The effects of intelligence and education on the development of dementia. A test of the brain reserve hypothesis

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ABSTRACT

Background. A number of recent epidemiological studies have shown that the prevalence and incidence of dementia are increased in population strata with low compared to high levels of education. This has been explained as a consequence of a greater 'brain reserve capacity' in people with a high level of education. Theoretically, however, brain reserve capacity is better reflected by intelligence than by level of education. Thus, the emergence of dementia will be better predicted by low pre-morbid intelligence than by low education.

Methods. This prediction was tested in a population based sample of elderly subjects ($N = 2063$; age range 65–84; Amsterdam Study of the Elderly) who were followed over 4 years. Dementia was diagnosed using the Geriatric Mental State examination (GMS). Pre-morbid intelligence was measured using the Dutch Adult Reading Test (DART), a short reading test which gives a good estimate of verbal intelligence, and is relatively insensitive to brain dysfunction. The effects of age, gender, occupational level, number of diseases affecting the central nervous system and family history of dementia or extreme forgetfulness were also examined.

Results. Logistic regression analysis showed that low DART-IQ predicted incident dementia better than low level of education. A high occupational level (having been in charge of subordinates) had a protective effect.

Conclusions. This result supports the brain reserve theory. It also indicates that low pre-morbid intelligence is an important risk factor for cognitive decline and dementia. Use of reading ability tests is to be preferred over years of education as estimator of pre-morbid cognitive level in (epidemiological) dementia research.

INTRODUCTION

Several studies have found a relation between level of education and prevalence of dementia (reviews: Katzman, 1993; Mortimer & Graves, 1993). Recent incidence studies of dementia confirm that low educational level increases the risk of Alzheimer's disease and other types of dementia (Canadian Study of Health and Aging 1994; Stern *et al.* 1994; Cobb *et al.* 1995; Glatt *et al.* 1996). Similar findings have been reported with respect to memory decline and cognitive decline in general (Blum & Jarvik, 1974; Scherr *et al.* 1988; Colsher & Wallace, 1991; Evans *et al.* 1993; Plassman *et al.* 1995; Snowdon *et al.* 1996; Schmand *et al.* 1997*a*).

This phenomenon has been explained by the concept of 'brain reserve capacity' (Mortimer, 1988; Katzman, 1993; Satz, 1993). People with a high level of education are presumed to possess a larger brain reserve capacity than people with less education. Given a particular insult to the brain, cognitive symptoms are more likely to emerge in people with less brain reserve. The brain reserve concept implicates the idea of a

threshold that has to be surpassed before symptoms of disease can become prominent. The concept is only loosely defined. One may think of it in terms of brain volume, intensity of brain metabolism, connectivity in neural networks (dendritic branching and synapse density), and efficiency of brain functioning. Satz (1993) reviews a wide range of empirical arguments in favour of the concept. Different kinds of brain damage, diseases of the central nervous system (CNS), systemic diseases affecting the CNS (such as diabetes mellitus, thyroid dysfunction, or AIDS), Alzheimer's disease, as well as the process of ageing itself, more specifically the atrophic processes that occur with ageing (e.g. Haug & Eggers, 1991; West, 1996), may all be viewed as causing brain lesions. These lesions are purported to be additive (Satz, 1993, p. 275). During the accumulation of different lesions, and during slowly progressive diseases, such as Alzheimer's disease, symptoms may arise several years later in persons with greater brain reserve than in people with small brain reserve (Satz, 1993; Schofield *et al.* 1995; Mori *et al.* 1997). This delay explains the epidemiological findings of reduced risk for dementia in population strata with high educational levels (Katzman, 1993).

According to the brain reserve theory, education is no more than a derivative of brain reserve. One may attain a high level of education if one's brain reserve capacity is large enough. However, intelligence 'might represent a more valid indirect measure of brain reserve capacity' than education (Satz, 1993, p. 290), since the latter is determined by other factors besides the capacities of the individual. For example, unfavourable socio-economic circumstances may limit the individual's opportunities to receive an appropriate education. Thus, the brain reserve theory predicts a stronger relationship between intelligence and the emergence of dementia than between education and dementia. It was the purpose of the present paper to test this prediction.

