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Cognitive process in preclinical phase of dementia

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Summary

Several recent prospective studies have demonstrated the existence of a preclinical stage of dementia, identifiable by neuropsychological assessment showing impairments with a great variety of cognitive tests. However, test scores are often colinear, largely because common cognitive components are involved in different tests; in spite of an apparent heterogeneity, it is still possible that a common cognitive component may be responsible for the deterioration shown in different tests in the preclinical phase. We studied the cognitive performances of 1159 elderly residents in the PAQUID (Personnes Agées quid*) cohort, at a fixed lag time of 2 years before the clinical diagnosis of dementia. Seven neuropsychological tests were administered (Mini-Mental Status Examination, Benton Visual Retention Test, Wechsler Paired-Associates Test, Isaacs Set Test, Zazzo's Cancellation Task, Digit Symbol Substitution Test and Wechsler Similarities Test). Among the initially non-demented 1159 subjects, 25 developed a dementia 2 years later, of whom 16 were classified as cases of Alzheimer's disease. In order to dissect the multicolinearity of the tests we used a multivariate approach with principal component analysis (PCA). The patients' loading on each of the first four PCA factors were subsequently correlated with the risk of dementia and Alzheimer's disease 2 years later. The logistic regression with backward stepwise selected only the first factor as an independent predictor of dementia or Alzheimer's disease. Analysis shows that there are good reasons to suspect that the first PCA factor represents a general factor corresponding to aspects of control in the tasks used. Our results therefore seem to show that preclinical deficits in dementia and Alzheimer's disease reflect the deterioration of a general cognitive factor, which may be interpreted as the disturbance of central, control processes.*

Keywords: cognition; dementia; preclinical signs; controlled processes

Abbreviations: BVRT = Benton Visual Retention Test; CI = confidence interval; DSST = Digit Symbol Substitution Test; IST = Isaacs Set Test; MMSE = Mini Mental State Examination; PCA = principal components analysis; WPAT= Wechsler Paired Associates Test; WST = Wechsler Similarities Test; ZCT = Zazzo's Cancellation Test

Introduction

Several recent studies have shown that impaired cognitive performances were predictors of dementia 1–13 years before the clinical diagnosis of the disease (Masur *et al.*, 1994; Jacobs *et al.*, 1995; Linn *et al.*, 1995). However, the neuropsychological measures found to be predictors of dementia or Alzheimer's disease were very different across studies: episodic memory and verbal fluency tests in the Bronx cohort (Masur *et al.*, 1994), abstract reasoning and confrontation naming ability in the North Manhattan Aging Project (Jacobs *et al.*, 1995), and verbal memory tests and immediate auditory attention on the Framingham cohort (Linn *et al.*, 1995). In previous papers on the PAQUID (Personnes Agées *quid*) cohort in the Bordeaux area (France), we found that global cognitive performance, short-term visual memory, verbal fluency performance (Dartigues *et al.*, 1997) and abstract reasoning (Fabrigoule *et al.*, 1996) were independent predictors of dementia or Alzheimer's disease, 1–3 years before the clinical onset. Therefore, a more or less long preclinical stage of dementia was demonstrated, corresponding certainly to a stage of the disease at which the pathology begins to have some repercussion on cognitive functioning, but when cognitive impairments are still not

sufficient for the dementia criteria to be reached. This has been identified by neuropsychological assessment but it has been associated with a great variety of impairment of cognitive functions. Three methodological reasons could explain this apparent heterogeneity: (i) the lag time between the evaluation of cognitive performances and the clinical diagnosis of dementia varies considerably between studies, and between subjects in a given study; (ii) the specific properties of various tests commonly used are not fully understood (Writing Committee, Lancet conference 1996), especially because each test involves several cognitive functions; (iii) test scores are often strongly colinear, essentially because common cognitive components are involved in different tests (e.g. attention). From a methodological point of view this colinearity could interfere with the results of the statistical analysis by over adjustment; from a theoretical point of view it is possible that a common cognitive component may be responsible for the deterioration shown by a number of different tests administered during the preclinical phase.

