Education Attenuates the Effect of Medial Temporal Lobe Atrophy on Cognitive Function in Alzheimer's Disease: The MIRAGE Study

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Abstract. Functional imaging and neuropathological studies suggest that individuals with higher education have better cognitive performance at the same level of brain pathology than less educated subjects. No *in vivo* studies are available that directly test how education modifies the effect of structural pathology on cognition in Alzheimer's disease (AD). The present study therefore aimed to measure this effect using data from a large multi-center study. 270 patients with AD underwent cognitive testing using the Mini Mental State Examination (MMSE), apolipoprotein E (APOE) genotyping, and cerebral magnetic resonance imaging. A linear regression analysis was used to examine the relation of medial temporal lobe atrophy (MTA), as a proxy of AD pathology, to MMSE score, adjusting for age, gender, APOE, cerebrovascular disease, ethnicity, education, and disease duration. An interaction term for MTA and education was introduced to test the hypothesis that education modifies the effect of MTA on cognition. There was a significant inverse association between MTA and cognition. Most interestingly, the interaction term between education and MTA was significant suggesting that education modifies the relation of MTA to cognition. At any level of pathology, cognition remained higher for better educated individuals.

Keywords: Alzheimer's disease, cognition, cognitive reserve, dementia, education, hippocampus, magnetic resonance imaging, medial temporal lobe atrophy

INTRODUCTION

The medial temporal lobe, which includes the hippocampus and parahippocampal gyrus (the latter includes the entorhinal cortex), is preferentially affected by Alzheimer's disease (AD) pathology, including neurofibrillary tangle formation [1], amyloid-β deposition [2], neuronal loss, and volume reduction [3].

Although magnetic resonance imaging (MRI) findings show some heterogeneity regarding their neuropathological basis [4], MRI medial temporal lobe atrophy (MTA) is a sensitive marker for pathologic AD stage [5]; MRI is able to detect MTA at early clinical stages of AD [6] and track its progression as the disease advances [7]. Furthermore, MTA is associated with cognitive impairment and decline over time and predicts AD in individuals with minor cognitive impairment [8]. The relationship between AD pathology and clinical symptoms, however, is not tight [9]. Elderly individuals may show a sufficient number of amyloid-β containing plaques and neurofibrillary tangles at autopsy to warrant a neuropathological diagnosis of AD but exhibit no symptoms of dementia during life [10]. The disjunction between pathology and symptoms is thought to indicate a variable capacity among individuals to withstand pathological change, which is referred to as brain reserve [11] or cognitive reserve (CR) [12,13]. Studies relating plaque counts at postmortem examination [14], regional blood flow [15–17], or metabolism [18–25] to clinical symptoms and biographical variables have consistently demonstrated that patients with higher pre-morbid intelligence, longer education, or greater occupational attainment have better cognitive performance at the same level of disease severity. Koepsell and colleagues [26], however, found no evidence of larger education-related differences in cognitive function in patients with more advanced AD neuropathology. The neurobiological substrate of CR is not known but may involve structural factors such as brain size, neuron numbers, and synaptic density as well as functional components including efficiency of neural networks and brain connectivity [27]. Only one study has explored the association between *in vivo* structural indices of AD pathology, education, and cognition so far. Kidron et al. [28] reported that education was a significant predictor of parietal atrophy, controlling for cognitive impairment, disease duration, age, and sex. There are, however, no other published reports that directly test whether educational attainment modifies the relationship between structural indices of AD pathology, such as MRI-based assessments of brain atrophy, and clinical symptoms. If such an effect were present, it would suggest that the influence of CR is powerful enough to offset significant amounts of brain tissue loss. The present study was undertaken to test the hypothesis that education modifies the association between MTA and cognitive performance in AD, taking into account other variables that are known to impact on cognitive ability, including age [29], apolipoprotein E (APOE) genotype [30], head size [31], cerebrovascular lesion burden [32], and duration of disease [33].

