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PARAHIPPOCAMPAL WHITE MATTER VOLUME PREDICTS AD RISK IN COGNITIVELY NORMAL OLD ADULTS

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Abstract

An *in vivo* marker of the underlying pathology in Alzheimer's disease (AD) is atrophy in select brain regions detected with quantitative MRI. Although gray matter changes have been documented to be predictive of cognitive decline culminating in AD among healthy older adults, very little attention has been given to alterations in white matter as a possible MRI biomarker predictive of AD. In this investigation, we examined parahippocampal white matter (PWM) volume derived from baseline MRI scans in two independent samples of 65 cognitively normal older adults, followed longitudinally, to determine if it was predictive of AD risk. The average follow-up period for the two samples was 8.5 years. Comparisons between the stable participants (N=50) and those who declined to AD (N=15) over time revealed a significant difference in baseline PWM volume ($p<0.001$). Furthermore, baseline PWM volume was predictive not only of time to AD (hazard ratio = 3.1, $p<0.05$), but also of baseline episodic memory performance ($p=0.041$). These results demonstrate that PWM atrophy provides a sensitive MRI biomarker of AD dementia risk among those with normal cognitive function.

Keywords

imaging; aging; perforant pathway; hippocampus; entorhinal cortex; structural MRI

1. INTRODUCTION

Recently, there has been increased interest in developing *in vivo* imaging biomarkers of risk of Alzheimer's disease (AD) in pre-clinical older adults (Sperling et al., 2011), since it is more likely that interventional strategies would be most effective in such individuals. In addition to biomarkers that predict decline from mild cognitive impairment (MCI) to AD, structural magnetic resonance imaging (MRI) investigations have demonstrated brain

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structural alterations before MCI (Dickerson et al., 2001; Saykin et al., 2006; Jessen et al., 2006; Smith et al., 2007, 2012; Chao et al., 2010) and in cognitively normal older adults (Apostolova et al., 2010; Martin et al., 2010; Dickerson et al., 2011), especially in medial temporal lobe regions.

Recent work from our laboratory has shown that cortical thinning in regions known to be affected in AD (Dickerson et al., 2009) can be detected in cognitively healthy older adults approximately a decade prior to developing AD dementia and is predictive of time to a diagnosis of AD (Dickerson et al., 2011). While cortical thickness measures provide information on alterations in gray matter, white matter changes, especially in the medial temporal region, also occur early in the disease process (Kalus et al., 2006; Rogalski et al., 2009; Salat et al., 2009, 2010; Wang et al., 2012) and may provide a sensitive imaging biomarker of risk of AD among healthy older individuals.

One of the cardinal features of AD is a decline in episodic memory critically dependent on the neuroanatomical components of the medial temporal lobe memory system such as the hippocampus, entorhinal cortex (EC) and the parahippocampal region in general (Squire and Zola-Morgan, 1991). Neurons of the EC receive multimodal sensory information from primary sensory and association cortices (Amaral et al., 1987; Van Hoesen and Pandya, 1975b; Van Hoesen et al., 1975) and relay this information to the hippocampus via the axons that make up the perforant pathway (Hyman et al., 1984; Van Hoesen and Pandya, 1975a). The integrity of this white matter tract is crucial for the proper information flow from neocortical regions to the hippocampus, and thus, for episodic memory function.

Work from our laboratory has demonstrated decreased parahippocampal white matter (PWM) volume in the region of the perforant pathway in people with amnesic MCI who are at risk of developing AD compared to controls (Stoub et al., 2006; Rogalski et al., 2009). However, it is unclear if PWM volume in the region of the perforant pathway could provide an imaging biomarker of risk of AD dementia even before a diagnosis of MCI. The present study was undertaken to examine this question in two samples of cognitively healthy older adults who entered independent longitudinal investigations with nearly identical demographic and cognitive characteristics. We chose to examine PWM volume since alterations in this region take place very early in the disease process, possibly due to cell loss in the EC (Hyman et al., 1984; Gomez-Isla et al., 1996; Kordower et al., 2001).

