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Longitudinal MRI and Cognitive Change in Healthy Elderly

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Abstract

Cross-sectional studies of normal aging indicate an association between memory and hippocampal volume, and between executive functioning and subcortical-frontal circuits. Much less is known, however, about the relationship between longitudinal MRI changes and cognitive decline. The authors hypothesized that longitudinal change in memory would be best predicted by change in hippocampal volumes, whereas change in executive functioning would be best predicted by cortical atrophy and progression of MRI markers of cerebrovascular disease. For this study, 50 healthy elderly subjects underwent structural MRI and cognitive testing at baseline and again at follow-up, with a mean follow-up interval of 45 months. Volumetric MRI measures were hippocampus, cortical gray matter, white matter signal hyperintensity (WMSH), and lacunae. Neuropsychological measures were psychometrically robust composite scores of episodic memory (MEM) and executive functioning (EXEC). Hierarchical multiple regression indicated that a decrease in hippocampus was associated with a decline in MEM, whereas decreased cortical gray matter and increased WMSH were independently associated with a decline in EXEC. Results suggest that in normal aging, cognitive functioning declines as cortical gray matter and hippocampus decrease, and WMSH increases. The association between WMSH and EXEC further highlights the cognitive sequealae associated with cerebrovascular disease in normal elderly.

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Keywords

normal aging; memory; executive function; hippocampal volumes; white matter signal hyperintensity

Normal aging is often associated with declining performance on cognitive tasks, particularly episodic memory and executive functioning (Buckner, 2004). Compared with younger controls, healthy elderly typically do less well on measures of delayed recall (Davis et al., 2003) and recognition (Huh, Kramer, Gazzaley, & Delis, 2006), although rates of forgetting may not change with age (Fjell et al., 2005). Older subjects also tend to perform less well on measures of novel problem solving (Davis & Klebe, 2001), fluency (Brickman et al., 2005), and mental flexibility (Wecker, Kramer, Hallam, & Delis, 2005).

The biological bases for these age-related cognitive changes are still unclear. Although multiple factors—including gene status (Wishart et al., 2006), neurotransmitters (Wu, Oh, & Disterhoft, 2002), and endocrine systems (Thilers, Macdonald, & Herlitz, 2006)—likely contribute, changes in brain structure are widely considered to be an important contributing factor (Buckner, 2004). It is well established that several brain regions critical for cognition—including the hippocampus (Jack et al., 2000) and cerebral cortex (DeCarli et al., 2005)—become smaller with age, with frontal cortex showing the greatest changes (DeCarli et al., 2005; Raz et al., 1997). There are also age-related increases in subcortical ischemic vascular disease that can independently contribute to cognitive decline and dementia (Román, Erkinjuntti, Wallin, Pantoni, & Chui, 2002). Population-based studies have reported "silent" (i.e., asymptomatic) lacunae in 11%–28% of clinically asymptomatic elderly (Longstreth et al., 1998; Price et al., 1997; Vermeer et al., 2003), whereas the prevalence of white matter signal hyperintensities on MRI has ranged from 30% to 100% across studies of healthy elderly samples (Breteler et al., 1994; Longstreth et al., 1998; Ylikoski et al., 2000). Diffusion tensor MRIs have shown a progressive reduction in fractional anisotropy and an increase in diffusivity with age (Charlton et al., 2006).