Although the theory assumes that intelligence and education are *consequences* of brain reserve capacity, there are also indications pointing in the opposite direction. Results of a number of experimental studies suggest that an enriched environment may promote brain development (Swaab, 1991). This holds true not only for the young but for the aged as well, and to some extent even for Alzheimer's disease patients (Swaab, 1991, p. 319). This 'use it or lose it' view reverses the causal direction. It implies that a thorough education and other favourable circumstances in early life are *causes* of a greater brain reserve capacity, and that stimulating mental activity during later life maintains or further increases the brain reserve. Indeed, an active life-style characterized by complex social functioning and diverse leisure activities has been found to protect against cognitive decline and dementia (Deeg *et al.* 1992; Kondo *et al.* 1994; Fabrigoule *et al.* 1995). Thus, if we want to investigate predictions made by the brain reserve theory, it is advisable to take into account the quality of mental activity during the post-education years as well.

We tested the above-mentioned prediction in a population sample of initially non-demented elderly people who were followed for a period of 4 years. Verbal intelligence of the respondents and their educational level were established at baseline. The intellectual level of their occupation and the number of subordinates of whom they had been in charge were used as proxy measures of the quality of post-education mental activity. The influences of age, gender, diseases affecting the CNS, and family history of dementia were also considered, since these influences may act as confounders. Age is the most important risk factor for cognitive decline and dementia (e.g. Henderson, 1986; Rocca *et al.* 1991*a*, *b*; Van Duijn, 1996). Female sex has been found to be a risk factor in a number of studies (see e.g. Van Duijn, 1996). As explained above, diseases affecting the CNS are considered to be lesions with a cumulative effect on brain reserve capacity. Finally, a positive family history of Alzheimer's disease is another established risk factor for dementia (Hardy *et al.* 1989; Canadian Study of Health and Aging 1994; Farrer *et al.* 1995; Van Duijn, 1996).

METHOD

Subjects

Participants were enrolled in the Amsterdam Study of the Elderly (AMSTEL), a population study on cognitive decline and dementia (Hooijer *et al.* 1992; Launer *et al.* 1993, 1995). Originally, a sample of 5666 subjects was drawn from 30

general practices throughout the city. The age range of the sample was 65 to 84 years, stratified in four 5-year age strata. This sample can be considered representative for the Amsterdam elderly population within each age stratum. Response rate was 71·5% ($N = 4051$). Non-responders were somewhat older, less educated, scored lower on cognitive function tests, and had a less favourable health status than responders (Launer *et al.* 1994). Dementia was diagnosed in 261 subjects (see next paragraph). These prevalent cases of dementia were dropped from the subsequent analyses.

After 4 years, 2063 subjects (54·4% of the remaining 3790) were available for re-evaluation; 9·7% had deceased; follow-up was refused by 16·2%; and 6·8% were too ill to participate. The remaining subjects either could not be contacted (10·1%) or had insufficient baseline data (2·9%).

Measurements

Participants were visited at home by trained lay interviewers who conducted a structured interview, including the Geriatric Mental State examination (GMS) (Copeland *et al.* 1976), and questions on education, occupation, medical history and chronic diseases, and family history of extreme forgetfulness or dementia. This interview was repeated after 4 years.

The presence of a dementia syndrome was derived from the GMS items. To that end, the GMS was used in conjunction with AGECAT, a computer program that mimics the diagnostic decision making process and records the presence of psychiatric syndromes at six levels of diagnostic confidence (Dewey & Copeland, 1986). An organic score of 3 or higher at syndrome level was considered to indicate organic brain disease or dementia (Copeland *et al.* 1976), and was used as the dementia criterion in the present study.