In order to understand the cognitive processes impaired during this preclinical stage better, we studied the cognitive performances of elderly community residents in the PAQUID cohort, with a fixed lag time of two years before the clinical diagnosis of dementia. We attempted to dissect the multicolinearity of the tests by analysing correlation and by using a multivariate approach with principal component analysis (PCA).

Method

The PAQUID cohort is a prospective study of a representative random sample of >4000 elderly people (all >65 years old) living in Gironde and Dordogne, two administrative areas around Bordeaux in south-western France. After a baseline screening, the subjects were followed-up at 1, 3 and 5 years. The general methodology of the study has been described elsewhere (Dartigues *et al.*, 1992). Subjects who agreed to participate in the study gave their informed consent; the study was approved by the Ethics Committee of the Centre Hôpitalier Universitaire de Bordeaux. They answered an interviewer-administered questionnaire, which included social and medical information, and underwent a neuropsychological assessment at each visit.

The neuropsychological battery administered by a psychologist comprised seven tests.

(i) The Mini-Mental Status Examination (MMSE) (Folstein *et al.*, 1975) can be considered as the sum of subscores that measure different cognitive components: orientation to time, orientation to place, registration of three words, attention and calculation, recall of three words, and language and visual construction. Possible scores range from 0 to 30.

(ii) The multiple-choice form (Form F) of the Benton Visual Retention Test (BVRT) (Benton, 1965) consists of 15 stimulus cards and 15 multiple choice cards. After the presentation of a stimulus card for 10 s, the subjects are asked to choose the initial figure among four options. Possible total scores range from 0 to 15.

(iii) The Wechsler Paired-Associates Test (WPAT) (Wechsler, 1945) involves the reading of 10 word pairs. After reading the list, the examiner reads the first word of each test pair and the subject is asked to provide the second word. Three learning trials and a delayed recall are performed. Six of the word pairs are easy associates (e.g. 'baby–cries') and four are difficult (e.g. 'school–grocery'). The easy pairs are given a score of 0.5 and the difficult ones a score of 1. For this paper we have considered scores of the first learning trial (WPAT1) and the delayed recall (WPATr) with a possible range from 0 to 7.

(iv) The Isaacs Set Test (IST) (Isaacs and Kennie, 1973) measures the ability to generate lists of words in four specific semantic categories (colours, animals, fruits, cities) in a limited time period. In our study and according to the Isaacs and Kennie initial rules, the maximum number of words to be generated in each category was limited to 10, thus possible total scores range from 0 to 40. To eliminate a major ceiling effect, we considered only the 15-s score in this analysis.

(v) Zazzo's Cancellation Task (ZCT) (Zazzo, 1974) measures the ability to cross out as fast and as exactly as possible, 125 target signs on a sheet of white paper containing 40 lines of signs. In our study, only the first eight lines comprising 29 target signs were performed. Two scores are considered in this paper: the number of signs correctly crossed out (ZCTtot) and the time spend to complete the test (ZCTtime). In PCA we used the speed measure (ZCTspd = 1/ZCTtime) so that, as with other variables, it decreases with impaired performance.

(vi) The Digit Symbol Substitution Test (DSST) (Wechsler, 1981) consists of assigning the correct symbol to digits ranging from 1 to 9 according to a code table displaying pairs of digits and symbols. The subject has to copy as many symbols as possible in a time period of 90 s. Possible scores range from 0 to 93.

(vii) In the Wechsler Similarities Test (WST) (Wechsler, 1981) the subject must explain in what way two things are alike (e.g. 'orange–banana'). In our study, only the first five pairs of the WAIS (Wechsler Adult Intelligence Scale) similarities subtest were considered. A score of two points is given for an abstract generalization, and one point if a response is a specific concrete likeness. Possible scores range from 0 to 10.

