Compensatory mechanisms in higher-educated subjects with Alzheimer’s disease: a study of 20 years of cognitive decline

Hélène Amieva,1 Hind Mokri,1 Mélanie Le Goff,1 Céline Meillon,1 Hélène Jacqmin-Gadda,1 Alexandra Foubert-Samier,1 Jean-Marc Orgogozo,1,2 Yaakov Stern3 and Jean-François Dartigues1,2

1 Inserm, U897, Bordeaux, F-33076 France; Univ Bordeaux Segalen, Bordeaux, F-33076 France
2 University Hospital, Department of Neurology, Bordeaux, F-33076 France
3 Cognitive Neuroscience Division, Department of Neurology, Columbia University, New York, NY 10032 USA

Correspondence to: Hélène Amieva,
INSERM U 897,
Univ Bordeaux Segalen,
146 Rue Leo Saignat - 33076 Bordeaux Cedex,
France
E-mail: helene.amieva@isped.u-bordeaux2.fr

A better knowledge of long-term trajectories of cognitive decline is a central feature of the study of the process leading to Alzheimer’s dementia. Several factors may mitigate such decline, among which is education, a major risk factor for Alzheimer’s disease. The aim of our work was to compare the pattern and duration of clinical trajectories before Alzheimer’s dementia in individuals with low and high education within the PAQUID cohort involving 20 years of follow-up. The sample comprises 442 participants with incident Alzheimer’s disease (27.2% were male)—171 with low education (mean age = 86.2 years; standard deviation = 5.3 years) and 271 with higher education (mean age = 86.5; standard deviation = 5.4)—and 442 control subjects matched according to age, sex and education. At each visit and up to the 20-year follow-up visit, several cognitive and clinical measures were collected and incident cases of Alzheimer’s disease clinically diagnosed. The evolution of clinical measures in pre-demented subjects and matched controls was analysed with a semi-parametric extension of the mixed effects linear model. The results show that the first signs of cognitive decline occurred 15 to 16 years before achieving dementia threshold in higher-educated subjects whereas signs occurred at 7 years before dementia in low-educated subjects. There seemed to be two successive periods of decline in higher-educated subjects lasting 7 years, characterized by decline concomitantly affecting specific and more global cognitive function along with alteration in functional abilities. This study demonstrates how early cognitive symptoms may emerge preceding Alzheimer’s dementia particularly in higher-educated individuals, for whom decline occurred up to 16 years before dementia. It also demonstrates the protective role of education in the clinical trajectory preceding Alzheimer’s dementia. We suggest that the initial decline in cognition occurs at the onset of comparable Alzheimer’s disease pathology in both groups, and is associated with immediate decline to dementia in the lower education group. In contrast, higher education protects against further cognitive decline for ~7 years until pathology becomes more severe.

Keywords: cognitive decline trajectories; education; compensatory mechanisms; Alzheimer’s disease
Introduction

