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Running title: Gender and education impact on brain aging

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Abstract:

In cognitive aging research, the study of a general cognitive factor has been shown to have a substantial explanatory power over the study of isolated tests. This work aimed at differentiating the impact of gender and education on global cognitive change with age from their differential impact on four psychometric tests using a new latent process approach, intermediate between a single factor longitudinal model for sum-scores and an item-response theory approach for longitudinal data. The analysis was conducted on a sample of 2,228 subjects from PAQUID, a population-based cohort of elderly subjects followed for 13 years with repeated measures of cognition. Adjusted for vascular factors, the analysis confirmed that women performed better in tests involving verbal component while men performed better in tests involving visuospatial skills. In addition the model suggested that women had a slightly steeper global cognitive decline with oldest age than men even after excluding incident dementia or death. Subjects with higher education exhibited a better mean score for the four tests but this difference tended to attenuate with age for tests involving a speed component.

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Introduction

The effects of gender and education on the change of cognitive performances with age have been an area of intense investigation. Population-based longitudinal studies with repeated measures of psychometric tests are considered to be the best way to examine these relationships (Morris, Evans, Hebert, & Bienias, 1999; Yesavage & Brooks, 1991). These studies allow the analysis of baseline levels and age-related changes of cognitive performance. However, there are limitations to the use of psychometric tests as surrogate markers of cognitive performance. In a battery of psychometric tests, each test only measures one or a few domains of cognition even when it is considered a global test such as the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975). Thus, when analyzing the effects of education or gender on change over time for a single test, it is not possible to determine whether results reflect relationships with global cognition, are specific to the domain(s) covered by the test, or reflect varying test-taking abilities.

Several studies have reported that different cognitive tests were differentially associated with gender and education. Females tend to have better performances than males on tests emphasizing verbal components such as verbal memory or verbal fluency tests, while males perform better on tests requiring visuospatial information processing (Collaer & Hines, 1995; Kramer, Delis, & Daniel, 1988; Reite, Cullum, Stocker, Teal, & Kozora, 1993; Wiederholt et al., 1993). Highly educated subjects perform better on a wide range of tests including the MMSE (Jorm, Scott, Henderson, & Kay, 1988; Launer, Dinkgreve, Jonker, Hooijer, & Lindeboom, 1993; Tombaugh & McIntyre, 1992). This observation was strengthened by community-based studies showing that the effect of education on numerous test scores remained significant after adjusting for confounding factors such as age (Elias, Elias, D'Agostino,

Silbershatz, & Wolf, 1997; Ganguli et al., 1991; Le Carret, Lafont, Mayo, & Fabrigoule, 2003; Fleishman, & Lawrence, 2003). These studies together would suggest that different cognitive performances across education in the elderly are mediated either by differential ability in developing test-taking skills between high and low educated subjects and/or by differential aging processes. In other words, the association between education and global cognitive level cannot be distinguished from the association between education and specific characteristics of the tools used to measure cognition or specific domain(s) covered by the test. An interesting method to disentangle these effects is to study the changes over time of the common cognitive factor underlying several psychometric tests considered simultaneously and measured repeatedly. Indeed such an approach makes it possible to separate effects of covariates on the change over time of the common factor from their specific effects on the change over time of each test.

The common factor or "general factor" theory is based on the empirical finding that psychometric tests used to measure cognition in aging studies are strongly correlated. The common or general factor is defined as the highest-order factor extracted from hierarchical factor models when using a large variety of cognitive tests. On cross-sectional data, it has been shown that most of the age differences in performance on a variety of cognitive variables may be mediated by a common factor (Salthouse, 1996; Salthouse & Czaja, 2000). Several longitudinal studies have confirmed that a large proportion of the variability in the rate of cognitive change was shared by various cognitive measures (Anstey, Luszcz, & Sanchez, 2001; Beckett, Tancredi, & Wilson, 2004; Sliwinski, Hofer, Hall, Buschke, & Lipton, 2003; Wilson et al., 2002). At last, using a principal components analysis on a battery of 8 psychometric tests widely used in aging studies, Fabrigoule et al. (1998) also found that only the first factor was an

independent predictor of dementia or Alzheimer's disease. The first factor explained 45% of the variance of the tests and was interpreted as a general cognitive factor, involving central and controlled processes, as all the tests were highly positively correlated with it.

Thus far, latent variable models have proven to be a powerful framework to investigate cognitive changes with age and the effects of covariates on aging processes. However, these models based on common factor theory still have some limitations. First Sliwinski, Hofer, Hall, Buschke and Lipton (2003) recommended interpreting the single common factor with caution since it may reflect several processes of decline as suggested also by Salthouse and Czaja (2000) through a hierarchical common factor model. These authors also stress that it is important to build a refined and appropriate measurement model of within-person change to avoid misleading interpretations of the common factor. Second models based on common factor theory usually assume linear relationships between the latent common factor and cognitive variables (Sliwinski & Buschke, 1999) or the composite scores (Beckett, Tancredi, & Wilson, 2004; Sliwinski, Hofer, Hall, Buschke, & Lipton, 2003; Wilson et al., 2002). Psychometric tests, however, often have different metrological properties, such as floor and ceiling effects and curvilinearity that composite scores do not necessarily correct (Morris, Evans, Hebert, & Bienias, 1999). Item-Response Theory (IRT) has countered the limitations associated with total sum-scores and particularly curvilinearity by working directly at the item level (Hambleton, Swaminathan, & Rogers, 1991; Mungas, & Reed, 2000). However, IRT requires a large number of parameters which may limit its application to a single scale rather than a battery of tests. Finally in latent structure models, cognition is often modeled as different latent variables at each observation time. We prefer define cognition as an individual characteristic that changes over

time using a single latent process rather than several latent variables. This process is continuous and may be measured at specific times with psychometric tests, though it is always defined.

In this paper, we utilized an approach that is intermediate between factor models of sum-scores and IRT models and assumes that cognition is a latent process (Proust, Jacqmin-Gadda, Taylor, Ganiayre, & Commenges, 2006). The model combines several sum scores as in a factor model of sum-scores but allows each score to have a curvilinear relationship with the latent process as in IRT, the relationship being estimated by nonlinear transformations. Change over time of the latent process that represents the common factor of the tests is described with a linear mixed model. Covariates can be associated both with change over age of the latent process and specifically with each psychometric test. That way, the model allows the examination of the effect of a covariate on specific abilities measured by individual tests and on the latent cognitive process itself. In the present work, we applied this approach to evaluate the impacts of gender and education on cognitive aging and sought to distinguish the effects of these covariates on mean cognitive change over age from their specific effects on psychometric tests. This analysis was conducted on the PAQUID study, a French population-based cohort of elderly subjects followed for 15 years with repeated measures of cognition. As we were specifically interested in differentiating education and gender effects on each test from their common effect on cognitive aging, we studied cognitive aging whatever the cause of the decline. However, as occurrence of dementia and attrition could be associated with effects of gender and education (Amieva et al., 2005; Letenneur et al., 1999), we performed secondary analyses excluding incident dementia and/or death during the course of the study. Finally, a section of this report addresses validation of the model.

Method

Population

PAQUID is a prospective cohort study initiated in 1988 in South Western France (Dordogne and Gironde) that aimed to explore functional and cerebral aging. In brief, 3,777 subjects over 65 years of age were randomly selected from electoral rolls and were eligible to participate if they were living at home at the time of enrollment. The subjects were extensively interviewed at home by trained psychologists at baseline (V0) and were followed up 6 times at year 1, 3, 5, 8, 10, 13 and 15 (respectively V1, V3, V5, V8, V10, V13 and V15) (with the exception for the 1 year where only subjects from Gironde were interviewed). At each visit a neuropsychological evaluation and a screening for dementia were carried out. A more detailed description of PAQUID is given by Letenneur, Commenges, Dartigues and Barberger-Gateau (1994).

Neuropsychological evaluation

A battery of psychometric tests was used to quantitatively assess cognition. Four tests (summarized as MMSE, verbal fluency, visual memory and psychomotor speed) conducted at each visit were used in the analyses:

(i) the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) is a test evaluating various dimensions of cognition (memory, calculation, orientation in space and time, language and word recognition). It is often used as an index of global cognitive performance and ranges from 0 to 30.

(ii) the Isaacs Set Test (Isaacs & Kennie, 1973), shortened to 15 seconds, mainly evaluates semantic verbal fluency and processing speed but also assesses memory. Subjects are required

to give a list of words (with a maximum of 10) belonging to a specific semantic category in 15 seconds. The four semantic categories are: cities, fruits, animals and colors. The score ranges from 0 to 40.

(iii) the recognition form of the Benton Visual Retention Test (Benton, 1965) evaluates immediate visual memory. After the presentation for 10 seconds of a stimulus card displaying geometric figures, subjects are asked to choose the initial figure among four possibilities. Fifteen figures are successively presented. The score ranges from 0 to 15.

(iv) the Digit Symbol Substitution Test (Wechsler, 1981) explores attention and psychomotor speed. Given a code table displaying the correspondence between pairs of digits (from 1 to 9) and symbols, subjects were asked to fill in blank squares with the symbol which is paired to the digit displayed above the square. The subjects are instructed to fill in as many squares as possible in 90 seconds. The score, representing the number of correct symbols, ranged from 0 to 76 in the PAQUID sample.

Statistical model

The response variables are the repeated measures of individual scores from the four psychometric tests. The statistical model assumes that the correlation between the four psychometric tests is induced by a latent cognitive process. The model has the same structure as a Structural Equation Model (SEM) (Muthén, 2002). It is divided into two parts: (i) a longitudinal model describes change over age of the latent cognitive process and evaluates the effects of covariates on the latent cognitive trajectory, and (ii) test-specific measurement models relate each administration of the psychometric tests with the latent cognitive process, taking into account test-specific associations with covariates.