After this evaluation, the psychologists completed a standardized questionnaire to obtain the A (memory impairment), B (impairment of at least one other cognitive function) and C (interference with social or professional life) DSM III-R (American Psychiatric Association, 1978) criteria for dementia (Forette *et al.*, 1989). In a second stage, subjects who met the first three DSM III-R criteria for dementia were seen by a senior neurologist who confirmed the DSM III-R criteria for dementia, added the NINCDS-ADRDA criteria (McKhann *et al.*, 1984) and the modified Hachinski score (Hachinski *et al.*, 1975) to specify the aetiology, i.e. as

Table 1 *Correlation coefficients between pairs of neuropsychological test scores (PAQUID cohort, 1989)*

	MMSE	DSST	BVRT	IST	WPAT1	WPATr	ZCTspd	ZCTtot	WST
MMSE	1.00								
DSST	0.43	1.00							
BVRT	0.42	0.54	1.00						
IST	0.43	0.59	0.45	1.00					
WPAT1	0.45	0.46	0.41	0.42	1.00				
WPATr	0.40	0.41	0.38	0.38	0.59	1.00			
ZCTspd	0.33	0.70	0.44	0.52	0.37	0.30	1.00		
ZCTtot	0.16	0.26	0.24	0.20	0.15	0.17	0.16	1.00	
WST	0.38	0.40	0.31	0.31	0.35	0.30	0.30	0.18	1.00

MMSE = Mini-Mental State Examination; DSST = Digit Symbol Substitution Test; BVRT = Benton Visual Retention Test; IST = Isaacs Set Test; WPAT(1/r) = Wechsler Paired Associates Test (1st/recall); ZCT(spd/tot) = Zazzo's Cancellation Test (speed/total number); WST = Wechsler Similarities Test. See text for a description of these variables.

probable or possible Alzheimer's disease, or as vascular or other type of dementia. The same procedure was applied at each follow-up visit of the cohort.

The present analysis was limited to 1159 subjects from Gironde considered as non-demented at the first year of follow-up of the cohort, who had performed the whole test battery at this date and who were followed-up 2 years later (for the third year of follow-up of the cohort). The first year of follow-up was chosen as the origin of time for the prediction of dementia because the neuropsychological assessment battery was the most complete, and because the subjects were being tested for the second time on this date. Therefore any misclassification bias for dementia as well as anxiety related to a first psychometric testing were minimized.

For each type of analysis we have considered (i) the risk of Alzheimer's disease, taking into account the subjects subsequently classified as Alzheimer's disease and (ii) the risk of dementia, taking into account all the subsequently demented subjects, whatever the type of dementia, including Alzheimer's disease (the number of subjects presenting other types of dementia was indeed too small to be analysed separately). The association between each test score performed at the first year of follow-up and the risk of subsequent dementia or Alzheimer's disease were assessed by calculating the odds ratio and its corresponding 95% confidence interval (95%CI). The model was the logistic regression. The Akaike criterion (Akaike, 1974) was applied to compare the predictive values of the models: the lower the Akaike criterion, the better the prediction. To prevent the harmful effect of the multicolinearity between scores on the selected neuropsychological tests, scores on the individual tests were subjected to a PCA. This is a multivariate statistical technique used to examine the relationships among a set of correlated variables, in this case, neuropsychological performances across different tests. It transforms the original set of variables into a new and smaller set of uncorrelated, i.e. independent, variables called principal components. The new variables are ranked in decreasing order of importance so that the first principal components account for the maximum amount of variation in the original data. This PCA did not take into account the information concerning the subsequent diagnosis of the subject (demented or not demented 2 years later). Individual patient weightings on each of these new variables were subsequently correlated with the risk of subsequent dementia by logistic backward stepwise regression and adjustment for age, gender and educational level. All statistical analyses were done with BMDP software (Bio Medical Data Program, Los Angeles, USA).

