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Authors

Carmichael, Owen T
Kuller, Lewis H
Lopez, Oscar L
et al.

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- **Title:** Cerebral ventricular changes associated with transitions between normal cognitive function, mild cognitive impairment, and dementia

- **Short Title:** Ventricle changes in normal-MCI-dementia transitions

- **Authors and author addresses:**

O. T. Carmichael Ph.D.[a], L. H. Kuller M.D. [b], O. L. Lopez M.D.[c], P. M. Thompson Ph.D.[d], R. A. Dutton [d], A. Lu [d], S. E. Lee [d], J. Y. Lee [d], H. J. Aizenstein M.D., Ph.D.[e], C. C. Meltzer M.D. [c e f], Y. Liu Ph.D.[g h], A. W. Toga Ph.D. [d], J. T. Becker Ph.D. [c i e]

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[a]Neurology Department, University of California, Davis, Davis, CA, 95616
[b]Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA, 15213
[c]Neurology Department, University of Pittsburgh, Pittsburgh, PA 15213
[d]Neurology Department, University of California, Los Angeles, Los Angeles, CA, 90095-1769
[e]Psychiatry Department, University of Pittsburgh, Pittsburgh PA 15213
[f]Radiology, Neurology, and Psychiatry Departments, Emory University, Atlanta, GA, 30322
[g]The Robotics Institute, Carnegie Mellon University, Pittsburgh, PA, 15213
[h]Radiology Department, University of Pittsburgh, Pittsburgh, PA, 15213
[i]Psychology Department, University of Pittsburgh, Pittsburgh, PA 15213

- **Corresponding author:**
Owen T. Carmichael
Center For Neuroscience
1544 Newton Court
Davis, CA, 95616
email: ocarmichael@ucdavis.edu
phone: (530) 754-9657
fax: (916) 734-6525

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Abstract

Expansion of the cerebral ventricles may occur at an accelerated rate in subjects with dementia, but the time course of expansion during transitions between normal cognitive function, mild cognitive impairment (MCI), and dementia is not well understood. Furthermore, the effects of cardiovascular risk factors on rate of ventricular expansion are unclear. We used a fully-automated segmentation technique to measure change rate in lateral ventricle-to-brain ratio (VBR) on 145 longitudinal pairs of magnetic resonance (MR) images of subjects in the Cardiovascular Health Study Cognition Study (CHS-CS) from the Pittsburgh Center. A multivariate model analyzed VBR change rate, accounting for dementia statuses at both imaging times (normal, MCI, or dementia), age, gender, education, race, MR-defined infarcts, CES-D depression score, baseline ventricular volume, and cardiovascular risk factors. VBR change was faster in subjects who were demented or transitioned from MCI to dementia, compared to subjects normal at both images and subjects who transitioned from normal to MCI or dementia. Diabetics had faster VBR change. Ventricular expansion may accelerate late in the progression from normal cognitive function to dementia, may be modulated by diabetes, and may be similar among subjects with varying MCI deficits.

1   Introduction

A growing body of longitudinal studies have demonstrated that atrophy of specific structures in the brain is accelerated in subjects with dementia. In particular, several authors have shown that subjects with Alzheimer's disease (AD) experience faster generalized brain atrophy and faster atrophy of specific structures in association with disease-related neuronal loss (for example, [1] [2]). Establishing normative atrophy rates for various brain structures has the potential to be clinically useful for early detection of dementia, monitoring of the disease course, and evaluating responses of critical brain structures to interventions.

However, the question of how brain structure atrophy rates are affected early in the process of cognitive decline is not well understood. In particular, while several studies have compared atrophy rates between cognitively normal subjects and subjects with dementia, fewer studies have examined the atrophy rates of subjects as they transition between normal cognitive function, mildly-impaired states such as mild cognitive impairment (MCI), and dementia. Studies to date in this area have generally focused on the characteristics of a small group of subjects or a single type of transition, for example, the transition from MCI to dementia

[3] [4] [5] [6]. Furthermore, the transition to dementia can be through a pure amnestic syndrome, or through a more widespread form of cognitive impairment. The majority of the epidemiological studies have found that the majority of the MCI cases have multiple cognitive deficits [7] [8]. Volumetric studies have found that the amnestic and the multiple cognitive domain types of MCI have cortical atrophy, although the mesial temporal lobe is more atrophic in the amnestic type [9]. Better understanding of how brain structure atrophy rates are differentiated between stable subjects– who remain cognitively normal or mildly impaired over a prolonged period– and declining subjects– who transition from normal cognitive function to various forms of MCI or dementia– have the potential to provide valuable indications of dementia risk and progression.

Additionally, an understanding of interactions between rates of cognitive decline and rates of brain structure atrophy could be useful for assessment of the time course of cognitive decline. Clinical studies have shown that the time course of conversion to dementia can be highly variable, since some subjects can remain in an MCI state for many years, while others convert to dementia rapidly, or improve over time [10][11]. A previous study from our group suggested that at baseline, normal subjects who subsequently developed dementia over the course of four years had brain structure characteristics that varied from those of other normal subjects [12]. However, while these results suggest that rapid decline from normal cognitive function to dementia may have distinct baseline structural correlates, the time course of structure atrophy in subjects undergoing rapid decline is unknown.

Furthermore, relationships between prevalent comorbidities and brain structure atrophy rates among subjects transitioning from normal cognitive function to dementia are unclear. For example, previous studies have suggested associations between cerebral ventricular volume and clinical conditions that are prevalent in the elderly, such as hypertension, diabetes, and depression [13] [14] [15]. But previous studies on brain structure atrophy rates in dementia progression vary with respect to accounting for these comorbidities.

This study analyzes the rate of expansion of the lateral ventricles between two magnetic resonance (MR) scans. Expansion of CSF spaces, especially of lateral ventricles, reflects many pathologic features, including cortical neuronal loss associated with dementia-related pathology. A loss of neurons could lead to a disruption of cell membranes, loss of myelin, and disruption of axonal processes, and consequently, to large lateral ventricles [16] [17] [18] [19] [20]. We focus on lateral ventricle expansion due to earlier longitudinal studies suggesting that fast ventricular expansion is associated with dementia, general cognitive decline, and higher loads of dementia-related pathology at autopsy [21] [22] [23] [18] [24] [16] [25] [26]. We feel that insight into ventricular expansion rates could complement studies on dementia-related atrophy

rates in the medial temporal lobe structures where early dementia-related pathology is prevalent [27] [5] [28]. Expansion of the ventricles was measured in terms of rate of change in the ventricle-to-brain ratio (VBR) between MR scans. An automated technique was used to estimate ventricular and brain volumes at the times of the first and second MR scans, VBR was computed by dividing ventricular by brain volume, and VBR change rate was computed by dividing interscan differences in VBR by the interscan interval. Statistical models then examined how VBR change rate were affected by dementia diagnoses at the times of the first and second scans (normal, MCI, or demented), as well as a variety of demographic and clinical factors.

This study was designed to test three hypotheses related to the time course of ventricular expansion in subjects experiencing cognitive decline. First, we note that AD was the most prevalent type of dementia in this cohort, and that associations between ventricular expansion rate and post-mortem levels of AD-related pathology have been suggested previously [25]. Assuming that MCI is associated with increased levels of AD-related pathological processes, and that AD-related pathologies accumulate steadily over time, our first hypothesis is that subjects who transitioned between MCI and dementia had faster ventricular expansion than subjects who transitioned between normal cognitive function and MCI, possibly reflecting increased pathological load. The second hypothesis, based on earlier findings that baseline ventricular volume was elevated among normal subjects who declined rapidly to dementia, is that baseline-normal subjects who declined rapidly experienced a time course of ventricular expansion during their decline that differed significantly from normal subjects who declined to MCI and normal subjects who remained normal [12]. The third hypothesis, based on earlier associations between cardiovascular risk factors and ventricular volume, is that subjects with prevalent cardiovascular risk factors, such as diabetes and hypertension, had faster ventricular expansion, possibly reflecting the impact of cerebrovascular disease on subcortical grey and white matter structures [29] [30] [31].