Change of the latent common factor with age

The trajectory of the common factor was modeled using a linear mixed model (Laird & Ware, 1982) which evaluates changes of a repeated outcome over time (here the latent cognitive process) and accounts for correlation between the repeated measures on each subject. The linear mixed model included a random intercept, age, and age squared in accordance with other longitudinal studies (Amieva et al., 2005; Hall, Lipton, Sliwinski, & Stewart, 2000) that showed quadratic cognitive trajectories with age. This quadratic trend allowed for an acceleration of the cognitive decline among the oldest subjects. The intercept and the linear and quadratic coefficients for age were subject-specific random coefficients that accounted for intra-subject correlation. A correlated Gaussian error was also added to the model to account for individual deviations from this quadratic trend, thus relaxing the parametric form of the model.

The test-specific models

The test-specific models defined the flexible links between the psychometric tests and the latent cognitive process. As an alternative to a linear relationship, we assumed that a test-specific nonlinear transformation of each test was a noisy measure of the level of the latent cognitive process adjusted for covariates, age, and test-and-subject specific variability. More specifically, the value of the nonlinear estimated transformation of each test at age t equaled:

- the latent cognitive level at age t,
- plus test-specific intercept and slope, and test-specific covariate effects, which accounted for effects of covariates at age t on the ability to perform each test after adjustment for the latent cognitive level,

- plus a test-and-subject-specific random intercept, which accounted for inter-individual variations of the ability to perform each test after adjustment for the latent cognitive level and the effects of covariates,
- plus an independent test-specific measurement error.

The nonlinear test-specific transformations which relate each psychometric test with the latent cognitive factor aimed at accounting for the global metrological properties of the tests. These transformations are covariate-and-time-invariant parametric functions depending on parameters that are estimated simultaneously with the other parameters in the model. Beta cumulative distribution functions were chosen as flexible transformations. These functions offered a large variety of shapes (concave, convex, sigmoid or simply linear) and thus accounted for the curvilinearity of the tests. Compared to the threshold models in IRT, this model only requires two estimated parameters per sum-score and thus it can handle a battery of psychometric tests without assuming the usual linear transformation. Before applying the Beta transformation, each test was rescaled to [0,1]. The latent cognitive process was also defined in [0,1]. In order to improve clarity, we multiplied the regression parameters by 100 so that the results are given in the [0,100] scale where 0 and 100 respectively correspond to the minimal and maximal latent cognitive level. The fact that the common factor is restrained to [0,1] prevents us from additional constraints as in the usual latent variable framework. The complete methodology and the link with SEM and IRT methodologies were previously described in Proust, Jacqmin-Gadda, Taylor, Ganiayre and Commenges (2006). The model used in the application is also detailed in the Appendix.

Explanatory variables

The time variable was age, more specifically (age-65)/10 so that the slopes measured the change in cognitive level for a decade and the simple effect evaluated the impact of covariates on the mean level at 65 years old. In addition to age and age squared, the model included education and gender, and their interactions with age and age squared. Educational level was included as a binary variable: subjects achieving at least the Certificat d'Etudes Primaires, e.g. the first French diploma after primary school *versus* less educated. This cut-off was previously validated to optimize the association between education with dementia on the PAQUID dataset (Letenneur et al., 1999). The two covariates were included as covariates both in the linear mixed model for the latent cognitive level and in the models for each psychometric test. Thus, we were able to estimate association of covariates with the underlying global cognitive process as well as on each test score adjusting for the latent process. Moreover, by summing these two estimates, we computed the global association between the covariate and each psychometric test without adjustment for the latent cognitive process but accounting for the correlation between psychometric tests. We present 3 kinds of estimates: (i) covariate effects underlying the global cognitive process directly derived from the mixed model, (ii) test-specific contrasts (or deviations) and (iii) test-specific covariate effects which are the sum of the linear mixed regression parameter previously mentioned and the test-specific deviation from this parameter.

For each covariate, we examined its impact both on the mean latent cognitive level and on its change with age (by including interaction terms between covariates and age or age squared). The latent cognitive level model was adjusted for vascular factors because they can confound the association between gender or education and cognitive aging, and they are associated with dropout and mortality. We considered the following potential confounding factors: history of stroke and high blood pressure (HBP) (self-reported usual systolic and

diastolic blood pressures higher than 140 and 90 mm Hg respectively or on HBP treatment) at the first year follow-up V1, and diabetes (self-reported history of diabetes or on treatment for diabetes by medication or diet), hypercholesterolemia (on diet or drug therapy for hypercholesterolemia) and smoking status (current or past smoker *versus* non-smoker) at the initial visit V0. The frequencies of some of these factors were markedly different between men and women. Only the significant factors (simple effects or interactions with age or age squared) were kept in the final model except that non significant effects of gender or education were maintained in the latent process model when the corresponding differential associations in the test-specific models were significant. Finally, the analysis was also adjusted for age at entry in the cohort to control for cohort effects.

Sample selection

Cognitive measurements at the initial visit (V0) were excluded from the analysis because of a first pass effect previously described (Jacqmin-Gadda, Fabrigoule, Commenges, & Dartigues, 1997). Indeed a test-retest improvement was observed between V0 and V1 possibly due to stress during the first evaluation or a learning effect observed after the first evaluation. From the 3,777 subjects in PAQUID, we retained the 3,043 subjects who were followed up after V0. We analyzed cognitive change between V1 and V13. The psychomotor speed test was not completed at V3, and since a sub-sample of PAQUID completed a nutritional questionnaire at V3 that may impact the fluency score for the fruit and animal categories, we excluded the measurements of fluency at V3. We retained in these analyses 2,252 subjects whose data included at least one measure of each neuropsychological test from V1 through V13 to ensure that test-specific parameters were informed by data from all the subjects. Finally, 24 subjects

with missing values for the covariates were excluded, leading to a sample of 2,228 subjects. The median number of measures was 4 for the MMSE (Inter Quartile Range (IQR)=2-5), 4 for visual memory (IQR=2-5), 3 for fluency (IQR=1-4), and 2 for psychomotor speed (IQR=1-4).

In addition to this sample, we selected two sub-samples for complementary analyses: the sample of 1800 subjects who were not diagnosed as demented during the follow-up and 2 years after the end of the follow-up (visit V15), and the sample of 848 subjects who were not diagnosed as demented and were alive at V15.

Results

Description of the sample

Characteristics of the sample are described in Table 1: 56.7% of the 2,228 subjects included in the sample were women and 73% had at least graduated from primary school. The mean age at V1 was 75.2 (SE=6.3) years old. Among the 2,228 subjects, 7 (0.4%) were demented at the beginning of the follow-up (V1) and 364 (16.3%) subjects were diagnosed with dementia in the subsequent visits. At baseline (V0), 7.8% had diabetes, 17.5% had hypercholesterolemia, and 38.1% were either current or former smokers. At V1, 7.1% had history of stroke and 82.9% had high blood pressure. Compared to the initial PAQUID sample of 3,777 subjects, our sample was more educated and included a smaller proportion of women (64.5% had at least graduated from primary school and 58% were women in the initial sample).

At V1, 1,604 subjects living in Gironde completed the MMSE with a median score of 28 (IQR=26-29), 1,603 completed the fluency test (median=28, IQR=24-33), 1,600 completed the visual memory test (median=11, IQR=10-13) and 1,596 completed the psychomotor speed test

(median=28, IQR=20-37) (See details for other visits in the supplemental material on the website of the journal, Table S1).

Multivariate longitudinal model

The final model included gender, education and their interaction with age squared in the latent process model and in the test-specific models. The vascular adjustment was only done for the common factor with antecedent of stroke, diabetes, smoking status, and diabetes and smoking status in interaction with age squared. For all the covariates, interactions with age were not significant and did not confound the other associations. Thus, only the interactions with age squared were kept in the final model so that in the following, "change" refers to interaction with age squared while "intercept" refers to the level at age 65.

Impact of gender on general aging

We first compared estimates of the multivariate model obtained with or without adjustment for vascular factors. Estimates and their 95% confidence intervals were nearly identical in both analyses except for the gender effect. When not adjusted for vascular factors, gender was not associated with latent cognitive intercept (β=0.078, p=0.39) or latent cognitive change (β=0.200, p=0.17). However, when adjusted for vascular factors, particularly smoking status, gender was still not associated with the latent cognitive intercept (β=-0.561, p=0.23) but was associated with latent cognitive change over age (β=0.614, p=0.002). Thus, in high age ranges, women had steeper cognitive decline compared with men (figure 1(a)). In the following, we comment only on estimates from the models adjusted for vascular factors.

