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Correlating Cognitive Decline with White Matter Lesion and Brain Atrophy MRI Measurements in Alzheimer's Disease

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Abstract

Background—Vascular risk factors are increasingly recognized as risks factors for Alzheimer's disease (AD) and early conversion from mild cognitive impairment (MCI) to dementia. While neuroimaging research in AD has focused on brain atrophy, metabolic function or amyloid deposition, little attention has been paid to the effect of cerebrovascular disease to cognitive decline.

Objective—To investigate the correlation of brain atrophy and white matter lesions with cognitive decline in AD, MCI, and control subjects.

Methods—Patients with AD and MCI, and healthy subjects were included in this study. Subjects had a baseline MRI scan, and baseline and follow-up neuropsychological battery (CERAD). Regional volumes were measured, and white matter lesion segmentation was performed. Correlations between rate of CERAD score decline and white matter lesion load and brain structure volume were evaluated. In addition, voxel-based correlations between baseline CERAD scores and atrophy and white matter lesion measures were computed.

Results—CERAD rate of decline was most significantly associated with lesion loads located in the fornices. Several temporal lobe ROI volumes were significantly associated with CERAD decline. Voxel-based analysis demonstrated strong correlation between baseline CERAD scores and atrophy measures in the anterior temporal lobes. Correlation of baseline CERAD scores with white matter lesion volumes achieved significance in multilobar subcortical white matter.

Conclusion—Both baseline and declines in CERAD scores correlate with white matter lesion load and gray matter atrophy. Results of this study highlight the dominant effect of volume loss, and underscore the importance of small vessel disease as a contributor to cognitive decline in the elderly.

Keywords

AD; MCI; cognitive decline; vascular disease; white matter lesions; atrophy

Introduction

Traditionally, there has been a dichotomous approach to Alzheimer disease (AD) and vascular dementia diagnosis [1]. However, more recent reports increasingly found that vascular risk factors (e.g., hypertension, diabetes mellitus, hyperlipidemia) and vascular disease per se (e.g., atherosclerotic, heart, peripheral vascular and cerebrovascular) are risk factors for AD suggesting a common etiologic or reciprocally synergistic pathophysiological mechanisms for both vascular pathology and plaque and tangle pathology [2, 3, 4, 5]. Vascular compromise may also interact with the amyloidogenic pathway in such a way as to exacerbate AD-type pathologic changes [6, 7], or may be the initial nidus for the formation of amyloid lesions [8]. Small vessel disease and hypoperfusion and hypoxia may also promote the deposition of amyloid plaques by damaging the blood-brain barrier and by up-regulating amyloid precursor protein and apolipoprotein E [9, 10]. In addition, coincident vascular pathology is more prevalent in AD than in other neurodegenerative diseases and leads to additional cognitive impairment [11]. The implication of these studies would be that aggressive treatment of the underlying cerebrovascular disease and associated vascular risk factors could delay or prevent the onset of dementia and slow down its progression.

White matter (WM) hyperintensities (WMH) on T2-weighted and FLAIR MRI images have been associated with mild cognitive impairment (MCI) [12–15] and dementia [13, 16, 17]. In one of these studies [13], the association between WMH and cognitive status was affected by both the extent and the spatial distribution of the lesions. For example, posterior periventricular and callosal lesions were associated with MCI and AD. Other associations, such as lesion load vs. regional atrophy, have been made between WMH and atrophy patterns seen in AD [18, 19]. For example, the presence and progression of periventricular WMH were found to be associated with progression of medial temporal lobe atrophy in a group of AD subjects [18]. Lesions affecting specific pathways, such as the entorhinal efferent and afferent pathways, may be particularly important [20]. In addition, previous studies suggest that concomitant WMHs may contribute to the severity of dementia in AD [13, 21]. However, the precise relation between spatial distribution and lesion load and their contribution to the dementia syndrome remains unclear [22, 23]. A variety of mechanisms have been described for the development of WMHs including wallerian degeneration secondary to neurodegenerative changes, vascular injury, and ischemia. Pathologically, the observed tissue damage range from mild perturbation of the matrix, all the way to demyelination and axonal loss in severe cases [24]. The most common etiology found at the tissue level appears to be infarction [25]. Some studies examined the association between longitudinal changes in global WMH and pathologic findings after death and demonstrated that arteriolosclerosis is the strongest pathologic correlate of accumulating WMH in aging [26].