Despite the co-occurrence of age-related cognitive decline and brain changes, associations between brain volume and cognitive ability in healthy subjects have been difficult to establish. Although several studies have reported that hippocampal atrophy is associated with poorer episodic memory performance in older subjects (De Leon et al., 1997; Golomb et al., 1996), an extensive review and meta-analysis by Van Petten (2004) noted considerable variability across studies. The common correlation between hippocampal volume and memory performance across 33 studies was statistically significant but quite low, leading to the conclusion that the evidence for a positive relationship between hippocampal volume and memory performance was weak. Divergent results have also been reported for global cognition and measures of executive functioning (Duarte et al., 2006). Cortical and frontal lobe atrophy have also been shown to correlate with global cognition and measures of executive functioning (Raz, Williamson, Gunning-Dixon, Head, & Acker, 2000). A significant association has been established between white matter signal hyperintensities and cognition in several studies (Baum, Schulte, Girke, Reischies, & Felix, 1996; Breteler et al., 1994; Cook et al., 2004; DeCarli et al., 2005; De Groot et al., 2002; Fukui, Sugita, Sato, Takeuchi, & Tsukagoshi, 1994; Kovari et al., 2004; Kramer, Reed, Mungas, Weiner, & Chui, 2002; Longstreth et al., 2005; Matsubayashi, Shimada, Kawamoto, & Ozawa, 1992; Ylikoski et al., 2000) but not in others (Boone et al., 1992; Burns et al., 2005; Fein et al., 2000; Wahlund, Almkvist, Basun, & Julin, 1996). Similarly, the role of lacunae in cognition has not been well defined, with some studies showing a negative relationship between lacunae and cognition (Gold et al., 2005; Kramer et al., 2002; Longstreth et al., 2005; Price et al., 1997), whereas others have not,

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particularly when accounting for the presence of other important pathological markers, such as white matter disease (Fein et al., 2000; Mungas et al., 2001).

To date, only a few longitudinal studies have attempted to directly link changes in brain structure to age-related declines in cognition in healthy subjects. Structural brain changes in healthy elderly found at baseline have been shown to predict a more rapid cognitive decline (Golomb et al., 1996; Prins et al., 2005; Rusinek et al., 2003) and higher rates of conversion to dementia. Increases in white matter lesions have also been associated with cognition decline (Longstreth et al., 2005; Schmidt et al., 2005), but because these studies primarily looked at white matter, it is unclear whether these effects might have been mediated by changes in other brain regions. In contrast, Ylikoski et al. (2000) and Cohen, Small, Lalonde, Friz, and Sunderland (2001) did not find any significant relationship between hippocampal atrophy and a decline in memory over time. Cook et al. (2004) reported that their normal elderly subjects showed a negligible cognitive decline over a 2-year study period despite evidence for subcortical brain changes. In sum, the handful of studies that have attempted to correlate a longitudinal change in brain volumes with changes in cognition have used variable imaging and psychometric methods and have yielded inconsistent results. The mechanisms underlying cognitive aging remain unclear. Inconsistencies in the extant literature might reflect differences in how brain volumes were obtained, how corrections were made for head size (Van Petten, 2004), ceiling effects or limited sensitivity in the cognitive measures, how carefully subjects were screened, and how *normal* was defined. The purpose of this study was to assess the relationship between cognition and changes in brain structure in a well-characterized sample of healthy elderly who received quantitative MRI and psychometrically robust scales of memory and executive functioning at baseline and at follow-up. We hypothesized that, based on previous studies (Mungas et al., 2001; Schmidt et al., 2005), a longitudinal change in memory would be best predicted by a change in hippocampal volumes, whereas a change in executive functioning would be best predicted by cortical atrophy and a progression of MRI markers of cerebrovascular disease, specifically white matter signal hyperintensities and subcortical lacunae.

Method

Subjects

Subjects were recruited from three academic dementia centers as part of a longitudinal study of ischemic cerebrovascular disease and aging. The institutional review boards at all participating institutions approved this study, and the subjects or their legal representatives gave written informed consent. All subjects received a comprehensive clinical evaluation that included a medical history, a neurologic examination, appropriate laboratory tests, a Clinical Dementia Rating Scale (Mattis, 1992) administered by a trained rater, and neuropsychological testing with a standardized test battery. In addition, subjects received a standardized MRI scan of the brain. At the completion of this clinical evaluation, a consensus diagnostic conference rated each subject as cognitively healthy, cognitive impaired but not demented, or demented. Longitudinal evaluations were scheduled annually for subjects with cognitive deficits or dementia, and every other year for cognitively healthy subjects.

Subjects were included in this study if they were healthy elderly controls as defined by (a) designation of cognitively healthy by the clinical team following completion of the clinical evaluation, (b) a Clinical Dementia Rating score of 0, and (c) a Mini-Mental State Examination (MMSE; Folstein, Robins, & Helzer, 1983) score greater than 25. There were 56 subjects with follow-up data who met these criteria. In addition, the neuroimaging and neuropsychological data for both the baseline and follow-up time points had to have been obtained within a 90-day window. If multiple follow-up evaluations were available, the subject's first follow-up with temporally contiguous neuroimaging and neuropsychological data was always selected.