After adjusting for the latent cognitive level, the gender effect was significantly different over the four tests both for the intercept ($\chi^2(3,N=2228)=43.85$, $p<0.0001$ for contrasts on

gender) and for the change with age ($\chi^2(3,N=2228)=27.89$, $p<0.0001$ for contrasts on gender×age squared). The overall effect of gender on each specific test (displayed in Table 3) was calculated by adding together the effect of gender on the latent cognitive process and the test-specific contrasts summarized in Table 2. Thus, women performed better than men on verbal fluency at 65 years old (β=-1.477, p=0.041) and their cognitive decline with age was not different with men (β=0.321, p=0.152) when not adjusting for the global cognitive process but accounting for the correlation between the psychometric tests. On the other hand, men performed better than women on visual memory at 65 years old (β=1.688, p=0.014) but had similar decline with age (β=0.394, p=0.095). For psychomotor speed, there was no gender effect at age 65 (β=-0.505, p=0.304), however, women tended to have a sharper decline with age than men (β=0.554, p=0.015). Finally, although women performed slightly better on the MMSE at 65 years old (β=-1.951, p=0.003), they had a much sharper decline (β=1.189, p<0.001) compared with men. Figure 1(b) represents these predicted mean trajectories with age for the four tests. The differences related to gender seemed small relative to the overall acceleration of cognitive decline. To improve understanding of this effect, we determined the number of years a man with particular covariates would need to age that equaled the difference attributable to gender. We did this for ages 80 and 90; results are shown in the top half of Table 4. Effects of gender were heterogeneous across the four tests. For visual memory, gender effect was roughly equivalent to the amount of change expected over 3 years both at age 80 and 90. In contrast, for the MMSE, gender effect was roughly equivalent to the amount of change expected over 1 year at age 80 but over 5 years at age 90.

Is the gender effect explained by attrition or occurrence of dementia?

We conducted a complementary analysis by excluding subjects diagnosed with dementia during the follow-up and 2 years after the end of the follow-up (N=1800, Tables 2 and 3) since it had been shown that there was a higher risk of dementia among older women,. The intensity of association between gender and latent cognitive decline was attenuated by 46%, but the sharper decline in oldest age among women was still statistically significant (p=0.002). The worse cognitive decline among women could also be explained by a higher rate of dropout due to death among men. We thus performed an analysis excluding subjects who died between V1 and V15 (N=848, Tables 2 and 3). The effect of gender on cognitive change with age remained significant, women having a steeper cognitive decline in older ages than men (β=-0.497, p=0.004). The effect of gender on individual tests was consistent across all analyses (see Table 2).

Impact of education on general cognition

As the effects of education did not change when adjusting for vascular factors, we focused on the adjusted model (Table 2). Subjects with higher education had on average a better latent cognitive level at age 65 than subjects with lower education (β=11.282, p<0.001) but had a sharper decline in older ages (β=-0.362, p=0.043) as shown in Figure 2(a).

The association between cognition and education was significantly different over the four psychometric tests both on the intercept of each test (χ^2(3,N=2228)=75.15, p<0.0001 for contrasts on education) and on the mean change with age (χ^2(3,N=2228)=18.77, p=0.0003 for contrasts on ×age squared). This suggested that education had an impact both on latent cognition and on the tools used to measure cognition. From the global measures of association between education and each test computed in Table 3, we found that the mean scores of subjects with

higher education were significantly better for the four tests at 65 years old but the impact of education was stronger for psychomotor speed (β=15.462, $p<0.001$) than for fluency (β=10.277, $p<0.001$), for the MMSE (β=9.838, $p<0.001$) or for visual memory (β=9.553, $p<0.001$). For fluency and psychomotor speed, the mean decline was significantly faster for subjects with high education compared to subjects with low education (β=-0.609, $p=0.010$ and β=-0.746, $p<0.001$ respectively). There was no significant difference in the rate of decline between the levels of education for the MMSE (β=-0.002, $p=0.399$) and visual memory (β=-0.091, $p=0.368$). These results are illustrated on Figure 2(b). As for gender differences, we determined the number of years an individual with higher education would need to age that equaled the difference in cognition attributable to education for ages 80 and 90; results are shown in the bottom half of Table 4. Across all tests and for the latent cognitive level, the education effect was large at any age. The education effect diminished with age more for speeded tests (fluency and psychomotor speed), such that low education effect was roughly equivalent to the amount of change expected over 6 years at age 80 and over 3 years at age 90 for fluency, and over 8 years at age 80 and over 4.5 years at age 90 for psychomotor speed.

Is education effect consistent when studying "normal aging"?

We conducted two complementary analyses to investigate whether association between education and cognitive aging could be explained by steeper declines of educated subjects in the pre-diagnostic phase of dementia as has been previously reported (Amieva et al., 2005). When considering only subjects who had not been diagnosed as demented during follow-up, the effect of education on cognitive decline in high age ranges was attenuated by 25% but remained significant ($p=0.010$). When looking at the test-by-test association, we found again a smaller

impact of education on mean score of visual memory at 65 years old and a stronger impact on psychomotor speed (and intermediate impact on MMSE and fluency). Finally, we determined whether the association between education and cognitive aging was significant when excluding subjects who died or were diagnosed with dementia during follow-up. On this reduced sample, education was no longer associated with latent cognitive change over age (p=0.369) but test-specific differences remained consistent with the other analyses (see Table 2).

Evaluation of the model assumptions

As in IRT or single factor models, our latent process model relies on the assumption that the correlation between the psychometric tests is mediated by a single latent process. We were not able to compare our model with a model including several latent processes. However, we compared the goodness-of-fit (using the Akaike information criterion (AIC)) of the latent process model to the goodness-of-fit of four univariate models estimated separately for each of the four psychometric tests. The combination of the four separate models assumed independence of the four psychometric tests but included fewer constraints on the change over age of each test compared to our latent process model (92 parameters for the four models *versus* 54 for the latent process model). The latent process model had a markedly better AIC (AIC= AIC=139,785) than the four separate models (AIC=142,951).

We also examined the proportion of variance of each test explained by the latent cognitive process (formula given in the Appendix). The proportion of variance explained was age-dependent. It was roughly 40% at 70 years old (41%, 37%, 37% and 45% for MMSE, fluency, visual memory and psychomotor speed respectively) and grew to 85% at 90 years old (86%, 83%, 83% and 87% for MMSE, visual memory and psychomotor speed respectively).

The model assumed that variance of the test-specific error is constant. Thus increasing variance expected with age in each test was captured by the latent process, and more of the variability in each test with age was explained by the latent process. We considered alternative models where the standard errors of the test-specific errors were linear, quadratic or logarithmic functions of age. However, in these more flexible models, the proportion of variance did not change by more than 1% for each test.

Estimated transformations between each test and the latent cognitive process (shown in Figure 3 with Bootstrapped confidence bands) exhibit clear nonlinearity, with exception for the fluency test for which the transformation was nonlinear according to the confidence bands but not far from the linear transformation. More generally, inclusion of nonlinear transformations compared to linear transformations clearly improved the goodness-of-fit of the model with a reduction of roughly 7850 points of Akaike information criterion. Misspecification of the model with linear relationships affected the estimates, especially the effects of gender and education on the latent cognitive trajectory (estimates changed by more than 25%) and their strength of associations.

Finally, goodness-of-fit of the model was evaluated by plotting estimated and observed scores of each test and by plotting a quantile-quantile plot of the marginal standardized residuals of the transformed tests (plots displayed in the website supplemental material Figure S1 and S2). Both showed strong support for model assumptions.

Discussion

Major findings

By applying a nonlinear latent process model (Proust, Jacqmin-Gadda, Taylor, Ganiayre, & Commenges, 2006) to the longitudinal psychometric data of the PAQUID cohort, we estimated the change with age of a comprehensive indicator of cognition and studied the impact of education and gender on change of this latent cognitive process over age. Since this indicator was defined as the common factor of psychometric tests, we could distinguish the impact of education and gender on the trajectory of the common factor with age (that is the latent cognitive process) from their impact on the trajectory of the four test-specific with age. Gender was found to have a differential effect on the four different tests. Adjusted for age, education and vascular factors, men performed better than women on the visual memory test, which is consistent with previous studies reporting that men are often better performers in tests involving visuospatial skills (e.g. Galea & Kimura, 1993; Reite, Cullum, Stocker, Teal, & Kozora, 1993; Voyer, Voyer, & Bryden, 1995 ;Wiederholt et al., 1993). In addition, we confirmed that women performed better than men on the verbal fluency test, which is in agreement with previous studies reporting that women tend to have better performances on tasks involving verbal skills (e.g. Reite, Cullum, Stocker, Teal, & Kozora, 1993; Wiederholt et al., 1993). We found that women had the same latent cognitive level as men at age 65 but displayed a slightly sharper decline in older age. Although moderated by socio-cultural (Weiss et al. 2003) and health and biological (Wahlin et al., 2006) factors, several studies suggest that sex differences would be present all along the lifespan with relative stability over age (Lövdén et al.,2004; de Frias, Nilsson, & Herlitz, 2006). Lövdén et al. (2004) did not find any difference in change over time of semantic and episodic memory related to gender. Gerstorf, Herlitz and Smith (2006) studied change over age of eight measures of cognition, and did not find any association between gender

and rate of cognitive decline with age. However, in both studies, the sample size was relatively small (N=361 and N=368) and the analysis was adjusted neither for confounding factors nor for pattern of attrition, which, as suggested by the latter authors, could mask gender differences. de Frias, Nilsson, & Herlitz (2006) also concluded to the stability of gender differences in cognition over a 10-year period. However, if they had a larger sample (N=625), they used only a linear model, did not separate age and cohort effects and only adjusted for education. In addition, the stability was found with a 1% significance level. At a 5% significance level, differences in sex effect over age in fluency and vocabulary were found. In the present study, the association between gender and cognitive decline was revealed only when the model was adjusted for smoking status. Indeed, 82% of the smokers in our cohort were men and smokers tend to have a greater cognitive decline with age. This result underlines the importance of adjusting for confounding factors that can mask associations between the factor of interest and cognitive change over time. When excluding incident cases of dementia, the significantly steeper decline of women in oldest age was attenuated but remained significant. Thus the excess risk of dementia in older women did not completely explain the association we found between gender and change of cognition over age. When both excluding incident cases of dementia and subjects who died during follow-up, women still had a steeper cognitive decline with age than men.