We analyzed a set of 145 image pairs from the community-based Cardiovascular Health Study (CHS), which we feel alleviates concerns related to small sample sizes and selection bias that may have limited some of the earlier studies in this area. Furthermore, we analyzed several types of cognitive state transitions– normal to MCI, MCI to dementia, and so on– in a single, unified statistical model in an attempt to capture relationships between ventricular structure and highly-variable rates of cognitive decline in a population-based sample. A reliable, fully-automated structure segmentation technique enabled analysis of the large set of images without the need for costly manual interaction with each image [32]. While previous studies

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have addressed longitudinal ventricular expansion rates in relatively large dementia clinic samples (*e.g.*, [33]), to our knowledge, no fully quantitative study of longitudinal ventricular expansion rates to date has combined a relatively large epidemiological sample with analysis of a rich set of cognitive state transitions and comorbidities.

2   Methods

2.1   Subjects

The Pittsburgh CHS Dementia Study, conducted between 1997 and 1999, identified 532 normal and MCI subjects at the Pittsburgh center. The Pittsburgh CHS Cognition Study (CHS-CS), a continuation of the CHS Dementia Study, was conducted from 2002 to 2005 to determine the incidence of dementia and MCI in that population of 532 subjects. The characteristics of the Pittsburgh CHS-CS have been described previously [29] [7], as well as the details concerning the longitudinal follow-up of the CHS participants [34] [35]. All participants completed neurological and neuropsychological examinations in 1998-99, 2002-03, and 2004-05. There were 388, 189, and 53 subjects who received high-resolution MR scans together with clinical evaluations in 1997-99, 2002-03, and 2004-05 respectively at the Pittsburgh center. Longitudinal pairs of 1997-99 and 2002-03 MR images were available for 107 subjects, and longitudinal pairs of 2002-03 and 2004-05 images were available for 43 subjects. 31 of the 43 subjects with 2002-03 and 2004-05 images also had a 1997-99 image. Complete demographic and clinical data was available for 145 of the 150 longitudinal image pairs, Demographic and clinical characteristics of the subjects in 2002-03 are shown in Table 1. Subjects were assigned to dementia progression groups according to dementia diagnoses at the times of the first and second scans (see Figure 1). We emphasize that there were two types of longitudinal image pairs, corresponding to scans acquired in 1997-99 and 2002-03 *vs.* 2002-03 and 2004-05 respectively.

2.2   Clinical examination

Neuropsychological examination.   The neuropsychological battery included tests of premorbid intelligence, memory, language, visuoperceptual/visuoconstructional, attention/executive, and fine motor control functions. Details of the neuropsychological battery, and normative data were previously published [7] [34].

Neurological exam. The neurological exam included a brief mental status examination, as well as cranial nerve testing, motor tone, abnormal movements, strength, deep tendon reflexes, release signs, plantar response and clonus, cerebellar testing, primary sensory testing, gait, and postural stability. After the mental status exam, the neurologist asked the participant about his/her performance on these tests, and the response was graded on a four-point scale. The examiner also completed the Unified Parkinsons Disease Rating Scale (UPDRS) [36] and the Hachinski Ischemic Scale (HRS) [37].

Psychiatric examination. Symptoms of depression were measured with the modified version of the Center for Epidemiology Studies Depression Scale (CES-D) 10-item version [38] and historical data were available through the CHS from 1992-1994 to 1998-99. The Neuropsychiatric Inventory (NPI) [39] was administered in 1998-99 and in 2002-03.

MCI criteria. MCI subjects were diagnosed following the CHS Cognition Study diagnostic criteria for MCI [7]. These were subjects who had impairments (defined as performance > 1.5 S.D. from controls) in delayed recall of verbal material, non-verbal materials, or both; or had impairments in at least one cognitive domain (other than memory) or one abnormal test (which could be a memory test) in at least two domains, without sufficiently severe impairment or loss of instrumental activities of daily living (IADLs) to constitute dementia. The cognitive deficits must represent a decline from a previous level of functioning. The diagnosis did not exclude individuals with mild defects on IADLs. Subjects were classified as probable MCI when there were no psychiatric, neurological (e.g., cerebrovascular disease, history of head trauma encephalopathy, infectious diseases, developmental disabilities) or systemic illnesses that may cause cognitive deficits, or possible when any comorbid condition was present.

Diagnosis of Dementia and Alzheimers disease. The diagnosis of dementia was based on a deficit in performance in two or more cognitive domains that were of sufficient severity to affect activities of daily living, and history of normal intellectual function before the onset of cognitive abnormalities. An abnormal domain was present when at least two tests of the same domain were abnormal [34]. The diagnosis of AD was made following the National Institute of neurological and Communicative Disorders and Stroke, and the Alzheimers Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable and possible AD [40].

2.3　MRI Acquisition and Processing

MRI acquisition　All MR images were collected from 1997 to 2005 on the same 1.5T Signa scanner (GE Medical Systems) with high performance gradients (4 G/cm and 150 T/m-s). The subjects were positioned in a standard head coil and a volumetric Spoiled Gradient Recalled Acquisition (SPGR) sequence with parameters optimized for maximal contrast among gray matter, white matter, and cerebrospinal fluid was acquired in the coronal plane (TE/TR = 5/25, flip angle = 40 deg., NEX = 1, slice thickness = 1.5mm/0mm interslice).

Automated ventricular and whole-brain volume estimation　Lateral ventricular volumes were estimated fully automatically on all scans using a technique described in a previous study [32]. In short, images were resampled to obtain 1x1x1 mm^3 voxels, anisotropically smoothed [41], skull-stripped [42], cropped to remove all-zero planes, and geometrically aligned to images on which the lateral ventricles had been delineated manually or automatically. The alignment technique used Levenberg-Marquardt optimization to estimate a series of geometric transformations of graduating complexity– a similarity transformation, followed by a piecewise-linear deformation, followed by a dense voxel-by-voxel flow– such that the aligned images minimized the voxel-by-voxel sum of squared differences between them (see [43] for details). For each longitudinal image pair, the first image was aligned to a single, randomly-selected subject image– the *cohort atlas image*– on which the lateral ventricles had been manually traced by a trained rater to include the frontal horn and body, as well as the temporal and occipital horns, using a tracing protocol described previously [44]. The second image in the longitudinal pair was aligned to the corresponding first image. The alignment between first image in the pair and the manually-traced subject image allowed the manual ventricle tracing to be transferred to the space of the first image. Consequently, the alignment between the first and second images allowed the manual-tracing-based ventricle delineation to be transferred from the first images to the second images. A whole-brain mask image, including parenchyma and ventricular and sulcal CSF spaces, was output by the skull-stripping procedure, and was used to estimate brain volume in each image. A typical lateral ventricle segmentation result is shown in Figure 2.