The Mini-Mental State Examination (MMSE; Folstein *et al.* 1975), and the Dutch Adult Reading Test (DART; Schmand *et al.* 1992) were also administered as part of the baseline interview. Missing MMSE item scores were set to zero (Fillenbaum *et al.* 1988). Pre-morbid intelligence was measured by the DART. This is the Dutch version of the National Adult Reading Test (NART; Nelson, 1982, 1991). It consists of a list of 50 words with irregular spelling which

have to be read aloud. The score is the number of correctly pronounced words. This raw score is transposed into an IQ-score. The DART (like the NART) gives a good estimate of verbal intelligence, and is relatively insensitive to brain dysfunction and mild dementia (Nelson, 1982, 1991; O'Carroll, 1995; Schmand *et al.* 1992; 1997*b*). The psychometric properties of both tests are comparable.

Level of education was measured in the conventional way as years of formal education, based on the answer to the question 'How old were you when you left school?'. Six years (age at which primary school was entered) were subtracted from the age at which school was finished to arrive at the years of education. People who indicated that they had done courses (general education, language, or professional courses) after finishing their formal education were assigned 1 year extra.

Occupational level was measured on a scale similar to the one used by Bickel & Cooper (1994). This scale expresses the intellectual difficulty of the occupation at five levels: (1) professionals, company directors, artists and similar occupations; (2) self-employed, highly skilled, or management occupations; (3) skilled workers and small tradesmen; (4) semi-skilled workers; (5) unskilled labour. Housewives were scaled according to the occupation they had practised before their marriage. Occupation was unknown in 30 respondents; these were scaled according to the occupation of their partner. The number of persons of whom the respondent had been in charge of was used as a second measure of occupational level. If unknown (80 respondents, mostly unskilled), the number of subordinates was set to zero.

The presence or history of the following diseases was assessed: stroke, transient ischaemic attack (TIA), myocardial infarction, cardiac arrhythmia, hypertension, closed head injury, epilepsy, Parkinson's disease, diabetes mellitus, cancer, rheumatoid arthritis, and chronic obstructive pulmonary disease. The number of diseases as reported by the respondents was counted. 'Don't know' answers were scored as disease not present.

Family history of severe forgetfulness or dementia in first-degree relatives was also based on self-report of the respondents. This variable was scored dichotomously (yes/no).

Data analysis

Logistic regression analysis was used to test the prediction that pre-morbid intelligence is stronger related than education to the emergence of dementia. Presence or absence of incident dementia as defined by GMS/AGECAT after 4 years was the dependent variable; age, gender, DART-IQ, years of education, occupational level, number of subordinates, number of diseases, and family history of dementia were the independent variables. To simplify the interpretation of the results, all continuous variables were dichotomized at the median of the sample: age at less than 75 years *versus* older; DART-IQ at less than 99 points *versus* higher; level of education at 8 years and less *versus* more than 8 years; occupational level at 1–3 *versus* 4–5; number of subordinates at zero *versus* at least one; and number of diseases at one *versus* more than one disease.

RESULTS

Incident dementia was found in 152 (7·4%) subjects according to GMS/AGECAT. Tables 1 and 2 present the demographic characteristics, test scores and distributions of occupational levels in the incident cases and those who remained normal. The dementia group was significantly older, less well educated, had a lower pre-morbid IQ and lower MMSE scores, and had a lower occupational level than the normal subgroup. The correlation between DART-IQ and years of education was 0·51; DART-IQ was not related to age ($r = 0·02$). The correlation between years of education and occupational level was $-0·62$; occupational level correlated $-0·46$ with number of subordinates. Table 3 shows the results of the logistic regression analysis. Age was the strongest predictor of incident dementia. DART-IQ was the second strongest predictor: a high IQ had a protective effect. Occupational level itself was not a significant predictor, but having been in charge of personnel had a protective effect. Level of education, number of diseases, and family history of extreme forgetfulness or dementia were not significant in this model. These results indicate that DART-IQ explained more variance of incident dementia than educational level. The results were substantively the same without dichotomization of the independent variables (part R's were as follows: age 0·201 ($P < 0·001$); DART-IQ $-0·075$ ($P = 0·005$); number of subordinates $-0·043$ ($P = 0·05$)). The results remained also the same when education was expressed on a scale reflecting the intellectual difficulty rather than mere duration of education. Since IQ, education and occupation were rather strongly correlated, the possible distortion due to multicollinearity was explored by repeating the analyses without either education or occupation. Again, this did not affect the pattern of results of the remaining variables.