A better knowledge of long-term trajectories of cognitive decline is a central feature of the study of Alzheimer’s disease, with dementia being the extreme end of dissolution of cognition. Nonetheless, cognitive decline is not restricted to those people evolving to dementia and also occurs in the non-demented population, with some cognitive functions more vulnerable to ageing than others. Cognitive decline preceding Alzheimer’s dementia has been the focus of several epidemiological longitudinal studies. These studies consistently showed that slight cognitive decline can begin up to a decade before Alzheimer’s dementia is clinically diagnosable and that memory function is affected along with other non-memory deficits (Jacobs et al., 1995; Elias et al., 2000; Chen et al., 2001; Hall et al., 2001; Amieva et al., 2005). However, several factors may mitigate the rate and pattern of cognitive decline. In the list of the potential influencing factors, education is probably one of the best candidates for at least two basic reasons. First, it is established that highly educated individuals achieve higher levels of cognitive performance in nearly all domains of cognition. It is reasonable to postulate that the duration of cognitive decline in Alzheimer’s disease before reaching the state of dementia depends on the level of performance at which such decline begins. Second, results from a considerable body of research have shown that low education is a risk factor for the onset of dementia and particularly for Alzheimer’s disease (Katzman et al., 1989; Zhang et al., 1990; Dartigues et al., 1991; Stern et al., 1994, 1999; Callahan et al., 1996; Letenneur et al., 1999; Qiu et al., 2001; Anttila et al., 2002; Karp et al., 2004). The cognitive reserve hypothesis is often proposed to explain such results (Stern et al., 1994; Stern, 2002). The so-called ‘cognitive reserve’ would be because of positive effects of early education and intellectually stimulating activities throughout life on cerebral and cognitive development. Such accumulated reserves would result in relative maintenance of cognitive function in the face of brain pathology in later life, including dementing illnesses. The cognitive reserve model would fit not only with the numerous results showing higher risks of Alzheimer’s disease in low-educated people, but also those results showing low correlation between observed pathological markers of Alzheimer’s disease and its clinical expression. In patients with Alzheimer’s disease matched for clinical severity, several studies showed negative correlations between resting regional cerebral blood flow and years of education or level of occupational attainment (Stern et al., 1992, 1995), such that higher cognitive reserve was associated with more depleted flow specifically in parietotemporal areas. A similar result was reported for white matter lesions by Brickman et al. (2011) who showed that for any given level of cognitive function, patients with Alzheimer’s disease with higher cognitive reserve had more white matter hyperintensities. Also, the study by Rentz et al. (2010) exploring the association between PET Pittsburgh compound B amyloid deposition and cognitive performances in 83 elderly subjects with cognitive impairment in various stages of severity found the expected significant association in low-educated subjects whereas no association was evidenced in high-educated subjects. These results showing that cognitive reserve mitigates the impact of Alzheimer’s disease pathology on cognition would be consistent with that reported by Hall et al. (2007). This analysis of the Bronx Ageing study consisted of applying a change point model to a verbal memory test repeatedly measured in 117 subjects who developed incident dementia during their participation in the study. The results showed that for each additional year of formal education, the rapid accelerated memory decline associated with oncoming dementia was delayed by ~2 months. However, after this first accelerated decline, memory decline was more rapid in better educated individuals. Later, a nearly identical effect for participation in cognitively stimulating leisure activities was reported in a subset of the same cohort (Hall et al., 2009). Taken together, these results suggest that for a given level of cognitive status, highly-educated individuals with Alzheimer’s disease would have more brain pathology than individuals with less education.

Therefore, integrating the cognitive reserve model to the study of the trajectories leading individuals to dementia can add to the understating of Alzheimer’s disease progression. If we assume that education is one of the stronger mediators of cognitive reserve, it may be predicted that on average, the duration between the first symptoms of cognitive decline and clinically diagnosable dementia will be longer in more educated individuals than in those with less education. This prediction can be tested by applying mixed effects linear models (Laird & Ware, 1982) to long-term longitudinal data. These models allow us to consider the date of Alzheimer’s dementia diagnosis as time zero and to look backwards in time at the cognitive trajectory that preceded diagnosis. Using these models, we have previously investigated, within the French prospective population-based study on ageing called PAQUID (Dartigues et al., 1992), the emergence of cognitive and non-cognitive symptoms through the pre-dementia phase and shown that cognitive decline exists 12 years before the onset of Alzheimer’s dementia (Amieva et al., 2008). With the still ongoing follow-up of the PAQUID cohort, we took advantage of the 20-year available follow-up of the cohort to directly compare the pattern and duration of trajectories of cognitive decline before dementia in higher and lower educated individuals.

