Brain size and the compensation of Alzheimer’s disease symptoms: 
A longitudinal cohort study
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Abstract

Background: 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.

Methods: 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).

Results: ICV was not directly associated with clinical worsening or atrophy progression. However, ICV attenuated the impact of atrophy and the apolipoprotein E e4 allele on clinical disease progression in aMCI.

Conclusion: 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.

Keywords: Intracranial volume; Head circumference; Atrophy; Apolipoprotein E; Dementia; Mild cognitive impairment; Cognitive reserve; Brain reserve; Magnetic resonance imaging

1. Introduction

The complementary hypothetical concepts of cognitive reserve and brain reserve are often used to account for individual differences in the clinical presentation of brain pathology. Brain reserve refers to the idea that individuals who start with more substrate are able to withstand more pathologic damage before symptoms manifest clinically. Cognitive reserve refers to the ability to mitigate the effect of brain pathology on its clinical presentation via compensatory strategies. Factors related to cognitive and brain reserve, such as education, occupation, social networks, as well as brain morphologic characteristics, have been repeatedly associated with a differential individual clinical expression of Alzheimer’s disease (AD) pathology [1]. Studies have consistently shown that higher estimates of reserve were related to less severe symptoms at comparable levels of AD pathology as measured by a wide range of techniques, including functional [2,3] and structural brain imaging [4], but also

1Data used in the preparation of this article were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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whether ICV modulates the relation between clinical disease impairment (aMCI) and healthy control subjects (CON) in patients with AD dementia or amnestic mild cognitive impairment. The impact of premorbid brain size on the association between AD pathology and cognitive deterioration over time, however, has not been explored. Therefore, the main aim of our study was to use a longitudinal approach to examine in patients with AD dementia or amnestic mild cognitive impairment (aMCI) and healthy control subjects (CON) whether ICV modulates the relation between clinical disease progression on the one hand and atrophy as well as APOE on the other.

2. Methods

2.1. Study design and participants

Study participants were between 55 and 90 years old, had a modified Hachinski score of ≤4, and at least 6 years of education. All patients with AD dementia met the criteria established by the National Institute of Neurological and Communicative Disorders and Stroke–AD and Related Disorders Association (NINCDS-ADRDA) [18], and had a Mini-Mental State Examination (MMSE) score of between 20 and 26 and a Clinical Dementia Rating (CDR) scale score of 0.5 or 1 at the baseline visit. For a diagnosis of aMCI, subjects showed MMSE scores of between 24 and 30, a global CDR score of 0.5, had memory complaints but no significant functional impairment, and objective memory impairment on the Wechsler Memory Scale—logical memory II. CON had MMSE scores of between 24 and 30, a global CDR score of 0, no evidence of depression, and no subjective memory complaints. After the baseline visit, subsequent visits were conducted at 6- or 12-month intervals until a maximum follow-up period of 60 months. The data used in this study were obtained from www.loni.ucla.edu/ADNI on October 20, 2011; all available subjects were included if cerebral magnetic resonance imaging (MRI) scans and follow-up data beyond the 6-month visit after baseline were available, resulting in a total of 674 subjects, including 204 CON, 144 AD dementia, and 326 aMCI, with a mean follow-up of 31.42 months (SD 13.12). The full list of inclusion/exclusion criteria can be accessed through the online ADNI protocol (pages 23–29) at www.adni-info.org/Scientists/ADNIScientistsHome.aspx.

2.2. MRI acquisition and apolipoprotein E genotyping

Structural MRI scans were acquired from 1.5-T MRI scanners with three-dimensional (3D) T1-weighted sequences according to individualized protocols for each scanner, as defined at www.loni.ucla.edu/ADNI/Research/Cores/index.shtml. Two high-resolution T1-weighted volumetric 3D sagittal magnetization prepared rapid gradient-echo (MPRAGE) scans were collected for each subject at baseline and follow-up visits. MRI measures of total ICV and total brain volume (TBV) were reconstructed using FreeSurfer software at the Multi-Modal Imaging Laboratory at University of California, San Diego, as described previously [19]. The TBV/ICV ratio was calculated as an estimate of brain atrophy (in the following referred to as atrophy) [20]. The apolipoprotein E (APOE) genotype was determined through analysis of blood samples using standard polymerase chain reaction methods.