2. MATERIALS AND METHODS

2.1. Participants

Participants included 65 older people (mean age = 74.2 ± 4.18) from two independent samples (as described in Dickerson et al., 2011), with nearly identical demographics and cognitive characteristics, who entered separate longitudinal studies as cognitively normal controls (CN) at Rush University Medical Center (N=32) and the Massachusetts General Hospital (MGH, N=33). Those from Rush were recruited by the Rush Alzheimer's Disease Center (RADC) for a longitudinal imaging project, from the community, the Religious Order Study (Bennett et al., 2013), or the Rush Memory and Aging Project (Bennett et al.,

2012). Participants from the MGH were recruited as community volunteers for a longitudinal investigation.

To be included in the present study, participants had to be ≥ 65 years of age during the baseline evaluation, performing within the 'normal' range on neuropsychological tests (based on clinicians' judgment and not below 1.5 standard deviation of age and education matched mean scores) and free of underlying medical, neurological or psychiatric illness (based on laboratory tests and comprehensive clinical evaluations). Individuals with major vascular risk factors or disease (i.e., atrial fibrillation, insulin dependent diabetes mellitus, cerebral infarcts, cardiac bypass graft surgery) at baseline were excluded.

As described in Dickerson et al. (2011), participants in both samples received clinical evaluations, neuropsychological testing and high resolution structural MRI scans at baseline. Composite episodic memory Z-scores were computed for multiple episodic memory tests carried out at both centers. For participants at the MGH, a composite episodic memory score was computed based on three measures, including the California Verbal Learning Test (CVLT, Delis et al., 1987) 'total learning' and delayed free recall measures, as well as the free and cued Selective Reminding Test (Grober and Buschke, 1987) delayed free recall measure. First we calculated standardized scores for each of these tests adjusted for age, gender, and education. For the present article, the standardized scores for the three memory tests were averaged into a single Episodic Memory Z-score. Thus, a standardized score of -1.0 indicates that the subject was 1 standard deviation below the expected mean for a CN subject of the same age, gender, and level of educational attainment.

As described in Dickerson et al. (2011), the episodic memory tests administered at Rush consisted of the immediate and delayed recall of the East Boston Story (Albert et al., 1991) and of Story A from the Logical Memory of the Wechsler memory scale-Revised (Wechsler, 1987). An additional test involved the learning and retention of a 10-word list from the CERAD battery (Morris et al., 1989). The three scores for this test included Word List Memory (the total number of words immediately recalled after each of three consecutive presentations of the list), Word List Recall (the number of words recalled after a delay) and Word List Recognition (the number of words correctly recognized in a four-alternative, forced-choice format, administered after Word List Recall). Summary scores were calculated for combined performance on episodic memory tests by standardizing each of the seven memory scores. We used the means and standard deviations of each test from the baseline visits of the first wave of 86 participants entered into our longitudinal project and averaged the standardized values to obtain a memory Z-score.

All participants and informants provided informed consent in accordance with the requirements of the Human Research Committee of MGH and the Human Investigation Committee of Rush University.

2.2. Longitudinal Clinical Evaluations

After the baseline evaluations, all participants in the two samples were followed yearly (combined mean follow-up period = 8.5 ± 3.2 years) with clinical examinations and were classified as a) cognitively healthy, b) having mild cognitive impairment or c) having

dementia. For the analyses presented in this paper, we included all participants in the two cohorts with a baseline status of 'cognitively normal' (CN) and at least 4 annual visits after the baseline MRI (1 Rush participant had 3 visits). Because of our focus on subtle neurodegenerative changes in pre-clinical AD, we restricted the sample for the present paper to individuals who remained CN at the most recent follow-up (CN-stable) and those diagnosed with AD dementia (CN-AD converter). Those with a follow-up diagnosis of MCI were excluded (since their long-term outcome was not yet known), as were those with a diagnosis of non-AD dementia. This resulted in a sample of 33 participants at the MGH (25 CN-stable, 8 CN-AD converters) and 32 at Rush (25 CN-stable, 7 CN-AD converters)

The clinical diagnosis of probable AD followed NINCDS/ADRDA guidelines (McKhann et al., 1984) and required a history of cognitive decline and neuropsychological test evidence of impairment in at least two cognitive domains, one of which had to be memory.