Materials and methods

Study population and protocol

The PAQUID study is a French epidemiological study relying on a population-based sample of 3777 community-dwelling individuals aged 65 or older (Dartigues et al., 1992). Subjects were evaluated at home at the initial visit (V0) and at 1 (V1), 3 (V3), 5 (V5), 8 (V8), 10 (V10), 13 (V13), 15 (V15), 17 (V17) and 20 years (V20). Each visit included a...
neuropsychological evaluation and a criteria checklist for dementia diagnosis completed by a psychologist. Individuals who met these criteria were seen by a neurologist who confirmed or rejected the diagnosis. The diagnosis was reviewed by a panel of specialized neurologists who applied the following criteria for each aetiological category: NINCDS-ADRDA criteria for Alzheimer’s disease (McKhann et al., 1984), NINDS-AIREN criteria for vascular dementia (Roman et al., 1993), standardized clinical criteria for fronto-temporal dementia (Lund and Manchester groups, 1994), Lewy body disease (McKeith et al., 1996), and a history of Parkinson’s disease for Parkinson’s dementia.

At each follow-up visit, several tests and scales of cognitive performances, cognitive complaints, functional abilities, and depressive symptomatology were administered to participants. For the present study, three tests have been analysed as markers of cognitive functioning: the Mini-Mental State Examination (MMSE; Folstein et al., 1975) was included in the analysis as an index of global cognitive performance. The Isaacs Set Test (IST; Isaacs and Kennie, 1973), measuring verbal semantic memory (the task requires generating words belonging to semantic categories in 15 s) was also included as it has been shown to be one of the earliest cognitive markers among the tests available in the PAQUID study. The Digit Symbol Substitution Test (DSST; Wechsler, 1981) was included as a global measure of processing speed. A previous study from the PAQUID cohort showed that both the IST and DSST had good sensitivity to measure cognitive changes in all levels of cognition (low or high) with minimal floor and ceiling effects (Proust-Lima et al., 2007). Instrumental Activities of Daily Living (IADL; Lawton and Brody, 1969) were assessed by the French version of Lawton’s scale. Four of the eight instrumental activities assessed by this scale shown to be associated with cognitive performance and free of confusion by sex were considered (telephone use, transportation, medication, domestic finances) (Barberger-Gateau et al., 1992). A score was calculated by summing the grades of dependency for these activities. A Memory Complaints scale (Dartigues et al., 1997) was administered and depressive symptomatology was assessed using the Centre for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977).

Selection of study sample

This study relies on two matched nested case-control samples selected within the cohort. Two groups of pre-demented Alzheimer’s individuals were constituted according to their level of education. Individuals with no schooling or incomplete primary school were considered as low-educated whereas those who achieved at least the primary certificate (end primary school diploma) or higher level were considered as high-educated. In France, among those born in the 1920’s, the primary school certificate was a critical graduation. Indeed, only pupils who graduated could pursue secondary education. This certificate was obtained after 6 years of schooling devoted to learning reading, writing, basic mathematics skills and a basic knowledge in biology, geography, history and music. Such classification of education level, i.e. participants with no schooling or incomplete primary school versus those who achieved at least the primary certificate or higher level, was previously found to be the best education-related predictor of dementia within the PAQUID study (Letenneur et al., 1999).

Data from the baseline screening visit (V0) were not included because of the ‘first-passing effect’ of neuropsychological tests previously described in the PAQUID cohort (Jacqmin-Gadda et al., 1997) which could bias cognitive trajectories of the subjects. Therefore, for this study, the first follow-up visit (V1) was considered as the baseline visit.

To be eligible, the ‘Alzheimer’s pre-demented’ subjects had to be (i) non-demented at the baseline visit (V1); (ii) diagnosed with Alzheimer’s dementia at any of the follow-up visits over the 20 years (i.e. at V3, V5, V8, V10, V13, V15, V17 or V20); and (iii) diagnosed as non-demented at the last visit preceding the dementia diagnosis. A control group was designed for each of the two pre-demented groups. Subjects included in the normal control groups, had to be (i) seen and free of dementia at the follow-up visit when the matched Alzheimer’s case was diagnosed; (ii) matched to the Alzheimer’s case according to age (± 5 years), sex and education (two classes: no diploma versus primary education level or higher); and (iii) seen and free of dementia at the following visit.