The Consortium to Establish a Registry for AD (CERAD) neuropsychological battery was developed to provide standardized and validated measures for the assessment of AD across the whole range of disease severity [27]. It is composed of five tests derived from previously established cognitive tests (Animal Naming, Modified Boston Naming Test [BNT], Mini-Mental State Examination [MMSE], Constructional Praxis, and Word List Memory). The CERAD battery has been found to be a valid and reliable measure of cognition in normal

aging and in AD [28]. It has also been shown that CERAD total score was superior to the MMSE or any single CERAD subtest in discriminating between the control and MCI groups [29].

The aim of this study was to correlate WMH and pre-selected ROIs in the gray matter (GM) with baseline and one year follow-up CERAD scores in subjects with clinical AD, MCI, and normal cognition (NC) diagnoses.

Materials and Methods

Subject Population

The proposed analysis was performed on existing data from the University of Pennsylvania's Alzheimer's Disease Core Center (ADCC)/ Center for Excellence in Research in Neurodegenerative Disease (CERND) [30] project database. This was a five-year project funded by the Commonwealth of Pennsylvania to assess the diagnostic and predictive utility of multiple biomarkers of interest in late-life dementia. More specifically, the intent was to use recruitment, evaluation and biomarker methods that might be widely implemented in the community rather than just at specialized research centers. Three hundred forty six subjects with NC, MCI, AD and other neurodegenerative diseases participated, of whom 101 had MRI scans and longitudinal cognitive, neurological and functional assessments. This study's subject population consisted of 57 subjects with AD, 66 subjects with MCI, and 35 healthy cognitively normal subjects.

All NC, MCI, and AD subjects participating in the ADCC/CERND protocol had also been participants in the University of Pennsylvania's ADCC's Clinical Core and had extensive clinical evaluations including completion of the National Alzheimer's Coordinating Center's Uniform Data Set [31]. The CERAD total score was obtained by combining the scores of its six subtests: Verbal Fluency modified Boston Naming Test, Word List Learning, Constructional Praxis, Word List recall and Word List Recognition, as previously described [27, 28]. Baseline and follow-up CERAD scores were computed on the basis of individual test scores. Follow-up testing occurred between 12 and 18 months from baseline.

MR acquisition parameters

MR data were acquired on a 1.5 T Siemens Sonata scanner (Siemens, Erlangen, Germany) and consisted of MPRAGE (T1-weighted), T2-weighted, proton density (PD), and FLAIR sequences. The MPRAGE sequence, acquired in the sagittal plane had the following parameters: TR = 3000 ms, TE = 3.55 ms, TI = 1000 ms, flip angle = 8°, matrix = 192 × 192 × 160, voxel size = 1.25 × 1.25 × 1.2 mm. The T2 and PD images were acquired as a dual echo sequence, and shared the following parameters: TR = 3000 ms, flip angle = 150°, matrix = 256 × 228 × 48, voxel size = 0.94 × 0.94 × 3.0 mm. They only differed by their echo times: 12 ms for PD, and 96 ms for T2.The FLAIR sequence had the following parameters: TR = 9840 ms, TE = 145 ms, TI = 2500 ms, flip angle = 180°, matrix = 256×204×48, voxel size = 0.86×0.86×3.0 mm.

Automatic WMH segmentation

Automatic WMH lesion segmentation was performed in all subjects using multimodality features and support vector machine classification as described and validated in previous studies (figure 1) (32). Necrotic lesions, i.e., abnormal foci exhibiting CSF signal, were not segmented with this method.

Once the lesions were segmented in an individual subject's space, the resulting masks were mapped in the parcellated template space using a nonlinear registration algorithm (33).

Regional Volumetric Maps

The images were processed with a freely-available published pipeline, which has been used in a variety of neuroimaging studies [9, 20, 21, 34, for software, see www.rad.upenn.edu/sbia]. Briefly, images were segmented into 3 tissue types: GM, WM, and cerebrospinal fluid (CSF), after initial removal of extracranial tissues. After a high-dimensional image warping to an atlas, tissue density maps for GM, WM and CSF were created, referred to herein as RAVENS maps. RAVENS maps constitute regional volumetric measurements of different tissues, and are used for voxel-based analysis and group comparisons. Using the same atlas warping procedures, regions of interest were defined on each MRI, allowing us to measure volumes of normal tissue and of lesions.