2.3. Outcome measures and predictor variables

All subjects received a standardized psychometric test battery at baseline and all available follow-up visits. For the purposes of the present study, deterioration rates per year were calculated for two different cognitive measures, the MMSE
and the AD Assessment Scale—cognitive subscale (ADAS-cog), and for one global clinical rating, the CDR—sum of boxes (CDR-sb). The rates of change on these three clinical measures were used as primary outcome measures (dependent variables). Atrophy was also considered as a dependent variable in additional models. The primary predictor variable (independent variable) was ICV. All models were adjusted for age, gender, years of education, APOE ε4 carrier status, and history of cardiovascular disease, stroke, or diabetes mellitus. Atrophy was considered as a further predictor variable except in the models using atrophy as the dependent variable.

2.4. Statistical analysis

All statistical analyses were performed using SPSS, version 19.0 (IBM Corp., Somers, NY), and R software (version 2.13.0) with the Q-Value package (http://genomics.princeton.edu/storeylab/qvalue/). All tests were two-sided with \( P < .05 \) considered significant. One-way analyses of variance (ANOVs) or Kruskal-Wallis tests and \( \chi^2 \) tests were used to compare the baseline demographic, clinical, and MRI variables between study groups. Longitudinal analyses were conducted by applying generalized estimating equations (GEEs) to examine the influence of ICV on clinical deterioration and atrophy progression. By treating each patient’s repeated measures as a cluster, GEE accounts for the possible correlation of variables measured in the same individual over time; furthermore, GEE allows for missing variables within one cluster and violations of the normality assumption [21]. Separate multivariate-adjusted models were constructed for each of the three study groups (CON, aMCI, and AD dementia). Two different sets of GEE models were constructed, the first set using one of the three clinical measures (MMSE, ADAS-cog, and CDR-sb) as the dependent variable and the second set using atrophy as the dependent variable. Independent variables were ICV and time (years from baseline); in addition, models were adjusted for possible confounding factors as specified previously (excluding atrophy as an independent variable from models in which atrophy was the dependent variable). The following interaction terms were tested in separate models (interaction terms including atrophy were not tested for models with atrophy as the dependent variable): (1) atrophy \( \times \) time; (2) \( APOE \times \) time; (3) ICV \( \times \) time (all other bivariate interactions were tested but are not reported here because of lacking significance); (4) atrophy \( \times \) ICV \( \times \) time; and (5) \( APOE \times \) ICV \( \times \) time. A significant ICV effect would suggest a difference in the dependent variable at baseline, whereas a significant time effect would suggest a change in the dependent variable over time. For models with one of the clinical measures as the dependent variable, a significant bivariate interaction term would suggest differential rates of clinical deterioration as a function of \( APOE \) or ICV, or atrophy. A significant interaction between three variables would suggest differential effects of atrophy or \( APOE \) on clinical deterioration in relation to ICV. For models with atrophy as the dependent variable, significant bivariate interactions would suggest differential atrophy progression rates as a function of \( APOE \) or ICV, whereas a significant interaction between three variables would suggest a differential effect of \( APOE \) on atrophy progression as a function of ICV. Quadratic terms of the interaction ICV \( \times \) time were added to the GEE models to test the hypothesis that patients with higher brain reserve experience faster cognitive decline than those with lower brain reserve [7]. Last, separate GEE models stratified according to gender were constructed to explore differential effects in women and in men.

3. Results

Baseline characteristics of the study sample are presented in Table 1. Compared with the CON group, the aMCI and AD dementia groups were characterized by a higher proportion of \( APOE \varepsilon4 \) allele carriers, lower MMSE scores, higher ADAS-cog scores, higher CDR-sb ratings, lower educational attainment, as well as lower Aβ(1-42) and higher t-tau as well as p-tau_{181} CSF concentrations (all \( P < .01 \)). ICV did not significantly differ between the three diagnostic groups (\( P = .23 \)). Baseline atrophy was significantly greater in aMCI and AD dementia compared with CON (\( P < .0001 \)).

