Dementia
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Cognitive Disorders

Cognitive Reserve: A SPECT Study of 132 Alzheimer's Disease Patients with an Education Range of 0–19 Years

Yi-Chu Liao[a, c, f]   Ren-Shyan Liu[d]   Evenly Lee Teng[h]   Yi-Chung Lee[a, b, g]
Pei-Ning Wang[a, c]   Ker-Neng Lin[c, e]   Chih-Ping Chung[a, c]   Hsiu-Chih Liu[a, c]

[a]Department of Neurology and [b]Institute of Clinical Medicine, National Yang-Ming University School of Medicine, [c]Neurological Institute and [d]Department of Nuclear Medicine, Taipei Veterans General Hospital, and [e]Department of Psychology, Fu Jen Catholic University, Taipei, [f]Department of Neurology, E-Da Hospital and I-Shou University, Kaohsiung, and [g]Department of Neurology, Taichung Veterans General Hospital, Taichung, Taiwan; [h]Department of Neurology, University of Southern California Keck School of Medicine, Los Angeles, Calif., USA

Abstract

This study examines the associations between education, cerebral perfusion, and cognitive test performance among 132 patients with Alzheimer's disease. The participants had had between 0 and 19 years of formal schooling, and had either mild or moderate dementia according to the Clinical Dementia Rating Scale. Cerebral perfusion was evaluated by the ^{99m}Tc-hexamethylpropylene amine oxime single photon emission computed tomography. The Mini-Mental State Examination and the Cognitive Abilities Screening Instrument were used to assess cognitive performance. For patients at each clinical dementia severity level, statistical parametric mapping was used to examine voxel by voxel the association between education and cerebral perfusion, and Pearson's correlation coefficients were calculated between education and cognitive test scores. Years of formal schooling had negative associations with cerebral perfusion and positive associations with cognitive test scores. The brain regions showing a significant education effect on perfusion involved bilateral posterior association areas in mild dementia, and bilateral parieto-temporo-frontal areas in moderate dementia. The present findings indicate that the cognitive reserve effect starts at the low end of the education range. They also suggest that the main effect of more education is a more facile use of alternative brain circuits instead of locally increased synaptic connections.

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Introduction

Little or no formal education is an important risk factor for dementia including Alzheimer's disease (AD) [1–3], and a 'cognitive reserve' hypothesis has been proposed to account for this phenomenon. In essence, this hypothesis suggests that more schooling, together with its associ-

Dr. Hsiu-Chih Liu
The Neurological Institute, Taipei Veterans General Hospital
201 Sec. 2, Shih-pai Road, Shih-pai
Taipei 11217 (Taiwan)
Tel. +886 2 2875 7492, Fax +886 2 2873 8696, E-Mail hcliu@vghtpe.gov.tw

ated conditions including more cognitively stimulating occupational and leisure activities, may result in richer synaptic connections and more facile utilization of a larger variety of alternative brain circuits for performing cognitive tasks [4, 5]. Consequently, higher education and a more cognitively stimulating lifestyle in general can delay or lessen the clinical manifestation of the pathological advances of AD. In other words, at comparable clinical levels of impairment, individuals with higher educational attainment have already sustained more advanced AD pathology. Consistent with this hypothesis, a lower prevalence rate [3], faster decline [6, 7], and higher mortality [8, 9] have been found among AD patients with higher education, and the association between cognitive functions and AD pathology also differed as a function of educational attainment [10].

Several functional imaging studies have shown that, at comparable dementia severity, lower perfusion or greater reduction in metabolic rate were associated with higher education among AD patients [11–13]. Since hypoperfusion or lowered metabolic rate are generally accepted to be indicators of AD pathology [14, 15], these findings also lend support to the cognitive reserve hypothesis. However, the majority of patients in these studies had at least some high school education. Therefore, it is unclear whether or not the cognitive reserve effect also extends to the lower ranges of education. In addition, these studies used cognitive test scores to indicate disease severity, but performance on cognitive tests is by itself influenced by education [16].