MATERIALS AND METHODS

Subjects and data collection

The MIRAGE Study was designed as a family-based multi-center study of genetic and environmental risk factors for AD, the details of which, regarding data collection and reliabilities of questionnaires, are published elsewhere [34–36]. Briefly, participants included in this investigation were ascertained through research registries or specialized memory clinics at 17 sites in the USA (14), Canada (1), Germany (1), and Greece (1) between February 2002 and November 2006. All individuals were diagnosed with probable AD according to the National Institute of Neurological and Communication Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria [37]. Medical history, risk factor information, blood samples for genetic analyses, and cranial MRI scans were collected from all study participants. The patients' educational level was dichotomized according to the highest level attained (low education: less than high school graduate; high education: high school graduate or higher), because the MIRAGE Study assesses levels of educational attainment which are not interval-scaled. A combination of informed written consent by patient and informed consent by proxy was obtained. Procedures involving experiments on human subjects were done in accord with the Helsinki Declaration of 1975. Cognitive ability was assessed in all patients using the Mini-Mental Status Examination (MMSE) [38]. For the present study only patients with an MMSE score lower than 26 were used to ensure diagnostic accuracy [39]. No other exclusion criteria were applied.

Acquisition of MRI scans

The MRI scanning procedures and analysis protocols have been described previously [40]. In brief, double spin echo, fluid-attenuated inversion recovery, and high resolution T1 images were acquired from each individual according to exactly the same protocol. All MRI were acquired on 1.5 T scanners and the sequences were modified to suit differences in machine manufacturers and operating systems. Qualitative rating scales were applied, which, by their simplicity, are relatively insensitive to measures at multiple sites [41]. In addition, all data were analyzed by a single rater (C.D.), who was blind to all clinical and genetic data, to reduce inter-rater variance [42]. The amount of MTA was determined from the high resolution T1 scans us-

ing a semi-quantitative visual scale [43], ranging from 0 (no atrophy) to 4 (most severe atrophy) that discriminates well between individuals with AD and cognitively healthy subjects, and has a high degree of inter-rater reliability [44]. Wahlung and colleagues [45] furthermore reported a high correlation between the visual rating and time-consuming volumetric procedures, and the visual rating had a higher diagnostic accuracy in the differentiation between patients with AD and healthy control subjects than the volumetric assessment. White matter hyperintensities (WMH) were rated from fluid-attenuated inversion recovery images on a 100 mm visual analogue scale, on which 0 stood for the total absence of WMH and 100 for the most severe degree of WMH. Examples of quantified abnormalities were incorporated as landmarks in the rating process. Finally, the presence or absence of MRI infarction (INF) was determined from the size, location, and imaging characteristics of the lesion, using information from all available scans according to a previously described standard protocol [46]. An overall rating of cerebrovascular disease (CVD) was created using a combination of WMH and INF data to describe the additive effects of both lesion types. CVD stands for the summed severity of WMH and INF; e.g., in the absence of INF, CVD equals WMH severity, whereas in the presence of accompanying INF, the CVD rating is obtained by summing the single scores for WMH and INF. Previous work found that MRI ratings of WMH and INF are associated with cerebrovascular abnormalities but not with AD pathology [4]. Wu et al. [47] reported a high correlation between the semi-quantitative visual rating and an automated quantitative rating on segmented brains.

APOE genotyping

APOE genotyping was performed using a standard polymerase chain reaction as reported elsewhere [48]. For the purpose of the present study, subjects were classified as APOE $\varepsilon4$ ($-$) or $\varepsilon4$ ($+$).

Measurement of head circumference

Head circumference was measured in a standardized manner by placing a measuring tape over the eyebrows and passing it around the head to fit snugly over the most posterior protuberance of the occiput [49].

