SHORT REPORT

Schooling mediates brain reserve in Alzheimer's disease: findings of fluoro-deoxy-glucose-positron emission tomography

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J Neurol Neurosurg Psychiatry 2006;**77**:1060–1063. doi: 10.1136/jnnp.2006.094714

Background: Functional imaging studies report that higher education is associated with more severe pathology in patients with Alzheimer's disease, controlling for disease severity. Therefore, schooling seems to provide brain reserve against neurodegeneration.
Objective: To provide further evidence for brain reserve in a large sample, using a sensitive technique for the indirect assessment of brain abnormality (^{18}F-fluoro-deoxy-glucose-positron emission tomography (FDG-PET)), a comprehensive measure of global cognitive impairment to control for disease severity (total score of the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery) and an approach unbiased by predefined regions of interest for the statistical analysis (statistical parametric mapping (SPM)).
Methods: 93 patients with mild Alzheimer's disease and 16 healthy controls underwent ^{18}F-FDG-PET imaging of the brain. A linear regression analysis with education as independent and glucose utilisation as dependent variables, adjusted for global cognitive status and demographic variables, was conducted in SPM2.
Results: The regression analysis showed a marked inverse association between years of schooling and glucose metabolism in the posterior temporo-occipital association cortex and the precuneus in the left hemisphere.
Conclusions: In line with previous reports, the findings suggest that education is associated with brain reserve and that people with higher education can cope with brain damage for a longer time.

The hypothesis of brain reserve capacity (BRC) was introduced almost 20 years ago to account for the repeated observation that pathology of Alzheimer's disease and its clinical symptoms are not tightly linked. Intelligence or life experience may provide reserve in the form of skills that allow some people to attenuate symptoms of neurodegeneration better than others. Epidemiological, clinical and neuropathological studies suggest education as an important factor of such life experience. Bennett *et al*[1] recently showed, for example, that the association between the Alzheimer's disease pathology and cognitive symptoms shortly before death was attenuated by the number of years of schooling. Better educated patients had more pathology than would have been predicted from their cognitive status. Epidemiological studies that support the BRC hypothesis show that the incidence of clinical Alzheimer's disease is lower in people with more years of school education and that higher educated patients with Alzheimer's disease experience faster cognitive decline.[2] Functional imaging studies also provide evidence for BRC. Considering reduced cerebral blood flow (CBF) and regional cerebral metabolic rate of glucose utilisation (rCGMglc) as indirect markers of Alzheimer's disease pathology, patients with more years of schooling consistently had more pronounced deficits in regions typically affected by the pathology of Alzheimer's disease.

We aim to provide further evidence for the BRC hypothesis using positron emission tomography (PET) imaging with ^{18}F-fluoro-2-deoxy-glucose (^{18}F-FDG) for the measurement of rCGMglc in patients with Alzheimer's disease. We hypothesised that years of schooling and rCGMglc should be inversely associated in brain regions affected by Alzheimer's disease pathology. We decided to readdress this issue for the following reasons:

- Most previous studies have used limited neuropsychological measures to control for clinical disease severity.
- Sample size was a limiting factor in some of the previous studies.
- Most of the previous studies used single-photon emission-computed tomography to measure CBF, although ^{18}F-FDG-PET was found to be more sensitive to early functional changes in Alzheimer's disease.[3]
- Some of the earlier studies focused on regions of interest.

A voxel-based approach, however, seems more appropriate, having no exact a priori hypothesis of brain regions with a marked association between education and rCGMglc.

METHODS

Study sample

In all, 93 consecutive patients with probable mild Alzheimer's disease[4] and 16 age-matched healthy controls[5] without memory complaints or objective cognitive deficits, who were all examined between 2001 and 2003 at a university-based outpatient unit for cognitive disorders, were identified in a pre-existing electronic database. All participants underwent a thorough diagnostic evaluation, which is described in detail by Drzezga *et al*.[6] The neuropsychological assessment was based on the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery (CERAD-NAB),[7] including the Mini-Mental State Examination (MMSE).[8] The total score of the CERAD-NAB was calculated for each patient according to recently published criteria (subtest addition method)[9] to control for cognitive status in