In the present study, we examined the association between education and cerebral perfusion among AD patients who had had between 0 and 19 years of formal schooling. To indicate dementia severity, we used ratings on the Clinical Dementia Rating (CDR) [17] scale that did not involve cognitive testing and were based on interview findings about the patients' functional level in their daily activities. For the identification of brain regions that show an education effect, we used the statistical parametric mapping (SPM) method to perform voxel-by-voxel analysis of single photon emission computed tomography (SPECT) images. The SPM method is more quantitative than visual inspection; it also avoids the limitations of the predetermined 'region of interest' approach [18]. The SPM method has been used successfully in comparing cerebral perfusion between AD patients who differed in clinical severity [19], and in identifying additional regions of hypoperfusion among AD patients who also had depression [20].

Methods

Subjects

The 132 participants of this study were recruited from the memory clinic of a large university-affiliated medical center. All patients at this clinic were screened for dementia and, if dementia was suspected, received further medical, neurological, neuropsychological, and psychiatric assessments. For the majority of these patients, neurological assessment included cerebral CT, or MRI, or both, in order to rule out intracranial pathology such as brain tumor or stroke that might have contributed to the cognitive decline. SPECT was not part of the routine workup.

The inclusion criteria for participation in the SPECT study were (1) a diagnosis of probable AD according to the NINCDS-ADRDA criteria (the criteria adopted by the National Institute of Neurological and Communicative Disorders and Stroke and by the Alzheimer's Disease and Related Disorders Association) [21], and (2) a rating of either 1 or 2 on the CDR scale [17, 22]. The exclusion criteria were (1) having possible additional causes of dementia as determined by history, neurological examination, imaging and blood studies; (2) an additional diagnosis of major depression or dysthymia, and (3) a lack of a responsible family member who could provide informed consent for study participation. The first criterion for exclusion helped ensure that all participants had reasonably pure AD.

CDR Staging

The CDR scale was designed to stage the severity of dementia. It assesses a patient's functional level in daily life in (1) recent and long-term memory; (2) orientation to time, place, and person; (3) judgment and problem solving; (4) community affairs; (5) home and hobby activities, and (6) personal care. The extent of cognitive impairment in each of the 6 areas is determined, and algorithms are provided for deriving an overall level of impairment that ranges from 0 (healthy) to 3 (severe) [17, 22]. CDR scores of 1 and 2 indicate 'mild' and 'moderate' dementia, respectively. A neuropsychologist, without knowledge of the patient's SPECT and cognitive test findings, assigned a rating on the CDR scale after conducting separate semistructured interviews with the patient and a knowledgeable informant.

SPECT Imaging and the SPM Method

All participants received a technetium-99m hexamethylpropylene amine oxime SPECT scan within 110 days (mean ± SD = 23.16 ± 21.12 days) of their CDR staging and cognitive testing. Imaging was conducted in a quiet, darkened room and started 30 min after the injection of a bolus of 740 MBq technetium 99m hexamethylpropylene amine oxime. A SPECT scanner (APEX-HELIX-HR, Elscint, Ltd.) was used to acquire the projection image. Image reconstruction was performed by filtered back projection using a Metz filter, and system resolution was measured to be 9.6 mm full width at half maximum. Correction for attenuation was made numerically with a uniform coefficient factor of 0.11/cm. The reconstructed images were analyzed by SPM (SPM99, Wellcome Department of Cognitive Neurology, London, UK) in Matlab 6.0 (Math Works, Natick, Mass., USA) [18]. The data were transformed into a standard three-dimensional space with the Talairach coordinates [23]. The images were spatially normalized with the template image supplied by SPM99 and smoothed with an isotropic Gaussian kernel with a full width at half maximum of

Table 1. Demographic data and cognitive test scores of the two AD patient groups that differ in clinical dementia severity

