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The protective role of brain size in Alzheimer disease

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SUMMARY

Evaluation of: Perneczky R, Wagenpfeil S, Lunetta KL, et al. Head circumference, atrophy, and cognition: Implications for brain reserve in Alzheimer disease. Neurology 2010; 75: 137-142.

The brain reserve hypothesis suggests that larger brain size is associated with a greater ability to tolerate pathological damage before showing any cognitive decline. This theory has been used to explain why many patients with Alzheimer's disease (AD) pathology are cognitively normal before death. The literature concerning the brain reserve hypothesis is however mixed with evidence both for and against this theory. Perneczky and colleagues tested the theory by assessing whether premorbid brain size, measured using head circumference, alters the relationship between brain atrophy and cognitive decline in 270 AD patients. They found that head circumference was associated with a reduced impact of atrophy on cognitive performance. Hence, for a given degree of atrophy, cognitive performance was better in patients with larger head circumference. These findings therefore support the brain reserve hypothesis. This evaluation will discuss the brain reserve concept and potential limitations and significance of this study.

Keywords

brain reserve; Alzheimer disease; head circumference; cognition; atrophy

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia affecting almost 40 million people world-wide [1]. Patients with AD typically show early episodic memory loss with progressive involvement of other cognitive domains and additional functional impairment. Progressive atrophy can be observed on magnetic resonance imaging (MRI), particularly involving the hippocampi and temporoparietal neocortex, and shows a tight correlation to the degree of cognitive impairment. However, a definitive diagnosis of AD can only be made at autopsy and is based on the finding of specific pathological hallmarks, namely the presence of amyloid plaques and neurofibrillary tangles. The majority of patients with a clinical diagnosis of AD do indeed have a pathological diagnosis of AD. Studies have found that the clinical diagnosis of AD has a high sensitivity and specificity for correctly predicting the presence of AD pathology at autopsy.

However, it has been shown that approximately 20% of patients with pathological AD are actually clinically normal before death [2]. It has been suggested that these patients do not manifest clinical changes of the disease because they are in some way protected against

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cognitive decline. In other words, they can tolerate more pathological damage before they become clinically affected than patients that do display clinical AD during life. One early study found that patients with AD pathology that were clinically normal had a greater brain weight and more large neurons than age-matched subjects without AD pathology [2]. This finding has led to the theory that a larger premorbid brain volume, with more neurons and synaptic connections, could provide protection against cognitive decline, often referred to as the "brain reserve (BR) hypothesis". Surrogates for premorbid brain volume include head circumference and measurements of intracranial volume on MRI. Evidence in support of this hypothesis comes from studies which have found that head size is related to the risk of developing AD, and correlates with cognitive impairment and age at onset in patients with AD [3]. However, there is disagreement in the field with other studies not finding evidence for the BR hypothesis [4,5]. It is likely that inconsistencies in the field relate to differences in study methodology, cohort characteristics, sample size, and in how well other confounding factors are accounted for in the analyses.

The concept of BR is therefore at present still contentious. It is however an important issue to resolve and has implications for the understanding of the relationship between pathology, cognition and atrophy in AD. Particularly, to increase understanding of factors that can help prevent or slow cognitive decline. The study under review aimed to test the BR hypothesis by assessing whether premorbid brain size alters the relationship between brain atrophy and cognitive decline in a large group of patients with AD [6]. This indirect approach to assessing the relationship between premorbid brain size and cognition furthers previous studies which tend to investigate the direct relationship between these features.

SUMMARY OF METHODS AND RESULTS

The authors assessed 270 patients with a clinical diagnosis of AD that were recruited from the Multi-Institutional Research in Alzheimer's Genetic Epidemiology (MIRAGE) study. These patients had been recruited from 14 sites in the US, one site in Canada and two sites in Europe. The degree of cerebral atrophy present on MRI was assessed using a visual rating scale. Premorbid brain size was measured using head circumference. The authors used linear regression to examine the association between cerebral atrophy and performance on the mini-mental state examination (MMSE), adjusting for head circumference and other demographic and clinical variables, including age, duration of AD symptoms, gender, APOE genotype, diabetes mellitus, hypertension, major depression and ethnicity. They also assessed whether head circumference modified the effect of atrophy on MMSE score by including an interaction term in the model.