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Fifty subjects (30 women and 20 men) met all of the inclusion criteria. Demographic data are summarized in Table 1. The mean follow-up interval was 45 months (*SD* =12.3; range =13–82 months). Fifteen of the subjects (30%) had evidence of a lacunar infarct on MRI at baseline.

Neuroimaging

MRI variables of interest were total hippocampal volume, cortical gray matter volume, volume of white matter signal hyperintensities (WMSH), and total lacunar volume. Structural MRI data were obtained at the San Francisco VA Neuroimaging Center on a standard 1.5 Tesla Siemens Vision System (Siemens, Islen, NJ). A sagittal T1-weighted localizer image was obtained, followed by oblique axial double spin-echo images parallel to the planum sphenoidale with these parameters: 3000/30,80/1 (repetition time/echo time/excitations), 3-mm-thick sections with no section gap, and in-plane resolution of $1 \times 1.4\ mm^2$. The spin-echo sequence yielded 43–46 sections covering the entire brain from the inferior cerebellum to the vertex. First, we extracted the scalp and skull from the images, and then we estimated and removed any radio frequency field inhomogeneity by using a low pass filter on each image section. Subtraction images (the difference between proton density– and T2–weighted images) and addition images (the sum of the proton density– and T2–weighted images) were created to enhance our ability to see the difference between cerebrospinal fluid (CSF) and non-CSF, and between gray and white matters, respectively.

Semiautomatic, computer interactive thresholding segmentation of the MR images into specific tissue and anatomic compartments was performed. All brains were segmented into areas of ventricular CSF, sulcal CSF, and total brain tissue and then further segmented into areas of cortical gray matter, subcortical gray matter, white matter, and abnormal white matter signal hyperintensities. Images were processed by two trained operators, both blinded to the subject's identity. Editing of subcortical gray matter regions and white matter signal hyperintensities was performed by one operator. In addition, total intracranial volume was computed by summing up the overall pixels within the intracranial vault.

WMSH appear as hyperintense areas on T2-weighted MRI in the periventricular and subcortical white matter. Lacunae were defined as small (>2 mm) areas of subcortical gray and white matter with increased signal relative to CSF on proton density MRI. Isointense lesions on pseudo proton density MRI at the level of the anterior commissure or inferior putamen were termed *perivascular spaces*; outside that region, they were defined as *cavitated lacunae* if they were ≥3 mm at maximum width.

Semiautomated hippocampal volumetry was carried out with a commercially available high-dimensional brain-mapping tool (Medtronic Surgical Navigation Technologies, Louisville, CO) that had been recently validated and compared with manual tracing of the hippocampus (Hsu et al., 2002). Measurement of hippocampal volume is achieved first by manually placing 22 control points as local landmarks for the hippocampus on the individual brain MRIs: one landmark at the hippocampal head, one at the tail, and four per image (i.e., at the superior, inferior, medial, and lateral boundaries) on five equally spaced images perpendicular to the long axis of the hippocampus. Second, fluid image transformation was used to match the individual brains to a template brain, and pixels corresponding to hippocampus were labeled and counted to obtain volumes (Christensen, Joshi, & Miller, 1997). This method of hippocampal voluming has well-documented reliability, with intraclass coefficients of .94 (Hsu et al., 2002).

Neuropsychology

All subjects received a standardized battery of neuropsychological tests. All personnel involved in test administration were trained in administration and scoring procedures, and cross-center

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observation and cross-scoring of test protocols were done to monitor quality of data collection. The MMSE and the Clinical Dementia Rating Scale were used as standard clinical measures of global function.