Statistical analysis

We performed two analyses including WMH ROI measurements, one determining the correlation of white matter ROIs lesion load with decline in CERAD score, the other examining the correlation of ROI volume with declines in CERAD scores. Logistic regression analysis was performed for each region (ROI lesion load or ROI volume). In each case, the analysis was performed using the whole population and also in subjects in each diagnostic group. For each ROI, the absolute lesion volume was normalized by the subject's brain volume. For both analyses, we used the approximate intracranial volume as a covariate to account for differences in head size. The average of left and right MRI measures for each ROI was used in the analysis. To minimize confounding effects, the brain volume was used as a covariate for the ROI lesion load analysis, and the total white matter load as a covariate for the ROI volume analysis. Correlations with each ROI WMH lesion load and ROI volume with the rate of decline of the CERAD score were evaluated using a mixed-effects model (33). The mixed-effects model takes into account within-subject correlations from repeated measurements of CERAD scores in the same subjects and for missing data points. Our model specified the intercept and the regression coefficient for the follow-up time as random effects such that subjects have a unique intercept and slope characterizing their individual trajectories. Population mean coefficients for the follow-up time were estimated by averaging across the subject-specific regression coefficients for the follow-up time. This population mean coefficient estimated the average annual change for the CERAD score over time. The interaction term "time × ROI WMH lesion load" (respectively "time × ROI volume") represents the effect of the ROI WMH lesion load (respectively ROI volume) on change in CERAD score over time. It can be interpreted as the annualized change in CERAD score for each one-unit change in a given ROI WMH lesion load (respectively ROI volume). All analyses were conducted using the statistical software packages SAS version

9.2 (SAS Institute Inc., Cary, North Carolina). All statistics tests were two-sided, and statistical significance was set at the $p < .05$ or lower.

For the voxel-based analysis, we built a regression model based on the RAVENS maps and the subjects' baseline CERAD scores, which determined the correlation of the gray matter tissue volume (or the white matter lesion load) at every voxel with the baseline CERAD score. In addition, a t-statistic map was generated, displaying the significance of the correlations.

Results

Demographic and clinical data

The clinical and demographics characteristics of the three groups are reported in Table 1. As expected, CERAD scores were significantly different between the three groups with the highest score in the NC group and lowest score in the AD group, while no significant differences arose with respect to age, gender, and education.

White matter lesion segmentation by ROI

The AD group showed greater WMH lesion load than the other groups, and that this was most evident in prefrontal subcortical white matter regions (Figure 2).

Voxel-based analysis and CERAD score

The gray matter voxels whose volume was most correlated with the baseline CERAD score were located in the left medial temporal lobe, especially in the region of the hippocampus, and in the adjacent insula, more on the left than the right (Figure 3). The WM regions whose correlation with the baseline CERAD score was strongest include bilateral frontal and parietal lobe deep and subcortical WM, as shown in Figure 4, which displays the WM voxels where the significance satisfies $p < 0.05$.

Rate of decline in CERAD score with regard to ROI lesion load analysis

There was an overall 1.43 decrease in mean CERAD score in all patients. AD and MCI patients showed a larger mean CERAD decrease than the controls (1.98, and 2.05 compared to 0.06, Figure 5).

From all WM ROIs defined in the template brain, the rate of decline in the CERAD was most significantly associated with lesion load located in the fornices ($p = 0.006$) when all subjects were included. There was no significant association if the MCI and Control groups were considered alone. When the analysis was performed within the AD group, the corpus callosum ($p = 0.03$) and the fornices ($p = 0.05$) yielded marginally significant values.

Rate of decline in CERAD score with regard to ROI volume analysis

There were many ROIs, the volume of which was significantly associated with declines in CERAD scores. Significant correlations between GM ROI volumes and declines in CERAD scores were found in the all subject group, and in the AD subgroup. No statistical significance was found in the MCI and in the control subgroups ($p>=0.05$). Including all

groups, statistical significance was reached for the temporal gray matter, amygdala, angular gyrus, hippocampus, inferior temporal gyrus, insula, lateral occipitotemporal gyrus, middle temporal gyrus, parahippocampal gyrus, parietal cingulate gyrus, precuneus, and uncus. In the AD subgroup, the following ROIs yielded statistical significance: inferior temporal gyrus, insula, lateral orbitofrontal gyrus, and lateral occipitotemporal gyrus. Details are found in Table 2.

