

ORIGINAL PAPER

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Factors associated with low cognitive performance in general practice

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Summary In the preparatory phase of a randomised controlled trial data were collected to assess the magnitude of changes on cognitive functions in 1628 volunteers (age range 45–75 years) that were recruited from general practitioners' patient population. Subjects were administered a short neuropsychological battery of tests including three paper-and-pencil tests, which assessed immediate recall, delayed memory, and attention. Being on antihypertensive medication was associated with low results for all three tests in every age group, and in all strata according to blood pressure levels. Psychotropic drug use was correlated with low results for all three tests. Differences between psychotropic drug users and nonusers increased with age. Antihypertensive treatment and psychotropic drug use seem to be important to consider in longitudinal studies of cognitive decline in aging.

Key words Ageing · Cognitive functioning
Hypertension · Psychotropic drug use

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Introduction

It is well established that cognitive function declines with age. However, there are important interindividual differences in age-adjusted cognitive ability, and this variability is only partly explained. Cross-sectional studies have shown that low cognitive performance is associated with low education [10, 13, 22], and a high level of depressive symptomatology [9, 14, 20, 21, 22]. Recent studies on the relationships between blood pressure, antihypertensive medication and cognitive performance in the elderly have shown conflicting results [5, 6, 7, 8, 23, 27]. The relationship between psychotropic drug use and decreased cognitive function has been demonstrated in young healthy volunteers [4, 15], but surprisingly no studies on the middle-aged and elderly population have focused on this question, and the effect of regular psychotropic drug use, especially benzodiazepines, on cognitive functioning remains to be documented. In view of the high prevalence of both psychotropic drug use and treatment for high blood pressure in elderly persons it is important to attempt to clarify whether they are risk factors of low cognitive performance.

The present study was conducted in general practice during the preparatory phase of a double-blind controlled trial. Its specific objective was to assess the magnitude of changes in cognitive function between 45 and 75 years of age on patients who consult family physicians (excluding those with serious medical problems), in order to estimate the mean and standard deviation of neuropsychological tests for sample-size calculation. These data allowed analysis of the relationships between antihypertensive treatment, use of psychotropic drug and cognitive performance, considering sex, age and level of education.

Subjects and methods

Subjects were recruited from general practitioners' (GP) patient population. A total of 800 GPs were contacted, and 634 of them agreed to participate in the study. After a brief training they were

asked to administer a short neuropsychological battery of tests to three persons, one person in each of the following three age groups: 45–54 years, 55–64 years and 65–75 years. In order to reduce selection bias only two consecutive days were allowed for each GP to recruit the three participants from his/her patients. Persons with a serious health problem, a history of stroke, heavy alcohol consumption, present or past mental disorder or severe head trauma were not eligible for the study. Psychotropic drug users were allowed to take part in the study if use was not associated with a psychiatric diagnosis. Subjects gave their written consent. The study began in January 1990 and ended in July 1990.

Neuropsychological testing

The battery [3] consisted of three paper-and-pencil tests assessing immediate recall, delayed memory and attention. In the *Morse Dictation* test, which explored immediate recall, subjects had to reproduce series of short and long sounds after hearing lists of one to ten sounds. The *Generic Words* test assessed delayed memory through recall of a ten-world list after approximately 15 min. The *Double Crossing* test probed attention, with the subject being asked to circle a letter and cross a digit.

The notation of the Morse Dictation and Generic Words tests was from 0 to 10 (10 = full score). In order to homogenize scores the Double Crossing notation was also calculated from 0 to 10. Scoring poorly was defined as belonging to the lowest 25th percentiles for each test. The 25th percentile was the score at or closest to the lowest 25th percentile of the subjects completing a test.

Covariates

In the analysis of the relationship between cognitive performance and age the following variables were considered: sex, level of education, blood pressure, use of antihypertensive prescriptions, use of psychotropic drugs and the main reason for visiting the doctor.

For the education covariate subjects were classified in one of the following three categories: elementary school (6 years of education or less), high school (7–13 years of education) or university (14 years of education or more). Systolic and diastolic blood pressure were taken by the GP during the examination. Blood pressure was studied in classes (5 classes for systolic blood pressure: SBP < 130 mmHg, 130 ≤ SBP < 140, 140 ≤ SBP < 150, 150 ≤ SBP < 160 and 160 ≤ SBP). The main medical reason for visiting the doctor was classified by the GP as somatic, psychological or mixed. Psychological motives included tiredness, headaches, insomnias and other complaints without organic disease, excluding psychiatric disease. For the treatment covariates, namely antihypertensive and psychotropic medications, subjects were classified according to whether they were receiving treatment at the time of testing. Psychotropic drugs included tranquilisers, antidepressives, sedatives and hypnotics.