Statistical analyses

Data were analyzed using the Statistical Package for Social Sciences (SPSS), v16.0 (SPSS Inc., Chicago, IL, USA). All p-values shown are two-sided and subject to a significance level of 0.05. Correlations (Pearson product-moment or Spearman's rank correlation coefficients) were calculated in order to explore dependencies in the dataset. More precisely, correlations were computed between the MMSE score and the MTA rating, education, and the CVD rating; and between age and the MTA, and the CVD ratings. The association of MTA and cognitive function was examined using multiple linear regression analysis with the MMSE score as the dependent variable. MTA score and other variables with a putative effect on cognitive function including age, education, gender, head circumference, APOE genotype, CVD rating, and duration of disease were considered as predictors. The regression model also included a trichotomous classification variable for ethnicity (Caucasian, African-American, and Asian-American) with Caucasian as the referent to control for ethnic differences in educational attainment. To control for differences in scanner sensitivity for WMH at the different study centers, variables for the main effect of study center and the interaction between center and WMH were also included in the regression analysis.

To determine whether education modified the effect of MTA on cognitive ability, an interaction term between education and MTA was added to the regression model. In this test of effect modification, the interaction term directly examines the extent to which education changes the effect of MTA on cognition. Thus, the interaction term is the primary focus of the analysis. In addition, to compare the distribution of the variable MMSE score with the normal distribution, a normal P-P plot of regression standardized residuals was generated, which compares the cumulative proportions of standardized residuals of the MMSE score with the cumulative proportions of the respective normal distribution. If the normality assumption is not violated, points are clustered around a straight line.

RESULTS

A description of the study sample is given in Table 1. A total of 270 patients with AD were included who had an average age of 75 years, a mean MMSE score of 17 (median 19, range 0–25, kurtosis 0.28, skewness 0.89), and a mean MTA rating of 2.5 (median 3, range 0–4,

Table 1
Description of the patient sample

Variable	Value
N	270
Age [years] *	75.23 (8.83)
Men: women	109: 161
Duration of disease [years] *	5.49 (4.42)
Caucasian: African-American: Asian-American	193: 41: 27
Educational level, high: low	166: 104
MMSE score *	17.38 (5.86)
MTA *	2.59 (1.19)
APOE $\varepsilon4$ (+): $\varepsilon4$ (−)	160: 110
CVD rating *	24.46 (24.95)
Head circumference [cm]	55.99 (2.67)

* mean (SD); MTA: medial temporal lobe atrophy; CVD: cerebrovascular disease; MMSE: Mini-Mental-State Examination; APOE: apolipoprotein E.

Table 2
Linear regression models examining the relation of MTA and education to global cognitive function

Model terms	Model 1		Model 2	
	β (SE)	P	β (SE)	P
MTA	−1.54 (0.41)	< 0.001	−0.75 (0.56)	0.18
Education	0.82 (0.88)	0.35	4.86 (2.13)	0.02
Age	−0.12 (0.06)	0.03	−0.13 (0.05)	0.02
Education x MTA	NA	NA	−1.57 (0.74)	0.03

Model 1 included separate terms for education and MTA to assess their independent contribution to global cognitive function, and Model 2 added an interaction term between education and MTA to determine whether education modified the relation of atrophy to level of cognitive function. Ethnicity and variables with a putative effect on cognition such as age, education, gender, head circumference, apoE genotype, and CVD rating were included in both models (only significant predictors are shown). β indicates the estimated effect and SE the respective standard error in the multiple regression analysis. Negative β represent an inverse interaction between the predictor and cognition performance, whereas positive β point to a positive interaction.
NA: not applicable.

kurtosis 0.80, skewness 0.42). Approximately 60% of the subjects were female, APOE $\varepsilon4$ allele carriers, and high school graduates. Correlation analysis revealed some plausible significant associations. In particular, a higher MMSE score was associated with a less severe MTA ($r = -0.31$, $p < 0.001$), and older age was correlated with both higher MTA ($r = 0.35, p < 0.001$) and CVD ($r = 0.36$, $p < 0.001$) ratings. There was no significant correlation between disease severity as indicated by the MMSE score as well as the MTA rating, education, and the CVD rating (MMSE: $r = 0.08$, $p = 0.43$; MTA: $r = 0.09$, $p = 0.16$; CVD: $r = 0.02$, $p = 0.76$).