Item response theory (IRT) analytic methods (Hambleton, Swaminathan, & Rogers, 1991) were used to create psychometrically matched scales of memory (MEM) and executive functioning (EXEC). The development and characteristics of these scales have been previously described by Mungas, Reed, and Kramer (2003). Briefly, item scores from a comprehensive neuropsychological test battery in a sample of 400 elderly persons who varied in cognitive status from cognitively healthy to mildly demented served as the basis for scale development. Within the IRT framework, scales are matched when they demonstrate equivalent reliability (test information values) over a similar range of measured ability. In the present case, the scales were constructed so as to have information values of about 14 over a −2.0 to +2.0 standard deviation range of ability. In terms of classical test theory this translates to a reliability coefficient of .93 for each scale; it also means that the scales have linear measurement properties (an absence of floor or ceiling effects) over this broad range of cognitive function. They also are near-normally distributed, which presents advantages for statistical analyses. Each scale was transformed so as to have a mean of 100 and a standard deviation of 15. Donor items for MEM came from the Memory Assessment Scale (Williams, 1991) list learning task and include immediate recall Trials 1 and 3, delayed free recall, and delayed cued recall. Donor scales for EXEC included the Initiation-Perseveration subscale of the Mattis Dementia Rating Scale, the FAS verbal fluency test (Delis, Kaplan, & Kramer, 2001), WAIS Digit Span Backward (Wechsler, 1997a), and WMS-R Visual Memory Span Backward (Wechsler, 1997b). A MEM score could not be computed for one subject because of missing data on a donor scale. Baseline and follow-up scores on each of these donor scales is available as supplementary online material.

Statistical Analyses

Paired sample *t* tests were used to evaluate interval changes in cognitive and MRI measures. Hierarchical multiple regression was used to test our primary hypotheses about predictors of change in MEM and EXEC. Because change scores often have skewed distributions, we selected follow-up MEM and EXEC scores as the dependent variables and entered baseline MEM and EXEC scores in the first step of each model. Demographic variables (age, gender, education), baseline MMSE, and total intracranial volume (to control for head size) were entered in the second step, followed by baseline measures of hippocampus, cortical gray matter, WMSH, and lacunae. In the final step of the model, we entered change in hippocampus, cortical gray matter, WMSH, and lacunae. Support for our hypotheses would be found if a decline in cortical gray matter and an increase in WMSH and lacunae contributed significantly to the remaining variance for EXEC, and if a decline in hippocampus contributed significantly to the remaining variance in MEM.

Results

Demographic, cognitive, and neuroimaging characteristics of the sample are described in Table 1. No interval changes were evident on the MMSE. EXEC and MEM scores fell slightly, but the changes did not reach statistical significance. There were significant declines in hippocampus ($t = 4.16$, $p < .001$) and cortical gray matter ($t = 3.60$, $p < .005$) and a significant increase in WMSH ($t = -3.49$, $p < .005$). The change in lacunae was not statistically significant ($t = -0.93$, $p > .35$).

Results of the regression analysis for EXEC are summarized in Table 2. In the first step of the model for EXEC, baseline EXEC scores explained 48.1% of the variance. Demographic variables and baseline MMSE and MRI volumes did not contribute significantly to the model.

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In the final step of the model, however, change in MRI volumes explained an additional 17.5% of the variance. As summarized in Table 2, the changes in cortical gray matter and in WMSH each contributed significantly to the model, with decreases in cortical gray matter and increases in WMSH associated with a decline in EXEC.

Regression results for MEM are summarized in Table 3. The baseline MEM scores that were entered in the first step of the model explained 44.7% of the variance. The baseline demographic, MMSE, and MRI variables entered in the next two steps did not contribute significantly to the model. In the final step of the model, the change in MRI volumes explained an additional 9.6% of the variance, with only the change in hippocampus making a significant individual contribution.

A review of the follow-up data indicated that the cognitive status of three subjects changed from healthy to mild cognitive impairment at the follow-up evaluation. The regressions were run again after excluding these three cases. The results were unchanged.

Discussion

The primary finding of this study was that in healthy elderly subjects defined by normative psychometric performance and absence of significant functional decline by proxy report, longitudinal change in brain structure was associated with longitudinal change in cognition over a mean follow-up interval of almost 4 years. A decrease in hippocampus was associated with a lower memory score. A decrease in cortical gray matter and an increase in WMSH were both independently associated with lower executive scores.