2.3. MRI data acquisition and analyses

MRI data were acquired in a very similar fashion for both the MGH and Rush samples using a General Electric (Milwaukee, WI) 1.5 Tesla scanner and a 3D T1-weighted spoiled gradient recalled (SPGR) echo pulse sequence. For the MGH sample, the parameters were: repetition time/echo time (TR/TE) = 35 msec/5 msec; field of view = 22 cm; flip angle = 45°; number of excitations = 1; slice thickness = 1.5 mm, 124 slices; matrix size = 256 × 256. For the Rush sample, the parameters were: TR/TE = 33.3 msec/7msec; field of view = 22 cm; flip angle = 35°; number of excitations = 1; slice thickness = 1.6 mm, 124 slices; matrix size = 256 × 192. For the present study, only the first baseline scan was analyzed. At the time of this scan all participants were healthy participants with no cognitive impairment.

2.3.1. Segmentation of Parahippocampal White Matter—Volumes of the PWM were manually segmented using a PC-based image analysis program (Analyze, Mayo Clinic Foundation) and computed separately for the right and left hemispheres from coronal slices oriented perpendicularly to the long axis of the hippocampal formation using a protocol developed in our laboratory (Rogalski et al., 2009). Although in the past we have used voxel based morphometry (Stoub et al., 2006) to investigate the PWM region, we preferred the use of an anatomically correct segmentation of the PWM in the region of the perforant pathway for the present paper. The boundaries and validation procedures used for quantifying PWM volume were published previously (Rogalski et al., 2009). Tracings began with the slice in which the gyrus ambiens, amygdala and white matter of the parahippocampal gyrus were first seen. The most caudal slice traced was one slice rostral to the first appearance of the lateral geniculate nucleus. The lateral border of the PWM was defined as the bend that signifies the junction between the PWM and the temporal stem. The medial border was defined as the point at which the white matter meets the gray matter of the entorhinal cortex as shown in Figure 1. All PWM tracings were carried out by TRS (who was trained to be within 95% of Emily Rogalski) and checked slice by slice by LdeTM. TRS's intra-rater reliability based on 10 samples was 98%.

To correct for individual differences in brain size, PWM volumes were divided by total intracranial volume, a measure of pre-morbid brain size, derived from sagittally formatted 5

mm slices using the Analyze program (i.e., normalized). To compute intracranial volume, the inner table of the cranium was traced in consecutive gapless sagittal slices spanning the entire brain. At the level of the foramen magnum, a straight line was drawn from the inner surface of the clivus to the most anterior extension of the occipital bone. Normalized PWM volume was determined using the following formula: (absolute volume in mm³/intracranial volume in mm³) × 1000.

2.3.2. Segmentation of the hippocampus and entorhinal cortex—We previously reported on measures of cortical thinning in gray matter regions, including in the medial temporal lobe (MTL) gray matter, in the two cohorts included in the present paper (Dickerson et al., 2011). Although the emphasis here is on PWM changes as a biomarker of risk of AD, we wanted to compare the efficacy of this marker with hippocampal and entorhinal cortex (EC) volumes previously shown in our laboratory to be sensitive markers of AD risk (deToledo-Morrell et al., 2004; Stoub et al., 2005). Hippocampal and EC volumes were segmented using our previously published and validated protocols (Goncharova et al., 2001; deToledo-Morrell et al., 2004).

