

No Protective Effects of Education During Normal Cognitive Aging: Results From the 6-Year Follow-Up of the Maastricht Aging Study

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Recent large-scale longitudinal aging studies question earlier claims that higher education protects against cognitive decline in older age. In the present study, the authors addressed this issue by determining whether educational level had an attenuating effect on the rate of cognitive change assessed with a broad range of neuropsychological tests in a community sample of 872 healthy individuals aged 49 to 81 years at baseline. The participants were followed for 6 years and were tested 3 times (at baseline and at 3 and 6 years after baseline). Results of linear mixed-model analyses showed that education had no significant effect on cognitive change over time. These results are discussed in terms of the age range of the sample, definition and range of education, cognitive measures used, length of the study and number of consecutive assessments, and confounding effect of health. The findings question the extent of the presumed protective effects of higher education on cognitive decline during normal aging.

Keywords: aging, education, cognitive reserve, longitudinal design

Several lines of research suggest that early-life mental abilities (Richards & Deary, 2005), cognitively stimulating activities (Wilson et al., 2005), and socioeconomic status (Everson-Rose, De Leon, Bienias, Wilson, & Evans, 2003) provide estimates of cognitive reserve capacity that have an attenuating effect on age-related cognitive decline. Because the most frequently mentioned and well-established proxy measure of reserve capacity in the aging brain is educational attainment (e.g., Richards & Deary, 2005; Ska & Joannette, 2006; Stern, 2002; Whalley, Deary, Appleton, & Starr, 2004), it is noteworthy that recent articles based on longitudinal data report conflicting results with respect to the relationship between educational level and normal age-associated cognitive decline (Alley, Suthers, & Crimmins, 2007; Anstey, Hofer, & Luszcz, 2003; Christensen et al., 2001; Gerstorf, Herlitz, & Smith, 2006).

Cognitive reserve can be seen as a moderator of the relationship between central nervous system integrity and clinical expression of

disease (Richards & Deary, 2005; Satz, 1993). Stern (2002) distinguished two classes of reserve models. First, he characterized passive models, which focus on brain reserve in terms of physical reserve capacity, which could be represented by, for instance, the neuronal network density. Second, he described active models, which focus on the ability of a person to recruit alternative cognitive capacity or on plasticity of the brain to reorganize cognitive networks when the central nervous system is compromised (Stern, 2002). Both active and passive components may play a role when the central nervous system is affected by aging. An individual's amount of cognitive reserve likely depends on genetics, but it also depends on factors such as a stimulating environment and active usage of the brain. Educational attainment is assumed to be an indirect measure of cognitive reserve and is thought to be influenced by innate (e.g., talent) and environmental (e.g., availability of education) factors.

Stern (2002) postulated that high cognitive reserve may allow individuals to cope more successfully with age-related brain changes on the basis of three studies performed in the mid-1990s (Albert et al., 1995; Butler, Ashford, & Snowdon, 1996; Farmer, Kittner, Rae, Bartko, & Regier, 1995). Anstey and Christensen (2000) reviewed not fewer than 14 longitudinal studies that reported effects of education on cognitive change over time, including those cited by Stern (2002). They found that in some studies, effects of education were observed only in subgroups (Butler et al., 1996; Colsher & Wallace, 1991; Farmer et al., 1995; Schmand, Smit, Geerlings, & Lindeboom, 1997), on only certain outcome measures (Arbuckle, Maag, Pushkar, & Chaikelson, 1998; Christensen et al., 1997; Schaie, 1989), or not at all (Carmelli, Swan, Larue, & Eslinger, 1997; Hultsch, Hertzog, Small, & Dixon, 1999). The researchers who did observe protective effects in subgroups reported effects within a restricted age range (Butler et al., 1996; Schmand et al., 1997), in women (Colsher & Wallace, 1991), or in participants with a certain level of cognitive function-

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ing (Mini-Mental State Examination [MMSE] score > 23; Farmer et al., 1995; Folstein, Folstein, & McHugh, 1975). However, the observed patterns in those studies have not been replicated in other studies. Overall, Anstey and Christensen (2000) concluded that the trends across studies that confirm effects of education on cognitive change over time should be interpreted with caution because of publication bias and methodological limitations. For example, the majority of studies examined cognitive decline by calculating a difference between two test occasions. However, the use of three or more assessments of longitudinal cognitive aging reduces measurement error and is the method of choice, especially when nonlinear effects are expected (see, e.g., Winkens, Schouten, Van Breukelen, & Berger, 2006). The inclusion of nonlinear predictors is important in this context because a significant Education \times Time interaction based on two assessments may lose significance if, after a third assessment, it would appear that there is a (non-significant) delay of cognitive decline in the higher educated group.

Recent articles on the relationship between educational attainment earlier in life and cognitive decline associated with aging that are based on longitudinal data collected over multiple time points (i.e., data from three or more assessments) offer mixed results. For example, a prospective longitudinal study covering 6 years with five assessments, by Alley et al. (2007), showed slower decline on a measure of general mental status for higher educated individuals but not on domain-specific cognitive tests (i.e., immediate and delayed verbal memory and working memory; Alley et al., 2007). In addition, reports based on 7 years and three time points of the Canberra Longitudinal Study (Christensen et al., 2001) and 13 years and five time points of the Berlin Aging Study (Gerstorf et al., 2006) did not find a relationship between education and cognitive decline at older age. Finally, data from the Australian Longitudinal Study of Aging spanning an 8-year period with three assessments showed a small to medium-sized correlation between education and decline in cognitive processing speed but not on verbal abilities and memory (Anstey et al., 2003). The conflicting results so far may be due to methodological differences between the studies, and therefore, we discuss next (a) the age range of the studied groups, (b) the definition and range of education, (c) the cognitive measures used, and (d) the length of the study and number of consecutive assessments.