Results

Six hundred and forty-five women and 514 men (mean age 72.9 years; range 66–102 years) were included in this study at the baseline screening. Six hundred and fifty subjects had a grade school level and 509 subjects a secondary or university level of education. As expected, almost all test scores were significantly correlated in pairs. The strongest correlation coefficient was found between ZCTspd and DSST ($r = 0.70$) and the lowest between ZCTtot and WPAT1 ($r = 0.15$) (Table 1).

Among the 1159 subjects, 25 had developed a dementia 2 years later. Of these, 16 cases were classified as Alzheimer's disease, seven as vascular dementia and two as Parkinson dementia. The test scores of future demented subjects were found to have been significantly lower than those of future normal subjects (Table 2). With a univariate logistic regression analysis, all psychometric scores were strongly related to the subsequent risk of dementia (all types confounded) and to the subsequent risk of Alzheimer's disease (Table 3). Hence, the risk of confounding and multicolinearity was maximal with this set of variables.

The PCA generated a one-factor solution with an eigenvalue >1, which accounted for 45.3% of the variance (Table 4) in test performance. This factor has high loadings (correlation coefficient >0.5) from the following test scores in order of importance: DSST, IST, BVRT, ZCTspd, WPAT1, MMS, WPATr and WST. With a cut-off of 0.75 for the eigenvalues, three more factors were generated which accounted for 29.2% of the variance. The second factor, with loadings very close to 0.5 from WPATr, and ZCTtot scores,

Table 2 *Tests scores of future demented and future normal subjects 2 years before clinical detection of dementia (PAQUID cohort, 1989) (1159 subjects)*

Variable	Future demented subjects	Future Alzheimer's disease subjects	Future normal subjects
MMS	25.04 ± 2.19*	24.25 ± 2.17*	27.63 ± 1.98
DSST	18.00 ± 9.03*	17.50 ± 7.06*	31.25 ± 11.43
BVRT	8.72 ± 2.54*	7.94 ± 2.54*	11.46 ± 2.23
IST	21.88 ± 4.13*	21.37 ± 3.93*	29.65 ± 5.61
WPAT1	2.54 ± 1.43*	2.22 ± 1.49*	4.29 ± 1.51
WPATr	4.14 ± 1.72*	3.28 ± 1.14*	5.76 ± 1.25
ZCTtot	26.80 ± 3.16	26.19 ± 3.71	27.88 ± 1.98
ZCTtime	131.16 ± 54.02*	130.31 ± 50.68*	76.76 ± 28.44
WST	4.32 ± 2.88*	3.87 ± 2.68*	7.42 ± 2.67

Data are presented as means ± SDs. See footnote to Table 1 for abbreviations. *$P < 0.0001$.

Table 3 *Relationships between each neuropsychological test score and risk of subsequent dementia or Alzheimer's disease*

Test score	Risk of dementia		Risk of Alzheimer's disease	
	Akaike criterion	Odds ratio (95%CI)	Akaike criterion	Odds ratio (95%CI)
MMS	216.2	1.5 (1.3–1.7)***	148.9	1.6 (1.4–1.9)***
DSST	204.4	1.2 (1.1–1.3)**	141.4	1.2 (1.1–1.3)**
BVRT	214.2	1.6 (1.3–1.8)**	140.0	1.8 (1.4–2.2)**
IST	197.4	1.3 (1.2–1.4)**	137.4	1.3 (1.2–1.5)**
WPAT1	211.6	1.1 (1.0–1.2)**	139.8	1.1 (1.1–1.2)**
WPATr	214.5	1.1 (1.0–1.1)**	128.6	1.1 (1.1–1.2)**
ZCTtot	239.4	1.2 (1.1–1.4)*	165.0	1.3 (1.1–1.5)*
ZCTspd	203.8	1.03 (1.0–1.1)**	146.2	1.0 (1.0–1.1)**
WST	219.4	1.4 (1.2–1.6)**	151.2	1.4 (1.2–1.7)**

Odds ratios, 95% confidence intervals and Akaike criteria were computed with univariate logistic regression. See footnote to Table 1 for other abbreviations. *$P < 0.01$; **$P < 0.001$; ***$P < 0.0001$.