The predictors of memory performance found in the present study are consistent with several cross-sectional studies of elderly patients and controls. Many investigators have described the relationship between hippocampal volume and memory performance in patients with mild cognitive impairment (Grundman et al., 2003; Muller et al., 2005; Saykin et al., 2006) and dementia (Kramer et al., 2004; Petersen et al., 2000), and baseline hippocampal atrophy is reported to be a risk factor for subsequent decline (den Heijer et al., 2006; Gluck, Myers, Nicolle, & Johnson, 2006). Cross-sectional studies examining brain-behavior relationships in healthy elderly have been more mixed (Lye et al., 2004Van Petten, 2004; Walhovd et al., 2004). The present study approaches the brain-behavior question with a longitudinal design. Our findings suggest that the relationship is fairly specific; hippocampus remained in the model predicting MEM, but cortical gray matter, WMSH, and lacunae did not. This lack of a significant contribution from WMSH and lacunae is similar to findings reported by Prins et al. (2005), who found that none of their markers of small vessel disease were related to decline in memory.

The relationships between executive functioning and brain structure appear more complex. We found that decreases in cortical gray matter and increases in WMSH were both associated with decline in EXEC. Cross-sectional and longitudinal studies have shown a relationship between cortical gray matter atrophy and EXEC decline in cognitive-impaired patients (Fein et al., 2000; Mungas et al., 2001, 2005). Van den Heuvel et al. (2006) reported recently that an increase in periventricular WMSH volume paralleled a decline in mental processing speed in a nondemented, high-risk cerebrovascular group. Our findings add to the literature by demonstrating MRI predictors of EXEC in a longitudinal study of healthy elderly.

Whether specific cortical regions are differentially involved in EXEC cannot be addressed by the present study. Certainly, several studies have highlighted the importance of frontal regions for set shifting, inhibition, fluency, and other executive tasks (Demakis, 2004; Goldstein, Obrzut, John, Ledakis, & Armstrong, 2004; Mc-Donald, Delis, Norman, Tecoma, & Iragui,

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2005; McDonald, Delis, Norman, Tecoma, & Iragui-Madozi, 2005), but anatomic specificity is far from established (Anderson, Damasio, Jones, & Tranel, 1991; Collette et al., 2005), and pathology in nonfrontal regions can affect frontal lobe activity (Tullberg et al., 2004).

Our results are consistent with other longitudinal studies linking white matter disease with cognition in healthy subjects (Longstreth et al., 2005; Schmidt et al., 2005). Longstreth et al. (2005), for example, showed that subjects with worsening white matter grade experienced a greater decline on the Digit Symbol Substitution Test (Smith, 1973) than did subjects with no change in white matter grade. The mechanisms underlying this effect are not clear but potentially include disruption of frontal-subcortical circuits (Cummings, 1998; Owen, 2004), cortical atrophy secondary to deinervation, or concomitant microvascular changes in the cortex.

We found that change in WMSH and not lacunae was related to EXEC. The opposite pattern was reported by Mungas et al. (2005), who found that WMSH was not associated with change in EXEC independent of cortical gray matter, lacunae, and hippocampus. One possible reason for the discrepant findings is that our study included only healthy controls, whereas Mungas et al. (2005) included subjects with cognitive impairment and dementia, and these subjects showed greater range in lacunae. In the present study of healthy controls, there was a very restricted range of change in lacunae that likely limited our ability to identify relationships between lacunae and cognition. Our findings are more compatible with Longstreth et al. (2005), who reported that subjects with worsening white matter grade, compared with those without, experienced greater cognitive decline even after controlling for stroke between scans or occurrence of transient ischemic attacks. The relative impact of subcortical lacunae versus white matter lesions on cognition continues to be a subject of debate, and the fact that lacunae and white matter disease are strongly related makes determining their differential contributions to cognition change more difficult.