One might argue that education has protective effects primarily in the young-old (e.g., younger than 70 years) because only in this age range do the brains of higher educated individuals still possess sufficient reserve resources to compensate. However, one can also argue that effects will only appear in the old-old (e.g., older than 70 or 80 years) because after that age, cognition becomes sufficiently impaired to reveal the benefits of reserve capacity. Studies published before 2001 were inconclusive about this issue: Some demonstrated protective effects across the life span starting as early as 18 years old (Farmer et al., 1995; Lyketsos, Chen, & Anthony, 1999), whereas others reported effects from studies including participants aged 65 and older (e.g., Evans et al., 1993) or up to 79 years (Arbuckle et al., 1998). In addition, two studies found differential effects of age such that protective effects were seen in younger (75–84) but not in older (84–102) years (Butler et al., 1996) or effects were found in those aged 65–70 and 76–80 but not in those aged 71–75 and 81–85 years (Schmand et al., 1997). The more recent studies do not help us further with this

issue because they all included participants of 70 years and older (except Anstey et al., 2003, who included a small proportion of individuals younger than 70 years) and showed no protective effects of education (Christensen et al., 2001; Gerstorf et al., 2006) or showed protective effects on only some measures (MMSE score, Alley et al., 2007; processing speed, Anstey et al., 2003).

Variability of the education measure may also influence study outcome. One might argue that failure to find an effect may have been due to restrictions in the range of education if not enough low-education participants were included (to observe decline in the dependent variable) or not enough high-education participants were included (with true cognitive reserve). Unfortunately, most studies do not give information on the number of participants in the higher or lower end of the distribution of education, and the older studies often do not even give the averages and standard deviations. Whether education is measured on a categorical scale or as the number of years of formal schooling does not seem to affect study outcome; neither does treating the education variable as two or three categories versus a continuous variable (Anstey & Christensen, 2000).

Another possibility is that education has protective effects on only some cognitive functions. Anstey and Christensen (2000) concluded that education appears to be more consistently predictive for crystallized abilities, memory, and mental status and less predictive for fluid abilities and speed (Anstey & Christensen, 2000), although recent studies have not confirmed this (Alley et al., 2007; Christensen et al., 2001; Gerstorf et al., 2006) or show the opposite (Anstey et al., 2003). Another possibility is that specific cognitive tests, in combination with a certain age range, may show the most protective effects of education. This is plausible given that several cognitive functions have differential age-related developmental patterns, such as lifelong decline (e.g., speed, episodic memory, and working memory), late-life decline (e.g., vocabulary, semantic knowledge, and short-term memory), and lifelong stability (e.g., implicit and autobiographical memory; Hedden & Gabrieli, 2004). Measures that are sensitive to functions that show late-life decline may only show protective effects in older populations, whereas those tapping functions that show slow gradual decline may be more difficult to pick up in small samples with high age ranges. This pattern, however, does not emerge when looking across all available studies.

Minimizing measurement error and modeling true trajectories of change in cognitive functioning due to aging are facilitated by longer studies with multiple assessments. Three studies included in the review by Anstey and Christensen (2000) that looked at the whole adult life span (≥ 18 years) covered 1, 45, and 28 years with two, two, and five assessments, respectively (Farmer et al., 1995; Lyketsos et al., 1999; Schaie, 1989, respectively). The remaining 11 studies included individuals from an older age (≥ 55 years) and had a mean duration of 4.1 years, with an average of 2.4 assessments and 1.7 years between assessments. Taken together, these studies offer some support for protective effects, but results must be interpreted with caution (Anstey & Christensen, 2000). The more recent studies were based on data collected over approximately 8 years (Anstey et al., 2003; Christensen et al., 2001; Gerstorf et al., 2006, respectively) or 13 years (Gerstorf et al., 2006). On average, these studies had four assessments and 2.25 years between assessments. Although the recent studies, which were primarily based on samples aged 70 years or older, had a

longer duration and multiple assessments, the general picture emerging from these studies indicates that protective effects of higher education during cognitive aging are not straightforward. The importance of the number of assessments becomes apparent when two different reports from the Canberra Longitudinal Study are compared. Effects of education on cognitive aging on some measures were found when two test waves were analyzed (Christensen et al., 1997) but were not found after a reanalysis that included three test waves (Christensen et al., 2001). This case convincingly shows that the number of follow-up measurements may have an effect on study outcome, and one might question the validity of multiple previously published studies based on difference scores from two assessments.

Somewhat related to number of assessments and the duration of the study is the choice of method of analysis. Most studies, especially those with only two assessments, have used traditional regression analysis or repeated measures analysis of variance techniques. However, more sophisticated analytic techniques, such as structural equation modeling (Albert et al., 1995), latent growth curve modeling (Alley et al., 2007; Christensen et al., 2001; Anstey et al., 2003), and multilevel modeling or linear mixed modeling (Gerstorf et al., 2006; Jacqmin-Gadda, Fabrigoule, Comenges, & Dartigues, 1997), are becoming more common. Because selective attrition in longitudinal aging studies is a clearly recognized problem (e.g., Van Beijsterveldt et al., 2002), the longer studies with more consecutive assessments generally apply more sophisticated techniques that do not rely on complete data across all assessments for each subject.

In summary, recent large longitudinal studies, in addition to data from studies included in the review by Anstey and Christensen (2000), do provide some evidence for protective effects of education during cognitive aging, but they also provide just as much data against such protective effects. Hence, we designed the present study to add another piece to the puzzle regarding the question of whether higher education may protect against age-related cognitive decline. To this end, we examined rate of cognitive change on a battery of neuropsychological tests in a community sample of 872 healthy individuals of ages 49 to 81 years at baseline. We specifically chose the neuropsychological tests to cover multiple cognitive domains that are known to decline as a function of age, including mental speed, several aspects of memory, and executive functions. The participants were followed for 6 years and were tested three times (at baseline and at 3 and 6 years after baseline), and linear mixed models were used to analyze the data. One of the differences between the above-mentioned recent studies and the present investigation is that we also included individuals younger than 70 years of age. This is important because educational status may cause differential trajectories of longitudinal cognitive change prior to the age of 70.

Method

Participants

Participants were enrolled in the Maastricht Aging Study (MAAS; Jolles, Houx, Van Boxtel, & Ponds, 1995; Van Boxtel et al., 1998), a longitudinal study regarding the determinants of cognitive aging. In the original sample, participants aged 24 to 81 years were randomly drawn from a patient register of collaborating

general practices in the province of Limburg, the Netherlands (Metsemakers, Hoppener, Knottnerus, Koeken, & Limonard, 1992). Individuals with conditions known to affect cognitive function (such as Alzheimer's disease [AD] and other neurological and psychiatric disorders) or who used psychotropic medication were not included. Participants were stratified according to age, sex, and level of occupational achievement. All participants were Caucasian and native Dutch speakers. The study was approved by the local medical ethics committee, and the participants gave written informed consent.