Briefly, both entorhinal and hippocampal volumes were computed separately (using the Analyze software, Mayo Clinic Foundation) for the right and left hemispheres from coronal slices reformatted to be perpendicular to the long axis of the hippocampus. For the EC, tracings began with the first section in which the gyrus ambiens, amygdala and the white matter of the parahippocampal gyrus first appeared visible. The superomedial border in rostral sections was the sulcus semi-annularis and in caudal sections the subiculum. The shoulder of the collateral sulcus was used as the lateral border. The lateral border was constructed by drawing a straight line from the most inferior point of the white matter to the most inferior tip of the gray matter. The last section measured was three 1.6 mm sections rostral to the image in which the lateral geniculate nucleus first appeared visible (see Goncharova et al., 2011 for details).

Tracings of the hippocampus started with the first section where it could be clearly differentiated from the amygdala by the alveus and included the fimbria, dentate gyrus, the hippocampus proper and the subiculum. Tracings continued on all consecutive images until the slice before the full appearance of the fornix (see deToledo-Morrell et al., 2004 for details).

All segmentations were carried out by an experienced tracer, TRS; his inter- and intra-rater correlation coefficients based on a sample of 10 were 0.97 and 0.97 respectively for the hippocampus and 0.99 and 0.99 for the EC. Volumes of the hippocampus and EC were normalized by dividing with intracranial volume as described above for the PWM.

2.4. Statistical analyses

The difference in normalized PWM volume, hippocampal volume and EC volume between the CN-stable and CN-AD converter groups was assessed with a two-tailed t-test. In addition, regression models were used to examine the utility of PWM volume for predicting the progression from CN to AD dementia, as well as contributing to the prediction of baseline episodic memory performance. Regression models were also used to compare

medial temporal lobe white and gray matter regions as predictors of the decline to AD dementia. For the regression analyses, we first used a univariate approach to investigate if the dependent variables were influenced by potential confounders such as age, education, gender, Mini Mental State Examination (MMSE) scores (Folstein et al., 1975) and APOE status. Confounders with statistically significant effects were then included in multivariate regression models.

3. RESULTS

Baseline demographic data, MMSE scores, episodic memory Z-scores, as well as APOE status, intracranial volume, normalized PWM, hippocampal and EC volumes for the two cohorts are presented in Table 1. As can be seen from this table and as reported previously (Dickerson et al., 2011), the two samples were remarkably similar, with MMSE scores being in the normal range and only one or two points from ceiling. Longitudinal clinical evaluations demonstrated that of the original 65 CN participants enrolled at both centers, 15 declined to develop AD during the follow-up period (8 at MGH and 7 at Rush). As can be seen from Table 1, the difference in PWM between the decliners and stable CN participants was similar, but more accentuated for the Rush sample compared to the MGH sample. Due to the similarity of the clinical characteristics of the two populations, the two samples were combined in the analyses reported below in order to have a larger sample.

3.1. Parahippocampal white matter as a predictor of decline to AD dementia

Figure 2 shows baseline PWM volume for the CN-stable and CN-AD converter groups. A comparison between the two groups revealed a significant difference in normalized PWM volume [$t(63)=4.1$, $p<0.001$]. To examine if the PWM volume measure could provide a sensitive marker of risk of AD among cognitively healthy older individuals, we first divided all participants into the following three groups based on PWM volume: 1) 1 SD below the cohort mean (low volume subgroup), 2) within 1 SD of the mean (average volume), 3) 1 SD above the mean (high volume). Of the 9 individuals with low volume, 6 declined and received a diagnosis of AD over nearly the next decade (67%). In contrast, of those with average volume, 9/46 declined to AD (20%), while none of those with high volume declined during the follow-up period, a highly significant difference ($X^2 = 12.25$, $p=0.002$). These results are shown in Figure 3.