Higher MMSE scores were associated with less severe atrophy ($r = -0.23$, $p<0.01$), shorter duration of symptoms ($r=-0.15$, $p<0.05$) and younger age ($r=-0.43$, $p=0.05$), although only atrophy and age were significant predictors of MMSE score in a linear regression model. No correlation was observed between MMSE and head circumference ($r=-0.12$, $p=0.77$). Head circumference was significantly associated with a reduced impact of atrophy on MMSE score ($p=0.04$, $\beta=-0.21$, standard error=0.01), such that the effects of atrophy on MMSE were more pronounced in patients with a smaller head circumference.

The authors concluded that their data supports the BR hypothesis, and suggests that larger brains protect against the clinical manifestations of the disease. Since the majority of brain growth occurs in the early years of life, the authors also suggest that improvement of prenatal and early life conditions could increase BR in the population and help protect against the effects of AD.

DISCUSSION

This study therefore suggests that although head circumference is not associated directly with cognitive function in patients with AD, it does modify the relationship between atrophy and cognition. Hence, for a given degree of atrophy, cognitive performance was better in patients with a larger head size. These findings are supported by the results from a previous study that assessed the relationship between AD pathology and cognitive function in men and women [7]. They found that AD pathology was more likely to be clinically expressed as dementia in women than men. Since it is well known that men have a larger head size than women, and atrophy provides an excellent marker of the degree of pathology [8], these results could also be interpreted to support the suggestion that head size modifies the relationship between atrophy and cognition. These findings would therefore suggest that cognition is not a good marker of underlying disease pathology in AD, since the degree of cognitive decline will be dependent upon premorbid brain size. Imaging measures of atrophy may instead provide more accurate markers of pathological stage, although it is possible that the degree of atrophy may also be affected by some sort of reserve mechanism.

While the current study accounted for a large number of variables that could have confounding effects on the analysis, one demographic variable that was conspicuous in its absence from the statistical model was education. Years of education could be an important confounder since it would have a direct influence on performance on cognitive testing, and some have suggested that it may correlate with head size [4]. Although perhaps more importantly, it has been hypothesized that subjects with greater cognitive reserve (CR) can withstand a greater degree of AD pathology without becoming demented, due to a greater efficiency in engaging brain networks or use of alternative functional strategies [9]. Hence, individuals with high CR perform better on cognitive tasks, and hence it takes longer before they are given a diagnosis of AD. Education or occupational attainment are commonly used as proxies of CR, with studies finding that a greater pathological burden is required in order to show an effect on cognition in subjects with more education [10]. Hence, one might expect the relationship between atrophy and cognition to be modified by the level of education, as well as head circumference, in AD. The relationship or interaction between these two reserve mechanisms is unclear and was not addressed in this study.

One other potential limitation of the current study was the relatively crude methods that were employed to measure premorbid brain size and atrophy. Head circumference is likely to prove inferior to detailed measurements of intracranial volume in assessing premorbid brain size. The degree of atrophy was measured using a simple visual assessment, with no reported intra-rater reliability. It is unclear whether the visual assessment provided equal weight to hippocampal and temporoparietal regions, or was predominantly biased towards the degree of hippocampal atrophy since it is easier to assess. This method of measurement could have introduced error into the statistical analysis and also did not allow the assessment of whether head size modifies the relationship between atrophy of specific regions of the brain and cognitive function. Automated techniques are available which would allow more accurate assessments of regional structures. Measurements of the degree of white matter hyperintensities could also be performed on MRI. Directly accounting for the presence of white matter hyperintensities could be important since this will influence the relationship between cognition and AD pathology [11].

EXPERT COMMENTARY AND FIVE YEAR REVIEW

Despite the methodological limitations of the study, it does provide solid evidence for the BR hypothesis. However, the concept of BR is still somewhat difficult to fully accept since if it were true then one would expect to observe clinical and prevalence differences in AD

across both genders and ethnic groups which are known to differ according to height and head size. This evidence is currently weak at best. In addition, the literature is still dogged by contradictory publications, with almost as many publications disproving the hypothesis as confirming it. It will therefore be important for these types of findings to be reproduced and validated in other AD cohorts, and in population-based cohorts. Ultimately, confirmation of the hypothesis will require studies that assess the degree of pathology in the brain, rather than using atrophy as a surrogate marker of pathology. Amyloid PET imaging could provide an invaluable way of assessing the degree of pathology, at least the degree of amyloid pathology, during life. Studies have already begun to use amyloid PET markers to assess the CR hypothesis in AD [12].