Using this latent process model, we also distinguished the effect of education on change of the general cognitive factor over age from its specific effect on the four different tests. The effect of education on cognitive performances has been reported in numerous cross-sectional studies where better performances were observed in highly educated subjects for tests assessing memory, executive functioning, or language abilities (Elias, Elias, D'Agostino, Silbershatz, &

Wolf, 1997; Ganguli et al., 1991; Le Carret, Lafont, Mayo, & Fabrigoule, 2003). In the present study, we found that subjects who graduated from primary school had higher mean performances on the general factor but that the difference was slightly reduced in older age. Moreover, the effect of education differed somewhat according to the cognitive test considered: the difference between a subject who graduated from primary school and a subject who did not graduate remained stable across all ages when considering the MMSE or the visual memory test. In contrast the differences by education decreased with age when considering the two tests involving a speed component (fluency and psychomotor speed test). The association between education and cognitive aging was only slightly reduced when analyzing the sample without the subjects in the pre-diagnostic phase of dementia but disappeared after exclusion of subjects who died. This suggests that the steeper cognitive decline with age of subjects with high education could be explained by a more rapid terminal decline before death among participants with a higher education (Wilson, Beckett, Bienias, Evans, & Benett, 2003). However, this result should be interpreted with caution because the size was reduced to a third of the original sample.

Choice of the population

A representative sample of the general population including subjects with normal cognitive aging and pathological aging (i.e. with incident dementia) was chosen because our objective was to evaluate the impact of gender and education on the change of a general cognitive factor over age whatever the cause of the decline. As we age, pathological effects on the brain accumulate, including cerebro-vascular lesions, Alzheimer disease-related lesions, and Lewy bodies. To better understand the progression of neurodegenerative diseases, one may argue that a separate evaluation of the impact of gender and education on normal cognitive aging and on pathological decline toward dementia would be more appropriate. However, several papers (Drachman,

2006; Jicha et al., 2006) suggest it is also relevant to study the cognitive change over time of the whole sample because there are important overlaps in brain lesions between demented and non-demented individuals (Jicha et al., 2006). Moreover, independent analyses of two samples (demented subjects and non demented subjects) at a given time point do not allow for rigorous comparison of normal and pathological aging. Non-demented subjects may include subjects in a prodromal phase of dementia (Jacqmin-Gadda, Fabrigoule, Commenges, & Dartigues, 1997; Sliwinski, Lipton, Buschke, & Stewart, 1996). Similarly, the selection of subjects followed up until a given time point may introduce selection bias. As complementary analyses, we contrasted results obtained from samples excluding subjects diagnosed with dementia and/or excluding subjects who died during follow-up. These demonstrated consistent findings. An appropriate way to distinguish normal aging from pathological aging processes may be to extend the nonlinear latent process approach developed here to jointly model the age at dementia diagnosis and the change over time of the latent process, as has been done for a single test (Jacqmin-Gadda, Commenges, & Dartigues, 2006).

Finally, when focusing on differential effects of covariates on the psychometric tests, there is no rationale to distinguish normal and pathological aging. Differential effects mostly underline differential sum-score functioning (test-taking abilities) rather than covariate effects on normal or pathological aging processes.

Special features of the statistical model

The latent process model we used in this analysis deviates from factor analysis in two ways: it permits nonlinear relationships between the psychometric tests and the latent quantity and assumes unidimensionality since only a single latent process is modeled. Our analyses suggested

that the model was correctly specified and fit the data well. Since many psychometric tests have curvilinear relationships with the overall cognitive ability as MMSE, Benton Visual Retention Test or even Digit Symbol Substitution Test (Proust-Lima, Amieva, Jacqmin-Gadda, & Dartigues, 2006), it is important to account for the nonlinear relationship with a latent quantity. Threshold models used in IRT correctly address this problem at the expense of many item parameters. Our approach offers a good compromise for handling sum-scores.

It is important to note that the common cognitive factor provided by our model was defined according to a limited set of psychometric tests. We selected tests that assess different domains of cognition (memory, calculation, language, verbal fluency, attention, speed of processing) and are frequently used in aging populations. In this way, the common factor described in this work may be interpreted as a general cognitive factor.

In this work, the residual test-specific variance was assumed to be constant over age while the variance of the latent process could vary with age thanks to the age-dependent random-effects and the correlated Gaussian error. When relaxing this assumption by allowing several forms of increasing test-specific variance with age, the proportion of variance explained by the common factor remained more or less the same, suggesting a decrease of test-specific proportion of variance with age. However, this result should be interpreted with caution and should not be used as an argument in favor of the de-differentiation theory (e.g. Ghisletta, & Lindenberger, 2003; Li, et al, 2004). Indeed, to address the specific question of de-differentiation, a thorough work on variance modeling would be required, including the use of flexible variance structures that assume different patterns of variance with age, comparison of several variance structures, and evaluation of the fit of the variance structure in addition to the fit of the mean structure. However, this is not possible with the model in its current form.

Our analyses assumed that missing data were ignorable. In other words, the probability that a measure was missing was assumed to be independent of the missing values after adjustment for the past observed cognitive scores and covariates. We increased the probability of satisfying the ignorability assumption by using information from several psychometric tests and adjusting models for vascular factors that may be associated with dropout. In any case, this assumption is not testable since missing data are not observed. An alternative would be to jointly model the probability of missing data but this would require other stringent and untestable assumptions regarding the association between missing values and the probability of missing data. Using such a joint model in a previous study of change over time of a single psychometric test (MMSE) in the PAQUID study, we found little difference with results obtained under the ignorability assumption (Jacqmin-Gadda, Fabrigoule, Commenges, & Dartigues, 1997).

Conclusion

In conclusion, using a new latent variable approach, we addressed the controversial question of the impact of gender and education on cognitive ageing. In particular, we showed how the associations of these factors with a general factor of cognitive ageing had to be distinguished from their association with each neuropsychological test. For instance, we did not find any difference between men and women on global cognitive level at age 65 but women better performed in tests involving a verbal component while men better performed in tests involving visuospatial skills, and women tended to have a more marked decline in oldest ages. On the other hand, subjects with higher levels of education exhibited a better mean score for the four psychometric tests but this difference tended to decrease with age for tests involving a speed

component. These findings are helpful to explain the conflicting results found in the literature. They also point out the need to use latent process models with appropriate methods to account for curvilinearity when evaluating association between risk factors and cognitive aging.

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Disclosure statement

There are no actual or potential conflicts of interest concerning this study.

Appendix: model specification

We considered *4* neuropsychological tests. For each test *k, k=1,…,4*, each subject *i, i=1,…,N* and each occasion j, *j=1,…,n_{ik}*, the measure of the neuropsychological test y_{ijk} is collected at time t_{ijk}, t_{ijk} being different for each test and each subject. The latent process which represents the common factor of the *4* neuropsychological tests is modeled using the following linear mixed model including a quadratic function of age and a Brownian motion $(w_i(t))_{t\geq 0}$ (type of correlated Gaussian error):

$$\Lambda_i(t) = \left(X_{0i}{}^T\beta_0 + \mu_0 + u_{0i}\right) + \left(X_{1i}{}^T\beta_1 + \mu_1 + u_{1i}\right)\times t + \left(X_{2i}{}^T\beta_2 + \mu_2 + u_{2i}\right)\times t^2 + w_i(t)$$

The vector of random effects $\mathbf{u_i}=(u_{0i},u_{1i},u_{2i})^T$ follows a multivariate normal distribution with mean vector **0** and variance covariance matrix *D*. The Brownian motion $w_i(t)$ has a $\sigma_w^2 t$ variance. The mean trajectory of the common factor is represented by the fixed effects μ_0, μ_1 and μ_2. The vectors of covariates $\mathbf{X_{0i}}$, $\mathbf{X_{1i}}$ and $\mathbf{X_{2i}}$ are respectively associated with the mean latent common factor level through the vector $\boldsymbol{\beta_0}$ or the mean common factor change over age through the vectors $\boldsymbol{\beta_1}$ and $\boldsymbol{\beta_2}$. In the application, $\mathbf{X_{0i}}$ included age at entry, gender, education and vascular factors while $\mathbf{X_{1i}}$ did not include any covariate and $\mathbf{X_{2i}}$ included gender, education and vascular factors.

The observed score value y_{ijk} is linked to the value of the common factor at the time of measurement $\Lambda_i(t_{ijk})$ through a nonlinear link function h_k which is a Beta Cumulative Distribution Function depending on two test-specific parameters $\boldsymbol{\eta_k}=(\eta_{1k},\eta_{2k})$to be estimated. This leads to the following measurement model:

$$h_k\left(y_{ijk};\eta_k\right) = \tilde{Y}_{ijk} = \Lambda_i\left(t_{ijk}\right) + X_i\left(t_{ijk}\right)^T\gamma_k + \alpha_{ik} + \varepsilon_{ijk}$$

where $\boldsymbol{X_i(t_{ijk})}$ is a vector of covariates associated with the neuropsychological tests through the vector of parameters $\boldsymbol{\gamma_k}$. In the application, $\boldsymbol{X_i(t_{ijk})}$ included gender and education as well as the quadratic function of time and the interactions between gender and education and t^2. The vector $\boldsymbol{\gamma_k}$ represents the differential association (or contrast) of $\boldsymbol{X_i(t_{ijk})}$ with the neuropsychological test k after adjusting for the common factor value $\Lambda_i(t_{ijk})$ $\left(\sum_{k=1}^{K}\gamma_{mk}=0,\forall m\right)$. The test-specific random intercept α_{ik} follows a Gaussian distribution with mean *0* and variance $\sigma_{\alpha k}^2$. It takes into account the residual individual variability between tests after adjustment for the latent common factor and the covariates. Finally, ε_{ijk} are independent Gaussian errors with mean *0* and variance $\sigma_{\varepsilon k}^2$.