Discussion

White matter lesions are associated with executive impairment and reduced information processing, and the most common histopathologic correlate in the elderly appears to be infarction with demyelination [24]. Our study showed that baseline white matter lesion load was strikingly increased in the frontal lobes of patients with AD compared to the MCI and CN groups. In addition, the ROI analysis demonstrates that WM lesions in the fornices, the frontal lobes and temporal lobes are correlated with decline in CERAD scores. These findings suggest that lesions found in connecting white matter tracks of the limbic system may be particularly significant in predicting decline in CERAD scores. The fornix, a major output pathway of the hippocampus, has been implicated in MCI and AD [36]. In addition, WM lesions close to the frontal lobe white matter-gray matter boundaries were also significantly correlated with decline in CERAD scores. This can be seen from the fact that the frontal lobe GM showed a significant relationship with the decline in CERAD scores. This significance in a GM ROI can be attributed to the intensity similarity between WML and the closest GM ROI, which results in a mislabeling of the WML as GM. In addition, we demonstrated that baseline CERAD scores correlated with atrophy affecting specific gray matter structures compared to white matter lesions. Focusing on the significant GM voxels, the temporal lobe appears to be especially important, with a striking asymmetry, favoring the left side in this study. For white matter, it appears that the subcortical WM of the anterior frontal and parieto-occipital lobes were most significantly correlated with baseline CERAD scores.

We have previously shown that AD imaging-based spatial patterns of brain atrophy, evaluated with sophisticated pattern analysis and recognition methods, may be useful in discriminating among NC individuals who are likely to be stable versus those who will show cognitive decline [37, 38]. Some of the previous studies also showed the independent contribution of WMHs to the transition to disability and dementia in initially in independently living elderly [39–41], however they also showed that neurodegeneration and atrophy is also independently related to cognitive decline [42, 43]. Considering the parallel effect of white matter changes and gray matter atrophy in the neurologic decline, prospective longitudinal cohort studies to focus on the mechanisms by which vascular and neurodegenerative mechanisms jointly contribute to the development and progression of aging-related cognitive disorders would be very important. Testing a combined mathematical approach to evaluate the effect of combined gray matter and white matter disease would be the next step.

Particular strengths of our study include the well-characterized cohort with longitudinal clinical data that were well-balanced in terms of demographic characteristics, the state-of-

the-art volumetric MRI approach incorporating both WM lesion and GM volumes. Limitations of this study include the fact that we looked at static distributions of WM lesions. Ideally, one would track the lesion load and the CERAD over multiple time points. Alternatively, one could distribute the subjects in groups of different CERAD scores, and identify the ROI lesion loads that best separate them. Such a study, however, would require a larger subject population that was not available for this work. In addition, although we used the total CERAD score in our study, we did not correlate different components of the score including verbal fluency, naming, word list immediate/delayed recall, constructional praxis, constructional praxis recall, and the Mini Mental State Examination (MMSE) due to the relatively small number of cases. We also used 1.5 Tesla MRI, however we do not consider it a significant limitation as prior studies have shown that the 1.5T and 3 T MRI are highly correlated in brain atrophy and WMH in aging and AD [44]. Despite these limitations, to our knowledge, ours is the only study correlating both WMH and GM atrophy with longitudinal changes in CERAD score.

Conclusion

Both baseline and declines in CERAD scores correlate with WM lesion load and GM atrophy. Results of this study underscore the importance of small vessel disease as a contributor to cognitive decline in elderly.

