Brain size and the compensation of Alzheimer's disease symptoms: a longitudinal cohort study.

Abstract: Greater intracranial volume (ICV) has been associated with less severe Alzheimer's disease (AD) symptoms at a given level of cerebral pathology. In this study we examine whether ICV modulates the association between clinical disease progression on the one hand and brain atrophy or the apolipoprotein E genotype on the other. Six hundred seventy-four subjects were studied from the AD Neuroimaging Initiative (ADNI). Subjects included 204 controls, 144 patients with AD dementia, and 326 with amnestic mild cognitive impairment (aMCI). Longitudinal analyses were conducted applying generalized estimating equations to examine the influence of ICV on clinical deterioration and atrophy progression. Follow-up data were available for up to 60 months after the baseline visit (mean 31.42 months, SD 13.12 months). ICV was not directly associated with clinical worsening or atrophy progression. However, ICV attenuated the impact of atrophy and the apolipoprotein E ?4 allele on clinical disease progression in aMCI. Greater ICV, that is, premorbid brain size, seems to protect against clinical deterioration in the face of AD-related brain atrophy in aMCI. The results support the theory of a compensatory role of brain reserve in contrast to a neuroprotective role. The protective effects of morphologic reserve seem to be limited to early clinical AD; once a certain threshold of neurodegenerative burden is passed,
a larger premorbid brain no longer offers an advantage in this context.