Abbreviations: BRC, brain reserve capacity; CBF, cerebral blood flow; CERAD-NAB, Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery; FDG-PET, fluoro-deoxy-glucose-positron emission tomography; MMSE, Mini-Mental State Examination; rCGMglc, regional cerebral metabolic rate of glucose utilisation; SPM, statistical parametric mapping

the regression analyses of ^{18}F-FDG-PET data. Briefly, total scores were obtained by summing scores from the individual subtests (excluding the MMSE score) into a total composite score (maximum for verbal fluency set at 24 points, maximum total score 100 points). This score was preferred to the MMSE score because it covers a wide spectrum of cognitive function. Educational levels of patients and controls were assessed as years of education, defined as years attending school plus years of apprenticeship, technical school, college and university. After the purpose and the procedures of the study had been fully explained to the participants, informed written consent was obtained from each of them in accordance with the Declaration of Helsinki. The local ethics committee and the radiation protection authorities approved the study protocol.

PET scan acquisition and data processing

Following exactly the same protocol, all patients and controls underwent PET scanning after being given an ^{18}F-FDG injection at rest. The detailed PET scanning procedure is described in Drzezga *et al*.[6] SPM software (SPM2, http://www.fil.ion.ucl.ac.uk/spm/software/spm2) based on Matlab, V.6.5, was used for image realignment, transformation into standard stereotactic space, smoothing and statistical analyses. Images were smoothed with a gaussian kernel (12 mm full-width at half-maximum). Individual global counts were normalised by proportional scaling to a mean value of 50 mg/100 ml/min.

Statistical evaluation

A voxel-based linear regression analysis of rCMRglc was conducted with years of schooling as independent variable, controlling for CERAD-NAB total score, age and sex. Findings reaching a threshold height of $p<0.001$ uncorrected for multiple comparisons were considered to be significant, as reported previously.[10] The extension threshold was set at 200 contiguous voxels for this type of analysis. Significant associations between years of school education and rCMRglc were only expected in brain regions known to be affected in patients with Alzheimer's disease.[11] Additionally, scatterplots between years of schooling and rCGMglc were also generated in SPM2 at the cluster with the strongest statistical correlation, and a regression line was fitted into these plots. The correlation coefficient was calculated in Matlab. Coordinates in Montreal Neurological Institute space (http://www.bic.mni.mcgill.ca) were transformed to Talairach space[12] using the Matlab function mni2tal (http://www.mrc-cbu.cam.ac.uk/Imaging). Anatomical regions were identified using the Talairach Demon Client, V.2.0 (http://ric.uthscsa.edu/recources). Demographics were also analysed in Matlab.

RESULTS

Table 1 presents the characteristics of the study sample. The MMSE score range of the group with Alzheimer's disease supported their diagnoses of mild Alzheimer's disease.[13] Years of school education ranged from 8 to 19 years in both groups.

At the significance value of $p<0.001$ uncorrected for multiple comparisons, the voxel-based regression analysis showed a significant negative association between years of schooling and adjusted rCGMglc (corrected for cognitive status and demographic characteristics) in an extensive cluster in the left hemisphere, encompassing the middle occipital gyrus, the superior temporal gyrus and the precuneus (cluster of 2172 contiguous voxels; table 2 and fig 1).

The fitted curve for the linear regression analysis has a negative slope (fig 1). The additional correlation analysis between the adjusted rCMRglc and years of schooling at the localisation of the most significant cluster showed a correlation coefficient of −0.39. We noted no marked positive correlation in any brain regions. Furthermore, we observed no association between education and rCGMglc in the control group.

Table 1 Characteristics of the study sample

Characteristic	AD group (n = 93)	Controls (n = 16)	p Value
Age in years*	69.63 (9.79)	67.88 (9.99)	0.51
Men:women	50:43	7:9	0.46
Schooling in years*	10.16 (2.79)	11.69 (4.01)	0.16
CERAD total score*	53.31 (11.09)	ND	NA
MMSE*	23.49 (2.26)	30 (0.00)	<0.001

*Data are reported as mean (SD).
AD, Alzheimer's disease; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; MMSE, Mini-Mental State Examination; NA, not applicable; ND, not done.