Validation of ventricular volume technique.　An earlier study reported the validation of the ventricle segmentation method by correlating automated VBR with semi-quantitative neuroradiological ratings of ventricular size on the entire set of 1998-99 high-resolution CHS scans at the Pittsburgh center (N= 388)

[12]. Briefly, trained neuroradiologists assigned each MR scan an integer score between 1 and 9, with lower scores corresponding to relatively small ventricles and higher scores corresponding to relatively large ones [45]. Agreement between the visual ratings and VBR was high ($R^2 = .698$). We augmented this validation data by investigating the effects of white matter hyperintensities (WMHs) on agreement between automated and visual ventricular assessments. This is an important validation issue because white matter hyperintensities (WMH) can appear similar to CSF in certain imaging sequences, and therefore periventricular WMHs could potentially be mislabeled as ventricle by our automated routine. The discrepancy between automated ventricular volume and visual ventricle rating was quantified by the standardized residual of the linear model that had been used to correlate the two measures. WMH grade was ascertained by radiologists using a 0-to-9 integer scale similar to the ventricular grade (see [45]), and WMH grade was then correlated with automated-radiological discrepancy to determine whether subjects with higher WMH load had higher discordance between visual and automated ventricular assessments.

We further validated the ventricular segmentation technique against expert manual tracings on a set of middle-aged brains with broad variability in ventricular volume. The manual tracings and images were taken from a previous study of spatial patterns of ventricular and callosal differences between middle-aged AIDS patients and controls [46]. Briefly, 31 AIDS patients and 19 HIV-seronegative controls (mean age 42.64 +/- 11.28 S.D.) underwent 3D MR scans on the same scanner as the CHS subjects, with the same acquisition parameters. The frontal horn, body, and temporal and occipital horns were manually traced using the protocol mentioned above [44]. 6 cohort atlas images were randomly selected from the set of 50 images, and each cohort atlas image was used in turn to segment the other 49 lateral ventricles in the image set. Lateral ventricle volume was computed based on the automated segmentations and expert manual tracings to assess the accuracy of the automated technique and its reliability with respect to selection of cohort atlas. For accuracy, the oneway, "consistency" type intraclass correlation coefficient (ICC, termed "ICC(1)" in [47]) was computed between manual-tracing-based volumes and automated volumes based on the cohort atlas that was used for segmentation of the CHS data set. For reliability, the ICC was computed between the automated volumes from the 6 cohort atlases. ICCs were computed using the `icc` function in the `irr` library of `R` version 2.3.1 [48].

Ventricular volume in each image was quantified using the ventricle-to-brain ratio (VBR), that is, the ratio of lateral ventricle volume to whole brain volume. However, we note that quantifying ventricular volume in terms of the raw ventricular volume– not normalizing by whole-brain volume– did not significantly alter

the results reported below. Ventricular expansion between first and second scans was quantified by the VBR change rate, that is, the difference between VBR in the first and second images divided by the interscan interval. Dividing by interscan interval normalized VBR change for differences in interscan interval between subjects.

2.4 Statistical Analysis

VBR change rate was analyzed as the outcome variable in a multivariate repeated-measures ANOVA model to account for the repeated measurement of VBR change rate in the 31 subjects who were scanned in 1997-99, 2002-03, and 2004-05. That is, for those 31 subjects, we repeatedly measured VBR change rate: once between 1997-99 and 2002-03; and again between 2002-03 and 2004-05. The following factors were fixed effects: age, gender, education level (up to *vs.* beyond high school level), race (white *vs.* non-white), appearance of infarcts on first or second images, CES-D depression score at the time of the first image (greater-than-or-equal-to *vs.* less than 8), dementia progression group (normal to normal, normal to MCI, *etc.*), VBR at the time of the first image (VBR1), and presence of heart disease, diabetes, and hypertension at the times of first or second images. These factors were chosen due to their previously-reported associations with ventricular volume in aging cohorts (for example, [49] [50] [26]). We chose VBR change rate as our univariate outcome measure, rather than incorporating VBR over time into a longitudinal outcome model such as random-effects regression, because the small number of subjects with more than two longitudinal measurements (31) precluded reliable parameter estimates of within-subject correlation in VBR over time [51]. Given our interest in a limited number of contrasts between dementia progression groups, *i.e.* between all initially-normal subjects and between subjects making normal-to-MCI, MCI-to-dementia, and normal-do-dementia transitions, the number of contrasts tested was modest relative to the number of data points. Additionally, we investigated differences the relationship between a dimensional measure of baseline cognitive function, the Modified Mini-Mental State Exam (MMSE) in the same ANOVA design as above but with the dementia progression group factor replaced with MMSE. Overall effects of factors were evaluated by omnibus F tests, and contrasts of interest between pairs of factor levels were evaluated by focused F tests. Effect size was determined by the contrast coefficient $r_{contrast}$ [52]. For the simple case of a contrast between two groups in a continuous outcome variable, the effect size correlation is the point-biserial correlation between the group membership (one group coded as 0, the other coded as 1) and the outcome variable. The contrast correlation is the generalization of effect size correlation to contrasts

between multiple groups measured by an omnibus F test; for the focused F tests of Table 4, the contrast correlation reduces to the effect size correlation after all modeled non-contrast variation has been removed. For Table 2, the omnibus F test on each fixed effect is based on the marginal (Type 3) sum of squares. We chose correlational measures of effect size to assess an overall effect size for each fixed effect, even if it has more than 2 effect levels (e.g. dementia progression); unfortunately more conventional effect size measures such as Hedges g and Cohens d cannot be computed from an omnibus F. Contrast correlation is standardized between 0 and 1. All statistical analyses were performed in R version 2.3.1 [48].

3 Results

Among the images of middle-aged controls and AIDS patients, lateral ventricle volume computed from manual segmentations ranged from 8824 to 95830 mm^3 (mean 27448 +/- 16809 S.D.), and was significantly higher in AIDS patients compared to controls (2-sided t-test with unequal variances: $p = 2.65e - 5$). The ICC between manual and automated volumes was high (ICC=.86, 95% C.I. = [.76,.92], $p = 6.05e - 16$, see Figure 4). We note that the automated technique appears to underestimate ventricular volume in AIDS patients with very large ventricles. The ICC for volumes based on the different cohort atlases was also high (ICC=.85, 95% C.I. = [.79,.90], $p = 1.77e - 81$). Correlation between WMH grade and visual-automated discrepancy in visual assessments was weak, $R^2 = .01369$, suggesting that there is little evidence that the automated ventricular volume measurement was systematically biased in subjects with high WMH load (Figure 6).

Mean and standard deviations of ventricular volume, brain volume, and VBR at the time of the first image are shown for each dementia progression group in Table 2. Longitudinal graphs of VBR change between the first and second scan are plotted for each image pair in Figure 3. The results of omnibus F tests in the ANOVA analysis are shown in Table 3. The VBR change rate varied significantly by dementia progression group, and was significantly higher among diabetics. VBR increased faster in subjects with MR-defined infarcts but the difference was not statistically significant. Table 4 shows the results of focused F tests for contrasts of interest between pairs of dementia progression groups. VBR change was significantly faster in demented subjects and in MCI subjects who declined to dementia, compared to normal subjects who declined to MCI. The rate of VBR change was also significantly higher in MCI subjects who declined to dementia compared to normal subjects who declined to dementia. VBR change was faster in demented

subjects compared to normal subjects who declined to dementia, but the difference was not statistically significant. No significant differences between groups of initially-normal subjects were seen. In the model with MMSE instead of dementia progression group, lower baseline MMSE was associated with higher VBR change rate, but the effect was not statistically significant ($p = .0988$).