The studied sample was determined as follows. First, individuals of 49 years and older were selected ($n = 1,024$). Next, cases with missing data on all dependent variables of interest and/or on the independent variable ($n = 4$) were excluded. It appeared that a total of 184 individuals were missing at the first follow-up. Reasons for being missing at the first follow-up were reported earlier (Van Beijsterveldt et al., 2002) and were death (28%) and refusal (72%). Most common reasons for refusal were "being too occupied," "feeling too ill," or "participation is too time consuming" (Van Beijsterveldt et al., 2002). Of these 184 individuals, 148 dropped out of the study and 36 returned for the second follow-up. On average, the group that dropped out was older ($M = 67.7$ vs. 63.3 years), was lower educated ($M = 9.4$ vs. 9.9 years of education), and had a lower MMSE score at baseline ($M = 27.3$ vs. 28.0), but both groups had similar gender distribution. We find it informative that average age, educational level, and MMSE did not significantly differ between the group that was tested at the first follow-up and the group that returned at the second follow-up after being absent at the first follow-up. At the second follow-up, data from an additional 129 participants were missing because of a number of deaths and refusals. Again, this group was older and less educated and had a lower MMSE at baseline and a similar gender distribution compared with the first follow-up group. Although the linear mixed statistical models that we used would not have excluded individuals who provided data only at baseline ($n = 148$) by default, as would be the case in traditional general linear models, they were excluded from the present analyses. The reason for excluding this group was that they would have affected only the cross-sectional estimates of the statistical models (the intercepts) and not our primary variable of interest, which was change over time (the slopes). Finally, data were included from 872 individuals at baseline, 836 at the first follow-up after 3 years, and 743 at the second follow-up after 6 years. The numbers of participants at each test occasion divided by education group and age are given in Table 1. The majority of the participants provided complete data for all three assessments ($n = 707$), whereas others were tested twice: at baseline and at either the first ($n = 129$) or second ($n = 36$) follow-up.

Level of education was determined by categorizing formal schooling according to a scale used in the Netherlands (De Bie, 1987), which is comparable to the International Standard Classification of Education (United Nations Educational Scientific and Cultural Organisation, 1976). The levels of education were defined by highest degree earned as 1 (*primary education*; $n = 149$), 2 (*lower vocational education*; $n = 259$), 3 (*intermediate general secondary education*; $n = 176$), 4 (*intermediate vocational education*; $n = 108$), 5 (*higher general secondary education*; $n = 38$), 6 (*higher vocational education*; $n = 110$), 7 (*higher professional*

education; $n = 6$), and 8 (university; $n = 26$). We dichotomized the total group using a median split procedure and dummy coded it into 0 (Levels 1 and 2 = low level of education) and 1 (Levels 3–8 = high level of education). The reason for dichotomizing level of education was that results are conceptually easy to interpret because the statistical models give an estimate for belonging to the high-educated group compared with the low-educated group. Information of level of education was missing for 10 participants, but we imputed the value of their partner instead. The number of years of education from these individuals (which were all available) indicated that they were correctly placed in the high ($n = 3$) and low ($n = 7$) education groups. The average years of formal schooling for the lower and higher educated groups were 8.3 ($SD = 1.6$) and 11.3 ($SD = 2.9$), respectively.

Demographic characteristics of the sample at baseline are given in Table 2. The higher educated group was significantly younger, $t(870) = 3.5$, $p < .001$; had a higher MMSE score, $t(858) = 3.5$, $p < .001$; and contained fewer women, $\chi^2(1, n = 872) = 25.36$, $p < .001$, than did the lower educated group.

Cognitive Measures

The Verbal Learning Test (Brand & Jolles, 1985; Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2005) is a modification of the word-list learning test by Rey (1958). Fifteen monosyllabic words were presented in five subsequent trials, with free recall immediately after each presentation. The total number of correctly recalled words after five trials was used as a measure of verbal learning. The number of correctly recalled words after a delay of 20 min served as a measure of long-term memory.

The Stroop Color–Word Test (Stroop, 1935; Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2006d) was used as a measure of interference control. Card 1 shows color words in random order (*red*, *blue*, *yellow*, and *green*) printed in black ink.

Table 1
Number of Participants Available at Each Test Occasion

Group	Baseline	Follow-up 1	Follow-up 2
49–59 years			
Low ed.	131	121	121
High ed.	198	193	182
60–69 years			
Low ed.	149	139	136
High ed.	153	150	93
70–81 years			
Low ed.	128	123	93
High ed.	113	110	83
Total low ed.	408	383	342
Total high ed.	464	453	401
Grand total	872	836	743

Note. Ed. = education. In the statistical analyses, age was treated as a continuous variable. For presentation in this table, the groups were divided by age at baseline (into three separate age groups: 49–59, 60–69, and 70–81 years). There were 14 participants older than 80 years at baseline of whom 13 returned at the first follow-up and 8 returned at the second follow-up.

Table 2
Descriptive Statistics of Total Sample Divided by Level of Education

Variable	Total sample	Level of education	
		Low	High
No. of women (%)	423 (49)	235 (58)	188 (41)
<i>M</i> age at baseline (<i>SD</i>)	63.3 (9.1)	64.5 (8.7)	62.2 (9.2)
<i>M</i> level of education (<i>SD</i>)	3.1 (1.8)	1.6 (0.5)	4.4 (1.5)
<i>M</i> years of education (<i>SD</i>)	9.9 (2.8)	8.3 (1.6)	11.3 (2.9)
<i>M</i> MMSE score at baseline (<i>SD</i>)	28.0 (1.7)	27.4 (1.8)	28.5 (1.5)
Total	872	408	464

Note. MMSE = Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975).

Card 2 displays solid color patches in one of these four basic colors. Card 3 contains color words printed in an incongruous ink color (e.g., the word *yellow* printed in red ink). The participants were instructed to read the words (Card 1), name the colors (Card 2), and name the ink color of the printed words (Card 3) as quickly and as accurately as possible. The dependent variable was calculated as the time needed to complete the color–word card minus the time needed to complete the color card and is hereafter referred to as interference control.