This latent process model can be summarized in a diagram as latent variable models. Figure 4 displays the diagram for the application explaining the link between the 4 psychometric tests and the latent process as well as the covariates associated with these quantities at a given time t. For clarity, we did not specify in the diagram the longitudinal aspect of the model. Maximum likelihood estimates were obtained using a Marquardt iterative algorithm. The estimation program NLMULTIMIX was written in Fortran90 and is available at http://biostat.isped.u-bordeaux2.fr.

Based on this model, the proportion of variance explained by the latent process can be computed for each test. This proportion of variance for test k (k=1,...,4) is time-dependent and defined as follows: $P_{Vk}(t)=\dfrac{Z(t)DZ(t)'+\sigma_w{}^2 t}{Z(t)DZ(t)'+\sigma_w{}^2 t+\sigma_{\alpha k}^2+\sigma_{\varepsilon k}^2}$, with $Z(t)=(1,t,t^2)$.

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Figure 1. (A) Predicted mean trajectories of the latent cognitive level with age according to gender for non-smoker with low level of education and without stroke or diabetes (with the 95% confidence bands (CB)) (B) predicted mean trajectories of each test (obtained by numerical integration) according to gender for non-smokers included in the study at 65 years old with a low level of education, no antecedent of stroke and no diabetes.

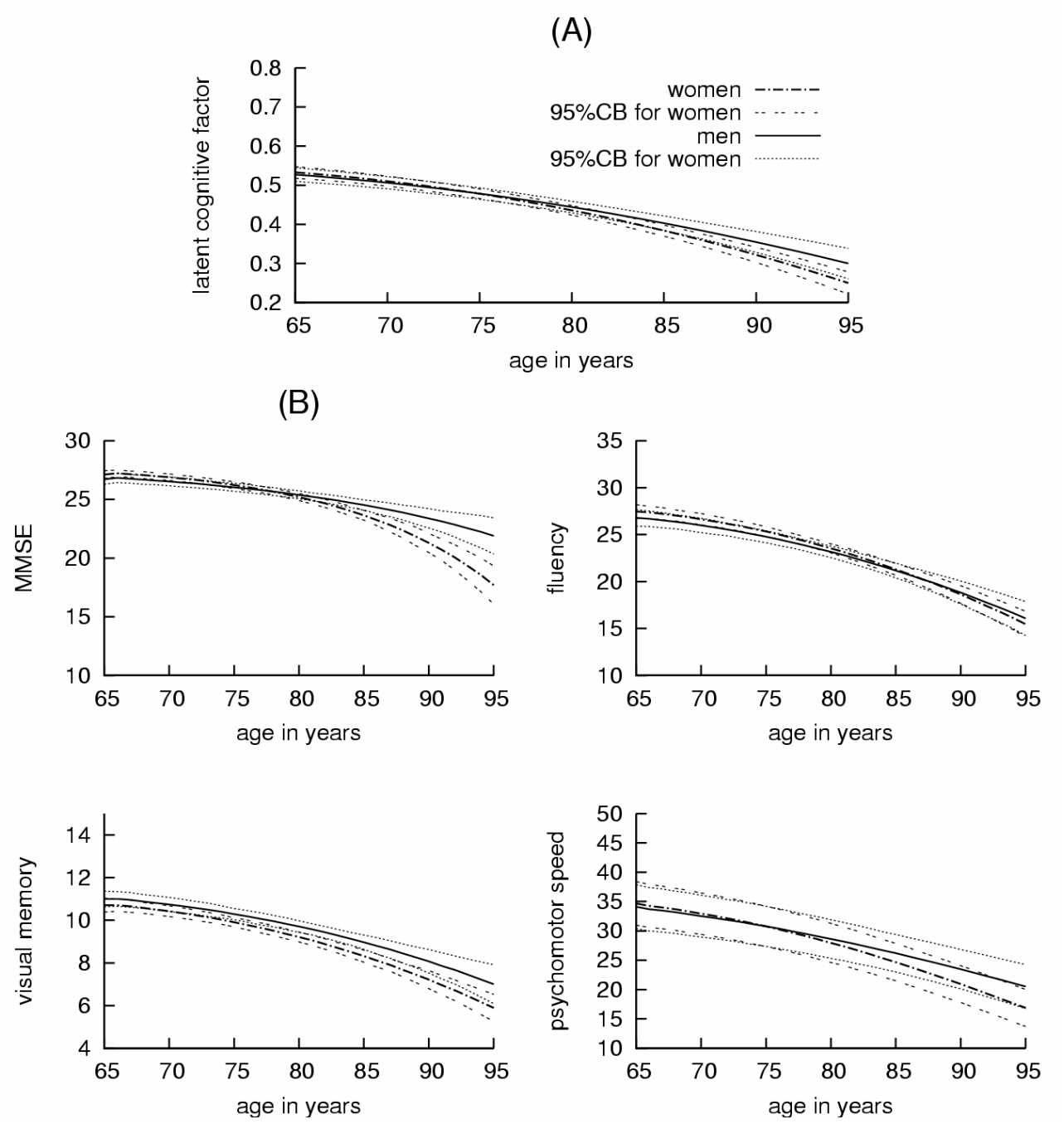


Figure 2. (A) Predicted mean trajectories of the latent cognitive level with age according to the education (EL+ or EL-) for non-smoker women without stroke or diabetes (with the 95% confidence bands (CB)) (B) predicted mean trajectories of each test (obtained by numerical integration) according to the level of education for a non-smoker woman of 65 years old at inclusion with no antecedent of stroke and no diabetes.

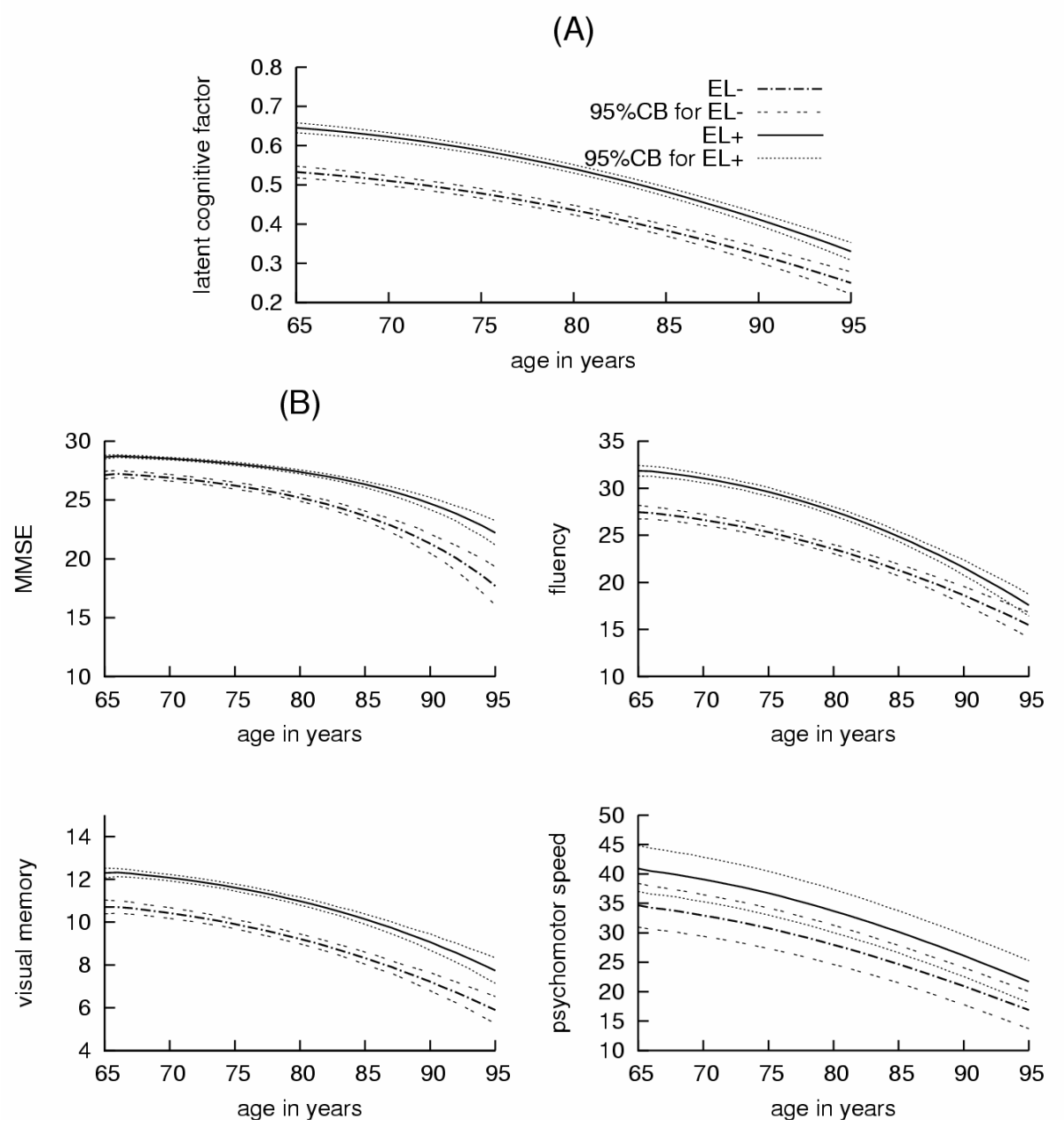


Figure 3. Estimated Beta transformations between each psychometric test and the latent common factor (with 95% confidence bands obtained by a Bootstrap method).