4 Discussion

The first key finding of this study is that ventricular expansion, measured via VBR change, was faster among subjects who were more advanced in the progression from normal cognitive function to dementia; specifically, VBR change was faster among subjects with dementia and subjects declining from MCI to dementia, compared to normal subjects experiencing no decline or declining to MCI. This supports our hypothesis that ventricular expansion may in part reflect continually-increasing pathological burden, and therefore accelerates late in the progression from normal cognitive function to dementia. The finding that ventricles expanded faster in demented subjects compared to normal subjects agrees with a variety of earlier longitudinal studies (*e.g.*, [21] [24] [22] [53]). In this study we were able to supplement these earlier findings by analyzing ventricular expansion during transitions between normal cognitive function, MCI, and dementia. MCI appears to represent a transitional state between the relatively slow ventricular expansion of normal cognitive function and the faster expansion of dementia.

The second key finding is that VBR increased significantly faster among MCI-to-dementia decliners compared to normal-to-dementia decliners. This finding may appear counterintuitive, since the transition from normal cognitive function to dementia represents more sudden cognitive decline that should presumably be accompanied by sudden changes in brain structure. However, based on earlier CHS findings that ventricular volume may represent a susceptibility factor for sudden decline, and in particular that normal-to-dementia decliners had significantly higher ventricular volume at baseline, we suggest that associations between cognitive decline and structural changes differ between sudden and gradual decliners [12] [35]. Our proposed model of the differences between sudden and gradual decliners is sketched in Figure 5. We speculate that both groups of decliners experienced similar time courses of dementia-related pathological processes that were reflected in initially slow, then fast, ventricular dilation. The normal-to-dementia decliners (shown in gray), with their initially-large ventricles, were especially susceptible to more severe cognitive changes earlier in the pathological process, so they experienced precipitous cognitive decline (*i.e.*, conver-

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sion from normal to dementia) early in the pathological time course, when ventricular dilation was still relatively slow. In the more gradual decliners, however (shown in black), the same time course of structural changes was associated with more gradual cognitive changes, so that the subjects transitioned from normal to MCI during the earlier, slower ventricular expansion, and from MCI to dementia during the later, faster expansion. It follows from this conjecture that if the normal-to-dementia decliners were scanned at a third time point in the future, we would expect to measure ventricular dilation between second and third scans that is as fast as a typical MCI-to-dementia decliner in this study. It also follows that if our MCI-to-dementia decliners had been scanned prior to their entry into the study, when they exhibited normal cognitive function, their ventricular volume at the time of the normal scan would have been lower than the ventricular volume of the normal-to-dementia decliners at the time of their normal scan. The first and second findings, together with previous CHS findings, suggest that ventricular volume may be related to both susceptibility to, and advanced progression of, cognitive decline. We have speculated that subjects with elevated ventricular volume at baseline are susceptible to faster cognitive decline relative to pathological load, but reasons for this association remain unclear. Results from previous studies have suggested that relationships between pathological burden and cognitive decline may be modulated by "brain reserve," that is, yet-unknown mechanisms that help the brain to compensate functionally in the presence of pathological damage [54] [55]. In the normal-to-dementia subjects, elevated ventricular volume may reflect a structural vulnerability– a lack of brain reserve– that prevents the brain from compensating functionally in the face of pathological insult. However, the neurobiological mechanisms that underlie associations between cognitive changes and pathological burden remain unclear.

The third key finding of this study is that in a model controlling for other cardiovascular risk factors, dementia status, and demographic factors, aging subjects with diabetes had higher rates of VBR change than subjects who did not. Earlier studies had reported increased cerebral atrophy or ventricular volume among elderly diabetics in cross-sectional studies [56] [57] [50] [58] [59]. However, the current study used MRI at multiple time points to confirm that ventricular dilation took place at a faster rate during the course of diabetes, regardless of dementia status or other comorbidities. Fast ventricular expansion in diabetics could be related to poor blood sugar regulation (see [60] and [61] for review). This structural change could contribute to the increased dementia risk among diabetics that was previously found in the CHS [F. Irie *et al.*, unpublished].

Preliminary data has suggested that increased ventricular volume may be strongly associated with mor-

tality in the CHS, so death is a possible confound in our analysis [62]. For example, an alternative explanation for relatively slow ventricular expansion among normal-to-dementia decliners is that normal-to-dementia decliners with quickly-expanding ventricles may have died before follow-up. However, while the relationship between ventricular volume and longevity is currently being investigated, the relationship between ventricular expansion rates and longevity has not been established.

The findings of this study were similar when change rate in raw ventricular volume, rather than VBR change rate, was analyzed, but we focused on VBR for two key reasons. First, we sought to provide a consistent presentation with our previous paper on baseline VBR in a super-set of the subjects presented here [12]. Second, we wanted to analyze ventricular expansion in a way that accounts for brain atrophy rate, which is already known to be faster in demented subjects (see Table . We recognize that VBR changes could represent brain atrophy, ventricular expansion, or a combination of both, but we note that rates of brain atrophy are similar among all groups that were normal at the first scan, along with the MCI-to-dementia group. Findings of significant differences in VBR between dementia progression groups in a model that accounts for brain atrophy rate suggests that aspects of ventricular expansion in these subjects may be independent of, or additional to, normal aging-associated global atrophy.

Table 5 shows the annual percent change in brain and ventricular volume in this report and a similar previous paper by Jack *et al.* [33]. Variability in both measures is generally higher in our sample; this could reflect differences in a variety of factors, including imaging data quality, data processing software, MCI diagnosis criteria, and population sampling. Given the similarity in median rates, we speculate that the latter factor may be the driving factor– there may be higher variability in subject characteristics in our epidemiological sample than the AD clinic sample of the earlier study. Median ventricle rates are broadly concordant between the two studies, although it was somewhat lower among normal decliners and higher in MCI stable in this study. Brain atrophy rates are lower in this sample, which we feel is likely to reflect differences in measurement methodology, with the earlier study using a method similar to the binary boundary shift integral (BBSI, see *e.g.* [24]), and this study measuring each brain volume independently.

Figure Legends

Figure 1: Breakdown of the subject pool in terms of their dementia diagnoses at the times of their first and second scans. **Figure 2:** Automated ventricle segmentation result on a typical CHS image. Three typical

axial slices are shown in superior-to-inferior order. The estimated ventricular boundary is shown in white.
Figure 3: Longitudinal change in VBR between the first scan (at time 0) and the second scan is shown for all image pairs. **Figure 4:** Scatter plot of manual vs. automated lateral ventricle volumes for AIDS and control subjects. The intraclass correlation coefficient (ICC) between manual and automated volumes is high (.86). **Figure 5:** Proposed model of VBR change in initially-normal subjects who decline gradually and suddenly, supported by data in this paper and previous CHS studies of the same cohort [12] [35]. See Section 4 for details. **Figure 6:** Scatter plot of discrepancy between visual and automated ventricle assessments (x axis) and automated ventricular volume (y axis). The relationship between the discrepancy and white matter grade was weak, $R^2 = .01369$.

Table Titles

- **Table 1:** Demographic data for subjects, broken out by dementia diagnosis at the times of the first and second MR scans. The results of between pairs of groups are indicated in the first column. Significant differences between normal and MCI, MCI and dementia, and normal and dementia subjects at the time of the first scan are indicated by $*$, $\dagger$, and $\ddagger$ respectively in the first column ($p < .05$, 2-tailed t tests for Age, Hachinski, UPDRS, MMSE; χ^2 tests for Gender, Race, Education, Diabetes, Hypertension, Heart Disease).

- **Table 2:** Ventricular volume, whole-brain volume, and ventricle-to-brain ratio (VBR) at the times of the first and second images, rate of change in these measures, and interscan interval are summarized for subjects in each dementia progression group. Mean $\pm$ standard deviation of each quantity are shown. * The MCI To Normal group included a single subject so standard deviation is not shown.