In addition, other imaging modalities are likely to play an important role in assessing other aspects and mechanisms of brain reserve, such as premorbid levels of metabolic activity measured using FDG-PET or functional connectivity measured using resting-state fMRI in the brain which could be as, or more, important than simple brain size. These modalities may also allow the assessment of compensatory mechanisms and connectivity in the brain, and perhaps even the degree of plasticity in the brain. A better understanding of these mechanisms will be crucial for development of future treatments for AD, including strategies which could potentially aim to modify and increase brain or cognitive reserve through environmental enrichment or targeted neurogenesis [13].

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REFERENCES

1. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. Alzheimers Dement. 2007; 3:186–191. [PubMed: 19595937]
2. Katzman R, Terry R, DeTeresa R, Brown T, Davies P, Fuld P, Renbing X, Peck A. Clinical, pathological, and neurochemical changes in dementia: a subgroup with preserved mental status and numerous neocortical plaques. Ann Neurol. 1988; 23:138–144. [PubMed: 2897823]
3. Wolf H, Julin P, Gertz HJ, Winblad B, Wahlund LO. Intracranial volume in mild cognitive impairment, Alzheimer's disease and vascular dementia: evidence for brain reserve? Int J Geriatr Psychiatry. 2004; 19:995–1007. [PubMed: 15449362]
4. Espinosa PS, Kryscio RJ, Mendiondo MS, Schmitt FA, Wekstein DR, Markesbery WR, Smith CD. Alzheimer's disease and head circumference. J Alzheimers Dis. 2006; 9:77–80. [PubMed: 16627937]
5. Christensen H, Batterham PJ, Mackinnon AJ, Anstey KJ, Wen W, Sachdev PS. Education, atrophy, and cognitive change in an epidemiological sample in early old age. Am J Geriatr Psychiatry. 2009; 17:218–226. [PubMed: 19454848]
6. Perneczky R, Wagenpfeil S, Lunetta KL, Cupples LA, Green RC, Decarli C, Farrer LA, Kurz A. Head circumference, atrophy, and cognition: implications for brain reserve in Alzheimer disease. Neurology. 2010; 75:137–142. [PubMed: 20625166]
7. Barnes LL, Wilson RS, Bienias JL, Schneider JA, Evans DA, Bennett DA. Sex differences in the clinical manifestations of Alzheimer disease pathology. Arch Gen Psychiatry. 2005; 62:685–691. [PubMed: 15939846]
8. Whitwell JL, Josephs KA, Murray ME, Kantarci K, Przybelski SA, Weigand SD, Vemuri P, Senjem ML, Parisi JE, Knopman DS, et al. : MRI correlates of neurofibrillary tangle pathology at autopsy: a voxel-based morphometry study. Neurology. 2008; 71:743–749. [PubMed: 18765650]
9. Stern Y. Cognitive reserve. Neuropsychologia. 2009; 47:2015–2028. [PubMed: 19467352]
10. Roe CM, Xiong C, Miller JP, Cairns NJ, Morris JC. Interaction of neuritic plaques and education predicts dementia. Alzheimer Dis Assoc Disord. 2008; 22:188–193. [PubMed: 18525294]

11. Brickman AM, Siedlecki KL, Muraskin J, Manly JJ, Luchsinger JA, Yeung LK, Brown TR, Decarli C, Stern Y. White matter hyperintensities and cognition: Testing the reserve hypothesis. Neurobiol Aging. 2009

12. Rentz DM, Locascio JJ, Becker JA, Moran EK, Eng E, Buckner RL, Sperling RA, Johnson KA. Cognition, reserve, and amyloid deposition in normal aging. Ann Neurol. 2010; 67:353–364. [PubMed: 20373347]

13. Sachdev PS, Valenzuela M. Brain and cognitive reserve. Am J Geriatr Psychiatry. 2009; 17:175–178. [PubMed: 19225275]

KEY ISSUES

- The brain reserve hypothesis suggests that larger brain size is associated with a greater ability to tolerate pathological damage before showing any cognitive decline.
- This concept has been extensively studied in Alzheimer's disease (AD) with mixed findings.
- Perneczky and colleagues assessed whether head circumference alters the relationship between brain atrophy and cognitive decline in AD. They found that head circumference was associated with a reduced impact of atrophy on cognitive performance.
- These findings provide convincing support for the brain reserve hypothesis.
- The study has the advantage that they accounted for many demographic, genetic and clinical features that could confound cognitive performance, although future studies will need to relate these findings to pathology, levels of education and use more sensitive measures of regional brain atrophy.