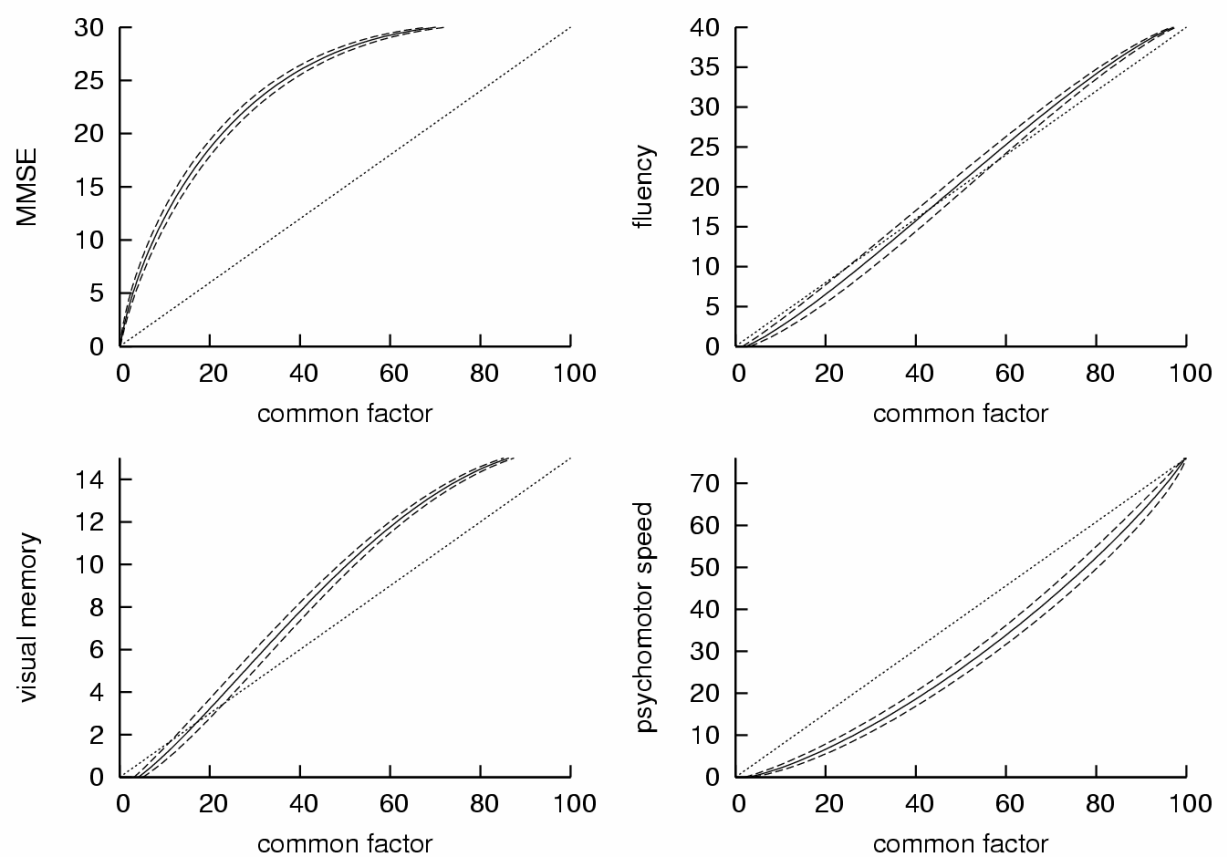


Figure 4. Diagram of the structure of relation between the 4 psychometric tests, the latent process and the covariates in the model at a given age t.

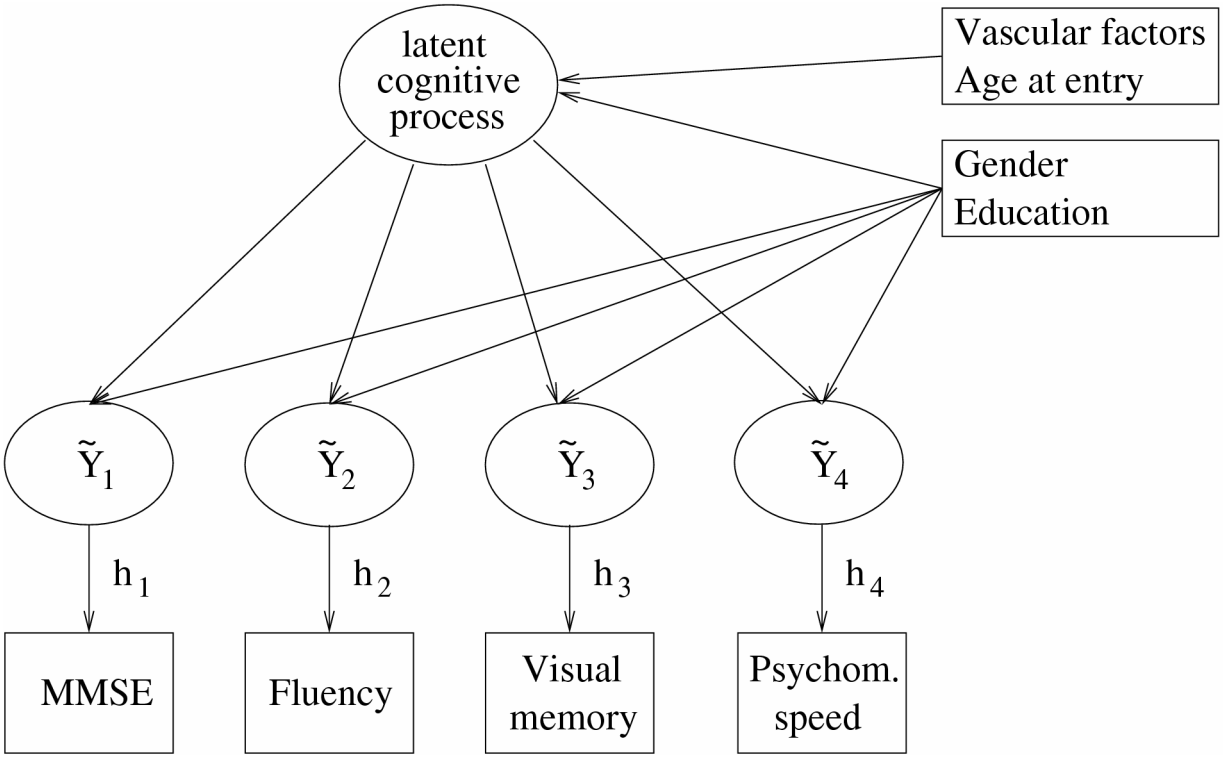


Table 1. Demographic and Health characteristics in the PAQUID cohort and the three sub-samples used in the analysis.

Variable	Main PAQUID sample (N=2228)		Non demented (N=1800)		Non demented and alive (N=848)		PAQUID cohort (N=3777)	
	N	%	N	%	N	%	N	%
Gender								
Male	964	43.3	815	45.3	322	38.0	1577	41.7
Female	1264	56.7	985	54.7	526	62.0	2200	58.3
Education								
No diploma	602	27.0	453	25.2	189	22.3	1342	35.5
CEP	1626	77.0	1347	74.8	659	77.7	2435	64.5
Prevalent dementia at V1	7	0.4	--	--	--	--	111	2.9
Dementia between V3 and V13	364	16.3	--	--	--	--	471	12.5
History of stroke at V1 (N=2967)	50	2.2	38	2.1	4	0.5	82	2.8
High blood pressure at V1(N=2967)	1847	82.9	1493	82.9	657	775	2490	83.9
Diabetes at V0 (N=3770)	174	7.8	138	7.7	36	4.3	316	8.4
Hypercholesterolemia at V0(N=3770)	389	17.5	313	17.4	158	18.6	594	15.7
Current or former smoker at V0 (N=3777)	849	38.1	715	39.7	274	32.3	1383	36.6
Age at entry (mean (SE))	73.7 (6.0)		73.4 (6.0)		70.7 (4.3)		75.5 (6.9)	

Table 2. Estimates, standard error (SE) and Wald test p-values of the regression parameters (multiplied by 100 for clarity) from the linear mixed model for the common factor adjusted for vascular factors and age at entry in the cohort (estimates for vascular factors in the cohort displayed in Table S2 in the website supplemental materials).