The GEE models showed that time had a negative effect on clinical status and atrophy over time in the aMCI and AD groups (\( P < .0001 \)). No association was observed between ICV and any of the dependent variables and no significant interaction effect between ICV and time, indicating that ICV per se has no impact on clinical deterioration or atrophy progression. A significant effect of \( APOE \) on clinical deterioration was observed in the aMCI group (\( P < .01 \)), but not in the AD dementia and CON groups. A significant interactive effect between atrophy and time on all three clinical outcome

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics of the study sample</th>
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<tbody>
<tr>
<td></td>
<td>CON</td>
</tr>
<tr>
<td>N</td>
<td>204</td>
</tr>
<tr>
<td>Age</td>
<td>75.9 (5.11)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>16.07 (2.85)</td>
</tr>
<tr>
<td>MMSE score</td>
<td>29.10 (1.02)</td>
</tr>
<tr>
<td>ADAS-cog score</td>
<td>9.32 (4.21)</td>
</tr>
<tr>
<td>CDR-sb score</td>
<td>0.29 (0.18)</td>
</tr>
<tr>
<td>Gender (N/% men)</td>
<td>106/51.96</td>
</tr>
<tr>
<td>( APOE \varepsilon 4 )</td>
<td>57/27.94</td>
</tr>
<tr>
<td>( N(% \text{ carriers}) )</td>
<td></td>
</tr>
<tr>
<td>ICV (cm³)</td>
<td>1464.47 (133.27)</td>
</tr>
<tr>
<td>TBV (cm³)</td>
<td>1001.29 (94.62)</td>
</tr>
<tr>
<td>TVB/ICV ratio (atrophy¹)</td>
<td>0.68 (0.03)</td>
</tr>
</tbody>
</table>

Abbreviations: CON, cognitively normal controls; aMCI, amnestic mild cognitive impairment; AD, Alzheimer’s disease; MMSE, Mini-Mental State Examination; ADAS-cog, Alzheimer’s Disease Assessment Scale—cognitive subscale; \( APOE \), apolipoprotein E; ICV, intracranial volume; TBV, total brain volume.

NOTE: Data presented as mean (SD) unless indicated otherwise.

¹Significant differences compared with the CON group at \( P < .05 \).

¹Higher values indicate less atrophy.
measures was detected in the aMCI and AD groups, indicating an increasing negative impact of atrophy on clinical status over time. All other independent variables (age, gender, and years of education, and history of cardiovascular disease, stroke, or diabetes mellitus) were not significant.

In the GEE model including the multivariate interactions atrophy × ICV × time or APOE × ICV × time, the interaction terms were significant for all three clinical measures as the dependent variable in the aMCI group, but not in the AD dementia group. The multivariate interaction APOE × ICV × time was not significant in the model with atrophy as the dependent variable in any of three study groups (Table 2). These results indicate that atrophy and APOE had less impact on clinical deterioration in aMCI patients with larger ICV. However, ICV did not affect the impact of APOE on atrophy progression (see also Figure 1). The quadratic terms of the interaction ICV × time were not significant in any of the GEE models. All other independent variables (age, years of education, and a history of cardiovascular disease, stroke, or diabetes mellitus) were also not significant. Stratifying the GEE models according to gender did not affect the findings.

4. Discussion

A protective effect of brain size against the expression of AD symptoms has been suggested by previous epidemiologic and clinical research. We aimed to extend the existing literature by exploring the association between ICV, atrophy or the APOE e4 allele and cognitive decline. Our results show that greater premorbid brain size attenuates the negative impact of AD pathology, as represented by brain atrophy and the APOE e4 allele in this case, on clinical disease progression, although no direct relation between ICV and cognitive performance was observed. Brain atrophy rates were not affected by ICV, which points to a compensatory rather than a neuroprotective effect of brain reserve. Our findings are in line with previous cross-sectional observations reporting that greater maximal adult brain size reduces the effects of atrophy and APOE e4 on cognition [11,12]. Our study also supports reports on a lower incidence [22] and prevalence [23] of cognitive impairment and AD dementia in individuals with larger head circumference and also a recent meta-analysis suggesting different cognitive trajectories in relation to biographic reserve variables [6].

