Longitudinal Structural MRI and Alzheimer Disease

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Background

Structural MRI enables sensitive detection of subtle global and subregional changes in the brain. In preclinical and prodromal late-onset Alzheimer disease (AD), such brain changes are useful indicators for detecting at-risk subjects; when combined with other biomarkers and risk-factors for the disease, they can enable significant enrichment and stratification opportunities for AD clinical trials—resulting in substantial reductions in required sample sizes. Of particular interest is age, the strongest risk factor for AD. Surprisingly, its effect on clinical and atrophic rates of decline in AD has been largely unexplored. Since the elderly population is growing, and proportionally growing faster with increasing age, it is important to better understand whether and how age interacts with the disease process to affect rate of decline and to assess the implications for clinical trial sample sizes. Finally, calculating rates of decline also allows us to model disease trajectories.

Materials and Methods

We examined longitudinal rates of change (1) ignoring age, and (2) as a function of baseline age, for measures of clinical decline and structural MRI-based regional brain atrophy, in 311 mild cognitive impairment (MCI) and 182 cognitively healthy (HC) older individuals from the Alzheimer's Disease Neuroimaging Initiative. For (1), we assessed the possibility of reducing sample sizes (enhancing power) when selecting subjects with respect to: (a) the primary genetic risk factor, APOE ε4; (b) cerebrospinal fluid densities of the AD-related proteins Aβ and ptau; and (c) baseline AD-like atrophy pattern V. We compared our MRI-based results with those from the best clinical measure, the Clinical Dementia Rating – Sum of Boxes score (CDR-SB). All sample sizes were for rates of change in the patient cohort relative to those in HCs free of Aβ-pathology. For (2), the effect of age was modeled using mixed effects linear regression. We used the age-specific annual rates of change, relative to HCs, in power calculations to estimate sample sizes needed to adequately power a clinical trial when individuals of a given age comprise the study sample. From baseline measures and rates of atrophy as a function of age, disease trajectories were modeled assuming the annual atrophy rate increases linearly with time.

Results

(1) Atrophy in medial temporal lobe regions of interest gave significantly enhanced power over CDR-SB. Further substantial reductions in sample size estimates were possible when selecting subjects with respect to positivity on single or multiple combined baseline biomarkers and risk factors. Baseline AD-like atrophy score, V, was the single most powerful biomarker. (2) There was pronounced deceleration with age in the rates of clinical and atrophic decline for AD and MCI individuals, while HCs showed evidence of an increase in rates of decline with age. This resulted in convergence in rates of change for HCs and patients near 90 years of age. Sample sizes based on rates of change in morphometic measures, relative to HCs, showed dramatic increases with age of study sample. Calculated disease trajectories show the rapid decline from HC to MCI to AD in ~10 years.

Conclusion

Structural MRI affords powerful biomarkers for outcome measures in AD clinical trials. The results on aging imply that the phenotypic expression of AD is relatively mild in individuals older than approximately 85 years. This may affect the ability to distinguish AD from normal aging in the very old. Our results also demonstrate that inclusion of older individuals in clinical trials can substantially reduce the power to detect beneficial effects of a disease-modifying treatment. Finally, plausible disease trajectories can be modeled based on longitudinal structural MRI.

References

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Figure 1

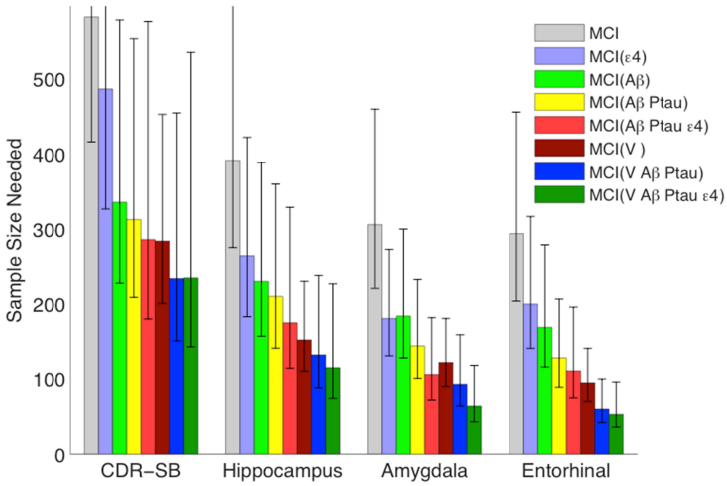

Figure 2