Acknowledgements

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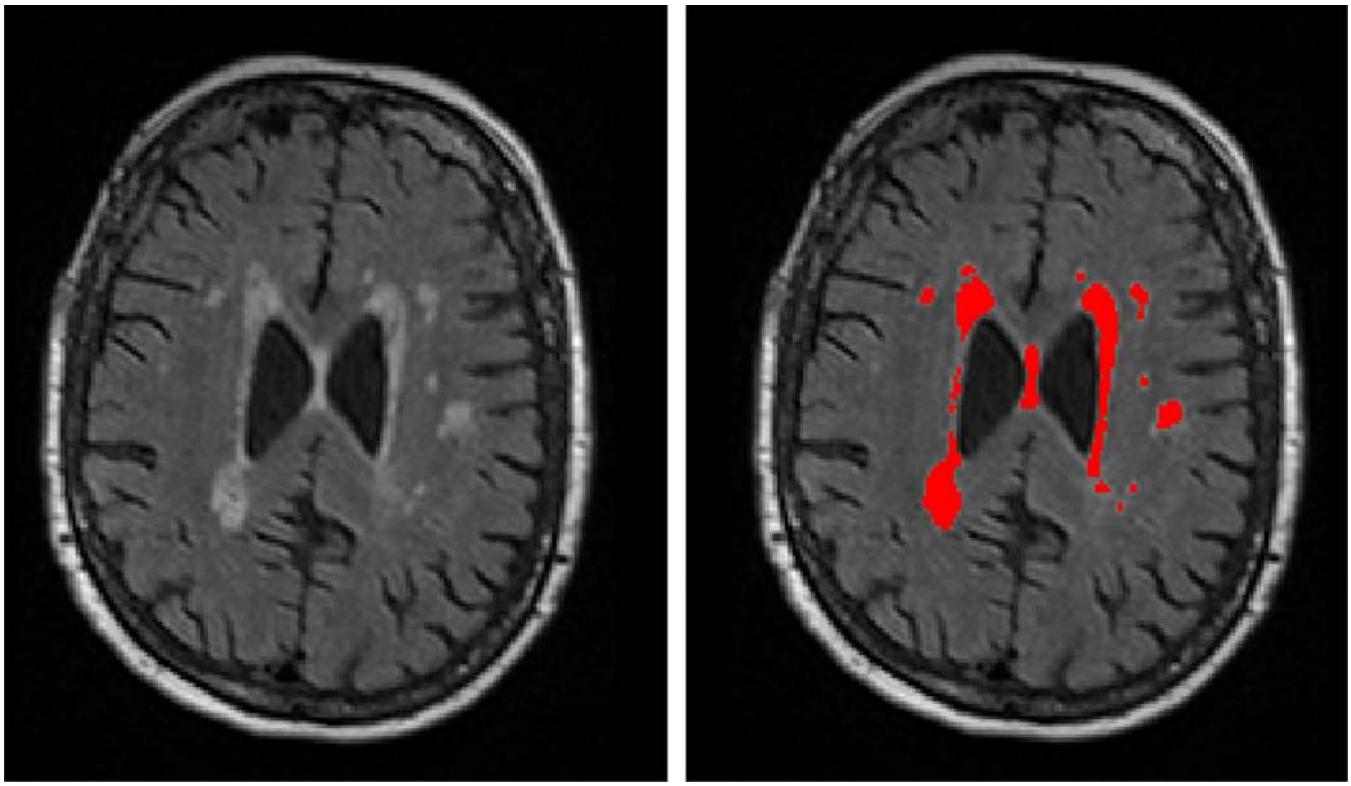

Figure 1.
Original T2/FLAIR image (left) with result of automatic WMH segmentation (right) on sample subject.