- **Table 3:** Overall factors in a model for rate of ventricular volume change over time. Factors with $p < .05$ are shown in bold. An omnibus F test evaluated the significance of each factor in a repeated-measures ANOVA design.

- **Table 4:** Differences between dementia progression groups in a model for ventricle expansion rate. Factors with $p < .05$ are shown in bold. For each test, the numerator and denominator DF were 1 and 21 respectively.

- **Table 5:** Comparison of brain and ventricle atrophy rates as reported by this paper and Jack et al

[33]. Data for the slowly declining group of demented subjects in [33] is shown. Data show median interquartile range in annual percent volume change in brain and ventricle. We cite the slowly declining dementia-to-dementia group from [33]. The normal declining" group in [33] had 2 normal-to-dementia decliners, which were lumped into the same group as the normal-to-MCI decliners.

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| Diagnosis At First Scan		Diagnosis At Second Scan		
Normal (N=104)		Normal (N=52)		
		MCI (N=29)	Amnestic (N=2)	
			MCD (N=27)	
		Dementia (N=23)	Possible-AD (N=6)	
			Probable-AD (N=15)	
			Non-AD (N=2)	
MCI (N=29)	Amnestic (N=3)	Dementia (N=3)	Possible-AD (N=2)	
			Probable-AD (N=1)	
	MCD (N=26)	Normal (N=1)		
		MCI (N=12)		
		Dementia (N=13)	Non-AD (N=4)	
			Possible-AD (N=2)	
			Probable-AD (N=7)	
Dementia (N=12)	Probable-AD (N=9)	Dementia (N=12)	Probable-AD (N=9)	
	Possible-AD (N=3)		Possible-AD (N=3)	

Figure 1: Subject pool
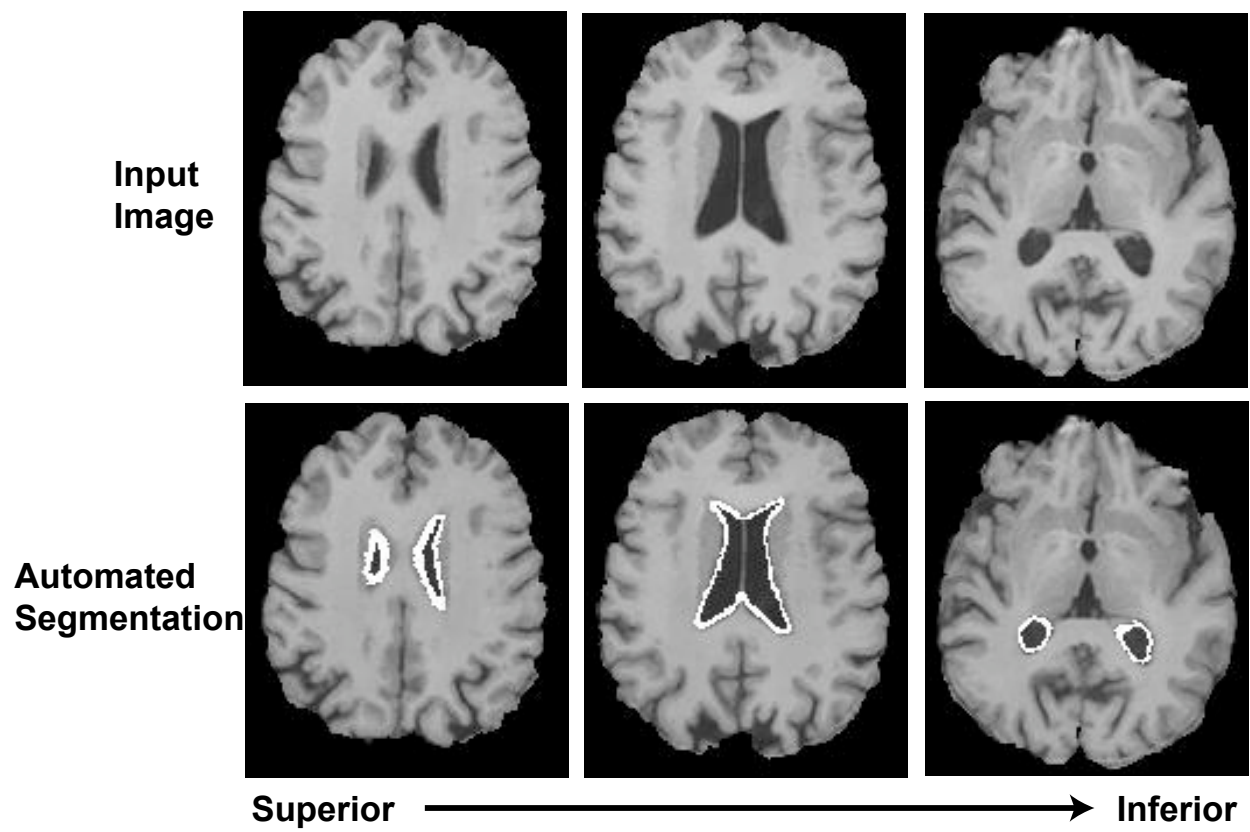
Figure 2: Automated ventricle segmentation result on a typical CHS image. Three typical axial slices are shown in superior-to-inferior order. The estimated ventricular boundary is shown in white.
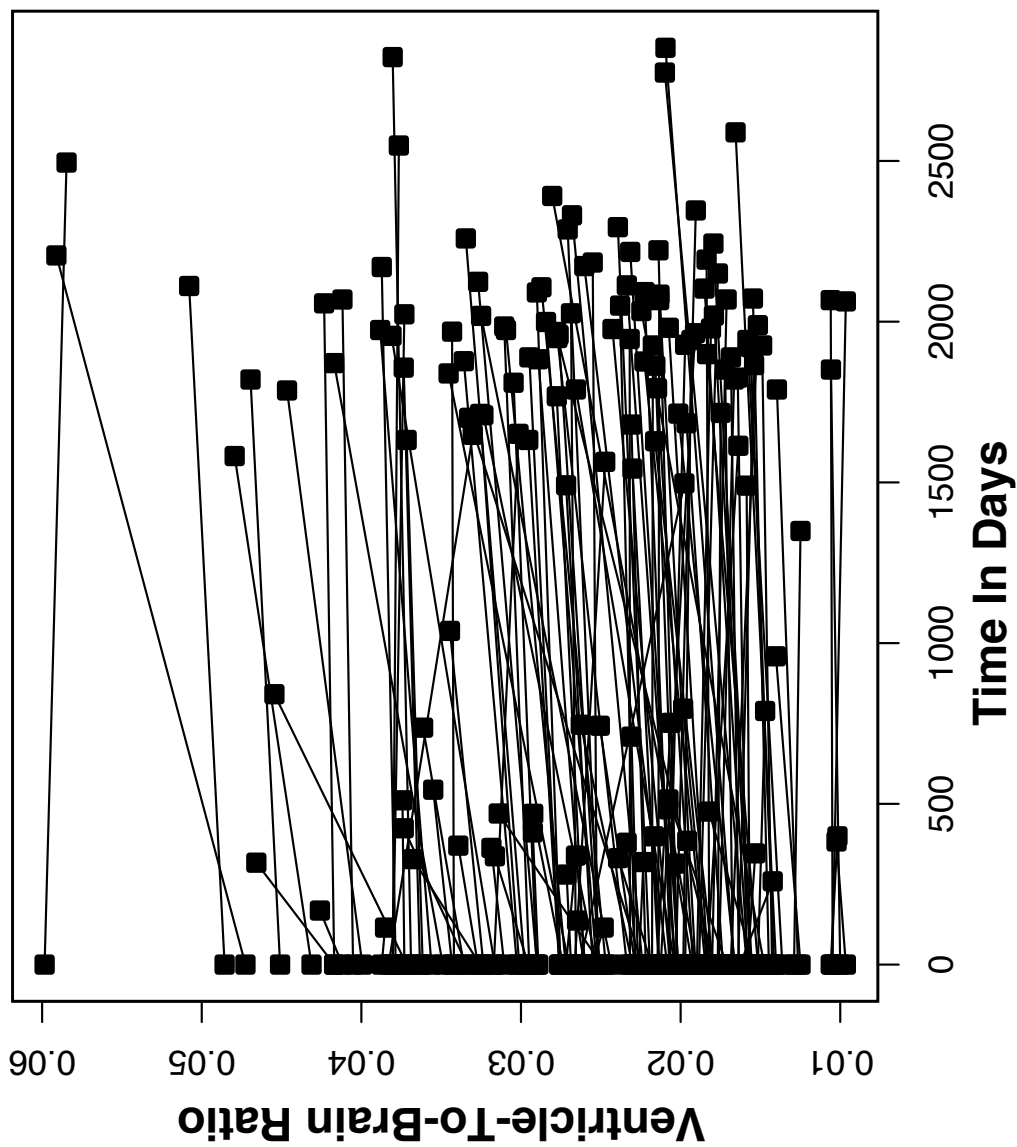
Table 4:

Table 5:

Figure 3: Longitudinal change in VBR between the first scan (at time 0) and the second scan is shown for all image pairs.
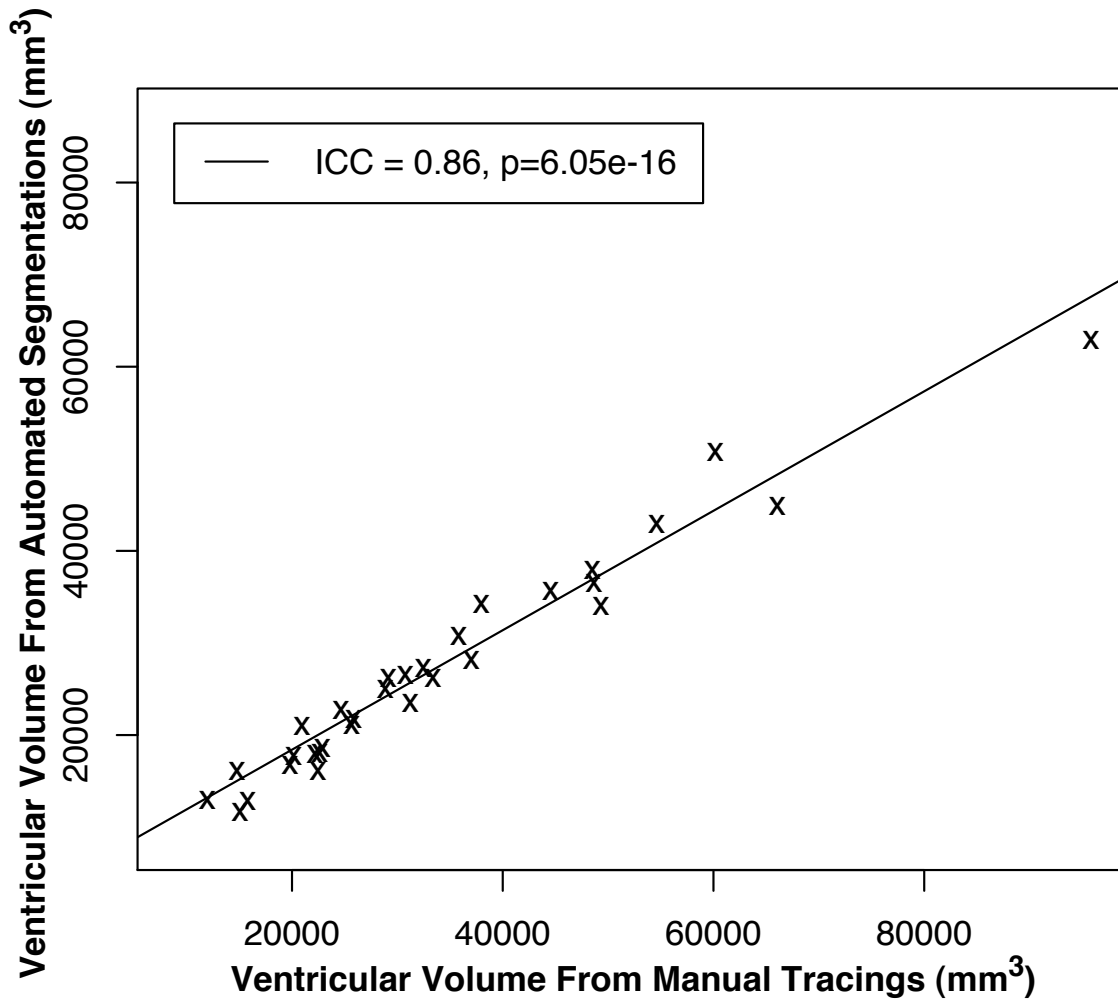
Figure 4: Scatter plot of manual vs. automated lateral ventricle volumes for AIDS and control subjects. The intraclass correlation coefficient (ICC) between manual and automated volumes is high (.86).
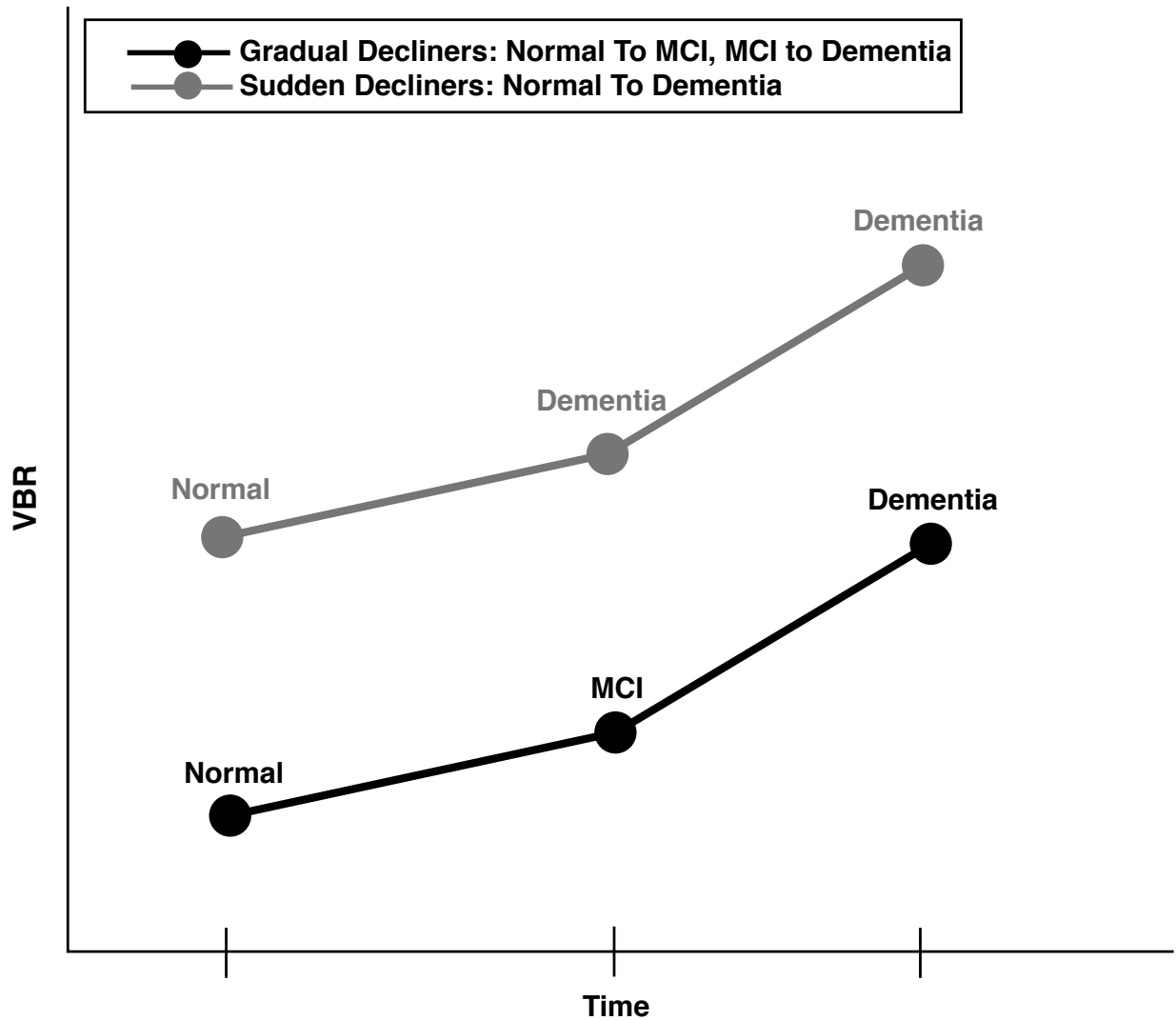
Figure 5: Proposed model of VBR change in initially-normal subjects who decline gradually and suddenly, supported by data in this paper and previous CHS studies of the same cohort [12] [35]. Both groups experience a similar, accelerating time course of ventricular expansion rate that may be triggered by dementia-related pathologies. However, the sudden decliners exhibit more rapid cognitive decline during this expansion, resulting in dementia diagnosis while expansion is still relatively slow. The accelerated cognitive decline in sudden decliners may be related to their significantly larger ventricles when they were normal, which could suggest a possible structural vulnerability or inability to compensate for pathology-related insult.
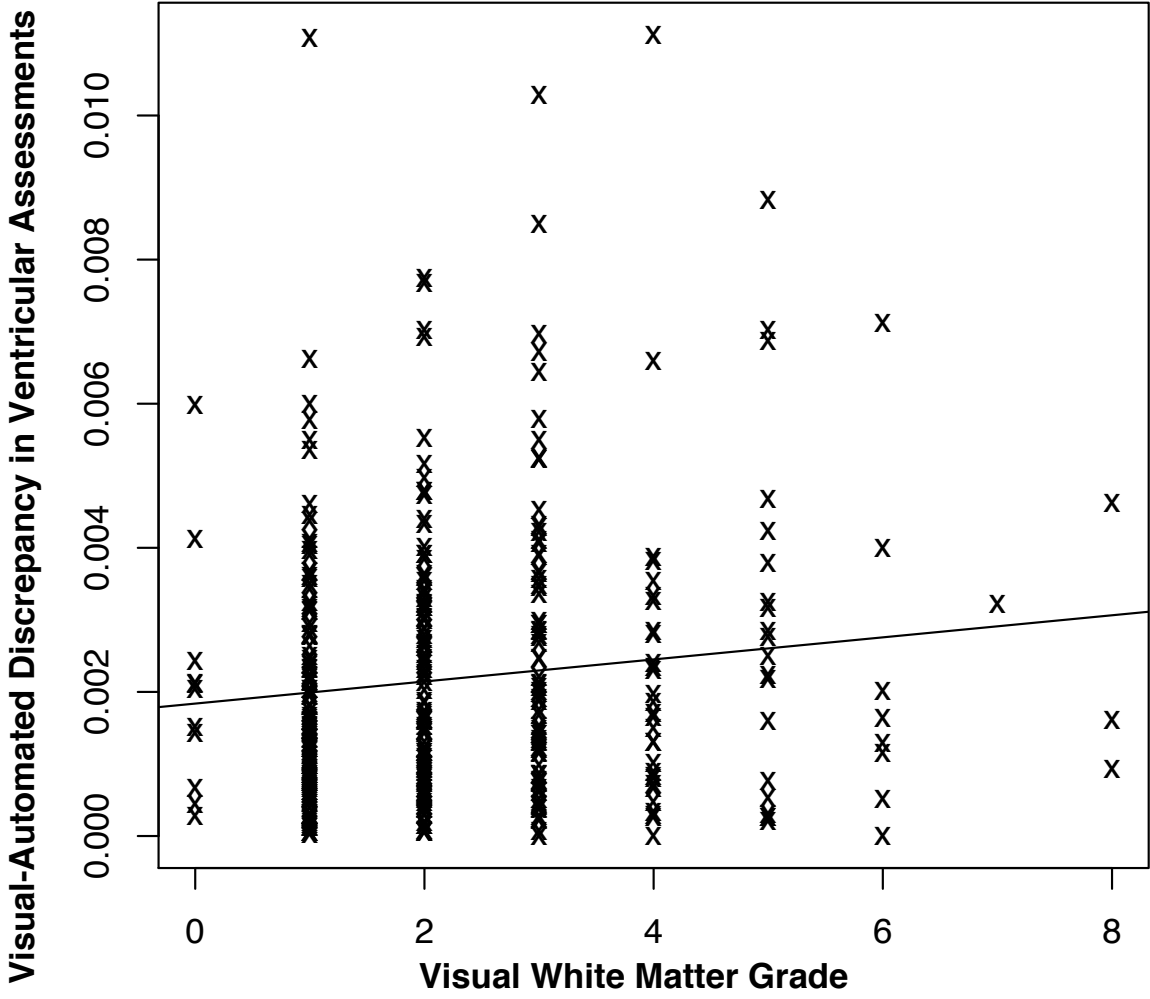
Figure 6: Scatter plot of discrepancy between visual and automated ventricle assessments (x axis) and automated ventricular volume (y axis). The relationship between the discrepancy and white matter grade was weak, $R^2 = .01369$.