DISCUSSION

Consistent with the BRC hypothesis, we found a marked inverse association between years of schooling and rCGMglc in brain regions typically affected by Alzheimer's disease pathology. This cluster encompassed the left posterior temporo-occipital association cortex, including the middle occipital gyrus, superior temporal gyrus and precuneus. The posterior temporo-occipital association cortex forms a cortical network responsible for the integration of information of different modalities. For the precuneus, a central role in a wide spectrum of highly integrated tasks, including visuo-spatial imagery, episodic memory retrieval and self-processing operations, is suggested by recent functional imaging studies on healthy controls. Reciprocal cortical connections between posterior association cortex and precuneus exist, and both structures are known to be affected by Alzheimer's disease pathology.[14]

Our findings are supported by other studies, although there is often no exact match between the results because of differences in sample characteristics and methods. Liao *et al*[15] recently reported a marked negative correlation between schooling and CBF in the temporal and parieto-occipital brain regions in patients with mild Alzheimer's disease and in the temporal, parietal and frontal regions in patients with moderate Alzheimer's disease. Stern *et al*[16] found that those patients with Alzheimer's disease who had the highest education showed most severe parietal CBF deficits when controlling for disease severity. In a recent study by Scarmeas *et al*,[17] the authors report a marked inverse association between schooling and CBF in the precuneus, middle temporal and middle frontal gyrus. No such association was found in their control group. The authors also report a marked negative correlation between the score of an instrument for the assessment of activities of daily living and CBF in the temporo–occipital–parietal association cortex. That the factors of everyday life experience other than school education may also provide reserve is further supported by a study reporting deficits of CBF in the parietal cortex in patients with Alzheimer's disease whose lifetime occupation was more demanding, again controlling for disease severity.[18]

One advantage of our study is the big and well-characterised study sample. We used a total score of the CERAD-NAB that allowed us to control for disease severity using a comprehensive assessment of cognitive functions. We controlled not only for age but also for sex, which seems to