Variable	Main PAQUID sample (N=2228)		Non demented (N=1800)		Non demented and alive (N=848)	
	Estimate (SE)	pvalue	Estimate (SE)	pvalue	Estimate (SE)	pvalue
Intercept at 65years	53.259 (0.757)	<0.001	57.882 (0.887)	<0.001	60.003 (1.396)	<0.001
Time	-3.474 (0.627)	<0.001	-4.273 (0.532)	<0.001	-3.829 (0.561)	<0.001
$time^2$ (t^2)	-1.981 (0.260)	<0.001	-0.454 (0.218)	<0.001	-0.467 (0.236)	0.056
gender	-0.561 (0.536)	0.231	-0.406 (0.539)	0.367	-1.057 (0.609)	0.088
gender × t^2	0.614 (0.190)	0.002	0.330 (0.152)	0.002	0.497 (0.166)	0.004
education	11.282 (0.530)	<0.001	10.837 (0.570)	<0.001	9.528 (0.746)	<0.001
education × t^2	-0.362 (0.172)	0.043	-0.271 (0.143)	0.010	0.065 (0.164)	0.369
age at entry	0.149 (0.039)	<0.001	-0.065 (0.034)	0.398	0.009 (0.055)	0.394
Contrasts for gender:	*p<0.0001*		*p<0.0001*		*p<0.0001*	
MMSE	-1.390 (0.354)	<0.001	-0.994 (0.419)	0.024	-1.202 (0.502)	0.023
verbal fluency	-0.916 (0.408)	0.032	-0.847 (0.431)	0.058	-1.237 (0.535)	0.028
visual memory	2.250 (0.375)	<0.001	2.102 (0.389)	0.000	2.170 (0.461)	<0.001
psychomotor speed	0.056 (0.409)	0.395	-0.261 (0.358)	0.306	0.270 (0.428)	0.327
Contrasts for gender×t^2:	*p<0.0001*		*p=0.004*		*p=0.005*	
MMSE	0.575 (0.111)	<0.001	0.434 (0.136)	0.002	0.633 (0.183)	<0.001
verbal fluency	-0.294 (0.124)	0.024	-0.331 (0.137)	0.022	-0.177 (0.181)	0.247

visual memory	-0.220	(0.124)	0.082	-0.179	(0.133)	0.160	-0.242	(0.173)	0.150
psychomotor speed	-0.061	(0.113)	0.346	0.076	(0.110)	0.315	-0.214	(0.136)	0.117
Contrasts for education:	*p<0.0001*			*p<0.0001*			*p=0.001*		
MMSE	-1.445	(0.440)	0.002	0.100	(0.569)	0.393	0.395	(0.691)	0.339
verbal fluency	-1.006	(0.511)	0.058	-0.680	(0.579)	0.200	-0.115	(0.776)	0.395
visual memory	-1.729	(0.472)	<0.001	-2.090	(0.533)	<0.001	-2.194	(0.638)	<0.001
psychomotor speed	4.179	(0.519)	<0.001	2.669	(0.549)	<0.001	1.914	(0.693)	0.009
Contrasts for education×t^2:	*p=0.0003*			*p=0.0002*			*p=0.001*		
MMSE	0.362	(0.122)	0.005	0.501	(0.157)	0.003	0.545	(0.215)	0.016
verbal fluency	-0.247	(0.138)	0.079	-0.262	(0.159)	0.103	-0.240	(0.221)	0.222
visual memory	0.271	(0.139)	0.061	0.201	(0.158)	0.177	0.246	(0.209)	0.199
psychomotor speed	-0.385	(0.131)	0.005	-0.440	(0.133)	0.002	-0.552	(0.167)	0.002

Note. These estimates are adjusted for vascular factors (history of stroke, diabetes, high blood pressure, hypercholesterolemia and smoking status). P-values given in the columns are derived from a Wald test. Time variable represents the number of decades past 65 years old (time=(age-65)/10); $time^2$=time × time. Gender is given as indicator for men (women as reference) and education, is given as the indicator that the subject graduated from primary school (no diploma as reference). Age at entry represents age at entry on the cohort. P-values for the contrasts (in italic) are derived from the Likelihood Ratio Test ($\chi^2(3,N)$).

Table 3. Estimates, standard error (SE) and Wald test p-values of the test-specific global association (multiplied by 100 for clarity) derived from the nonlinear latent process model using MMSE, IST15, BVRT and DSST with adjustment for vascular factors and age at entry in the cohort. Estimates for 3 samples: 2228 subjects; 1800 subjects (only subjects free of dementia until V15) and 848 subjects (only subjects free of dementia and alive at V15).

Test-specific effect		Main PAQUID sample (N=2228)			Non demented (N=1800)			Non demented and alive (N=848)		
		estimate	(SE)	p-value	estimate	(SE)	p-value	estimate	(SE)	p-value
Gender	MMSE	-1.951	(0.630)	0.003	-1.399	(0.692)	0.052	-2.259	(0.805)	0.008
	verbal fluency	-1.477	(0.694)	0.041	-1.252	(0.709)	0.084	-2.294	(0.847)	0.010
	visual memory	1.688	(0.654)	0.014	1.696	(0.658)	0.014	1.112	(0.745)	0.131
	psychomotor speed	-0.505	(0.685)	0.304	-0.666	(0.613)	0.221	-0.787	(0.704)	0.214
Gender×t^2	MMSE	1.189	(0.217)	<0.001	0.764	(0.208)	<0.001	1.130	(0.259)	<0.001
	verbal fluency	0.321	(0.231)	0.152	-0.001	(0.210)	0.399	0.320	(0.253)	0.180
	visual memory	0.394	(0.233)	0.095	0.150	(0.207)	0.306	0.255	(0.246)	0.233
	psychomotor speed	0.554	(0.216)	0.015	0.405	(0.171)	0.024	0.283	(0.182)	0.118
Education	MMSE	9.838	(0.649)	<0.001	10.937	(0.794)	<0.001	9.923	(1.000)	<0.001
	verbal fluency	10.277	(0.757)	<0.001	10.157	(0.835)	<0.001	9.413	(1.105)	<0.001
	visual memory	9.553	(0.700)	<0.001	8.748	(0.756)	<0.001	7.334	(0.920)	<0.001
	psychomotor speed	15.462	(0.765)	<0.001	13.506	(0.799)	<0.001	11.442	(1.060)	<0.001
Education×t^2	MMSE	-0.002	(0.202)	0.399	0.230	(0.215)	0.225	0.610	(0.280)	0.037
	verbal fluency	-0.609	(0.224)	0.010	-0.533	(0.220)	0.021	-0.175	(0.284)	0.330
	visual memory	-0.091	(0.228)	0.368	-0.070	(0.219)	0.379	0.311	(0.276)	0.212

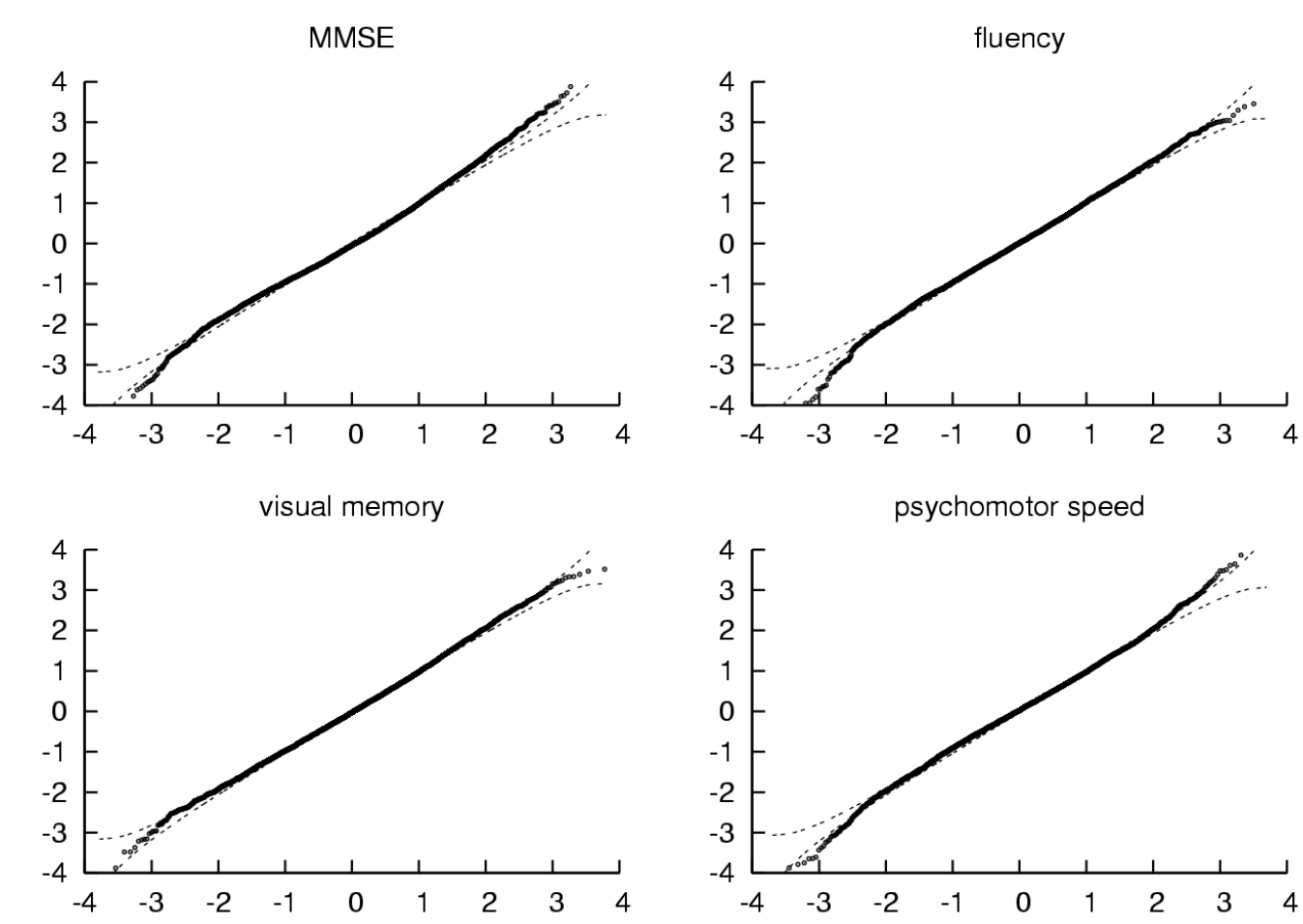
psychomotor speed	-0.746	(0.212)	<0.001	-0.711	(0.179)	<0.001	-0.487	(0.197)	0.019

Note. These estimates are adjusted for vascular factor (history of stroke, diabetes, high blood pressure, hypercholesterolemia and smoking status) and age at entry in the cohort. P-values given in the columns are derived from a Wald test. $t^2 = ((age-65)/10)^2$ with age in years. Gender is given as indicator for men (women as reference) and education is given as the indicator that the subject graduated from primary school (no diploma as reference).