Of 2144 subjects who had neuropsychological testing by the GPs 516 were excluded for the following reasons: in 378 testings data did not satisfy quality-control requirements. In 46 cases main covariates (age, sex or educational level) were missing, and 92 persons were outside the age limit for eligibility.

Statistical analysis

The effects of the main covariates on neuropsychological test scores were studied by variance analysis with one or several factors. Interaction between age and other variables was added in models to examine whether the relationships were similar across age groups. Crude Pearson's correlation coefficients and partial coefficients were computed. In order to quantify relationships between neuropsychological testing and covariates logistic regression was used to compute adjusted odds-ratios, with the dependent variable being scoring poorly for each test.

Results

Characteristics of sample

The sample included 679 men and 949 women, almost evenly distributed in the three age groups. The level of education was rather high, with 23% having some education beyond high school; it was more elevated amongst men, and was strongly negatively correlated with age in both sexes (Table 1). The main medical reason for visiting the doctor was given by 1504 subjects: it was mainly somatic in 65.6%, psychological in 25% and mixed in 9.4%.

Antihypertensive medications were usually prescribed to 30.4% of the sample ($n = 495$). This proportion was similar in both sexes, increased markedly with age and decreased when educational level rose (38.8%, 28% and 17.9%, respectively, in low, middle and high level). In the 1289 subjects for which blood pressure measures were available mean systolic blood pressure (SBP) increased with age (Table 1) and decreased when educational level rose (141 ± 14 mmHg; 137 ± 14 and 134 ± 14 ; $P < 10^{-4}$). The decrease observed with educational level was less important when controlling for age, but remained significant ($P < 10^{-3}$). Among subjects whose SBP was < 130 mmHg, 6.7% were on antihypertensive treatment, this proportion growing to 78.1% for subjects whose SBP was ≥ 160 mmHg. The same relationships were found with mean diastolic blood pressure.

A psychotropic treatment was regularly taken by 274 subjects (16.8% of the sample size), with 232 taking one of these drugs and the other 42 taking two drugs or more. Tranquilisers ranked first (51%), followed by hypnotics

Table 1 Sociodemographic characteristics of test sample, blood pressure and treatment use by age group; P value is comparison between the three groups. SBP systolic blood pressure (mean \pm SD); DBP diastolic blood pressure

	45–54 years ($n = 542$)	55–64 years ($n = 551$)	65–75 years ($n = 535$)
Gender			
Men (%) ^a	38.8	45.2	41.1
Educational level ^{b, ***}			
Low (%)	27.1	45.6	58.5
Middle (%)	36.0	35.8	28.0
High (%)	36.9	18.7	13.5
SBP (mmHg) ^{***}	133 ± 13	138 ± 14	144 ± 14
DBP (mmHg) ^{***}	78 ± 9	80 ± 8	82 ± 7
Antihypertensive treatment (%) ^{***}	14.8	30.5	46.2
Psychotropic drug use (%) [*]	13.5	18.2	18.9

^a P value not significant

^b Low level: elementary school; middle level: high school; high level: university

^{*} $P < 0.05$

^{***} $P < 0.001$

(27%). Use of psychotropic treatment was more frequent among women (19.4% vs 13.3%), increased after 55 years and was twofold higher in the low- and middle-educational levels than in the high. As expected the relationship between motive of consultation and psychotropic treatment was strong: psychotropic drug use was found in 11.2% of somatic cases, 25.2% of psychological, and 34.5% of mixed.

Neuropsychological test scores

In all three tests the mean score decreased with age (1.0 for Morse Dictation, 1.3 for Generic Words and 1.0 for Double Crossing between younger and older groups; all $P < 10^{-4}$) (Table 2). Mean scores increased when educational level rose (1.5, 1.7 and 1.0, respectively for Morse Dictation, Generic Words and Double Crossing between lower and higher levels; all $P < 10^{-4}$). Gender differences were found in only one test, Generic Words, where women performed better than men (0.3 point; $P = 10^{-2}$). In univariate analyses age explained 5–7% of the variance according to the tests, and educational level explained 7–10%. For Morse Dictation and Double Crossing decreases with age were similar in each educational level. Only for Generic Words was a decrease in score more important in high levels.