	Normal at First Scan	Normal To Normal	Normal To MCI	Normal To Dementia	MCI At First Scan	MCI To Normal	MCI To MCI	MCI To Dementia	Demented
Age At First Scan (Mean ± S. D). ∗‡	83.9 ± 3.86	83.62 ± 4.41	84.25 ± 3.28	84.26 ± 3.22	86.38 ± 5.14	84.29	89.69 ± 4.77	84.03 ± 4.20	88.29 ± 2.70
Gender (Female, Male) †‡	69 , 35	32, 20	20, 9	17, 6	20 , 9	0, 1	7, 5	13, 3	6 , 6
Race (Caucasian, African-American) ∗‡	78 , 26	40, 12	19, 10	19, 4	19, 10	1, 0	7, 5	11, 5	5 , 7
Education Level (Up to, beyond high school) †	34 , 70	15, 37	8, 21	11, 12	10 , 19	0, 1	3, 9	7, 9	7 , 5
Hachinski Ischemic Scale (Mean ± S. D., N/A)	1.04 ± 1.29 , 1	0.90 ± 1.16 , 0	1.10 ± 1.18 , 0	1.27 ± 1.70, 1	1.10 ± 1.37 , 0	1.00	0.67 ± 0.89 , 0	1.44 ± 1.63 , 0	1 ± 1.13 , 0
Unified Parkinson Disease Rating Scale (UPDRS; Mean ± S.D., N/A)	3.60 ± 3.60 , 1	3.31 ± 3.75 , 0	4.03 ± 3.06 , 0	3.73 ± 3.98, 1	4.69 ± 2.93 , 0	9.00 , 0	4.42 ± 2.15 , 0	4.62 ± 3.36 , 0	4.08 ± 5.05 , 0
Modified Mini Mental State Exam (3MSE; Mean, S.D. ∗†‡	96.38 ± 3.85	97.60 3.49	95.83 3.98	94.35 3.56	92.07 ± 5.44	97.00	91.17 5.41	92.44 5.60	88.08 ± 5.52
History of Diabetes (No, Yes) ‡	86 , 18	46, 6	20, 9	20, 3	25 , 4	1, 0	10, 2	14, 2	11 , 1
History of Hypertension (No , Yes)	54 , 50	28, 24	15, 14	11, 12	17 , 12	0, 1	9, 3	8, 8	6 , 6
History of Heart Disease (No , Yes)	92 , 12	46, 6	27, 2	19, 4	27 , 2	1, 0	10, 2	16, 0	11 , 1