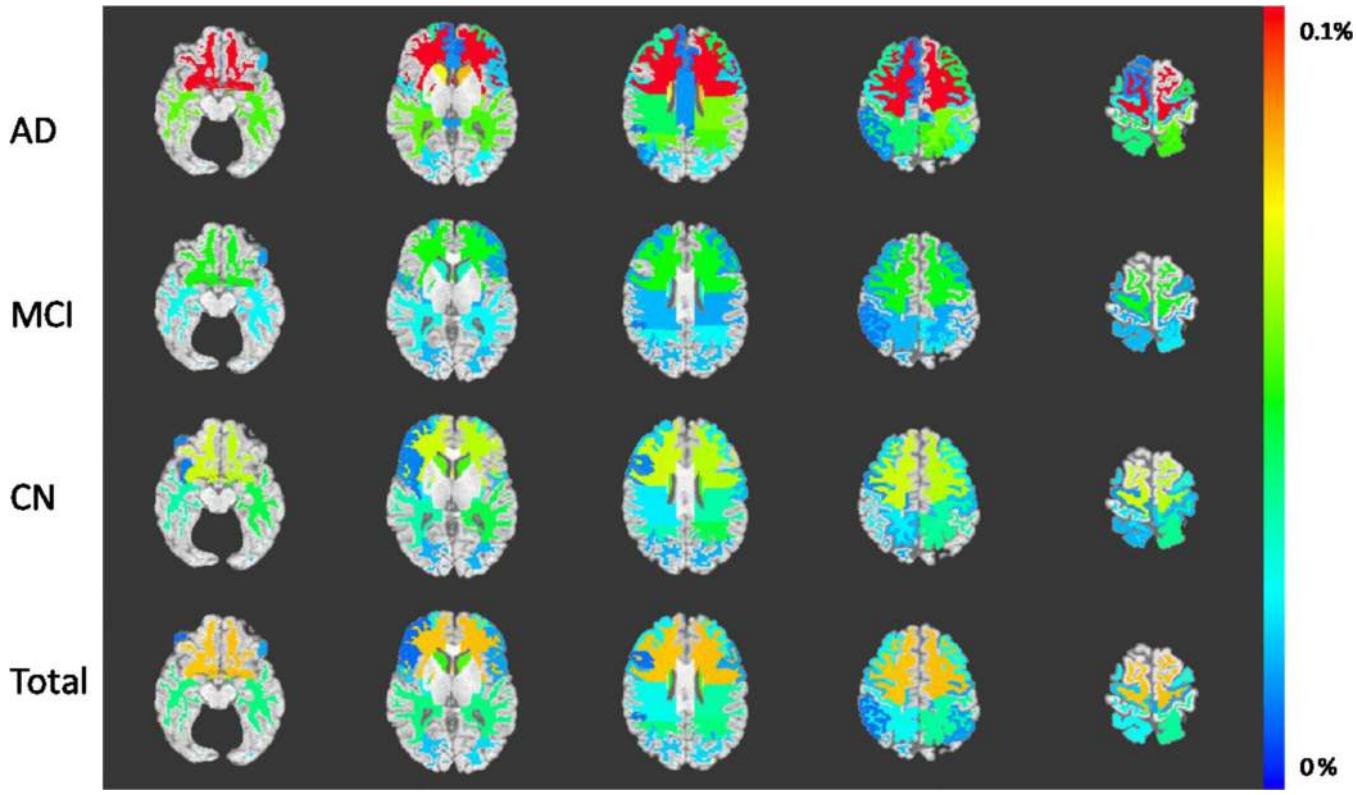

Figure 2.

Average normalized lesion load in each ROI across different diagnostic groups. The color scale indicates the extent of WMH lesions in each ROI indicating the highest lesion load shown as red and vice-versa for blue. The WMH lesion loads obtained for each subject were normalized by its Total Brain Volume (TBV) to reduce the effect of head size across subjects. Additionally, the lesion loads below 0.01% of TBV were eliminated to focus on ROIs showing higher lesion loads. The images represent axial brain images from inferior to superior. The images are in radiological convention. The average is computed over all subjects in a given diagnostic group, and the laterality is preserved, whereby no average is performed over a specific ROI and its contralateral counterpart.

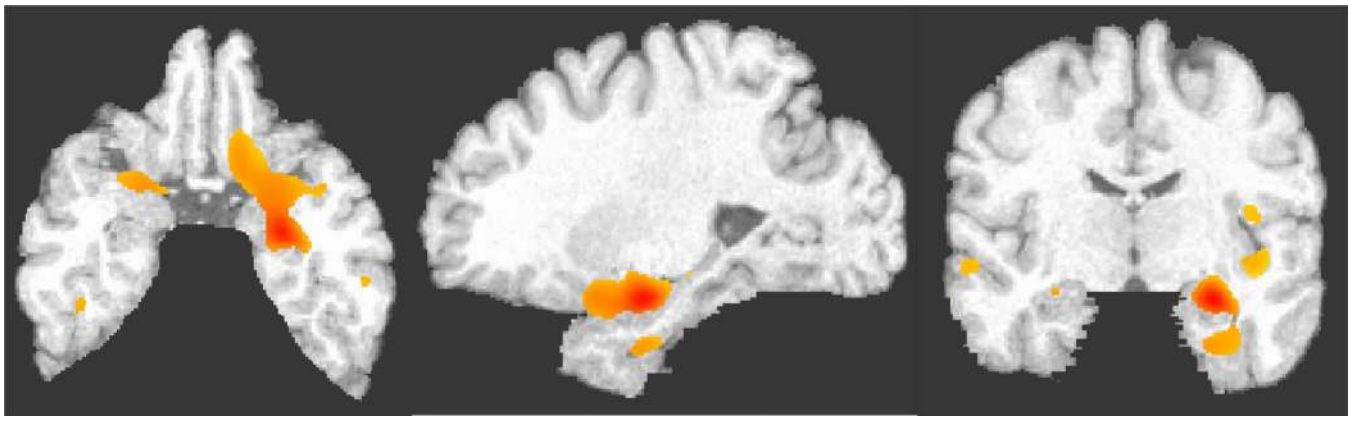

Figure 3.