Statistics

The evolution of clinical measures is described throughout 19 years of follow-up. The time of follow-up ranges from T – 19 years to T0, where 0 is the time of diagnosis for incident cases of dementia of Alzheimer’s type (and for a non-demented subject, the follow-up visit when the matched case is diagnosed). Longitudinal analyses of the different measures were done using a semi-parametric extension (Jacqmin-Gadda et al., 2002) of the mixed effects linear model (Laird et al., 1982), a model that has previously shown its usefulness in the description of the evolution of psychometric measures without having restrictive assumptions on the shape of the curve (Amieva et al., 2005). This model has also been adapted for longitudinal ordinal data (Jacqmin-Gadda et al., 2010). In this model, the mean changes of the scores with time are assumed to be smooth curves, approximated by cubic-splines. An auto-regressive error structure is introduced in the model to take into account the correlation between responses of the same subject. Parameters are estimated by penalized likelihood and confidence intervals (CI) for the mean curve are obtained using the Bayesian approach. The smoothing parameter, which controls the balance between the fit of the data and the smoothness of the mean curve, is estimated by cross-validation. The mean scores at baseline for control and pre-demented subjects were compared with a t-test.

Results

Sample description

Four hundred and forty-two subjects of the PAQUID cohort fulfilled the inclusion criteria of the pre-demented Alzheimer’s cases detailed above. Among them, 120 (27.2%) were male. One hundred and seventy-one (38.7%) were considered as low-educated and 271 (61.3%) as high-educated. Mean age at diagnosis of lower-educated and higher-educated pre-demented Alzheimer’s cases was 86.2 years (standard deviation (SD) = 5.3) and 86.5 years (SD = 5.4), respectively. The difference was not statistically significant. As described above, the pre-demented Alzheimer’s cases were matched to 442 elderly control subjects according to age, sex and education. Because of missing data for some of the measures, the sample size slightly varied according to the measures presented.

Clinical trajectory before Alzheimer’s dementia

Figure 1 displays the estimated change in DSST, IST, MMSE, Memory Complaints, CESD and IADL scores over the 19 years of follow-up for the Alzheimer’s pre-demented individuals and normal control subjects. Figure 1A presents the clinical trajectories for higher educated participants and Fig. 1B for those with low education.
Clinical trajectory in higher-educated subjects

The DSST score decreased from 34 to 15 over the 19 years preceding dementia. Baseline score of pre-demented individuals was roughly similar to that of normal control subjects with overlap of 95% CI. The curves become completely distinguishable with no further overlap of 95% CI from T = 17 years. A progressive decline can be observed in the Alzheimer’s pre-demented individuals with a slightly accelerated decline ~5 years before diagnosis.

Figure 1  Estimated change in DSST, IST, MMSE, Memory Complaints, CES-D and IADL scores over the 19 years of follow-up for the pre-demented Alzheimer’s individuals in red and their matched normal controls, in blue. (A) Estimated change in DSST, IST, MMSE, Memory Complaints, CES-D and IADL scores over the 19 years of follow-up for the pre-demented Alzheimer’s individuals with high education (n = 271) and their matched normal controls (n = 271). (B) Estimated change in DSST, IST, MMSE, Memory Complaints, CES-D and IADL scores over the 19 years of follow-up for the pre-demented Alzheimer’s individuals with low education (n = 171) and their matched normal controls (n = 171).
The IST score decreased from 33 to 19 in the Alzheimer’s pre-demented individuals. Baseline score of pre-demented individuals was similar to that of normal controls with full overlap of 95% CI. From ~T – 16 years forward, the scores were statistically different between the two groups with no overlap of 95% CI. A regular decline in the pre-demented individuals may be seen with slight acceleration ~4 years before diagnosis.

The MMSE score decreased from 28 to 20 in the pre-demented individuals. The baseline scores were not different between the two groups and the curves remain indistinguishable until ~T – 7 years. From this time forward, the scores and the slope of decline become different. An accelerated decline appeared close to diagnosis. In normal controls, there was almost no decline over the 19 years of follow-up.