	Mild dementia (n = 87)	Moderate dementia (n = 45)	Statistical results of group comparisons
Men, %	51	49	$\chi^2 = 0.03$, p = 0.85
Education, years	8.3 ± 5.6 (0–19)	8.3 ± 6.0 (0–16)	$t = -0.03$, p = 0.97
0	n = 18	n = 9	
1–6	n = 19	n = 11	
7–12	n = 29	n = 12	
13	n = 21	n = 13	
Age, years	75.0 ± 7.2 (44–89)	76.6 ± 7.1 (55–88)	$t = -1.19$, p = 0.24
CASI score	62.1 ± 15.4 (20–90)	41.0 ± 17.6 (3–77)	$t = 7.13$, p < 0.001
MMSE score	18.1 ± 5.3 (7–28)	11.5 ± 5.5 (1–23)	$t = 6.63$, p < 0.001

Figures in parentheses indicate ranges.

12 mm [24]. To adjust for scan-to-scan variations, for each patient local flow rates were scaled to the mean voxel value of the cerebellum. The cerebellum activities were calculated with the template method reported by Soonawala et al. [25] who established the validity of using cerebellum as the reference region for AD patients. Although the presence of plaques and neurofibrillary tangles in the cerebellum had been reported, SPECT studies showed that the cerebellum was scintigraphically unaffected before the advanced stage of AD [26, 27].

At each clinical severity level, voxel-by-voxel analysis of the association between education and perfusion was performed. The associations between years of formal schooling and cerebral blood flow were computed twice, once with and once without the inclusion of age, gender, and the Mini-Mental State Examination (MMSE) and Cognitive Abilities Screening Instrument (CASI) scores as confounding covariates. Locations reaching statistical significance of a corrected p value of <0.05 at the cluster level were displayed on three orthogonal projections [28]. Anatomical localization was determined according to the Talairach coordinates obtained from M. Brett's transformations (www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html).

Cognitive Test Performance
Chinese versions of the MMSE [29] and the CASI were administered and scored by research assistants who did not know the CDR stage or the SPECT findings. The CASI has more items and more refined scoring than the MMSE; it provides 9 domain scores (attention, concentration, orientation, recent memory, long-term memory, language abilities, visual construction, list-generating fluency, and abstraction and judgment) that sum to a total score of 100 [30]. Each of the 9 domain scores, as well as the CASI total score, showed significant differences between different patient groups who differed in their CDR stage [31]. Partial correlation coefficients were calculated to show the association between years of education and cognitive test performance after partialling out age and gender.

Comparison of Demographic Data and Cognitive Test Scores between the Two Patient Groups of Mild (CDR = 1) and Moderate (CDR = 2) Dementia
Significance of group differences in mean age, education, and the MMSE and CASI scores was checked by the t test. Significance of group differences in gender ratio was checked by the χ^2 test. The SPSS software, version 11.5, was used. Statistical significance was set at the two-tailed p value of 0.05.

Results

Demographic data and cognitive test scores for the mild and the moderate dementia groups are shown in table 1. The two groups are comparable in gender ratio, education, and age. The mild dementia (CDR = 1) group had better cognitive test scores than the moderate dementia (CDR = 2) group.

Negative associations between years of formal schooling and cerebral perfusion were found in bilateral parietal regions and some adjacent occipital and temporal regions among patients with mild dementia, and in bilateral parieto-temporo-frontal regions among patients with moderate dementia (table 2, fig. 1). Nearly identical findings were obtained with the inclusion of age, gender, and cognitive test scores as covariates in the calculations.

Scatterplots between education and cerebral perfusion are shown in figure 2a. In order to avoid visual clutter, at each CDR level only data at the two brain loci that showed the strongest negative associations with education are presented. No brain region showed a statistically significant positive association between education and cerebral perfusion.