The fact that brain reserve effects on clinical disease expression were limited to the aMCI group in our study is an interesting but not entirely unexpected finding. aMCI often represents a transitional stage between normal cognitive aging and AD dementia [24]. Several lines of evidence indicate that neural impairment and compensation coexist in this stage. For example, functional connectivity deficits between posterior cingulate cortex and regions within the default mode network are accompanied by increased connectivity between posterior cingulate cortex, medial prefrontal cortex,
and anterior cingulate cortex [25]. Blood flow increases in brain regions including the medial temporal lobe have also been observed alongside flow decreases in other AD-typical regions in MCI [26]. These compensatory mechanisms seem less relevant in further advanced clinical stages of AD. In line with these observations, our results may suggest that a larger premorbid brain helps to offset the impact of AD on cognition during the transitional stage of aMCI; the protective effect, however, is outweighed by the neurodegenerative burden in more advanced AD. The concept of faster cognitive deterioration in patients with higher brain reserve compared to those with lower reserve is not supported by our findings (Figure 2 depicts the theoretical model).

We hypothesized that ICV is a proxy of structural reserve components. At 6 years of age, brain growth is largely complete [27]; indices such as adult ICV or head circumference therefore mainly reflect cerebral development during early childhood. Hence, our results may suggest that one basis for high brain reserve is provided by an optimal brain growth [28], which is determined by a mixture of genetic factors [29,30] and external influences, including infections, inflammations [31], nutrition [32], and perinatal injury [33]. Larger brains may offer protection by providing quantitative and/or qualitative advantages such as high synapse/neuron count [34] or better connectivity. Regardless of the underlying mechanisms, improving prenatal and early life conditions could significantly increase brain reserve in the population, which in turn may have an impact on the prevention of AD.

Limitations of our study include the recruitment of participants at specialized memory clinics, which restricts extrapolation of the findings to the general population. No neuropathologic data were available but the reliability of clinical diagnoses established at specialized centers is usually very good [35]. ICV is only an approximation of the real premorbid brain size, but this baseline information is rarely available in clinical cohorts. Strengths of the study are the longitudinal design and the inclusion of a large number of individuals with normal and impaired cognition. The use of automated procedures to measure atrophy and ICV provided data that was not affected by rater-dependent variability. Furthermore, ICV is a closer approximation to maximal adult brain size than head circumference [36], which

Fig. 1. Predicted Mini-Mental-State Examination score decline in the amnestic mild cognitive impairment group in: (A) patients with large intracranial volume and severe atrophy versus patients with small intracranial volume and mild atrophy; and (B) patients with large intracranial volume carrying the apolipoprotein E ε4 allele versus patients with small intracranial volume not carrying the ε4 allele. APOE, apolipoprotein E; ICV, intracranial volume. Models adjusted for covariates as specified. ICV and brain atrophy were dichotomized for illustrative purposes. Small ICV was defined as the first tertile of the distribution, whereas large ICV was defined as the third tertile. Severe atrophy was defined using a cut-off ≤0.66 derived from an ROC analysis comparing the Alzheimer’s disease dementia group with the healthy control group. It can be seen clearly that patients with large intracranial volume experienced slower cognitive deterioration as compared with patients with small intracranial volume despite having more severe brain atrophy or carrying the APOE ε4 allele.

Fig. 2. A theoretical model of brain reserve. Theoretical illustration of how brain reserve may offset the negative impact of brain atrophy on cognitive performance over time. Our model predicts that brain atrophy increases at the same rate over time in individuals with high and with low brain reserve (estimated by intracranial volume in our study). In the mild cognitive impairment stage, cognitive decline will be faster in individuals with low reserve, but individuals with high reserve will have a similar rate of deterioration in the AD stage. Therefore, cognitive performance will be better in the high brain reserve group at any given level of brain atrophy than in the low brain reserve group.
was often used in previous studies [11]. There is some disagreement whether ICV should be corrected for body size, but previous research shows that the association between ICV, brain volume, and cognition in old age was actually not affected by adjusting for height [37].

In conclusion, our study suggests that premorbid brain size protects 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 brain reserve seem to be limited to early clinical AD; once a certain threshold of neurodegenerative burden is passed, larger premorbid brains no longer offer an advantage in this context. Although these observations strongly support the hypothesis of a structural component of reserve, the issue of the exact neurobiologic substrates still needs to be resolved. A complex interplay between brain functional and structural factors most likely determines the individual level of brain reserve [38].

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