The Memory Complaints score slightly increased over the 19 years preceding dementia. The scores were not different between the two groups until ~T – 7 years. From this time forward, the score increased in the pre-demented group with no further overlap of 95% CI. The CES-D score slightly increased from 6 to 11 over the 19 years preceding dementia.
The scores of the two groups were not different until \( T - 7 \) years. From then, the score slightly increased in the pre-demented group with no further overlap of 95% CI. Finally, for the IADL scale, the baseline score of the predemented remained similar to that of normal controls until \( T - 6 \) years. From then, the score substantially increased in the pre-demented group until diagnosis.

**Clinical trajectory in lower-educated subjects**

The DSST score decreased from 25 to 12 over the 19 years preceding dementia. The baseline score of the pre-demented group was not different to that of their matched normal control subjects, with 95% CI overlapping until \( T - 8 \) years. From this time forward, the score was significantly different to that of normal controls and regularly decreased until dementia diagnosis. The IST score decreased from 27 to 18 over the 19 years preceding dementia. The pattern of evolution was very similar to that observed with the DSST. The baseline score of the pre-demented group was not different to that of normal control subjects, with 95% CI overlapping until \( T - 7 \) years. From this time forward, the score was different to that of control subjects and decreased until dementia diagnosis.

The MMSE score decreased from 26 to 19 in the pre-demented group. As for the other two tests, baseline score of Alzheimer’s pre-demented individuals was not different to that of normal control subjects, with 95% CI overlapping until \( T - 8 \) years. From this time forward, there was no overlap of 95% CI and the score decreased until dementia diagnosis with acceleration in the last 3 years. In normal controls, there was almost no decline over the 19 years of follow-up.

The Memory Complaints score of the pre-demented individuals was similar to that of normal control subjects at baseline and all through the follow-up. There was almost no change over the 19 years. A similar result was observed for the CES-D score with no difference between the two groups and very little change all through the follow-up.

Finally, for the IADL scale, the scores were not different to that of normal control subjects until \( T - 5 \) years. From then, the score of the pre-demented individuals substantially increased until Alzheimer’s dementia diagnosis.

We attempted to quantify the difference of trajectories of cognitive scores by calculating the mean difference in DSST and IST scores per year between the pre-demented individuals and normal control subjects estimated by the semi-parametric mixed effects model, considering separately the first potential period of decline (i.e. between \( T - 17 \) years and \( T - 7 \) years before dementia) and the second period of decline (i.e. between \( T - 7 \) years before dementia and \( T_0 \)). The mean differences in DSST and IST scores for individuals with low education, and those with high education are presented in Table 1. As may be seen, for the higher educated group, during the first period of decline (between \( T - 17 \) years and \( T - 7 \) years before dementia), there is a clear difference

<table>
<thead>
<tr>
<th></th>
<th>Higher educated subjects</th>
<th>Low educated subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Between ( T - 17 ) years and ( T - 7 ) years before dementia</td>
<td>Between ( T - 7 ) years before dementia and ( T_0 )</td>
</tr>
<tr>
<td>DSST</td>
<td>-4.59</td>
<td>-7.63</td>
</tr>
<tr>
<td>IST</td>
<td>-2.15</td>
<td>-4.97</td>
</tr>
</tbody>
</table>

**Figure 2** The cognitive reserve model. (A) The original cognitive reserve model by Stern (2009). (B) The cognitive reserve model amended according to the present findings.
between normal controls and pre-demented subjects (mean difference of 4.59 points per year for DSST and 2.15 points per year for IST) while there is almost no difference between normal control subjects and pre-demented subjects in the low educated group (mean difference of 0.78 points per year for DSST and 1.20 points per year for IST). During the second period of decline (between $T - 7$ years before dementia and $T_0$), there is a clear mean scores difference between pre-demented subjects and normal control subjects for both education groups.