Table 4 *PCA for the neuropsychological tests (PAQUID cohort, 1989) (1159 subjects)*

Variable	Factor				
	1	2	3	4	5
MMS	0.67	–0.26	–0.07	–0.19	0.53
DSST	0.82	0.28	0.20	0.01	–0.12
BVRT	0.71	0.12	0.01	0.07	0.36
IST	0.74	0.16	0.19	0.09	0.08
WPAT1	0.71	–0.43	–0.06	0.20	–0.18
WPATr	0.66	–0.47	–0.15	0.33	–0.21
ZCTtot	0.35	0.47	–0.78	0.16	–0.03
ZCTspd	0.71	0.37	0.38	0.01	–0.20
WST	0.58	–0.12	–0.20	–0.72	–0.26

See footnote to Table 1 for abbreviations.

accounted for 10.8% of the variance. The third factor, with high loadings from ZCTtot score, accounted for 10.1% of the variance. The fourth factor, with high loadings from the WST score, accounted for 8.3% of the variance.

The patients' loadings on each of these four PCA factors were subsequently correlated with the risk of dementia and Alzheimer's disease 2 years later with adjustment for age and educational level. Thus, four new variables were created corresponding to the four PCA factors. The logistic backward stepwise regression selected only the first factor as independent predictor of dementia and as independent predictor of Alzheimer's disease. For a decrease of one point of the PCA score the odds ratio for the risk of dementia was 2.31 (95%CI, 1.82–2.95), $P < 0.00001$); it was 3.25 (95%CI, 2.18–4.8, $P < 0.00001$) for the risk of Alzheimer's disease. The other factors did not reach the significance level. The Akaike criterion, computed with a univariate logistic regression analysis, taking into account only the first PCA factor (Factor 1), was 153.6 for the risk of dementia and 80.5 for the risk of Alzheimer's disease, which was far better than the Akaike criterion related to each psychometric test score alone (Table 3).

The graphical projection of the individual values of the first two PCA factors confirmed the strong predictive value of the first factor score, since all future demented subjects were in the same left part of the graph (Fig. 1). Future Alzheimer's disease subjects were among the subjects with a lower PCA Factor 1 score, while other dementia subjects