Table 2 Neuropsychological test scores according to sociodemographic characteristics and treatment use (mean \pm SD)

	Morse Dictation ^a (<i>n</i> = 1628)	Generic Words ^a (<i>n</i> = 1626)	Double Crossing ^a (<i>n</i> = 1571)
Mean test score	7.6 \pm 2.0	5.9 \pm 2.2	6.4 \pm 1.6
Gender	NS	**	NS
Men	7.7 \pm 1.9	5.8 \pm 2.2	6.5 \pm 1.6
Women	7.6 \pm 2.0	6.1 \pm 2.3	6.3 \pm 1.6
Age (years)***			
45–54	8.1 \pm 1.7	6.6 \pm 2.2	6.8 \pm 1.5
55–64	7.6 \pm 1.9	5.9 \pm 2.2	6.5 \pm 1.5
65–75	7.1 \pm 2.1	5.3 \pm 2.1	5.8 \pm 1.5
Educational level***			
Low	7.0 \pm 2.1	5.2 \pm 2.2	6.0 \pm 1.5
Middle	7.8 \pm 1.8	6.2 \pm 2.1	6.5 \pm 1.5
High	8.5 \pm 1.5	6.9 \pm 2.1	7.0 \pm 1.5
Antihypertensive treatment***			
No	7.8 \pm 1.9	6.2 \pm 2.3	6.5 \pm 1.5
Yes	7.2 \pm 2.1	5.3 \pm 2.1	6.1 \pm 1.6
Psychotropic drug use***			
No	7.7 \pm 1.9	6.0 \pm 2.2	6.4 \pm 1.6
Yes	7.2 \pm 2.2	5.5 \pm 2.3	5.9 \pm 1.6

^a All subjects took Morse Dictation, two did not take Generic Words and 57 did not take Double Crossing

** $P < 0.01$

*** $P < 0.001$

A positive correlation was observed between the three tests. The Pearson correlation coefficient (r) was equal to 0.34 between Morse Dictation and Generic Words; $r = 0.28$ between Morse Dictation and Double Crossing, and $r = 0.34$ between Generic Words and Double Crossing (all $P < 10^{-4}$). When controlling for age and educational level the correlation values decreased, but remained significant, with partial correlation coefficients being equal to 0.24, 0.20 and 0.26 (all $P < 10^{-4}$).

Neuropsychological test scores, antihypertensive treatment and blood pressure

A significant difference in test scores was observed between groups on and off antihypertensive treatment. Subjects who were treated for arterial hypertension performed the worst, with the differences being equal to 0.7 in Morse Dictation, 0.9 in Generic Words and 0.4 in Double Crossing (all $P < 10^{-4}$). The effect of antihypertensive treatment was similar in the three age groups. When controlling for age and educational level the difference observed according to antihypertensive treatment was equal to 0.3 for Morse Dictation ($P = 10^{-3}$), 0.5 for Generic Words ($P = 10^{-4}$) and 0.1 for Double Crossing (n.s.). When studying test results according to SBP classes a clear decreased was observed for all three tests with increasing SBP, but this effect remained significant only for one test, Morse Dictation, when considering age and level of education. To distinguish between the effect of high blood pressure and antihypertensive treatment test results were studied according to antihypertensive treatment in SBP classes. Results were poorer in subjects on antihypertensive treatment than in subjects off for all three tests, but the difference was not clear in high levels of SBP. This effect of antihypertensive treatment across SBP classes remained significant for two tests (Morse Dictation and Generic Words) when considering the effect of age and level of education, whereas only a decreasing trend was observed for the SBP class for one test (Morse Dictation; $P = 0.09$), as shown in Fig. 1. These results were nearly the same for diastolic blood pressure.

Neuropsychological test scores and psychotropic drug use

Compared to nonusers subjects using psychotropic drugs had mean scores less than 0.5 for each of the three tests ($P < 10^{-4}$ for Morse Dictation; $P < 10^{-3}$ for the two other tests). When studying the effects of psychotropic treatment across age groups we found a significant interaction between age and psychotropic treatment. The observed difference increased significantly with age for two tests, and there was a trend for the third ($P < 0.05$ for Morse Dictation and Double Crossing; $P < 0.10$ for Generic Words). When testing differences between psychotropic drug users and nonusers within each age group they were significant only in the older group (Fig. 2). Whether the