Voxels where correlation between ROI volume and baseline CERAD score resulted in p values less than 10^{-8}. The low p-value was selected to display only the voxels with most significant correlation.

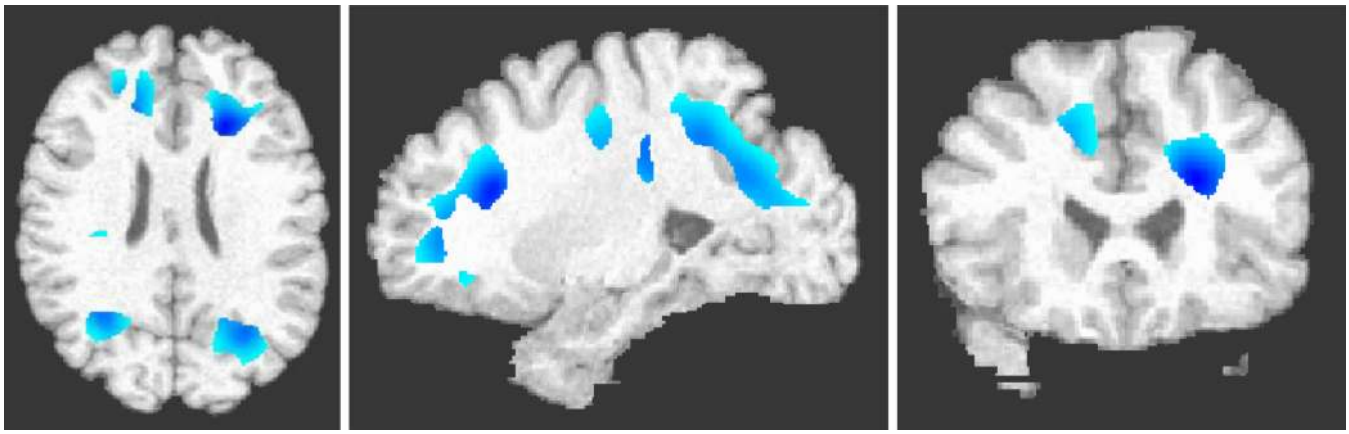

Figure 4.
Voxels where correlation between WMH lesion volume and baseline CERAD score resulted in p values less than 0.05.