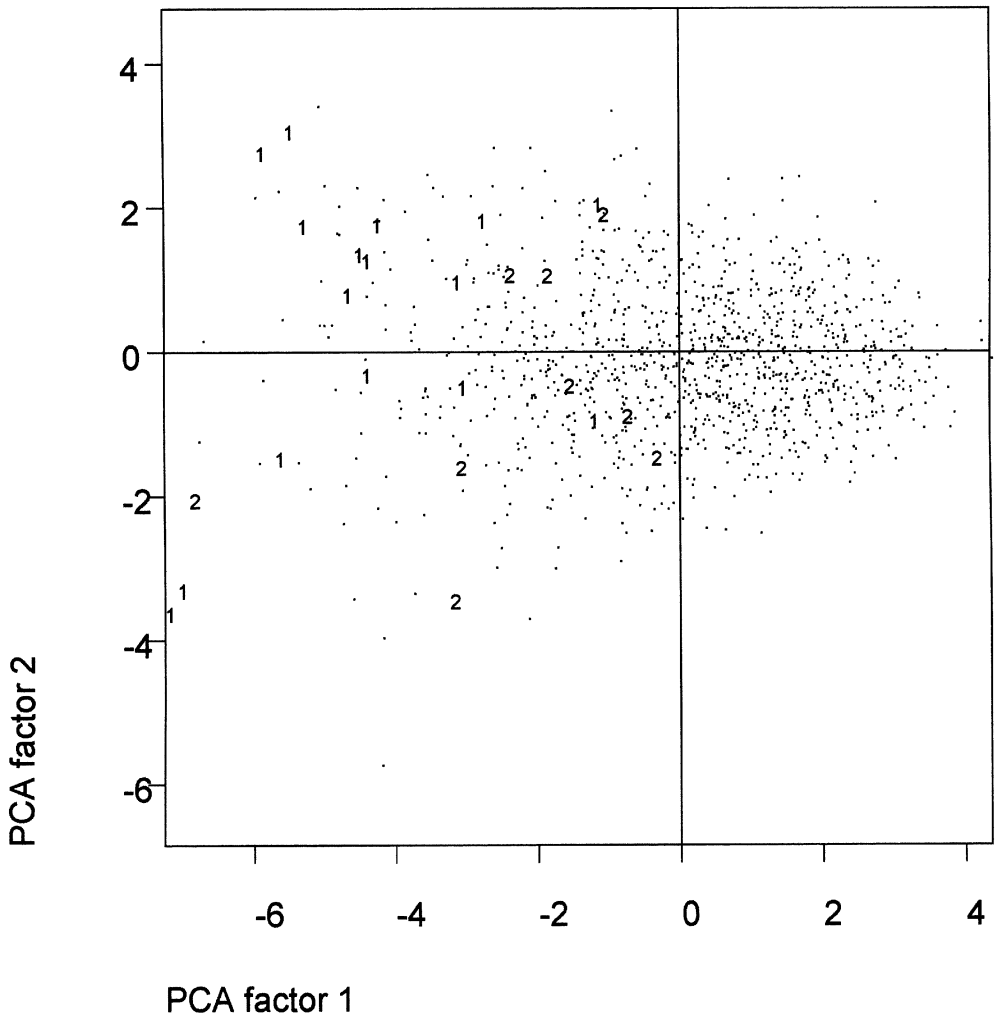

Fig. 1 Graphical projection of individual values of the first two factors from the PCA. Dots show data from normal subjects; 1 = subject with future dementia of the Alzheimer's type; 2 = subject with future dementia of another type.

had an intermediate value. It is interesting to note that the only case of non-Alzheimer's disease dementia having a very low PCA Factor 1 score was verified with autopsy, and the histopathological diagnosis was amyloid angiopathy.

Discussion

Our findings confirm that the clinical diagnosis of dementia or Alzheimer's disease was preceded by a preclinical stage of at least 2 years detectable by psychometric testing. As found previously (Masur *et al.*, 1994; Jacobs *et al.*, 1995; Linn *et al.*, 1995), all psychometric performances were associated with the subsequent risk of dementia and with the subsequent risk of Alzheimer's disease. Despite this apparent heterogeneity, the clinical impairment of cognition seems to be homogeneous, since only one component of the neuropsychological pattern of the subjects was a strong independent predictor of dementia and Alzheimer's disease.

The major problem is, of course, to interpret what the first factor generated by the PCA represents. Eight psychometric scores among 11 tested were highly correlated with this factor. This could be in favour of the effect of a general factor. However, it should be stressed that the eight tests had different loadings on Factor 1; in addition, it is interesting to take into account their relative loadings on the different PCA factors, as used by Horn and Cattell (1967). On the basis of this rule, DSST and IST scores characterize PCA Factor 1 better than the other test scores, since their loadings on this factor were at least twice as large as their loadings on any other factor; BVRT and ZCTtime scores are very close to fulfilling this criteria.

Therefore, the cognitive processes involved in these tests could help in understanding what component they might share. Visuospatial perception, selective attention, response speed, visuomotor coordination and incidental memory of digit–symbol pairs association may play a role in digit symbol substitution test performances. In the ZCT, visuospatial perception, selective attention and response speed contribute to the subject's performances. This test shares many components with the Digit Symbol Substitution Test, but it

is more simple in that a single target has to be detected among distractors, and unlike the digit symbol test, it may give way to automatization with practice. Our score does, however, reflect the controlled part of the test because subjects completed only the first eight lines, and at this stage, the automatization process has only just begun. The IST is a categorical fluency test in which production depends on the integrity of semantic memory networks as well as the ability to initiate systematic search and retrieval strategies; it also involves short-term memory in keeping track of what words have already been said. Moreover, response speed contributes to the subject's performance as in the two previous tests.

