Longitudinal Study of Cerebral Ventricular Atrophy Rates in the Cardiovascular Health Study

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Introduction: Automated analysis of cerebral ventricle expansion rates in an elderly cohort

A growing body of longitudinal studies have demonstrated that atrophy of specific structures in the brain is accelerated in subjects with dementia. Establishing normative atrophy rates for various brain structures among elderly subjects has the potential to be clinically useful for early detection of dementia, monitoring the course of cognitive decline, and evaluating responses of critical brain structures to interventions. However, relationships between brain structure atrophy rates and transitions between normal cognitive function, mild cognitive impairment (MCI), and dementia are not well understood. Furthermore, interactions between prevalent late-life comorbidities, dementia processes, and brain structure atrophy rates are unclear. This study addressed these issues by using automated computational techniques to measure expansion rates of the lateral ventricles among subjects in the Cardiovascular Health Study (CHS) who received multiple clinical evaluations and magnetic resonance (MR) image scans.

Data: 145 longitudinal pairs of MR images and clinical evaluations

There were 388, 189, and 53 subjects who received clinical evaluations and high-resolution MR scans in 1997-99, 2002-03, and 2004-05 respectively as part of the Cardiovascular Health Study Cognition Study 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. Subjects were assigned to dementia progression groups according to dementia diagnoses at the times of the first and second scans (see Figure 1).

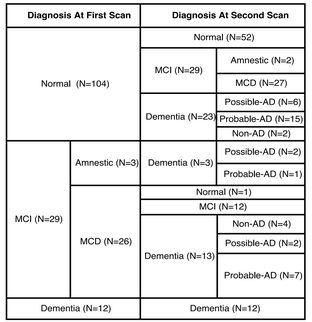

Figure 1: Subject categorization by dementia progression
Subjects were placed into categories based on whether they were diagnosed with MCI or dementia, or were cognitively normal at the times of the first and second scans.

Methods: Automated lateral ventricle segmentation and statistical modeling of expansion over time

Lateral ventricular volumes were estimated fully automatically on all scans using a technique described in a previous study and validated against quantitative and qualitative manual ratings ([1] [2], See Figures 2 and 3). 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. 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 inter-scan interval. VBR change rate was the outcome variable in multivariate mixed-effects statistical models that properly accounted for the repeated measurement of VBR change rate in the 31 subjects who were scanned in 1997-99, 2002-03, and 2004-05.

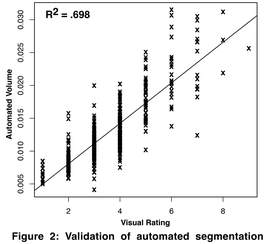

Figure 2: Validation of automated segmentation against radiological ratings
Ventricular volume was computed by the automated method on 377 CHS subjects and compared to the visual ratings of ventricular dilation that were part of the CHS neuroradiological evaluation. Agreement between the visual ratings and VBR was high (R^2 = .698) [1].

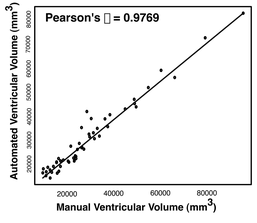

Figure 3: Validation of automated segmentation against manual tracings
Ventricular volume was computed by the automated method on 55 images of middle-aged controls and AIDS patients with a wide range of ventricular volumes. Automated volume was compared to volume computed from manual tracings. Agreement was high (r = .9769).

Results: Faster ventricular dilation among decliners from MCI to dementia, dementia subjects, and diabetics

The ventricular expansion rate varied significantly by dementia progression group, and was significantly higher among diabetics. Ventricles expanded faster in subjects with MR-defined infarcts but the difference was not statistically significant. Ventricles expanded significantly faster in demented subjects and in MCI subjects who declined to dementia, compared to normal subjects who remained normal and normal subjects who declined to MCI. Ventricular expansion was faster in demented subjects compared to normal subjects who declined to dementia, but the difference was not statistically significant. Likewise, MCI subjects who remained MCI had faster ventricular expansion than normals who remained normal and normals who declined to MCI, but the differences were not statistically significant. No significant differences between groups of initially-normal subjects were seen (see Figure 4)..

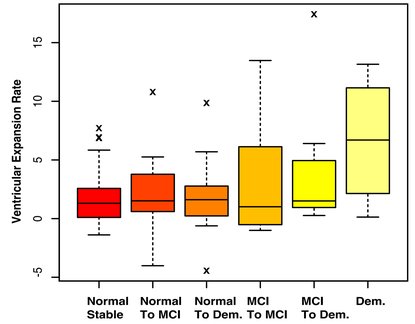

Figure 4: Ventricular expansion rates
Box plots show the distribution of ventricular expansion rates broken out by dementia progression group. Expansion rates are shown uncorrected for factors in the statistical model.

Discussion: The time course of ventricular expansion during cognitive decline

The key finding of this study is that ventricles expanded faster among subjects with dementia and subjects declining from MCI to dementia; expanded slower in initially-normal subjects, regardless of dementia progression, and expanded at highly-variable rates for MCI subjects who remained MCI. This suggests that ventricular expansion may be an effect of pathological processes that occur relatively late in the gradual progression from normal cognitive function to dementia. MCI appears to represent a transitional state between the relatively slow ventricular expansion of normal cognitive function and the faster expansion of dementia (Figure 5). Our earlier study suggested that ventricles were significantly larger in normal subjects who went on to transition rapidly to dementia over a 4-year period [1], while the current study suggests that their ventricular expansion was no faster than among other normal subjects. We speculate that rapid cognitive decline may involve a distinct time course of brain structure changes. Faster ventricular expansion among diabetics may reflect damage to periventricular white matter.

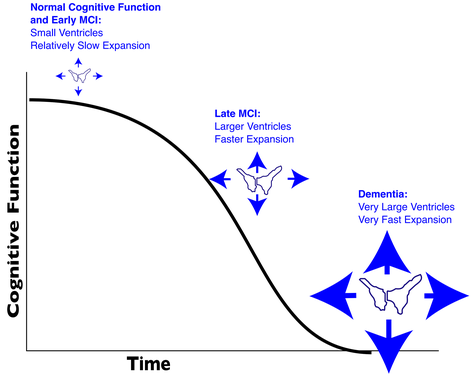

Figure 5: Schematic view of ventricular expansion during gradual cognitive decline
The following general time course of ventricular expansion during gradual transitions between normal cognitive function, MCI, and dementia is suggested by our studies of lateral ventricle size in the CHS. Ventricle size grows steadily and relatively slowly early in the decline process and accelerates as MCI progresses to dementia.

References

1. O. Carmichael, L. H. Kuller, O. L. Lopez, P. M. Thompson, A. Lu, S. E. Lee, J. Y. Lee, H. J. Aizenstein, C. C. Meltzer, Y. Liu, A. W. Toga, J. T. Becker. Ventricular volume and dementia progression in the Cardiovascular Health Study. In press, Neurobiology of Aging.
2. O. Carmichael, H. J. Aizenstein, S. W. Davis, J. T. Becker, P. M. Thompson, C. C. Meltzer, Y. Liu. Atlas-Based Hippocampus Segmentation In Alzheimer's Disease and Mild Cognitive Impairment. NeuroImage, V. 27 (4), October 2005, pp 979-990

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