, the sample size of this study was smaller than most epidemiological studies of aging. Future studies with a larger sample size are warranted to replicate these findings and to assess the associations between maintenance in multiple cognitive domains and rapidity of brain function/morphology changes over time.

Conclusions and implications

Our findings indicate that the volume of the medial temporal area and microstructure of the cingulate cortex might enable maintaining cognitive performance late in age. Recent works indicate that these two areas are susceptible to late life-style changes that also promote maintenance of cognitive function (Colcombe and Kramer, 2003; Colcombe et al., 2006; Dishman et al., 2006; Erickson et al., 2009; McCloskey et al., 2001; Rosano et al., 2010). Future studies are warranted to explore whether maintaining cognitive function among very old adults is mediated by changes localized within memory-related and executive control-related regions. Longitudinal studies with neuroimaging and cognitive follow-up are needed to explore the interaction of factors of cerebral reserve capacity, such as education, occupation, and socioeconomic status, with anatomical markers and their effects on cognitive function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Population's characteristics at time of MRI.

	Cognitive maintainers (average 3MS slope of >0)	Cognitive decline (average 3MS slope of <0)
N	153	105[a]
3MS at study entry	92.4 (5.6)	91.4 (7.3)
3MS at time of MRI	96.2 (4.1)**	88.6 (6.9)
Age, mean years, (SD)	81.53 (2.6)*	82.34 (2.6)
Race, N black (%)	52 (34)**	58 (55)
Gender, N female (%)	90 (60)	54 (52)
Education, N>high school education (%)	82 (54)	54 (51)
Current smoker, N (%)	3 (2.0)	1 (1)
Mod-vigorous exercise, N (%)	71 (46)	44 (42)
BMI, mean kg/m^2, (SD)	27.58 (4.4)	27.21 (4.4)
Systolic blood pressure, mean mm Hg (SD)	132.45 (18.8)*	137.22 (18.1)
Myocardial infarction, N (%)	18 (12)*	21 (20)
Cardiovascular disease, N (%)	42 (28)	34 (32)
Diabetes, N (%)	35 (22.9)	31 (29.0)
Self-reported health (poor/fair), N (%)	85 (56)*	64 (60)
Depression score >16, N (%)	7 (4.6)^	11 (10)
APOE e4 carrier, N (%)	42 (26.1)	25 (25)
Gray matter volume of all brain, mean mm^3 (SD)	531.5 (54.3)^	518.4 (55.1)
White matter hyperintensities of total brain, mean mm^3 (SD)	3.18 (3.5)^	4.26 (4.9)
Atrophy index (intracranial volume–parenchyma volume), mean mm^3 (SD)	59.79 (115.34)	54.21 (137.14)
Mean diffusivity of normal appearing gray matter of total brain, mean, (SD)×1000	1.293 (0.104)	1.314 (0.0106)
Fractional anisotropy of normal appearing white matter of total brain, mean, (SD)	0.359 (.0132)	0.357 (.0158)

** Difference between groups is significant at p<0.002 using 2 tailed χ^2 tests.

* Differences between groups are significant at 0.002<p<0.05 using 2 tailed *t*-test and χ^2 tests for continuous and binary variables respectively.

^ Differences between groups are significant at 0.05<p<0.06 using 2 tailed *t*-test.

[a] Results are similar when n=14 with decline of >1 SD were excluded from this group.

Table 2

Gray matter volume (voxel number) and mean diffusivity of brain areas are reported for groups stratified by presence/absence of cognitive maintenance. See text for areas hypothesized to differ between groups.

Brain MRI measures[a]		**Cognitive maintainers (average 3MS slope of >0) Mean (SD)**		**Cognitive decline (average 3MS slope of <0) Mean (SD)**		**Between-groups Mean differences (95% CI), p value**
Medial temporal lobe [a]	Gray matter volume	24151.21	(3059.27)	23011.73	(3064.42)	1139.48 (379.60, 1902.37) 0.004
	Mean diffusivity	9.138	(1.286)	9.470	(1.259)	−0.332 (−0.653, −0.011) 0.04
Cingulate cortex [a]	Gray matter volume	25558.08	(3320.84)	24956.58	(3105.80)	601.49 (−210.66, 1413.65) 0.15
	Mean diffusivity	10.385	(0.987)	10.734	(1.082)	−0.349 (−0.608, −0.091) 0.008
Dorsolateral prefrontal cortex [b]	Gray matter volume	26946.02	(3320.84)	26334.50	(3097.58)	611.52 (−193.67, 1416.71) 0.14
	Mean diffusivity	2.162	(0.236)	2.192	(0.223)	−0.030 (−0.088, 0.028) 0.31
Posterior parietal cortex [b]	Gray matter volume	43533.11	(6224.00)	42817.84	(5487.59)	715.26 (−782.47, 2213.0) 0.35
	Mean diffusivity	7.781	(0.937)	7.787	(0.856)	−0.006 (−0.234, 0.222) 0.96
Sensorimotor cortex	Gray matter volume	36199.01	(6219.68)	35138.78	(4755.40)	1060.23 (−370.26, 2490.72) 0.15
	Mean diffusivity	4.828	(0.447)	4.829	(0.448)	0.002 (−0.111, 0.115) 0.97
Cingulum	Fractional anisotropy	0.794	0.045	0.781	0.058	−0.013 (−0.026, −0.000) 0.045
Uncinate fasciculus	Fractional anisotropy	0.645	0.052	0.653	0.055	0.008 (−0.006, 0.021) 0.25
Superior longitudinal fasciculus	Fractional anisotropy	0.710	0.039	0.706	0.043	−0.004 (−0.014, 0.006) 0.441

[a] Gray matter volume is in voxel numbers. Mean diffusivity is in $mm^2/s \times 1000$. Higher mean diffusivity indicates lower tissue integrity.

[b] Brain areas hypothesized to significantly differ between groups.

Table 3

Association of MRI measures with the likelihood (standardized odds ratio and 95% confidence interval) of maintenance of cognition.

	Model 1: Adjusted for intracranial volume	**Model 2: Further adjusted for age, race, total brain gray matter volume**	**Model 3: Further adjusted for total WMH volume**	**Model 4: Further adjusted for systolic blood pressure, myocardial infarction, self-reported health**
Medial temporal area, gray matter volume	3.88 (1.53, 9.86)	3.65 (1.13,11.76)	3.67 (1.13, 11.76)	3.80 (1.16, 12.44)
Cingulate cortex, mean diffusivity	0.72 (0.54,0.96)	0.63 (0.44, 0.89)	0.65 (0.45, 0.94)	0.66 (0.46, 0.97)
Total brain, gray matter volume		0.74 (0.44, 1.25)	0.75 (0.44, 1.27)	0.75 (0.44, 1.29)
Total brain, WMH volume			0.92 (0.69, 1.22)	0.94 (0.70, 1.26)

WMH: White matter hyperintensities.