In the linear regression analysis, MTA ($p < 0.001$) and age ($p = 0.03$) were inversely associated with cognitive performance (indicated by a negative β) (Table 2). The other independent variables were not significant (gender: $p = 0.47$; APOE genotype: $p = 0.92$; head circumference: $p = 0.74$; CVD: $p = 0.78$; education: $p = 0.35$; Asian-American ethnicity: $p = 0.15$; African-American ethnicity: $p = 0.07$; duration of disease: $p = 0.07$; study center: $p = 0.36$, study center * WMH: 0.52).

Most interestingly, in the model with an added interaction term between MTA and education, the interaction term showed a statistically significant inverse association with the MMSE score ($p = 0.03$), indicating that education attenuated the impact of MTA on cognitive performance (again, indicated by a negative β). In this model, age ($p = 0.02$) and education ($p = 0.02$) were significant predictors of cognitive performance (Table 2). MTA and the other independent variables did not show significant effects (MTA: $p = 0.18$; gender $p = 0.42$; APOE genotype: $p = 0.90$; head circumference: $p = 0.67$; CVD: $p = 0.62$; Asian-American ethnicity: $p = 0.11$, African-American ethnicity: $p =$

0.09; duration of disease: $p = 0.09$; study center: $p = 0.48$, study center * WMH: 0.43). The normal P-P plot of regression standardized residuals supported the normality assumption (Fig. 1).

DISCUSSION

The present study suggests that educational attainment modifies the association between ratings of MTA and cognitive performance in patients with AD, taking into account other factors which may have an impact on cognition, including age, gender, APOE genotype, head size, and cerebrovascular lesion burden. In well-educated patients, the effect of MTA on cognition was weaker than in less-educated subjects. This finding is consistent with the concept of CR [12,13]. It is also in line with previous studies relating functional and structural indicators of neurodegeneration, including metabolism, cerebral blood flow or brain atrophy, with cognitive ability and education as a measure of CR. These studies have consistently demonstrated that the association between *in vivo* pathological indices and cognitive impairment was weaker in better educated individuals with AD [15,16,18,21,28], dementia with Lewy bodies [22], frontotemporal dementia [50], and non-fluent progressive aphasia [20]. In addition, clinico-pathological studies have suggested that not only functional alterations but also morphological brain changes have a less negative effect on cognitive ability shortly before death in patients with greater CR [51]. In line with these studies, our findings suggest that the
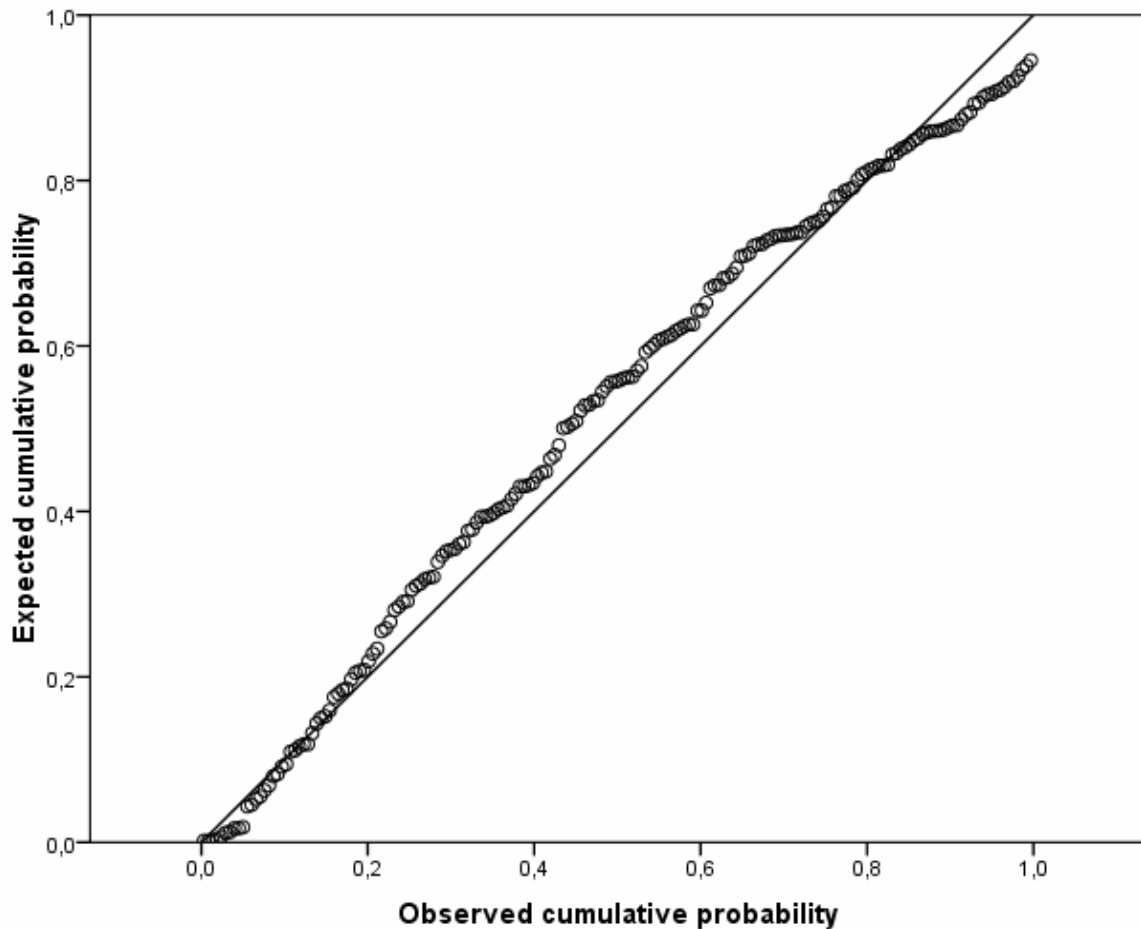
Fig. 1. Normal P-P Plot of regression standardized residuals (dependent variable: MMSE).