## Discussion

This study of elderly, community-dwelling subjects prospectively followed-up for 20 years provides an illustrative demonstration of the role of education in the clinical trajectory of Alzheimer’s disease, with results closely espousing the theoretical model of cognitive reserve (Stern, 2009; Fig. 3). Higher education has been proposed to contribute to delay onset of clinically diagnosable dementia (Katzman et al., 1989, 2004; Stern et al., 1994, 1999; Callahan et al., 1996; Qiu et al., 2001), modulate the relationship between markers of brain pathology and cognitive status (Knopman et al., 2003; O’Brien et al., 2003; Rentz et al., 2010; Landau et al., 2012), and delay accelerated post-onset decline (Hall et al., 2007) with little effect in severely impaired levels of Alzheimer’s disease pathology (Koeppe et al., 2008).

In agreement with this set of results, the present study provides a global and comprehensive vision of such trajectories of decline over a substantial follow-up period and the opportunity to model several cognitive and non-cognitive measures. From the first signs of cognitive decline, subjects with a higher education decline for $> 15$ years before achieving the threshold of dementia criteria whereas subjects with a low education decline for $\sim 7$ years before dementia onset. The observed differences concern not only duration but also pattern of decline. In higher-educated subjects, a visual examination of the results suggests two successive periods of decline. Such visual interpretation is supported by the estimated mean difference in DSST and IST scores during the first period of decline (i.e. between $T - 7$ years and $T - 7$ years before dementia). Indeed, in the higher-educated group, during this period of decline, there is a clear difference in DSST and IST scores between normal control subjects and pre-demented individuals, whereas in the low-educated group there is almost no difference between control subjects and pre-demented individuals. Therefore, it seems that in higher-educated subjects, decline starts $> 15$ years before dementia with subtle impairment restricted to some cognitive tests, i.e. tests involving psychomotor speed and verbal fluency. Tests scores, although exhibiting a significant decline compared to controls, remain within the « norms » for 7 to 8 years with no impact on global cognition as reflected by the absence of difference in the MMSE, cognitive complaints, or activities of daily living scales compared to their counterparts. Then, there seems to be a second phase of decline occurring $\sim 7$ years before dementia. At this time, we can see the beginning of global cognitive abilities deterioration, along with difficulties dealing with complex activities of daily living, the increase in self-perceived difficulties and depressive symptoms. On the other hand, lower-educated subjects who eventually developed Alzheimer’s dementia seem to present a single period of decline lasting $\sim 7$ years, characterized by decline affecting concomitantly specific and more global cognitive function along with alteration of functional abilities. The other difference in the pattern of the pre-dementia phase between higher and lower-educated subjects is the absence of increase in cognitive complaints and depressive symptoms in the latter.

Such results touch on some fundamental issues that are important for understanding the relationship between cognition and the ageing brain, especially as it undergoes degeneration. Regarding normal aging, the effect of education on age-related cognitive decline has been inconclusive. The more recent studies report a positive effect of education on cognitive level performance as may be expected, but a lack of association with rate of cognitive decline (Schaele, 1996; Christensen et al., 2001; Backman et al., 2003; Carmelli et al., 2004; Hultsch, 2004; Muniz-Terrera et al., 2009; Zahodne et al., 2011). Therefore, the question of interest is how education modifies the cognitive decline occurring with Alzheimer’s disease pathology. The first explanation could be basically because of the difference in pre-morbid level of performance. As higher-educated subjects achieve higher premorbid levels of cognitive performances, the delay in reaching dementia threshold is longer but education per se would have no particular effect on the rate of decline. The second hypothesis is that education acts against the Alzheimer’s disease process through active reserve or compensatory capacity by facilitating recruitment of alternative networks after Alzheimer’s disease lesions until an individual threshold is reached and the amount of brain damage overpowers cognitive reserve mechanisms. Our study showing a first period of decline in higher-educated subjects, where only subtle decline in limited tests can be seen with no impact on global cognitive function, memory complaints or functional abilities, clearly supports the concept of an active mechanism of compensation. That is, we suggest that this early subtle decline indicates the onset of Alzheimer’s disease pathology at a much earlier time before the onset of dementia in the higher versus lower educated individuals who eventually developed Alzheimer’s disease. Moreover, these results suggest that higher-educated subjects compensate for the developing Alzheimer’s disease pathology up to 7 to 8 years after the beginning of cognitive decline until the exhaustion of cognitive reserve capacities, entailing a second period of decline characterized by a more pronounced general cognitive and functional decline accompanied by memory complaints and depressive symptoms. In contrast, we hypothesize that elderly subjects lower cognitive reserve succumb more immediately to Alzheimer’s disease pathology without this initial compensatory period.