Table 1: Demographic data for subjects, broken out by dementia diagnosis at the times of the first and second MR scans. Significant differences between normal and MCI, MCI and dementia, and normal and dementia subjects at the time of the first scan are indicated by ∗, †, and ‡ respectively in the first column ($p<.05$, 2-tailed t tests for Age, Hachinski, UPDRS, MMSE; χ^2 tests for Gender, Race, Education, Diabetes, Hypertension, Heart Disease).

Dementia Progression Group (N	First Image			Second Image			Change Rate			Interscan Interval (days)
	Ventricular Volume (cm^3)	Brain Volume (cm^3)	VBR	Ventricular Volume (cm^3)	Brain Volume (cm^3)	VBR	Ventricular Volume (cm^3/day)	Brain Volume (cm^3/day)	VBR (units/day)	
Normal To Normal (52)	30.66 ± 12.55	1366.24 ± 149.36	0.0221 ± 0.0079	33.60 ±13.97	1284.41 ±153.75	0.0238 ±0.0082	1.77 ± 2.19	-0.07 ±0.10	7.23e-07 ±1.64e-06	1839.08 ±603.79
Normal To MCI (29)	33.05 ±14.28	1304.55 ± 130.79	0.0249 ± 0.0094	35.92 ±15.35	1225.01 ±126.24	0.0265 ±0.0099	1.87 ± 2.91	-0.14 ±0.29	7.39e-07 ±2.66e-06	1652.38 ±674.71
Normal To Dementia (23)	36.13 ±16.60	1313.52 ± 144.21	0.0271 ± 0.0112	39.46 ±16.04	1228.11 ±150.39	0.0293 ±0.0106	1.89 ± 2.73	-0.05 ±0.04	1.00e-06 ±2.56e-06	1802.79 ±294.33
MCI To Normal (1) *	31.68	1568.51	0.0202	34.23	1499.25	0.0214	1.15	-0.03	1.57e-07	2222.00
MCI To MCI (12)	34.64 ± 16.18	1296.70 ± 183.78	0.0259 ± 0.0095	35.96 ±17.14	1212.03 ±164.09	0.0266 ±0.0101	4.11 ± 5.84	-0.40 ±0.45	3.55e-06 ±5.08e-06	859.37 ±743.55
MCI To Dementia (13)	33.80 ± 13.41	1284.57 ± 111.48	0.0261 ± 0.0097	38.72 ±16.61	1189.13 ±66.59	0.0297 ±0.0122	4.68 ± 6.47	-0.09 ±0.15	2.72e-06 ±5.06e-06	1669.50 ±574.11
Dementia To Dementia (12)	35.28 ± 8.60	1390.75 ± 136.08	0.0254 ± 0.0060	37.76 ±11.30	1252.48 ±135.66	0.0269 ±0.0083	4.61 ± 5.34	-0.45 ±0.22	7.21e-06 ±1.08e-05	446.25 ±217.79

Table 2: Ventricular volume, whole-brain volume, and ventricle-to-brain ratio (VBR) at the times of the first and second images, rate of change in these measures between images, and interscan interval are summarized for subjects in each dementia progression group.. Mean ± standard deviation are shown. * The MCI To Normal group included a single subject so standard deviation is not shown.

Factor	F	numDF	denDF	p	$r_{contrast}$
VBR In First Image	1.4892	1	20	0.2365	0.2633
Age	0.0002	1	20	0.9894	0.0030
Gender	0.9731	1	108	0.3261	0.0945
Education	1.9354	1	108	0.1670	0.1327
Race	1.4239	1	108	0.2354	0.1141
Infarcts	2.8726	1	20	0.1056	0.3544
CES-D Score	2.8592	1	108	0.0937	0.1606
Dementia Progression	**2.7163**	**6**	**20**	**0.0428**	**0.3458**
Heart Disease	0.0072	1	108	0.9327	0.0081
Diabetes	**3.9903**	**1**	**108**	**0.0483**	**0.1888**
Hypertension	0.0150	1	108	0.9027	0.0118

Table 3: Overall factors in the model for rate of ventricular volume change over time. An omnibus F test evaluated the significance of each factor in a repeated-measures ANOVA design.

Dementia Groups	Difference In Model Coefficients	F	p	$r_{contrast}$
Normal To Normal (N=52) *vs.* Normal To MCI (N=29)	2.886e-07	0.1774	0.6779	0.0915
Normal To Normal (52) *vs.* Normal To Dementia (23)	-2.632e-07	0.1186	0.7340	0.0749
Normal To MCI (29) *vs.* Normal To Dementia (23)	-5.518e-07	0.4665	0.5021	0.1474
Normal To MCI (29) *vs.* MCI To Dementia (13)	**-2.739e-06**	**9.6928**	**0.0053**	**0.5620**
Normal To MCI (29) *vs.* Dementia To Dementia (12)	**-2.526e-06**	**6.0524**	**0.0226**	**0.4730**
Normal To Dementia (23) *vs.* MCI To Dementia (13)	**-2.187e-06**	**5.6077**	**0.0276**	**0.4591**
Normal To Dementia (23) vs. Dementia To Dementia (12)	-1.975e-06	3.4769	0.0763	0.3769
MCI To Dementia (13) *vs.* Dementia To Dementia (12)	2.127e-07	0.0359	0.8516	0.0413

Table 4: Differences between dementia progression groups in the model for ventricle expansion rate. The table summarizes the results of focused F tests between pairs of groups. For each test, the numerator and denominator DF were 1 and 21 respectively.

	Jack *et al.* [33]		This Paper	
	Brain	Ventricle	Brain	Ventricle
Normal stable	.4 ± .3	1.7 ± .9	.20 ± .86	1.94 ± .287
Normal declining	.8 ± .5	3.4 ± 1.6	Normal2MCI: .12 ± .67 Normal2Dem: .19 ± .47	Normal2MCI: 2.2 ± 3.71 Normal2Dem: 2.3 ± 2.32
MCI stable	.4 ± .4	2.6 ± 1.3	.41 ± 1.1	3.83 ± 6.77
MCI declining	.8 ± .5	3.4 ± 2.8	.21 ± .53	3.41 ± 4.98
Demented	.6 ± .7	4.3 ± 3.3	.46 ± .70	4.51 ± 5.56

Table 5. Comparison of brain and ventricle atrophy rates as reported by this paper and Jack *et al* [33]. Data show median ± interquartile range in annual percent volume change in brain and ventricle. We cite the "slowly declining" dementia-to-dementia group from [33]. The "normal declining" group had two normal-to-dementia decliners in [33], which were lumped into the same group as the normal-to-MCI decliners.