In contrast, education showed statistically significant (p < 0.01) positive associations with cognitive test scores. Scatterplots between education and cognitive test scores are shown in figure 2b. Also shown are partial correlation coefficients between education and test scores after partialling out age and gender.
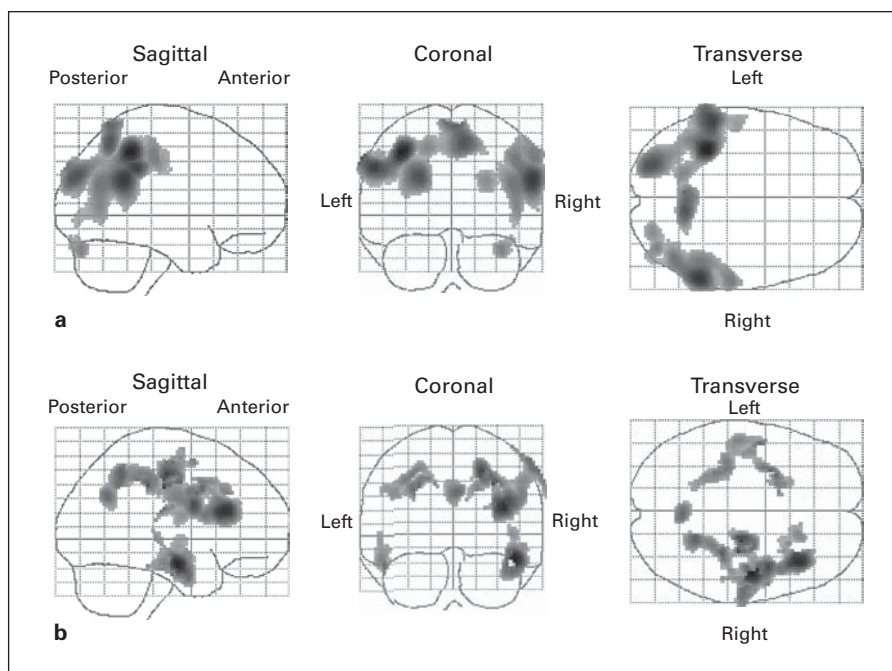
Fig. 1. Areas with significant negative correlations between years of education and cerebral perfusion. **a** Mild dementia (CDR = 1). **b** Moderate dementia (CDR = 2).

Table 2. Regions and peaks that show a significant correlation between years of education and local perfusion

CDR = 1					CDR = 2				
brain regions	Talairach coordinates			Z value	brain regions	Talairach coordinates			Z value
	x	–y	z			x	–y	–z	
Lt inferior parietal lobule	–36	–40	46	4.51	Lt parietal, subgyral	–30	–27	44	3.99
Lt occipital, cuneus	–24	–78	32	4.01	Lt frontal, subgyral	–26	9	35	4.26
					Lt middle temporal gyrus	–50	–5	–18	4.10
					Lt superior temporal gyrus	–51	–10	–5	3.44
Rt parietal, supramarginal gyrus	59	–45	26	4.27	Rt parietal, precuneus	22	–48	45	4.43
Rt parietal, postcentral gyrus	61	–21	40	3.60	Rt parietal, postcentral gyrus	32	–29	38	4.46
Rt middle temporal gyrus	50	–61	25	3.64	Rt temporal, subgyral	46	–10	–16	5.50
					Rt temporal, fusiform gyrus	44	–3	–23	4.28
					Rt frontal, subgyral	38	24	17	5.25

The scatterplots show three main points: (1) cerebral perfusion (scaled to the mean cerebellum perfusion), as well as cognitive test scores, were in general lower in moderate dementia than in mild dementia; (2) at each dementia severity level, education had negative associations with cerebral perfusion, but positive associations with cognitive test scores, and (3) the effects of education on cerebral perfusion and cognitive test scores cover the entire education range of 0–19 years.