Since participants in the study had different follow-up periods, Cox regression models were performed to investigate the utility of PWM volume for the prediction of progression from CN to AD dementia. As previously described (Dickerson et al., 2011), the mean time to a diagnosis of AD dementia in the pooled sample was 8 (± 1.9) years. Univariate Cox regression models of covariates indicated that gender was a predictor of time to dementia (greater risk for males, $p<0.005$), but age, education, APOE status and MMSE were not ($p>0.1$), at least in this sample. A forward conditional Cox regression model was conducted in which gender was entered in block one and PWM volume was included in the forward conditional block two. This overall model was statistically significant ($X^2=19.5$, $p<0.001$): the PWM variable entered the model (HR=3.1 for one SD decrease in PWM volume; 95% CI, 1.2–7.8; $p<0.05$). Figure 4 presents a survival plot illustrating these results.

Previous findings from our laboratory have demonstrated that in addition to hippocampal volume, PWM volume in the region of the perforant pathway is a significant predictor of episodic memory performance in people with MCI (Stoub et al., 2006). Due to the fact that this region is important for memory function since it relays multi-modal sensory information to the hippocampus, we carried out regression models to investigate if PWM volume is predictive of baseline episodic memory Z-scores (dependent variable) in cognitively healthy older adults. None of the covariates such as gender, age, education and APOE status were predictive of baseline memory Z scores, but total normalized PWM volume was [$F(1,64)=4.34$, $p=0.041$; Beta coefficient=0.254]. A scatter plot showing the relation between episodic memory Z-scores and PWM volume for each participant is presented in Figure 5.

3.2. Comparison of parahippocampal white matter volume with entorhinal cortex and hippocampal volumes as markers predicting decline to AD dementia

As was the case for PWM volume, the CN stable and CN-decliner groups differed from each other in both normalized hippocampal and EC volumes [$t(63)=3.489$, $p<0.001$] and [$t(63)=5.205$, $p<0.001$ respectively].

When three separate models were run, one for each independent volumetric variable, all three separate regions under consideration, namely normalized PWM, EC and hippocampal volumes each predicted conversion to dementia. The model for PWM volume was described above. Similarly to the PWM results, the two gray matter volumes produced significant, albeit weaker models. The model for EC volume was significant overall ($X^2=19.1$, $p<0.001$), with a HR of 2.4 (CI 1.3–4.4, $p<0.005$). The model with hippocampus was significant overall ($X^2=14.8$, $p=0.001$), with a HR of 1.6 (CI 1.0–2.5, $p<0.05$). When a stepwise model was constructed with all three variables entered in a stepwise block, only the PWM entered the model with the two gray matter volumes not entering the model ($p>0.1$), indicating that they did not explain additional variance beyond that explained by the PWM volume.

In addition, we examined the relation between EC volume and PWM volume in the CN-AD decliner group to determine if the alterations in PWM could be explained by the death of cells in the entorhinal cortex which give rise to the perforant pathway. There was a strong relationship between the two volumes ($r=0.810$, $p=0.0025$), indicating that reductions in PWM volume among decliners could reflect cell body degeneration in the EC which takes place very early in the disease process. The relation between hippocampal volume and PWM volume in decliners was not as strong, but still significant ($r=0.635$, $p=0.01$).

4. DISCUSSION

The major aim of this paper was to investigate if, in addition to subtle alterations in AD-signature gray matter regions as reported by us previously (Dickerson et al., 2011), changes in white matter can predict risk of AD dementia in cognitively healthy older individuals. We were especially interested in white matter changes in the anterior medial portion of the parahippocampal gyrus, since the perforant pathway, located in this region, conveys multi-modal sensory information to the hippocampus and is pathologically affected very early in

the disease process due to cell loss in layer II of the entorhinal cortex (Hyman et al., 1984; Braak and Braak, 1991; Gomez-Isla et al., 1998; Kordower et al., 2001). In addition, we compared the strength of PWM volume as a predictor of decline, with medial temporal lobe gray matter such as the entorhinal cortex and the hippocampus, areas known to be pathologically affected very early in the disease process.