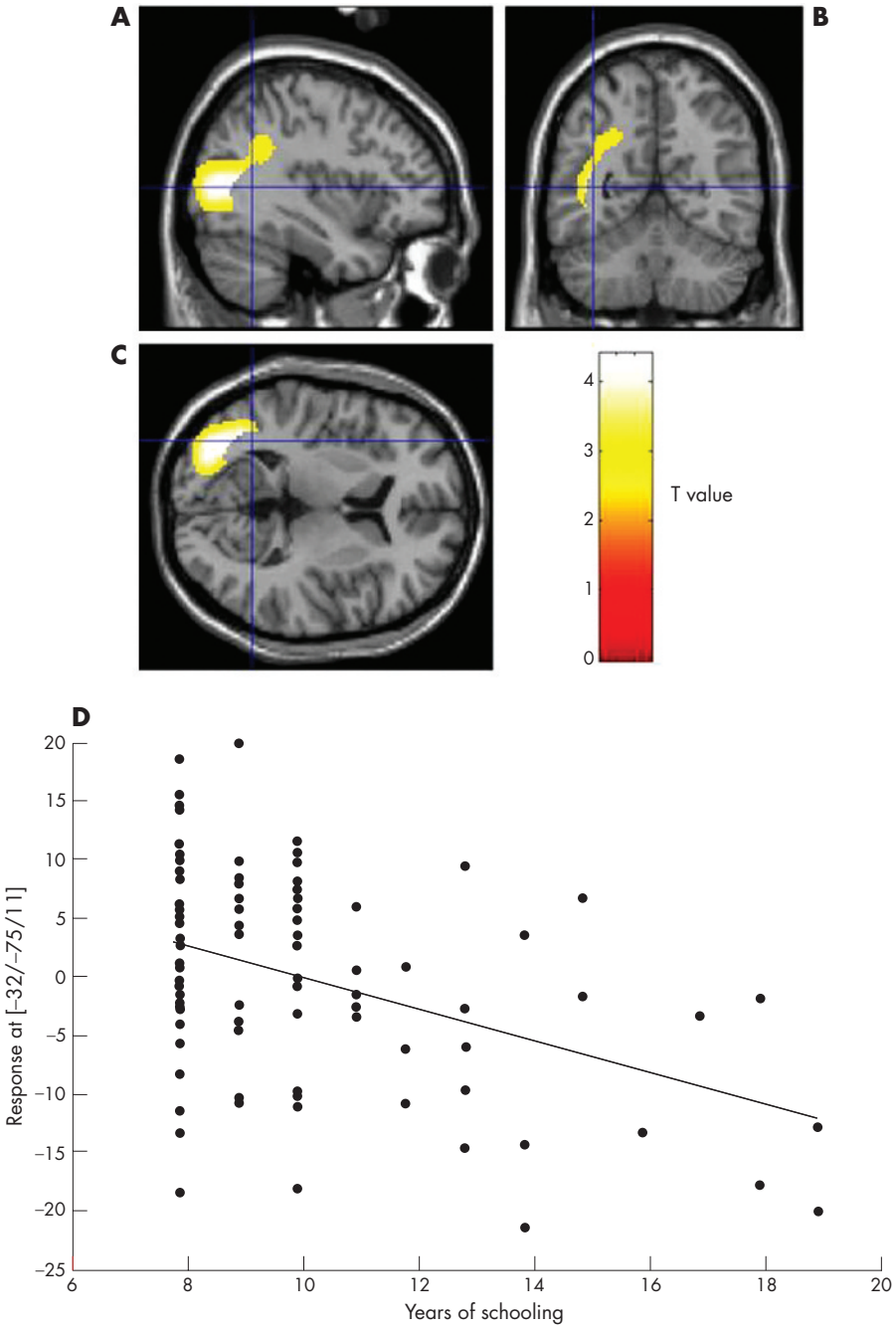

Figure 1 Inverse association between regional cerebral metabolic rate of glucose utilisation (rCMRglc) and years of schooling. Anatomical localisation of the significant clusters (maximum at Talairach coordinates x/y/z −32/−75/11, left medial occipital gyrus, $p<0.005$ uncorrected or multiple comparisons for display purposes), as projected on (A) sagittal, (B) coronal, (C) axial sections of a normal magnetic resonance imaging, spatially normalised into Montreal Neurological Institute's template (colour bar indicating the corresponding T values) and (D) regression analysis of fitted and adjusted rCMRglc response in arbitrary units as dependent variable and years of school education as independent variable at the position of the most significant cluster.

affect BRC. Barnes *et al*[19] reported that the association between neuropathology of Alzheimer's disease and clinical Alzheimer's disease was considerably stronger in women than in men. Each unit of Alzheimer's disease pathology increased the odds of clinical Alzheimer's disease more than 20-fold in women compared with a threefold increase in men.[19] Results were unchanged after controlling for potential confounders as school education. By using ^{18}F-FDG-PET scanning in combination with SPM methods, we established a sensitive in vivo measure avoiding the limitations of the predetermined region of interest approach. Our study by no means indicates that education provides protection against Alzheimer's disease pathology. Rather, it provides further evidence that neurodegeneration and clinical symptoms are not tightly linked and that education is associated with people's ability to cope with brain damage.

ACKNOWLEDGEMENTS

This study was partly funded by the Federal Ministry of Research and Education as part of a national collaboration on dementia

Table 2 Peak correlations of regional cerebral metabolic rate of glucose utilisation and schooling in the group with Alzheimer's disease

Anatomical region	Coordinates in Talairach space x	y	z	Peak z value
Left middle occipital gyrus	**−32**	**−75**	**11**	**4.17**
Left precuneus	−14	−45	38	3.02
Left superior temporal gyrus	−28	−47	34	3.02

Bold markings delineate the cluster.
Non-bold markings identify further peaks in the same cluster.

(Kompetenznetz Demenzen), grant no 01GI0420. The sponsors played no part in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review or approval of the manuscript. We thank Dorottya Ruisz and Suzanne Rodger for proof reading.

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Competing interests: None.

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Received 3 April 2006
Revised version received 18 April 2006
Accepted 11 May 2006
Published Online First 18 May 2006

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J Neurol Neurosurg Psychiatry 2006 77: 1060-1063 originally published online May 18, 2006
doi: 10.1136/jnnp.2006.094714