DISCUSSION

Pre-morbid intelligence appears to be a more powerful determinant of incident dementia than level of education. This result supports the brain reserve theory, which states that intelligence reflects brain reserve capacity more directly than education (Satz, 1993). As far as we are aware,

Table 1. *Demographic characteristics and test scores of the subjects who remained normal at follow-up after* 4 *years and those who developed a dementia syndrome by Geriatric Mental State* (*GMS*) *criteria; mean* (*S.D.*)

	Normal (N = 1911)	GMS-dementia (N = 152)	Significance*
Female %	62·5%	64·5%	0·62 χ^2
Age, years	74·1 (5·5)	77·5 (5·0)	0·000 *t* test
Education, years	9·1 (3·0)	8·0 (1·8)	0·0001 M–W
DART-IQ	100·3 (14·3)	94·9 (13·9)	0·000 *t* test
Number of diseases	1·3 (1·2)	1·3 (1·2)	0·63 M–W
Family history	18·1%	21·7%	0·27 χ^2
MMSE baseline (1990)	28·2 (1·7)	26·2 (2·4)	0·0000 M–W
MMSE follow-up (1994)	27·3 (2·5)	21·0 (5·4)	0·0000 M–W

* Level of significance (two-tailed) by χ^2, Mann–Whitney, or *t* test.

Table 2. *Distribution of occupational levels and numbers of subordinates of those who had worked in management functions*

	Normal	GMS-dementia	Significance*
Occupational level			
1 professional	75 (4·0%)	2 (1·3%)	
2	167 (8·8%)	15 (10·0%)	
3	440 (23·3%)	22 (14·7%)	
4	746 (39·5%)	52 (34·7%)	
5 unskilled	460 (24·4%)	59 (39·3%)	0·0003
No management	1173 (63·7%)	110 (75·3%)	
1–4 subordinates	191 (10·4%)	13 (8·9%)	
5–9	145 (7·9%)	7 (4·8%)	
10–19	136 (7·4%)	6 (4·1%)	
20–49	119 (6·5%)	7 (4·8%)	
⩾ 50	77 (4·2%)	3 (2·1%)	0·004

* Level of significance (two-tailed) by Mann–Whitney test.

Table 3. *Result of logistic regression analysis with GMS/AGECAT incident dementia as dependent variable, and age, gender, years of education, pre-morbid intelligence (DART-IQ), occupational level, management function, number of diseases, and family history of extreme forgetfulness and dementia as independent variables*

Variable*	B (S.E.)	P	R	Odds ratio (95% CI)
Age	1·242 (0·194)	0·000	0·189	3·46 (2·37–5·07)
Gender	−0·319 (0·200)	0·111	−0·023	0·73 (0·49–1·08)
Education	−0·150 (0·214)	0·482	0·000	0·86 (0·57–1·31)
DART-IQ	−0·495 (0·204)	0·015	−0·060	0·61 (0·41–0·91)
Occupation	−0·053 (0·239)	0·824	0·000	1·05 (0·66–1·68)
Management	−0·537 (0·225)	0·017	−0·058	0·58 (0·38–0·91)
Number of diseases	−0·032 (0·179)	0·859	0·000	0·97 (0·68–1·37)
Family history	0·218 (0·210)	0·298	0·000	1·24 (0·82–1·89)

* All variables were entered in a single step. Continuous variables were dichotomized at their respective sample medians.
B, regression coefficient; S.E., standard error of B; P, level of significance; R, partial correlation; CI, confidence interval; sex: male is scored as 1, female as 2.

this is the first epidemiological study to report an effect of pre-morbid intelligence on the development of dementia. The importance of intelligence has remained unnoticed until now, perhaps because epidemiological studies on cognitive decline and dementia typically use education or occupation as proxies of pre-morbid cognitive functioning, instead of directly measuring intelligence. Our results also suggest that continued mental stimulation during the post-education years has an independent protective effect with respect to the development of dementia. This was expressed by whether or not one had exerted some kind of managerial function.