Although much is still unknown regarding the biological bases of such compensation, numerous animal studies, in a wide array of species including monkeys, have demonstrated changes in the morphology of the brain, as well as in the general cognitive ability of animals raised in enriched environments. Changes included thickness of cerebral cortices (Markham and Greenough, 2004), amyloid load (Lazarov et al., 2005), cortical capillary formation (Black et al., 1987), neurogenesis (Kempermann et al., 1997), dendritic and synaptic growth (Kozorovitskiy et al., 2005), along with less cognitive decline (Jankowsky et al., 2005). Obviously, no
such effects have been demonstrated in humans, however, a recent study using the voxel-based morphometry technique in a population-based sample of 331 non-demented elderly subjects showed morphological differences according to education (Foubert-Samier et al., 2012). Indeed, higher-education was significantly associated with greater cerebral volume of both grey and white matter. The difference in grey matter volume was the more prominent and bilaterally located in the temporoparietal lobes and in the orbitofrontal lobes. Although such results do not capture the whole complexity of cognitive reserve capacities, they show that morphological differences in critical regions for cognition and Alzheimer’s disease pathology do exist between higher- and lower-educated subjects. Such brain characteristics could help in bearing the burden of accumulating Alzheimer’s disease lesions as well as facilitating recruitment of alternative/compensatory networks (Habeck et al., 2003; Steffener et al., 2011). In addition, higher education and other life exposures associated with higher cognitive reserve are thought to result in enhanced cognitive capacities that increase the efficiency and capacity of cognitive networks as well as allow for the ability to recruit alternative/compensatory strategies as needed.

Our findings must be viewed in light of some limitations. The first is the lack of IQ measures. A possible explanation of the results observed in our study could be a difference in premorbid cognitive level of the participants with low and high education. Therefore, in the absence of such measures, it is not possible to determine whether the longer compensation period observed is really because of higher education or higher premorbid IQ. Such a question should be addressed in longitudinal studies having collected both education status and estimated IQ measures. Another limitation is the visual interpretation of the results. In particular, the semi-parametric mixed effects model with semi-parametric extension model used in this study does not allow us to statistically assess the change in the slope of the curves. Therefore, our conclusions regarding the different phases of decline in higher- and lower-educated subjects are based on the visual examination of the curves and the emergence of the different symptoms. Another obvious limitation is the lack of biomarkers, which would contribute to a better understanding of the observed clinical trajectories. Nonetheless, the strengths of this study include its population-based design, the flexibility of the model, the large number of pre-demented subjects investigated, the particularly long follow-up, as well as the variety of clinical measures included. Taken together, this study evidenced the earliness of cognitive symptoms preceding Alzheimer’s dementia, particularly in higher-educated subjects for whom decline occurred almost 20 years before dementia, and provided an illustrative demonstration of the role of education in the clinical trajectory of patients with Alzheimer’s disease. Such work could be carried out in other forms of dementia to examine whether the concept of ‘cognitive reserve’ is applicable to other dementias, or specific to Alzheimer’s disease.

Funding

The PAQUID study is supported by Novartis, IPSEN and Conseil Régional d’Aquitaine.

References