The results presented here demonstrate that volumetric changes in the parahippocampal white matter region of interest can provide a sensitive imaging marker of risk of AD dementia in cognitively healthy individuals nearly a decade prior to cognitive decline culminating in AD. Such quantitative MRI measures provide a surrogate marker of the underlying pathological changes taking place years before the actual appearance of clinical symptoms and are useful not only as an index of risk of AD, but also for predicting time to dementia.

It is important to note that the data reported here for the PWM in cognitively healthy older adults are remarkably similar to those we published previously for AD-signature gray matter thinning in the same cohort as predictors of decline to AD approximately a decade ahead of the diagnosis of dementia (Dickerson et al., 2011). As was the case for cortical thinning in AD-signature regions, individuals with low PWM volume were more likely to decline and receive a diagnosis of AD dementia over the follow-up period. Similarly, baseline PWM volume provided a good predictor of time to dementia in individuals who were cognitively normal at the time they were scanned.

In addition to gray matter thinning reported by us in the same two cohorts (Dickerson et al., 2011) in the medial temporal lobe region, in the present paper we compared models based on the strength of PWM volume in predicting decline with entorhinal and hippocampal volumes segmented in an anatomically precise manner. Although both gray matter regions were predictive of decline in cognitively healthy individuals, PWM volume provided stronger predictive value. The fact that the model based on EC volume was stronger than the one based on hippocampal volume may reflect the pathological involvement of the EC before the hippocampus in the disease process (Braak and Braak, 1991; Stoub et al., 2005).

The exact underlying mechanism of the volume loss in the PWM region of interest cannot be determined *in vivo* with the tools available to us. One may speculate that some of the observed volume change may reflect partial loss of fibers of the perforant pathway that arise from cells in the entorhinal cortex since, as discussed above, these cells degenerate very early in the disease process. The strong relationship we report above between EC volume and PWM volume supports the possibility of such Wallerian degeneration. Furthermore, white matter volume change may reflect not only loss of afferent and efferent fibers in the region of the parahippocampal gyrus, but also partial age- or disease-related demyelination in remaining fibers (Bartzokis, 2004). In addition to volume loss, diffusion tensor imaging (DTI) has been used by us and others to assess micro-structural alterations in remaining white matter fibers (Rogalski et al., 2009, 2012; Yassa et al., 2010; Salat et al., 2010; Ziegler et al., 2010; Wang et al., 2012) that can further amplify the disruption in information flow from one region of the brain to another and affect cognitive function. Unfortunately, baseline DTI scans were not available for all members of the cognitively healthy cohort

followed by us for almost a decade. It is possible that combined measures of PWM volume loss and DTI abnormalities may provide an even more sensitive imaging biomarker of risk of AD.

Regression models reported in this paper also demonstrate that baseline PWM volume is predictive of performance on baseline episodic memory tests. This finding is consistent with the results of a previous paper from our laboratory showing that both hippocampal volume and PWM volume were significant predictors of episodic memory function in participants with amnesic MCI (Stoub et al., 2006). Here we demonstrate that PWM volume is predictive of episodic memory performance in an even earlier stage than MCI, in the pre-clinical stages of AD. The results reported here further demonstrate that alterations in PWM fibers contribute to episodic memory function by affecting normal multi-modal sensory information flow to the hippocampus.

In summary, the data presented in this paper show that in addition to cortical thinning in AD-signature regions (Dickerson et al., 2011), or EC and hippocampal volume, white matter volume loss in the parahippocampal region that includes the perforant pathway provides a sensitive biomarker of risk of AD approximately a decade ahead of time. These results are especially timely and of interest in view of a recent publication demonstrating that the parahippocampal gyrus links the medial temporal lobe with nodes of the default-mode cortical network (Ward et al., 2013). These authors conclude that sensitive measures of parahippocampal connectivity may provide a biomarker of network dysfunction related to AD. In this paper we provide one such measure of parahippocampal connectivity that predicts decline to AD in cognitively healthy individuals.