effect of CR, whatever its nature, is robust enough to offset the consequences of brain tissue loss on cognitive ability.

Some limitations of the study should be considered in the interpretation of the results. First, our patient sample was generally well-educated and was recruited from memory clinics or similar institutions, so that the results may not be generalizable. This may be one of the reasons for the underrepresentation of CVD in the study sample. Particularly, cerebral infarction was rather rare, so that the CVD rating predominantly represents WMH. Therefore, effects of CVD on cognition may have been underestimated. Second, MTA was assessed using a visual rating procedure which may not be sensitive to minor or non-linear changes. Therefore, the analysis might be improved by volumetric MTA measurements. Third, we considered education level as a dichotomous outcome and may not have captured

non-linear effects of years of schooling or identified a level of education that is optimal for assessing the effect of education on the association of MTA with cognitive performance. Furthermore, it has to be noted that education might not be the ideal proxy for CR, although it has been used as such in most studies. Other demographic factors, such as intelligence [18], lifetime occupation [17], leisure activities [15], or social networks [52] may also contribute to CR in a way that is yet to be understood. Forth, the MMSE was used to rate cognitive impairment in the MIRAGE study. Although it is a reliable assessment scale in AD, more sensitive tests may have further improved the results.

In conclusion, the present study strengthens the concept of CR by demonstrating that manifest morphological brain changes have a less negative effect on cognition in patients with AD and greater educational attainment. Therefore, education is not only associat-

ed with a cognitive advantage such that well-educated individuals have better cognitive function and require more pathology to reach any given level of cognitive impairment; education also modifies the association between pathology and cognition at any given level of brain damage. Future studies using more precise volumetric measures of MTA in a larger sample are needed to refine and extend the results of the present study.

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