Discussion

This study examined cerebral perfusion and cognitive test performance of AD patients in relation to their educational attainment. It differed from prior studies [11–13] in that we used a larger sample size and covered a wider education range, extending its low end to include no or few years of formal schooling. In addition, we used functional level in daily life instead of cognitive test scores to indicate
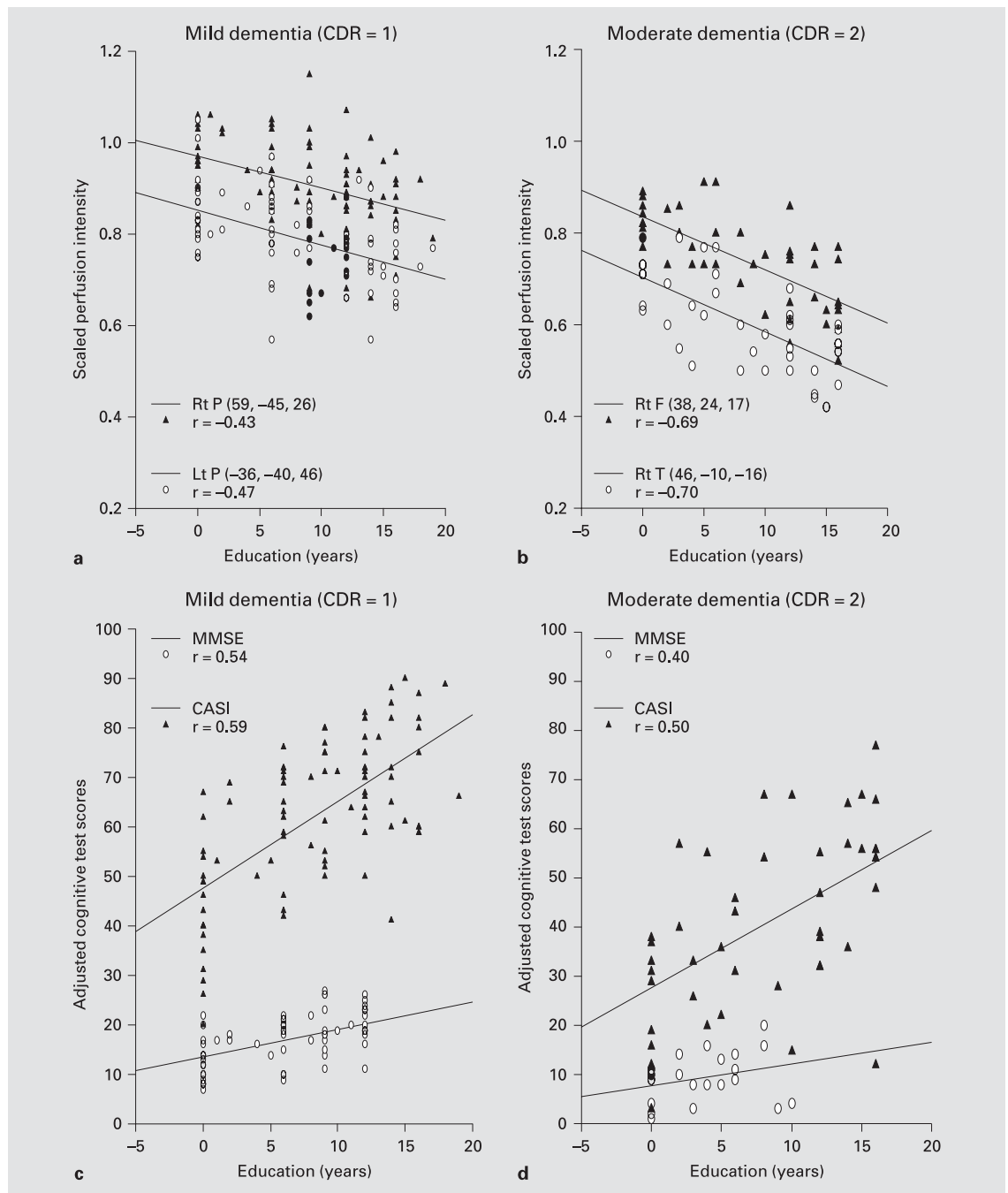
Fig. 2. a Scatterplots between years of education and scaled perfusion intensity at two locations that showed the most significant correlations. F = Frontal lobe; P = parietal lobe; T = temporal lobe. Numbers in parentheses are Talairach coordinates. **b** Scatterplots between years of education and cognitive test scores, and partial correlation coefficients between education and test scores after partialling out age and gender.

the clinical severity of dementia. The main findings were the following: (1) at each of two severity levels and throughout the education range of 0–19 years, patients with more years of formal schooling had lower cerebral perfusion but

higher cognitive test scores, and (2) the brain regions showing an education effect involved bilateral posterior association areas in mild dementia, and bilateral parieto-temporo-frontal areas in moderate dementia.