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Figure 1.
A coronal MR image of the medial temporal lobe showing the parahippocampal white matter region of interest.

Figure 2.

Bar graph showing total, normalized parahippocampal volume for the CN-stable group compared to the CN-AD converter group. Vertical bars represent the standard error of the mean.

Figure 3.

AD dementia risk as a function of baseline parahippocampal white matter (PWM) volume. None of the 10 individuals with 'high' PWM volume developed AD dementia during the follow-up period while 9 of the 46 participants with 'average' volume (20%) and 6 of the 9 with 'low' volume (67%) declined to a diagnosis of AD dementia (see text for details).

Figure 4.

Univariate survival plot of predicted time to AD dementia for hypothetical average study participants with PWM volume in the lowest (smallest) tertile, middle tertile and highest tertile. The displayed survival curves are model predictions and do not directly represent subject results. PWM volume was predictive of progression from normal cognition to AD dementia (hazard ratio=3.1 for one standard deviation decrease in volume; 95% CI, 1.2–7.8; $p<0.05$) in the model.

Figure 5. Scatter plot showing the relationship between PWM volume and episodic memory Z-scores for all participants.

Table 1

Demographic and Clinical Characteristics of Participants

Sample Group	MGH		Rush		Combined MGH and Rush	
	CN -Stable (n=25)	CN -AD (n=8)	CN -Stable (n=25)	CN -AD (n=7)	CN -Stable (n=50)	CN -AD (n=15)
Gender Male Female	9 16	5 3	3 22	4 3	12 38	9 6
Age (in years) (Mean ± SD)	71 ± 4	72 ± 2	76 ± 6	78 ± 5	73.8 ± 6	73.7 ± 5
Education (in years) (Mean ± SD)	15 ± 2	14 ± 3	16 ± 3	15 ± 3	15.3 ± 3	14.8 ± 3
APOE (% e4 carriers)	4 (16)	2 (25)	3 (12)	1 (14)	7 (14)	3 (20)
Baseline MMSE (Mean ± SD)	29 ± 1	29 ± 1	29 ± 1	28 ± 1 ^a	29.1 ± 1	28.7 ± 1
Baseline Memory (Z) (Mean ± SD)	0.29 ± 0.7	-0.28 ± 1.1 ^b	0.64 ± 0.5	-0.13 ± 0.5 ^c	0.49 ± 0.6	-0.04 ± 0.9 ^d
Follow-up (in years) (Mean ± SD)	10.4 ± 3.1	11.1 ± 2.5	8.3 ± 3.1	7.1 ± 1.1	8.8 ± 3.4	7.7 ± 2.6
Intracranial Volume (Mean ± SD)	1532499.5 ± 136897.2	1527104.9 ± 179723.1	1401460.5 ± 111231.5	1518768.6 ± 127152.8	1466980.0 ± 140069.9	1523214.6 ± 151979.6
Normalized PVM Volume (Mean ± SD)	1231 ± 204	1100 ± 100 ^e	1481 ± 277	921 ± 135 ^f	1356 ± 272	1017 ± 146 ^f
Normalized Hippocampal Volume (Mean ± SD)	4010 ± 537	3782 ± 541	4412 ± 408	3517 ± 714 ^f	4211 ± 513	3658 ± 619 ^f
Normalized Entorhinal Cortex Volume (Mean ± SD)	1000 ± 166	798 ± 214 ^a	1133 ± 211	729 ± 146 ^f	1066 ± 200	766 ± 183 ^f

^aSignificantly different from CN-Stable p<0.01

^bTrend-level effect p<0.1

^cSignificantly different from CN-Stable p<0.05

^dSignificantly different from CN-Stable p=0.01

^eTrend-level effect p=0.09

^fSignificantly different from CN-Stable p<0.001