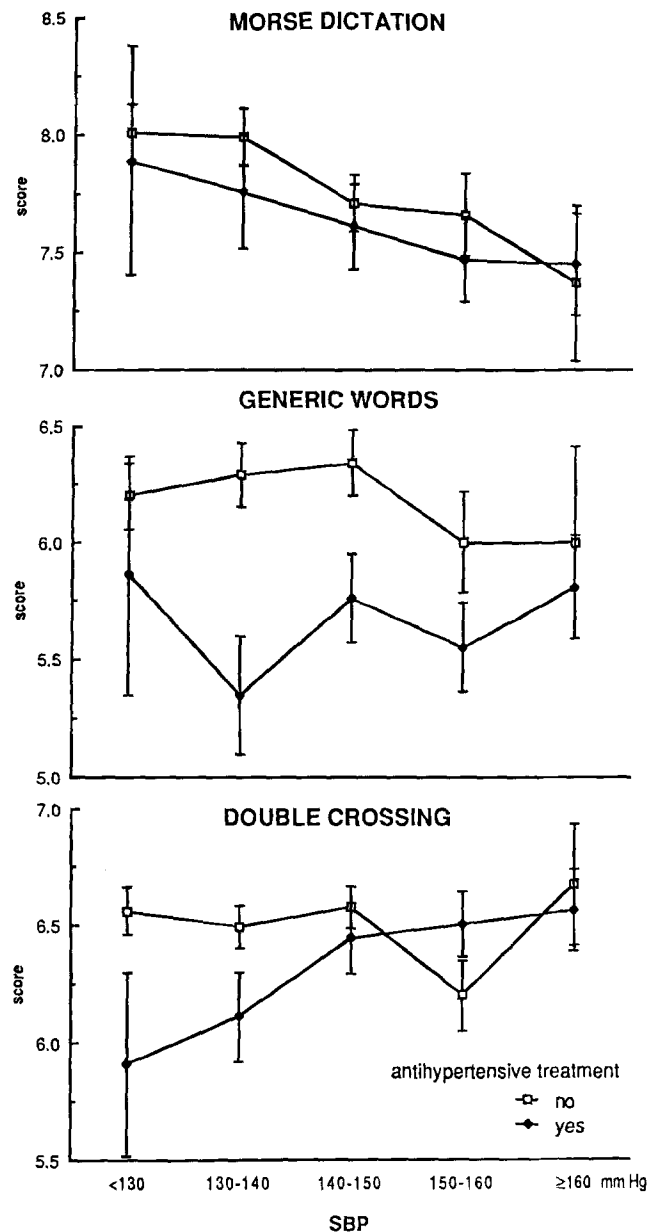


Fig.1 Neuropsychological test scores by systolic blood, blood pressure (SBP) class and hypertensive treatment, controlling for age and educational level (mean \pm SEM)

main reason for the consultation was somatic or psychological, psychotropic drug users had lower results than nonusers, but amongst subjects whose motive was somatic interaction between age and psychotropic drug use was not significant.

Risk of scoring poorly

A total of 84 subjects was in the lowest 25th percentiles in all three tests, with 841 subjects in the highest 75th percentiles. In multiple logistic regression increasing age, low educational level, hypertensive treatment and psychotropic drug use were predictive variables for scoring