The Concept Shifting Test (Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2006a; Vink & Jolles, 1985) is a modification of the Trail Making Test (Reitan, 1958) and was used as a measure of switching between attentional sets (numbers and letters). The test consists of three cards with 16 small circles that are grouped in a larger circle. The small circles contain digits (Card 1), letters (Card 2), or both digits and letters (Card 3). The participants are instructed to cross out the digits as quickly as possible in ascending order (Card 1), letters in alphabetical order (Card 2), and the digits and letters in alternating order (Card 3). The dependent variable was obtained by subtracting the average time to complete Card 1 and Card 2 from the time to complete Card 3. Hereafter, this measure is referred to as set shifting.

We used verbal fluency tests (Lezak, Howieson, & Loring, 2004; Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2006c) to measure semantic fluency and phonemic fluency. For semantic fluency, the participants were required to name as many professions as possible in 60 s. Phonemic fluency involved naming as many four-letter words beginning with the letter S as possible. The total score for each test was the number of correct items produced in 60 s.

The Letter Digit Substitution Test (Jolles et al., 1995; Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2006b) is a modified version of the Digit Symbol Modality Test (Smith, 1982) and Symbol Digit Substitution subtest of the Wechsler Adult Intelligence Test (Wechsler, 1945). Participants were required to replace random letters with the appropriate digits according to a given key. The total number of correct substitutions after 60 s served as a measure of mental speed.

In addition to these cognitive tests, the MMSE (Folstein, Folstein, & McHugh, 1975) was administered as a screening measure of general cognitive status. The above-described tests (or equivalents) have all been reported to show protective effects of education during cognitive aging in previous studies, and the set of tests

is broad enough to cover the cognitive domains that are known to show lifelong decline (e.g., mental speed) and late-life decline (e.g., verbal fluency) during aging (Hedden & Gabrieli, 2004). To minimize training effects, we used different parallel versions of the Verbal Learning Test and Concept Shifting Test at each test wave. There was no counterbalancing across occasions, the different versions of the Verbal Learning Test were considered to be parallel after pilot experiments (Brand & Jolles, 1985), and the versions of the Cognitive Screening Test differed only with respect to the different random location of the test items on the test cards (Vink & Jolles, 1985).

Health Measures

Because cognitive functioning is known to be affected by physical (Carmelli et al., 1997) and mental health (Comijs, Jonker, Beekman, & Deeg, 2001), we included two measures of health as covariates in the statistical analyses. The RAND 36-Item Health Survey (RAND-36; Van der Zee, Sanderman, Heyink, & de Haes, 1996), which is a translation of the 36-Item Short-Form Health Survey (SF-36; Ware & Sherbourne, 1992), was available. We selected the first of eight subscales of the RAND-36, which measures limitations in physical activities because of health problems in 10 items that are scored on a 3-point scale. The subscale has a range between 10 and 30, with higher scores indicating fewer health problems. From the Symptom Checklist-90 (SCL-90, Arrindell & Ettema, 1986), we selected the subscale measuring symptoms of depression in 16 items on a 5-point scale. This subscale has a range between 16 and 80, with higher scores indicating more depressive symptoms. From both the RAND-36 and the SCL-90, the score at the first follow-up was used because it reflects a status of health at approximately the middle of the current analysis period. When data were missing on the RAND-36 and SCL-90, the average value at baseline and the second follow-up was used. For 12 out of 872 participants, there was no score of the RAND-36 available at any assessment, and in those cases, we imputed the average of the rest of the group. The RAND-36 and SCL-90 measures are hereafter referred to as physical health and mental health, respectively.

Analysis

We used linear mixed models to evaluate the effects of level of education on rate of cognitive change over time. We obtained fixed effects (i.e., average effects for the group) and random effects (i.e., individual deviation from the fixed effects) to model cognitive change at both the group level and the individual level. Individual change is assumed to follow the mean path of the group, except for random effects that cause the initial level of functioning to be higher or lower and the rate of change to be faster or slower (Hox, 2002).

The model presented in this article includes fixed terms for the intercept (baseline performance for an individual with value zero on all predictors), time (time in years since baseline), age (at baseline centered around the mean), sex (0 = *male*, 1 = *female*), and education (0 = *low level of education*, 1 = *high level of education*). We included quadratic terms for time and age to capture nonlinear trends. The term of primary interest for the present article is the Time \times Education interaction, which reflects whether the high- or low-education groups differ in the rate of

change in cognitive performance over time. Although there is a long-held view that aging trajectories for men and women are generally similar (Kaufman, Kaufman-Packer, McLean, & Reynolds, 1991), which was recently confirmed (Gerstorff et al., 2006), we did include the Time \times Sex interaction to take possible differences in rate of change between men and women into account. Because rate of cognitive change is likely to be determined by age (with the older participants showing the greatest decline), the Time \times Age interaction was also included, as was the interaction between time and the quadratic term for age. To control for effects of physical and mental health on cognitive functioning, we included the physical health subscale of the RAND-36 and the depression subscale of the SCL-90 as covariates, as well as the interaction terms of these scales with time.

Random effects were calculated using an unstructured covariance matrix. To correct for the use of multiple comparisons, we considered *ps* below .01 statistically significant and *ps* between .01 and .09 a trend. SPSS Base software for Windows (Version 14.0.1) was used for all analyses. One methodological issue in longitudinal studies is the phenomenon of retest effects (i.e., improved performance over time because of repeated test exposure), which can be modeled under specific data conditions by including dummy variables representing the retest effects. When age and retest effects are highly correlated, as was the case in the present dataset, this is not possible (Ferrer, Salthouse, Stewart, & Schwartz, 2004). Therefore, we were not able to differentiate aging effects from retest effects. Because the vast majority of the participants underwent similar experimental conditions (e.g., the same tests were used, number of assessments for the majority of participants was equal), this assumption permits relative comparisons between groups (Thorvaldsson, Hofer, Berg, & Johansson, 2006). By definition, the effect of time (cognitive change over time) is the net effect of retest and aging.

Results

Table 3 shows the correlations between the cognitive measures at baseline, Table 4 shows the results of the linear mixed model analyses, and Figure 1 gives a visual representation of the trajectories of cognitive change as function of age and education. Below, first the fixed effects of the linear mixed models are presented (i.e., average effects for the group), followed by the random effects (i.e., individual deviation from the fixed effects).