In our sample, MRI volumes showed greater age-related changes than did the cognitive and EXEC measures. The relationship between age and cognition in healthy elderly is somewhat controversial. Although group means on MEM and EXEC tests typically decline (Buckner, 2004; Davis et al., 2003; Wecker et al., 2005), interpretation is confounded by increased variability and the fact that a large percentage of individuals demonstrate relative stability in cognitive scores over time (Cook et al., 2004; Royall, Palmer, Chiodo, & Polk, 2005). Our sample was a well-screened group of healthy elderly that for the most part appeared to remain healthy during the follow-up period. Despite this, changes on MRI were measurable, and these changes were still associated with changes in MEM and EXEC.

This study has several strengths. First, all subjects were carefully evaluated clinically both at baseline and follow-up to ensure that they were cognitively and functionally healthy. The assessments also included informant reports and consensus diagnoses at the study sites. These methods make it less likely that our findings were influenced by a few subjects with incipient neurodegenerative disease, although such a possibility cannot be entirely ruled out. Second, several MRI variables were considered simultaneously as predictors of cognitive change. The importance of considering multiple MRI variables is highlighted by Schmidt et al. (2005), who found that the association between changes in white matter lesion load and cognitive functioning were no longer significant when whole brain volume was added to the model. In our study, changes in both WMSH and cortical gray matter made significant contributions to declines in EXEC, implying that multiple brain components are relevant in understanding age-related cognitive change. These findings also emerged after carefully controlling for numerous other factors, including baseline cognitive performance, demographic variables, and baseline MRI measures. Third, all MRI variables were quantitative rather than semi-quantitative ratings. Fourth, our ability to discern brain-behavior relationships was likely enhanced by using psychometrically robust measures that were reliable and fairly normally distributed and did

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not have ceiling effects. This was particularly important given that cognitive changes in normal aging tend to be quite small and often not statistically significant (Cook et al., 2004). The strong psychometric properties of our measures also enabled us to look separately at EXEC and MEM and determine that the neuroanatomical correlates of cognitive change were different for the two cognitive domains.

Age-related atrophy in the hippocampus and cerebral cortex are well documented, but the causes are not clear. It is not known to what degree atrophy can be attributable to normal aging or whether there are underlying neuropathological changes that reflect a disease state. One of the important implications of the current data is that at least for EXEC, one likely contributing factor to declining performance in healthy elderly is ischemic white matter disease. Accordingly, MRI markers of cerebrovascular disease should not be considered benign, even in a sample of healthy elderly, and reducing cerebrovascular risk factors such as high blood pressure, hypercholesteremia, diabetes, and smoking may be an important step toward optimizing cognitive stability.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Demographic, Cognitive, and MRI Variables at Baseline and Follow-Up

Variable	Baseline	Follow-up
Education	15.5 (2.8)	
Age	73.9 (6.6)	77.5 (6.3)
MMSE	29.1 (1.0)	29.2 (1.1)
MEM	104.4 (12.5)	102.7 (14.6)
EXEC	98.0 (11.5)	97.6 (14.5)
MRI measures		
HC	4.6 (0.6)	4.4 (0.7)
CGM	510.6 (46.7)	491.3 (50.3)
WMSH	8.0 (9.1)	10.4 (12.2)
LAC	0.2 (0.6)	0.3 (1.0)

Note. Values shown are means (with standard deviations in parentheses). MRI measures are in cubic centimeters. MMSE = Mini-Mental State Examination; MEM = episodic memory; EXEC = executive functioning; HC = hippocampus; CGM = cortical gray matter; WMSH = white matter signal hyperintensity; LAC = lacunae.

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Table 2

Predictors of Executive Functioning (EXEC) at Follow-Up

Variable	β	*p*
Baseline EXEC	.586	.000
ΔHC	.135	.242
ΔCGM	.368	.003
ΔWMSH	−.261	.022
ΔLAC	−.171	.164

Note. HC = hippocampus; CGM = cortical gray matter; WMSH = white matter signal hyperintensity; LAC = lacunae.

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Table 3

Predictors of Episodic Memory (MEM) at Follow-Up

Variable	β	*p*
Baseline MEM	.537	.000
ΔHC	.282	.048
ΔCGM	.234	.104
ΔWMSH	−.093	.490
ΔLAC	−.163	.291

Note. HC = hippocampus; CGM = cortical gray matter; WMSH = white matter signal hyperintensity; LAC = lacunae.