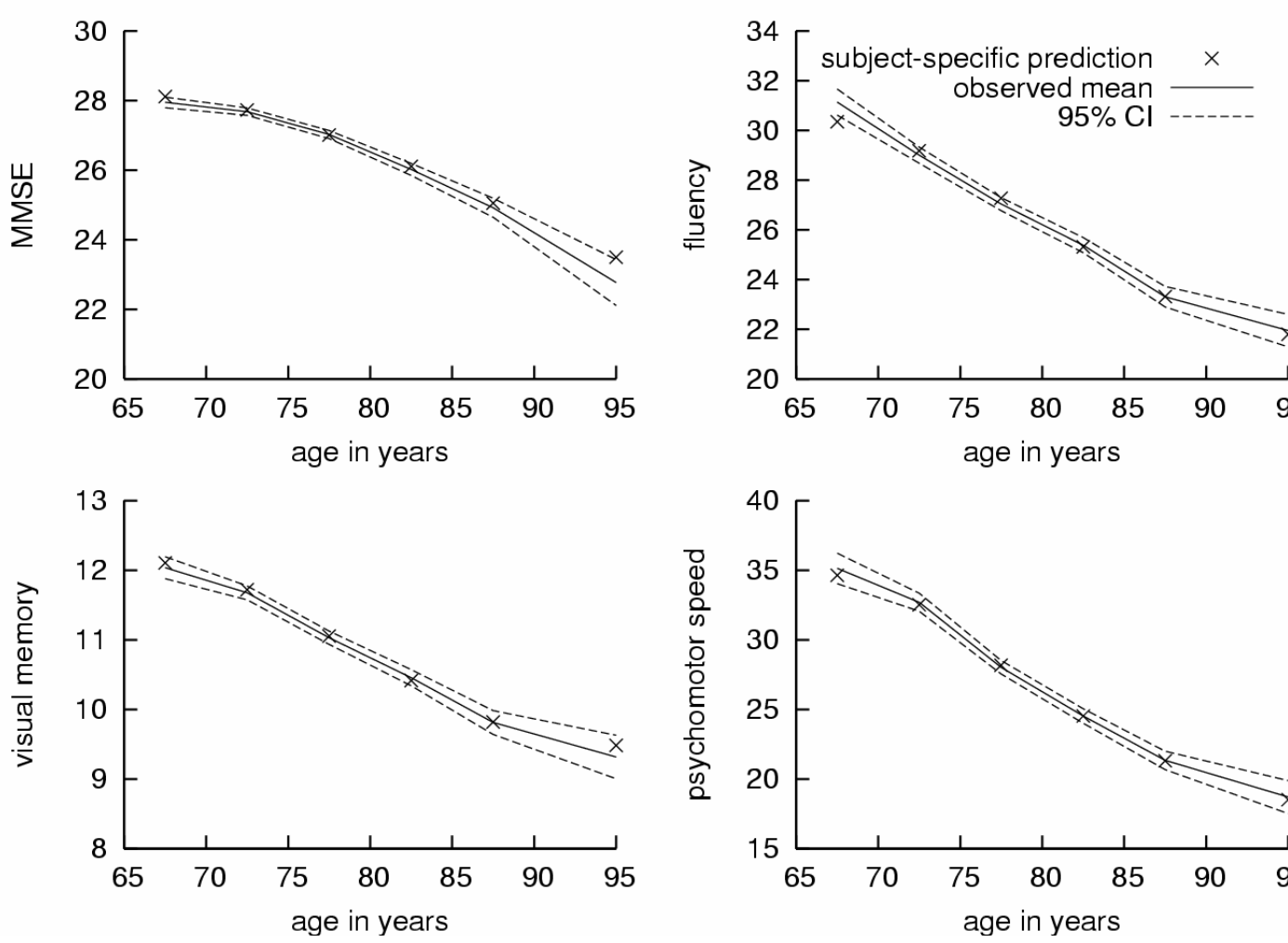
Table 4. Number of years 80 or 90 year old men (or subjects with high education) would have to age to reach the cognitive level of 80 or 90 year old women (or subjects with low education) with the same covariates. These values are averaged over the covariate distribution.

		Common factor	MMSE	verbal fluency	visual memory	psychomotor speed
Gender at:	80 years old	0.87	1.00	-0.76	2.83	0.65
	90 years old	2.39	5.18	0.36	3.34	1.74
Education at:	80 years old	7.19	7.89	5.89	7.33	7.79
	90 years old	4.65	6.05	3.16	5.31	4.56

Supplemental material Figure S1. Quantile-quantile plot of the predicted standardized residuals for the four transformed psychometric tests.



Supplemental material Figure S2. Mean change over age of the observed scores (plain line) with confidence bands (dashed lines) for each of the four tests compared to the mean trajectories of the subject-specific predictions (x) derived from the nonlinear latent process model using MMSE and tests of verbal fluency, visual memory and psychomotor speed with adjustment for vascular factors and age at entry in the cohort.



Supplemental material Table S1. Psychometric tests distribution (mean, standard-error (SE), minimum (min), first quartile (Q1), median, third quartile (Q3) and maximum (max)) over the follow-up.

Test	Visit	N	mean (SE)	min	Q1	median	Q3	max
MMSE	1	1604	27.12 (2.46)	12	26	28	29	30
	3	1815	27.00 (2.81)	0	26	28	29	30
	5	1707	26.97 (3.08)	0	26	28	29	30
	8	1336	26.53 (3.91)	0	25	28	29	30
	10	1242	25.64 (4.93)	0	24	27	29	30
	13	924	25.95 (5.55)	0	23	27	28	30
verbal	1	1603	28.50 (6.01)	9	24	28	33	40
fluency	5	1596	26.68 (6.17)	1	23	27	31	40
	8	1292	25.94 (6.32)	4	22	26	30	40
	10	1157	25.24 (6.68)	5	21	25	30	40
	13	858	25.14 (6.66)	1	21	26	30	40
visual	1	1600	10.99 (2.50)	0	10	11	13	15
memory	3	1690	11.09 (2.43)	0	10	11	13	15
	5	1571	11.14 (2.43)	1	10	11	13	15
	8	1208	10.76 (2.49)	1	9	11	13	15
	10	1086	10.68 (2.61)	2	9	11	13	15
	13	795	10.60 (2.57)	1	9	11	13	15
psychomotor	1	1596	28.68 (12.04)	0	20	28	37	76
speed	5	1373	28.95 (11.21)	0	21	28	36	68
	8	1082	26.78 (11.04)	1	18	25	34	68
	10	933	26.03 (10.43)	0	18	25	32	68

13	688	26.06 (10.13)	2	19	25	33	59

Supplemental material Table S2. Estimates, standard error (SE) and Wald test p-values of the regression parameters (multiplied by 100 for clarity) in the linear mixed model for the common factor using MMSE, fluency, visual memory and psychomotor speed with adjustment for vascular factors and age at entry in the cohort. Estimates for 3 samples: 2228 subjects; 1800 subjects (only subjects free of dementia until V15) and 848 subjects (only subjects free of dementia and alive at V15). Compared to the table given in the manuscript, this table includes the estimates for the vascular factors.

Variable	Main PAQUID sample (N=2228)		Non demented (N=1800)		Non demented and alive (N=848)	
	Estimate (SE)	pvalue	Estimate (SE)	pvalue	Estimate (SE)	pvalue
Intercept at 65years	53.259 (0.757)	<0.001	57.882 (0.887)	<0.001	60.003 (1.396)	<0.001
Time	-3.474 (0.627)	<0.001	-4.273 (0.532)	<0.001	-3.829 (0.561)	<0.001
time^2 (t^2)	-1.981 (0.260)	<0.001	-0.454 (0.218)	<0.001	-0.467 (0.236)	0.056
gender	-0.561 (0.536)	0.231	-0.406 (0.539)	0.367	-1.057 (0.609)	0.088
gender × t^2	0.614 (0.190)	0.002	0.330 (0.152)	0.002	0.497 (0.166)	0.004
education	11.282 (0.530)	<0.001	10.837 (0.570)	<0.001	9.528 (0.746)	<0.001
education × t^2	-0.362 (0.172)	0.043	-0.271 (0.143)	0.010	0.065 (0.164)	0.369
Age at entry	0.149 (0.039)	<0.001	-0.065 (0.034)	0.398	0.009 (0.055)	0.394
stroke history	-4.174 (1.252)	0.002	-3.150 (1.230)	0.003	-3.573 (3.147)	0.209
Diabetes	-2.015 (0.789)	0.015	-1.745 (0.797)	0.087	-1.467 (1.187)	0.186
diabetes× t^2	-0.720 (0.304)	0.024	-0.443 (0.249)	<0.001	-0.429 (0.297)	0.140
smoking status	1.355 (0.543)	0.018	1.110 (0.540)	0.215	2.056 (0.626)	0.002
smoking status× t^2	-0.716 (0.196)	<0.001	-0.422 (0.156)	<0.001	-0.363 (0.167)	0.037

Note. P-values given in the columns are derived from a Wald test. Time variable is age in years minus 65 by 10 years (time=(age-65)/10); t^2=time × time. Gender is given as indicator for men (women in reference) and education, the indicator that the subject who graduated from primary school (subjects who did not graduate in reference). Age at entry represents age at entry in the cohort. Vascular factors are the binary indicators of history of stroke, diabetes, hypercholesterolemia and smoking status).