Fixed Effects

First, there was a significant improvement in performance over time on tests of verbal learning and long-term memory and a trend for improvements in set shifting. These increased scores over time are most likely due to retest effects.¹ On the contrary, scores of interference control showed a trend for a decline over time as the study progressed. On four measures, the quadratic term for time was significant in such direction that, with increasing time, there was less retest effect (verbal learning,

¹ Higher average scores at the second or third assessment could also be due to selective dropout of poor performers. However, including only complete cases in the analyses yielded comparable retest effects, which indicates that individuals who did not drop out of the study really showed improved performance over time.

Table 3
Pearson Correlation Coefficients Between the Cognitive Measures at Baseline

Measure	1	2	3	4	5	6	7	8
1. Verbal learning	1.00 (871)							
2. Long-term memory	0.82** (870)	1.00 (870)						
3. Interference control	-0.34** (859)	-0.30** (858)	1.00 (860)					
4. Set shifting	-0.07* (852)	-0.08* (851)	0.07* (840)	1.00 (852)				
5. Semantic fluency	0.27** (871)	0.23** (870)	-0.24** (860)	-0.11** (852)	1.00 (872)			
6. Phonemic fluency	0.30** (870)	0.29** (869)	-0.27** (860)	-0.19** (851)	0.31** (871)	1.00 (871)		
7. Mental speed	0.43** (868)	0.39** (867)	-0.46** (857)	-0.21** (849)	0.38** (869)	0.37** (868)	1.00 (869)	
8. MMSE	0.41** (871)	0.37** (870)	-0.34** (860)	-0.16** (852)	0.25** (872)	0.31** (871)	0.42** (869)	1.00 (872)

Note. MMSE = Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975). The number of observations after pairwise deletion are given in parentheses. Higher scores indicate better performance, except for interference control and set shifting.

* $p < .05$. ** $p < .01$.

long-term memory, and set shifting) or a more accelerated decline (semantic fluency). Second, higher age had a significant negative effect on all cognitive measures except for phonemic fluency. The quadratic term for age was significant for verbal learning, long-term memory, and interference control, indicating that the negative cross-sectional effect of age increased in later life. Third, women outperformed men on verbal learning and long-term memory, and men outperformed women on semantic fluency. Finally, the cross-sectional estimate of educational status showed that the higher educated group scored significantly better on all cognitive tests.

The Time \times Age interaction tells us whether cognitive change over time varied with baseline age. The rate of change

appeared to be significantly related to baseline age on each cognitive test except for MMSE score. The direction of this association indicated that there were fewer retest effects for older participants on the measures of verbal learning and long-term memory. For measures of interference control, set shifting, semantic and phonemic fluency, and mental speed, the association was indicative of faster decline in function during the study for individuals with higher age. The interaction between time and the quadratic term for age showed a trend for interference control and mental speed, indicating accelerated decline on these measures during the study in the oldest participants. In addition, the Time \times Sex interaction was significant for interference control and semantic fluency, suggesting that cognitive change over

Table 4
Models of Longitudinal Change in Cognitive Measures

Variable	Verbal learning	Long-term memory	Interference control	Set shifting	Semantic fluency	Phonemic fluency	Mental speed	MMSE
Fixed effects								
Intercept	41.20***	9.10***	52.37***	20.57***	14.40***	4.63***	26.01***	27.65***
Time	2.00***	0.62***	2.47 [†]	-1.73 [†]	0.15	-0.01	-0.19	0.08
Time ²	-0.22***	-0.06***	-0.02	0.26***	-0.06***	-0.03 [†]	-0.03 [†]	0.00
Age	-0.35***	-0.11***	0.89***	0.19***	-0.07***	0.00	-0.31***	-0.06***
Age ²	-0.01**	0.00***	0.04***	0.00	0.00	0.00	0.00	0.00
Sex	4.57***	1.35***	-3.26 [†]	0.76	-1.16***	-0.10	-0.08	0.21 [†]
Physical health	0.02	-0.01	-0.21	-0.18 [†]	0.07 [†]	0.04	0.05	0.01
Mental health	-0.12**	-0.04**	0.13	-0.01	-0.02	0.00	-0.06 [†]	-0.02 [†]
Education	3.67***	0.97***	-9.91***	-4.13***	2.55***	2.45***	4.82***	1.03***
Time \times Age	-0.024***	-0.007***	0.128***	0.032**	-0.013***	-0.014***	-0.024***	-0.003 [†]
Time \times Age ²	0.000	0.000	0.004 [†]	0.001	0.000	0.000	-0.001 [†]	0.000
Time \times Sex	-0.152	-0.011	-0.765**	0.126	0.123***	0.109 [†]	0.042	0.021
Time \times Physical Health	0.002	-0.002	-0.065 [†]	-0.006	-0.001	0.003	0.019**	0.001
Time \times Mental Health	-0.007	-0.006**	0.030	0.031**	-0.002	0.004	-0.003	-0.001
Time \times Education	0.111	0.061 [†]	0.025	0.016	-0.015	0.012	0.083 [†]	-0.027
Random effects								
Variance of intercept	42.91***	3.90***	228.32***	41.15***	15.44***	13.90***	24.35***	1.10***
Variance of slope	0.38**	0.016 [†]	5.62***	1.30***	0.059 [†]	0.043	0.070 [†]	0.020**
Cov of intercept and slope	-0.014	0.11	22.01***	-2.03	-0.64***	0.039	0.42**	-0.027

Note. MMSE = Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975); intercept = baseline performance for an individual with value zero on all predictors; time = years since baseline; age = age at baseline centered around the mean; sex = 0 (*male*) or 1 (*female*); education = 0 (*low level of education*) or 1 (*high level of education*), slope = change over time; cov = covariance. Higher scores indicate better performance, except for interference control and set shifting.

[†] $p < .09$. ** $p < .01$. *** $p < .001$.