Besides these three timed tests, we find the Benton visual retention test which may best be characterized by its memory component. This test used in recognition involves visuospatial perception, visual conceptualization, immediate memory span, and a form of selective attention, because the memorized stimulus has to be selected among three very similar distractors.

This description of the processes involved in the four tests which are the most specific of PCA Factor 1 shows that it has to do with processing speed and selective attention as well as with the more controlled aspects of memory functioning, i.e. the 'central executive' of working memory described in Baddeley's model (1986) and/or the strategic aspect of memory retrieval proposed by Moscovitch (1992). Therefore, there are good reasons to suspect that PCA Factor 1 represents a general factor corresponding to the controlled aspects of the tasks used, and that the other factors of PCA correspond to other components of the same tasks, but which are more automated.

Taking into account the distinction introduced a century ago by Huglings-Jackson (Taylor, 1932) between automatic and controlled processes, new neuropsychological theories of information processing, e.g. from Norman and Shallice (1986) and Moscovitch and Ulmita (1990), incorporate examples of control functions at a central level which modulate more automatic systems. In a review paper, Jorm (1986) hypothesizes that relative deterioration of controlled processes as opposed to preservation of automatic ones constitutes one of the first sign of dementia. Following Jorm's hypothesis, our results seem to show that the controlled/automatic distinction may be relevant in the characterization of the early deterioration of cognitive functioning in the preclinical phase of dementia and Alzheimer's disease.

Our results, therefore, seem to show that beyond the apparent heterogeneity shown by the predictive value of a variety of psychometric tests, preclinical deficits in dementia and Alzheimer's disease are homogeneous and reflect the deterioration of a general cognitive factor, reinterpreted as the involvement of central, controlled processes. Two methodological limitations could interfere with these findings. First, the number of incident cases of dementia or Alzheimer's disease was quite low (25 dementia, 16 Alzheimer's disease) even if the population at risk was larger ($>$1000 subjects) than most studies on this topic. Even if this number reflects the real proportion of incident cases in our population-based study, it could induce a lack of power and, therefore, explain the non-significant relationships between the other PCA components and the risk of dementia. Secondly, the number of psychometric tests applied to our sample was limited and some fields of cognition, particularly those related to language, were not explored. Concerning our conclusions, we did not dispose of any true automatic tasks.

At a more theoretical level, one can argue that the deterioration of controlled processes is classically associated with damage to the prefrontal structures. Such structures are not supposed to be the first to deteriorate in dementia and especially in dementia of the Alzheimer type. Yet different authors (Damasio *et al.*, 1990; Moscovitch and Umilta, 1990) argue that many neuropsychological deficits occur in Alzheimer's disease as a consequence of the disruption of corticocortical and corticolimbic connectivity and its disruptive effect on the integrative system. Even if the frontal cortex is not directly damaged at an early stage of dementia, very early deterioration of the functioning of control processes might therefore be considered to be a disconnection syndrome.

It must also be emphasized that our results are not in contradiction with the demonstration of clinical heterogeneity in Alzheimer's disease (Martin *et al.*, 1986; Joanette *et al.*, 1989; Grafman, 1992). One may argue that the early preclinical signs of Alzheimer's disease correspond to a disconnection syndrome giving way to disruption in the integrative system, and that with the progression of the disease, a differential distribution of pathological features occurs in different brain structures, giving way to different clinical patterns of functional deficits.

In conclusion, a preclinical stage of dementia or Alzheimer's disease could be detected by a neuropsychological assessment. From a neuropsychological point of view, this stage seems to be characterized by an homogeneous impairment of cognition that could be interpreted as a deterioration of control processes. The follow-up of the PAQUID cohort, and particularly the evolution of PCA Factor 1, should enable a better understanding of these findings.

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