The GMS is not an expert's diagnosis. However, it is less endangered by the educational bias inherent in two-phase epidemiological studies on dementia. In these studies a large population sample is screened for dementia using the MMSE, followed by a second, diagnostic phase in which a subsample of 'screen positives' is examined by experts. Educational bias of the MMSE may affect inclusion in the second phase, and thus distort the relationship between education and dementia. With the GMS a diagnosis is obtained for all respondents in the first phase of the study. The GMS was, therefore, very useful for our research purpose. Moreover, it allowed calculations on large numbers of subjects. Our results probably would not have been very different, had we used a conventional dementia criterion. First, the number of 152 new cases amounts to a roughly estimated incidence of 18 per 1000 person-years, which is comparable to other European studies (Van Duijn, 1996). Secondly, the percentage of agreement between the GMS dementia diagnosis and the DSM-III-R

diagnosis is at least 85% (Fichter *et al.* 1995; Schmand *et al.* 1995). Thus, it is unlikely that our results were seriously distorted by the GMS dementia criterion.

The use of reading tests like the NART as measures of pre-morbid intelligence is not without criticism (e.g. O'Carroll, 1995). Recent studies have shown that reading ability is not so well preserved in dementia as it was originally claimed to be (Stebbins *et al.* 1990; Fromm *et al.* 1991; Patterson *et al.* 1994). The NART appears to underestimate pre-morbid IQ with about one standard deviation in patients with moderately severe dementia (MMSE scores below 15; Stebbins *et al.* 1990; O'Carroll *et al.* 1995). However, this criticism does not concern the present study since the DART was administered at baseline, where all demented subjects were excluded. Moreover, a follow-up study after 6 years in part of our sample ($N = 314$) showed that the DART remains stable in the prodromal phase of dementia, even until a mild dementia syndrome has developed (Schmand *et al.* 1997*b*). Others have reached a similar conclusion (Berger *et al.* 1996). Our finding cannot therefore be an artefact of prodromal decline of the DART-IQ.

We did not find any effect of number of diseases, or of family history of dementia. This may be a consequence of the crude way in which we measured these two variables. Under-reporting of disease may be expected in demented patients, but as stressed above, the baseline dementia cases were excluded from the analyses. Moreover, most of the diseases that were counted are clear entities which can not be missed very easily, not even by people who suffer from mild forgetfulness. Thus, this disease measure probably is a valid one. We used self-report on presence or absence of first-degree relatives suffering from dementia or extreme forgetfulness as a measure of genetic burden. No further distinctions were made in terms of the number of afflicted family members, since the value of such a refinement is questionable. The number of affected family members does not only depend of the genetic risk, but also of the size of the family and of the age that family members have reached.

Our results coincide with two recent publications which also found that cognitive functioning in old age and the development of dementia are more strongly associated with pre-morbid intelligence than with education. The first is a study in which the IQs of veterans, as measured during World War II, were correlated with their mental status 50 years later (Plassman *et al.* 1995). This correlation was slightly higher than the correlation between education and mental status ($r = 0.46$ and $r = 0.41$, respectively). The other is a study of aged catholic nuns, who had to write a structured autobiography before taking their religious vows (Snowdon *et al.* 1996). Verbal ability, especially the 'idea density', as expressed in these autobiographies, was more strongly associated than education with cognitive functioning some 60 years later. Idea density was even related to the number of neurofibrillar tangles in various regions of the brain.

Our results are also in accordance with some other studies showing that a low level of occupation is a risk factor for Alzheimer's disease and vascular dementia (Stern *et al.* 1994; Mortel *et al.* 1995). Stern *et al.* (1995) suggested that education may not be as important as later life experiences with respect to the build-up of brain reserve. They found that the interpersonal skills which are generally required at higher levels of occupation are a particularly important aspect. Their suggestion was corroborated in our study.

We conclude that our findings not only support a prediction derived from the brain reserve theory, but also indicate that low pre-morbid intelligence is an important risk factor for cognitive decline and dementia. Use of NART or similar tests is to be preferred over years of education as estimator of pre-morbid cognitive level in (epidemiological) dementia research.

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