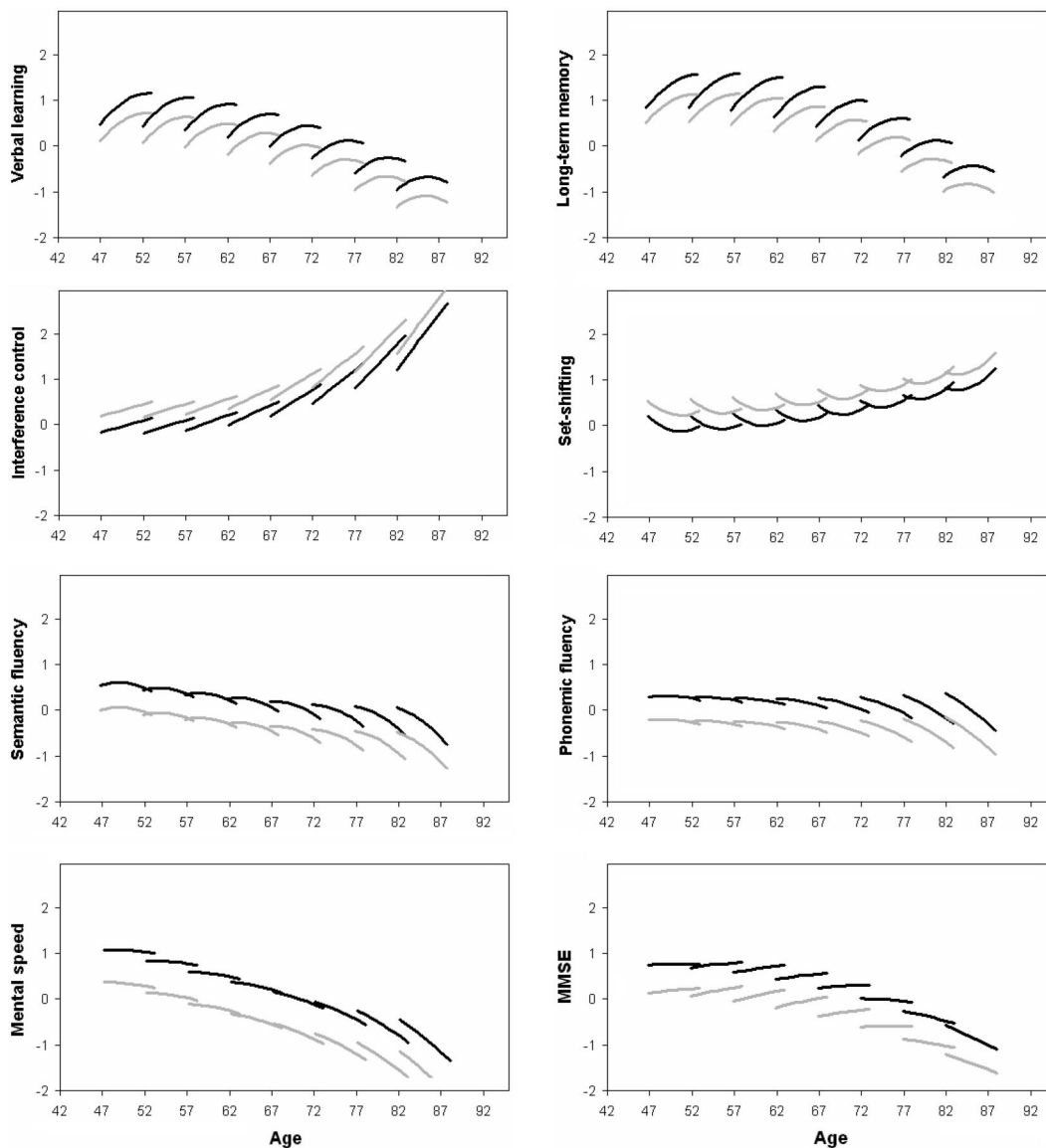


Figure 1. Normalized predicted 6-year paths of change on each cognitive measure for individuals aged 47, 52, 57, 62, 67, 72, 77, and 82 years at baseline divided by level of education. The black lines are estimates for individuals with high education; the gray lines are estimates for individuals with low education. Note that higher scores indicate better performance, except for interference control and set shifting. MMSE = Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975).

time for women was somewhat faster, although they started out on a slightly higher level at the beginning of the study. Finally, the Time \times Health interactions showed a faster decline on mental speed when physical health was poorer and a faster decline on long-term memory and set shifting when mental health was poorer.

The Time \times Education interaction was of primary interest in this study and reflects whether the high- and low-educated groups differed in the rate of change in cognitive performance over time. Although there was a statistical trend toward faster decline in long-term memory ($p = .05$) and mental speed ($p = .085$) in the low-educated group, the Time \times Education interaction was not statistically significant for any of the cognitive tests.²

Random Effects

The variance of the random intercept of each cognitive function was significant, indicating differences between individuals at baseline. The variance of the random slope was significant for verbal learning, interference control, set shifting, and MMSE score and

² To be certain that we did not miss any effects because of the way we treated the education variable, we reanalyzed all data (a) with education as an ordinal scale with eight levels; (b) with three educational groups of approximately same size, with 8.3, 10.0, and 13.2 mean years of education; and (c) with years of education as a continuous variable. The results from those analyses did not differ from the presented results.

showed a trend for long-term memory, semantic fluency, and mental speed, which is indicative of individual differences in change over time for these functions.

The covariance between the random intercept and slope was statistically significant for interference control, semantic fluency, and mental speed, indicating that baseline scores were associated with rate of change over time. The direction of these associations suggests that poor functioning at baseline corresponds with more decline over time in interference control and semantic fluency. Furthermore, high functioning at baseline was associated with more retest effects on the test for mental speed.

Discussion

We examined rate of cognitive change on a broad range of neuropsychological tests in a community sample of 872 healthy individuals of ages 49 to 81 years at baseline. The participants were followed for 6 years and were tested three times (at baseline and at 3 and 6 years after baseline). As expected, level of education had a large cross-sectional effect on performance on all cognitive tests. However, the Time \times Education interaction was not statistically significant for any measure, suggesting that there were no effects of educational attainment on cognitive change over time.

Effects of Aging and Retest Effects

Cross-sectional estimates indicated that age had a significant negative effect on performance on all cognitive tests except for phonemic fluency. This is in line with the well-documented phenomenon that so-called fluid mental abilities, such as learning new information, decline when age increases, whereas crystallized abilities, such as semantic knowledge, are relatively spared (Craik & Bialystok, 2006; Hedden & Gabrieli, 2004; McArdle, Ferrer-Caja, Hamagami, & Woodcock, 2002; Schaie, 2005; Wilson, Beckett, Bennett, Albert, & Evans, 1999). Trajectories of cognitive change over time showed, on average, significant improvement of scores on tests of verbal learning and long-term memory, which are most likely due to retest effects. Retest effects are common when the same subjects are repeatedly tested (Mitrushina & Satz, 1991), and previous studies have also found these effects to be larger for memory-related tests and smaller for tests of speed (Ferrer et al., 2004). It is interesting that our data reveal nonlinear effects of time for verbal learning, long-term memory, set shifting, and semantic fluency, indicating that retest effects leveled off at the third assessment, which took place approximately 6 years after baseline. Another study also found retest effects in individuals older than 65 years to diminish after a second test occasion (Jacqmin-Gadda et al., 1997), although a recent study showed that retest effects continued to accumulate after more than 8 years (Wilson, Li, Bienias, & Bennett, 2006). The apparent retest effects in the present study indicate that our results underestimate age-related cognitive decline, a phenomenon clearly recognized by others (e.g., Ferrer et al., 2004).