Since cerebral hypoperfusion is generally accepted to be an indicator for AD pathology [14, 15], our first finding indicates that, despite greater AD pathology, patients with more education still had better cognitive test performance than, and could maintain comparable functional levels as, patients with less education. Previous studies have shown that, with comparable cognitive test scores, AD patients with higher education showed lower cerebral perfusion [11–13]. However, it is likely that individuals with more years of schooling are just more used to and apt at taking cognitive tests. In addition, since most cognitive tests are designed by academics, some test items may tap abilities (e.g. reading and writing) poorly developed by individuals who had no or few years of formal schooling. Consequently, individuals with more years of schooling will typically score higher on cognitive tests, with or without AD, and greater AD pathology is needed to cancel the benefits of education on test scores. Instead of cognitive test scores, the present study used interview findings about the patients' functional level in their everyday life to indicate dementia severity. Therefore, our findings have provided stronger support for the cognitive reserve hypotheses.

Patients in previous SPECT studies had an average education level of around 15 years [11–13], and few individuals with little or no formal schooling were included. Therefore, it was unclear whether or not the cognitive reserve effect supported by their findings would extend to the low end of the education range. The present study covered an education range of 0–19 years, and the findings are supportive of a cumulative effect of education that starts at the very low end of the education range.

The neural effect of education for cognitive reserve has been hypothesized to include either enriched synaptic connections, or a more facile use of alternative neural circuits, or both [4, 5]. Findings from this and other SPECT studies seem to favor the second hypothesis. If the main neural effect of education was denser synaptic connections, we would have found positive associations between years of schooling and cerebral perfusion.

The exact brain sites that showed an education effect were different between the mild dementia and the moderate dementia groups, as well as between the present and previous findings [11–13]. In fact, there was no exact agreement in location between any two of the studies. For example, Stern et al. [11] identified parieto-temporal regions, Scarmeas et al. [12] identified precuneus, middle frontal gyrus, and middle temporal gyrus, and Alexander et al. [13] identified right prefrontal, bilateral premotor and left parietal association regions. These differences are attributable to the many differences among the studies in measurement and analysis methods, as well as in patient characteristics. In the SPM analysis of SPECT data, only locations that show significant perfusion differences were identified. In other words, regions that are equally poorly perfused or equally well perfused in relation to education will not be identified. Therefore, the findings are sensitively influenced by the patients' general stage of AD progression. Many PET and SPECT studies have reported that the parieto-temporal cortex is affected early in AD and the pathology spreads to frontal lobes with disease progression [32, 33]. Findings in figure 1 are consistent with this trend and indicate that the pathological changes in AD do progress from posterior association areas towards anterior ones [34]. However, in this study we compared two groups of patients who differed in dementia severity. Our conclusions will become stronger when the findings are confirmed with longitudinal follow-up.

Impairment in recent memory is the earliest and most prominent cognitive deficit in AD, and the hippocampi are critically important for recent memory. It may appear unexpected that our study did not find significant associations between hippocampal perfusion and education. The reason may be that, by the time a diagnosis of AD could be made, recent memory and hippocampal structures were already severely impaired in all participants regardless of their educational attainment, therefore no negative association between education and hippocampal perfusion was found.

To summarize, this study has provided stronger support for the cognitive reserve effect of education, has extended it to the low end of the education range, and favors a 'flexible neural circuitry' interpretation of the education effect. Finally, although years of formal schooling has been used as the explanatory variable in data analysis, it should be noted that other associated conditions including cognitively more stimulating occupations [6, 35] and leisure activities [36, 37] are also implicated.

Acknowledgements

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