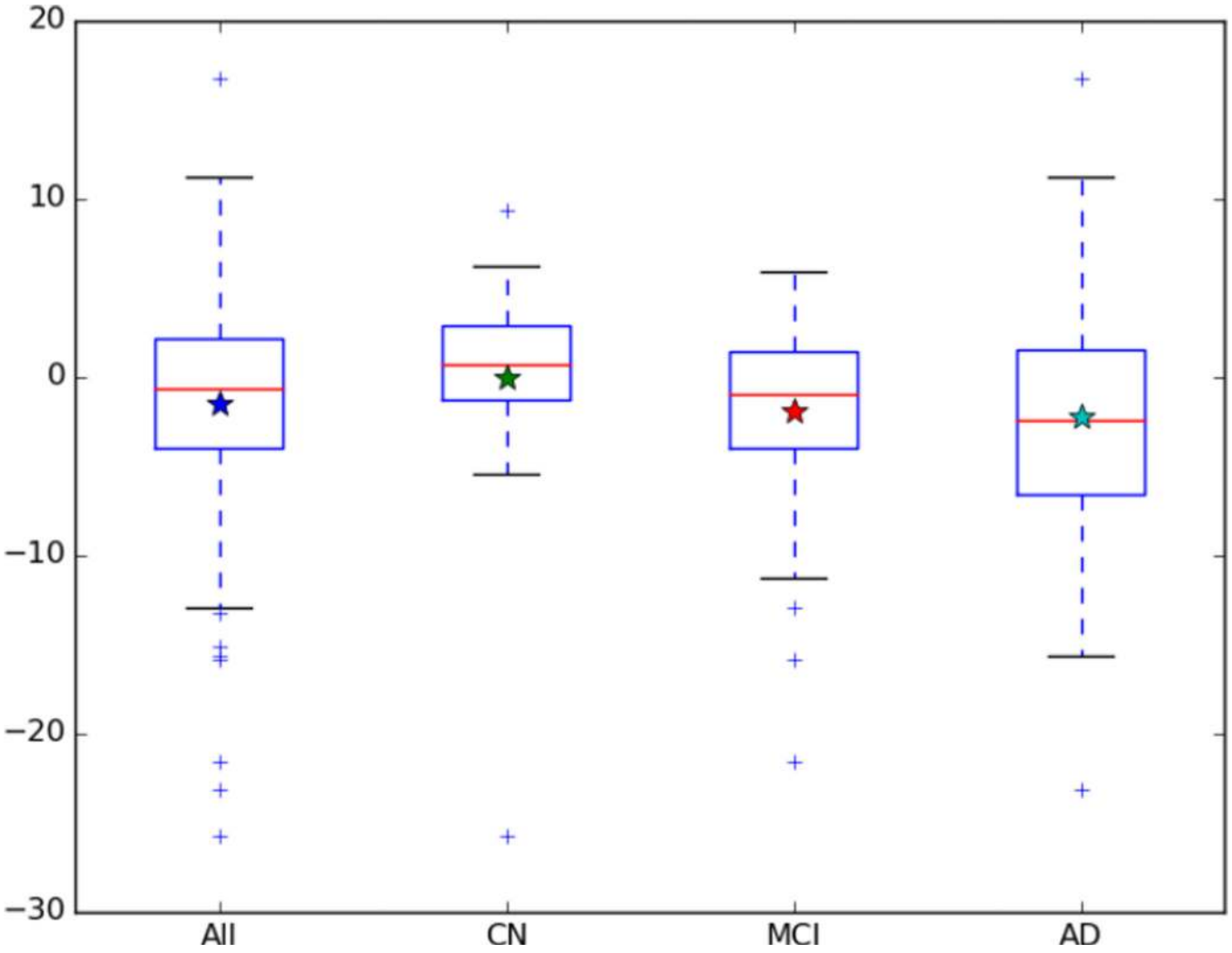

Figure 5.

Boxplot of rate of change of CERAD score over time (slope) for all diagnostic groups. The red bar indicates median, the star indicates mean.

Table 1

CERAD score and demographic characteristics in AD, MCI and NC subjects.

	AD	MCI	NC
Count	57	66	35
Age [Mean (SD) yrs]	75.3 (10.1)	70.1 (8.6)	69.5 (9.9)
Education [Mean (SD) yrs]	12.6 (4.4)	12.5 (5.5)	14.3 (4.7)
Sex [male]	35.10%	37.90%	20%
Race			
Black	15.80%	7.60%	11.40%
White	64.90%	65.20%	60%
Multi-Racial	15.80%	27.30%	28.60%
Other	3.50%	0%	0%
Ethnicity			
Latino	21.10%	39.40%	40%
CERAD [Mean (SD)]	41 (15.9)	59.6 (11.9)	80.1 (12)

Table 2

GM ROI volumes significantly correlated with declines in CERAD scores. The p-value was selected at 0.01 to account for multiple correlations.

ALL		AD	
Temporal GM	**0.002**	Temporal GM	0.021
Amygdala	**0.0004**	Amygdala	0.022
Angular gyrus	**0.0008**	Angular gyrus	0.018
Hippocampus	**0.001**	Hippocampus	0.1788
Inferior temporal gyrus	**0.0004**	Inferior temporal gyrus	**0.0007**
Insula	**0.0009**	Insula	**0.0019**
Lateral orbitofrontal gyrus	0.018	Lateral orbitofrontal gyrus	**0.0049**
Lateral occipitotemporal gyrus	**0.0003**	Lateral occipitotemporal gyrus	**0.0090**
Middle temporal gyrus	**0.0086**	Middle temporal gyrus	0.1182
Parahippocampal gyrus	**0.0082**	Parahippocampal gyrus	0.0797
Parietal cingulate gyrus	**0.002**	Parietal cingulate gyrus	0.022
Precuneus	**0.0039**	Precuneus	0.0689
Uncus	**0.0042**	Uncus	0.1090