Although statistical analysis of retest effects and its relation to age is beyond the scope of the present article, one can see from the graphs in Figure 1 that the upward learning curve seems to flatten out and even bend downward for verbal learning and long-term memory. This downward pattern is especially pronounced at higher ages, indicating that as age advances, the effect of cognitive

aging exceeds retest effects. The literature is ambiguous regarding whether retest effects are related to age (Hickman, Howieson, Dame, Sexton, & Kaye, 2000; Lovden, Ghisletta, & Lindenberger, 2004) or not (Wilson et al., 2006). Future analysis should be aimed at unraveling effects of aging and of repeated testing in further detail and, more important for the current topic, should also investigate whether level of education is related to the extent of retest effects. We believe that potential differences in retest effects between higher and lower educated participants would have augmented the Time \times Education interaction (the indicator of protective effects) and therefore cannot have masked potentially protective effects of education in our sample.

Lack of Protective Effects of Education in Cognitive Change Over Time

The lack of significant effects in the present study are discussed in terms of (a) the age range of the sample, (b) definition and range of education, (c) cognitive measures used, (d) length of the study and number of consecutive assessments, and (e) confounding effect of health.

The recently published study by Alley et al. (2007) included a large number of participants aged 70 years and older and found that higher educated older adults showed faster decline of memory than did lower educated older adults. The authors considered the possibility that the lower educated group may have shown greater cognitive decline in the years before the age of 70 (when the higher educated group remained stable), indicating a delayed onset of decline in the higher educated. A related issue is that education may cause differential cognitive decline in either young-old or old-old. Because our sample included a large number of participants younger and older than 70 years, we were able to test these hypotheses. These hypotheses require that the Time \times Education interaction differs between different age groups, and we tested this by adding the Time \times Education \times Age interaction to our model. The results did not yield significant effects for this three-way interaction on any cognitive measure (not tabulated), and therefore, the delayed-onset hypothesis and the idea of effects restricted to certain age ranges are not supported by our data.³

In previous articles, details of the distribution of levels of education were mostly limited to the mean years of education and standard deviation ($M = 9.3$, $SD = 2.8$, Anstey et al., 2003; $M = 11.1$, $SD = 4.6$, Gerstorf et al., 2006), the mean and the range ($M = 11.1$, range = 0–17, Alley et al., 2007), or the studied educational groups (<10 years, 10–12 years, >12 years, Christensen et al., 2001). In the present study, a comparable variability in level of education and years of formal schooling was obtained ($M = 9.9$, $SD = 2.8$, range = 4–24 years of education), and we can see that some studies did pick up an effect of education (Alley et al., 2007; Anstey et al., 2003), whereas other studies, with perhaps somewhat more higher educated participants, did not (Christensen et al., 2001; Gerstorf et al., 2006). One could argue

³ To be sure not to have overlooked any effect that may have been due to smaller numbers of participants in the highest age range, we repeated all analyses separately in three age groups (49–59, 60–69, and 70–81 years at baseline). The results from those analyses did not differ from the presented results.

that education is more predictive of cognitive aging among samples with lower levels of education (e.g., Anstey & Christensen, 2000), but the results of the present study, which included a high proportion of lower educated participants, do not support this idea. A related issue is that we know that the proportion of very highly educated individuals (e.g., with a college degree or higher) is low in the present study, and it is possible that this relatively small group may not have had enough weight to yield significant effects in the overall analysis. Therefore, we performed an "extreme group" analysis in which we contrasted the 34 individuals with college education or higher (Levels 7 and 8) with the 149 individuals from the lowest educational level (Level 1).⁴ Besides some minor changes in the trends,⁵ the results were not different from those of the main analysis. Nevertheless, because the proportion of highly educated participants is known to be low in the present study but is unknown in any previous study, it is possible that protective effects of education over time are only found when large numbers of highly educated participants are included.

In the present study, MMSE score revealed no differential effects of change over time as a function of education. This result is in contrast with several earlier studies in which cognitive decline was defined as the difference between two assessments (Anstey & Christensen, 2000). However, considering the comparable or better methods used in the present study, we believe that our result may reflect a true null finding of education on decline of MMSE scores. In a recent large multi-assessment cognitive aging study, a telephone version of the MMSE did show slower decline for older individuals with higher education (Alley et al., 2007). However, it is important to note that in the same study, aging trajectories for high- and low-educational groups were the same on a measure of working memory and even in the opposite direction on a memory test for immediate and delayed recall (Alley et al., 2007). In the present study, seven domain-specific cognitive measures were analyzed besides the MMSE, but no significant change in cognitive performance as function of education was found. On two of our measures (long-term memory and mental speed), there was a statistical trend toward protective effects of higher education. Our results confirm neither the protective effects on measures of processing speed reported by Anstey et al. (2003) nor the faster decline for the higher educated group found by Alley et al. (2007) and are in line with the findings from Christensen et al. (2001) and Gerstorf et al. (2006), who found no significant effects.

As mentioned in the introduction, longer study duration and inclusion of three or more assessments allowed us to model true aging trajectories and to minimize measurement error. The present study covered 6 years with three assessments and used linear mixed models to analyze the data. One may argue that analyses including only two assessments or the use of another statistical method may show different results. To investigate this, we performed an additional set of analyses. First, we analyzed data from two assessments using the model displayed in Table 2, omitting time squared because this variable is redundant when there are only two assessments (note that it will ignore the nonlinear effects of time, which we know to be present from our primary analyses). We then selected only the values of either Assessments 1 and 2, or 2 and 3, or 1 and 3 and reran the linear mixed models for each cognitive measure. The results did not differ from the results of our main analyses. Second, we performed repeated measures analyses of covariance with the change scores between two assessments as

the dependent variables; level of education as between-subjects factor; and age, age squared, sex, physical health, and mental health as covariates. We did this separately for change scores between Assessments 1 and 2, 2 and 3, and 1 and 3. We found no effects of education between Assessments 1 and 2 and nonrelevant trends between Assessments 2 and 3 and Assessments 1 and 3.⁶ Thus, these additional analyses did not give different results than the main analyses presented in this article, indicating that several analysis methods produce the same null results.

The current study shows that there was faster decline in mental speed when physical health was poorer and a faster decline in long-term memory and set shifting when mental health was poorer. Therefore, it seems that health factors have an effect on cognitive change over time, which in the present dataset is more evident than effects of education. In this light, it is interesting that from the studies reviewed by Anstey and Christensen (2000), only 4 out of 14 (30%) explicitly mentioned that health factors were included as covariates (Albert et al., 1995; Arbuckle et al., 1998; Carmelli et al., 1997; Christensen et al., 1997), as opposed to three out of four (75%) of the more recent studies (Alley et al., 2007; Anstey et al., 2003; Christensen et al., 2001). A comparison of analyses with and without health variables in the current study showed that including health variables reduced the variance that is explained by education and its interaction with time.⁷ This may explain the limited protective effects of higher education in other studies that included health covariates. It might even imply that if there is a protective effect of education, this effect is less potent in samples containing old-old individuals, in whom health factors start playing a larger role. Thus, it is very conceivable that, although higher educated individuals may initially have a slight benefit of greater cognitive reserve, they are not protected against the effects of cognitive aging once they acquire certain physical or mental diseases.

Potential Confounding Effect of Cases With Prodromal AD

Of relevance for the present study are consistent findings in longitudinal studies that higher educated individuals show faster

⁴ We also contrasted the same 34 individuals with 34 randomly chosen individuals from the lowest educational level. The results from those analyses did not differ from the presented results.

⁵ The trends for protective effects of higher education on long-term memory and processing speed from the main analysis disappeared ($p < .40$ and $p < .80$, respectively), and a new trend emerged for a protective effect on set shifting ($p = .073$).

⁶ There was an effect of education for MMSE between Assessments 2 and 3 ($p = .026$), indicating that the lower educated group showed an improvement from 27.67 to 27.83 (average predicted values, corrected for covariates), with the higher educated showing stability with 28.82 and 28.76, respectively. There were two outcome variables that showed a trend for differences between Assessments 1 and 3 in the direction of protective effects of higher education on cognitive change over time: verbal learning ($p = .065$) and mental speed ($p = .065$).

⁷ When we excluded the health variables from the model, the significance levels of the Time \times Education interaction changed from .050 to .035 for long-term memory and from .085 to .015 for mental speed, indicating that health variables play a significant role in change in cognitive functioning during aging.

decline of cognitive functions once they are diagnosed with AD (Andel, Vigen, Mack, Clark, & Gatz, 2006; Hall et al., 2007; Roe, Xiong, Miller, & Morris, 2007; Scarmeas, Albert, Manly, & Stern, 2006; Stern, Albert, Tang, & Tsai, 1999; Wilson et al., 2004). This faster rate of decline is thought to be caused by a more advanced stage of neuropathology at diagnosis in AD patients with higher education, compared with patients with less education. Thus, in the recent literature, protective effects of education are found more consistently in AD than in normal aging. For example, Andel et al. (2006) showed differential effects of education on cognitive change over time in AD with a study covering half the time span of our study, with fewer participants, and with MMSE as dependent variable. Perhaps once the central nervous system is substantially damaged by a disease such as AD, differential cognitive trajectories of change between higher and lower educated groups are found that are not as apparent in normal cognitive aging.

More important, when older individuals without dementia and AD patients are included in the same sample, effects of educational status may be leveled out because the current literature predicts that higher education causes cognitive decline over time to be slower in normal aging (e.g., Stern, 2002) but faster in AD (e.g., Andel et al., 2006). Although none of the individuals in the present study had a diagnosis of dementia at the time of testing, it is possible that individuals in a prodromal stage of a progressive neurodegenerative disease, such as AD, may have distorted the data. To take this possible confounding factor into account, we labeled individuals who may have been in a prodromal stage of a progressive neurodegenerative disorder. This was done by identifying cases with a relatively rapid decline in MMSE score (i.e., more than one unit decline per year). Omitting these cases ($n = 43$) from the analysis did not change the results, however.

Limitations of the Current Study and Future Directions

Our study has a number of limitations. First, it is possible that with increasing study duration, subtle effects of education on cognitive change over time may start to become apparent. Second, the evident retest effects on the test for verbal learning and long-term memory may suggest that we have measured change in test scores rather than change in the underlying cognitive functions. Third, the number of old-old and higher educated individuals was relatively low.

In the next few years, all 12-year follow-up data of MAAS will become available, and future analyses may shed more light on the issues of sufficient range in age and education. Future studies may reveal that a combination of large numbers of participants with higher education and large numbers of participants in higher age ranges will show protective effects of education on certain outcome measures. For future articles on longitudinal aging data, we advise not only reporting mean, *SD*, and range of age and education but also giving insight into the number of participants at the low and high ends of the distributions. In addition, future longitudinal studies should ideally include a so-called time-lag design (McArdle & Woodcock, 1997) or refreshment samples (Schaie, 2005) to disentangle retest effects from true aging effects. This will give the opportunity not only to analyze true aging effects but also to determine whether retest effects depend on educational level. Finally, although the trajectories of cognitive change were identical for high- and low-educated groups in the present study, the

brains of these participants may show differential structural changes over time that may be masked or compensated for by functional reorganization (Persson et al., 2006). It must be recognized that the precise mechanisms underlying structural or functional brain changes due to aging and the role of education are still unknown. A recent study using functional magnetic resonance imaging showed that brain activation was higher during an episodic memory task in older individuals with higher education, compared with their lower educated counterparts (Springer, McIntosh, Winocur, & Grady, 2005). It is especially interesting that test performance in that study was not affected by education but extent of brain activation was. Longitudinal aging studies including functional imaging techniques that are currently underway will most likely address these issues.

Overall Conclusion

We found no statistically significant protective effects of higher education on cognitive change over time in normal aging. These findings, together with several other recent longitudinal aging studies based on multiple time points, question the extent of the presumed protective effects of higher education on cognitive decline in normal aging.

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