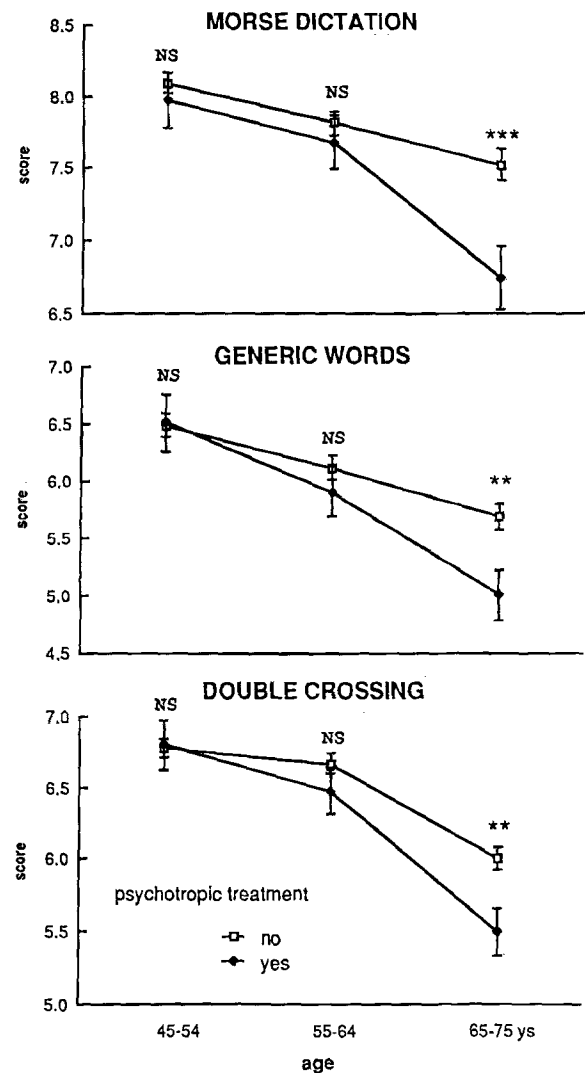


Fig.2 Neuropsychological test scores by age group and psychotropic treatment, controlling for education level, (mean \pm SEM). *P* value according to psychotropic drug use, for each age group: NS; ***P* < 0.01; ****P* < 0.001

poorly (Table 3). Age effects might be quantified by adjusted odds-ratios: their values were approximately 1.3 for the 55–64 age group and higher (1.6–3.0) for the 65–75 group. Considering the higher level as a reference the middle-educational level group was associated with a twofold higher probability of scoring poorly, and the low group with a fourfold probability. Adjusted odds-ratios according to hypertension were equal to 1.4 for Morse Dictation and Generic Words, and 1.3 for Double Crossing, the first two significantly higher than 1 (*P* = 0.08 for the third). According to psychotropic drug use adjusted odds-ratios were equal to 1.3 for Morse Dictation and Generic Words, no significantly higher than 1 (*P* = 0.08 and *P* = 0.09), and equal to 1.5 for Double Crossing (significantly higher than 1). Within age groups odds-ratios associated with psychotropic drug use were higher among older subjects (1.6, 1.6 and 1.7, respectively, for Morse Dictation, Generic Words and Double Crossing, all of

Table 3 Adjusted odds-ratios (OR) associated with the probability of scoring poorly (belonging to the 25th lower percentiles; OR CI 95% for each test)

	Morse Dictation (<i>n</i> = 1628)	Generic Words (<i>n</i> = 1626)	Double Crossing (<i>n</i> = 1571)
Age (years)			
45–54	1.00	1.00	1.00
55–64	1.32 (0.97–1.81)	1.33 (0.97–1.83)	1.23 (0.89–1.70)
65–75	1.70 (1.24–2.33)	1.61 (1.17–2.21)	2.96 (2.16–4.05)
Educational level			
Low	4.53 (3.05–6.73)	3.57 (2.46–5.20)	4.11 (2.77–6.10)
Middle	2.42 (1.60–3.65)	1.64 (1.10–2.45)	2.67 (1.77–4.03)
High	1.00	1.00	1.00
Antihypertensive treatment			
No	1.00	1.00	1.00
Yes	1.44 (1.12–1.85)	1.36 (1.06–1.76)	1.26 (0.97–1.62)
Psychotropic drug use			
No	1.00	1.00	1.00
Yes	1.30 (0.97–1.75)	1.30 (0.96–1.76)	1.51 (1.12–2.04)

them higher than 1). All these results were similar either by excluding subjects who did not take a test or considering them as scoring poorly.

Discussion

Through general practitioners it has been possible to analyse factors related to low cognitive performance in 1628 patients 45–75 year old. Besides the classical decline of neuropsychological test scores with age and the strong effect of the educational level, the most interesting findings of this cross-sectional study lies in that antihypertensive medication and psychotropic drug use were both associated with low scores. These associations were independent of the educational level. For psychotropic drugs analysis suggested an interaction between age and the magnitude of the difference between users and nonusers. This analysis was made on data collected during the preparatory phase of a randomised placebo-controlled trial in general practice and raised some methodological issues. The aim of this phase was to verify feasibility and estimate the mean and standard deviation of neuropsychological tests for sample-size calculation. The sample consisted of volunteers who had no serious medical problems and agreed to take part in the study. The distribution of educational level gave evidence of selection bias, in that 23% of the subjects had 14 years of education or more. However, proportions of subjects receiving antihypertensive medications [7, 23, 27] of those using psychotropic drugs [2, 28] did not suggest any other major selection bias neither did relations of cognitive performance to age, sex and education. As expected older subjects were more frequently on antihypertensive treatment and used more psychotropic drugs. In accordance with Farmer we observed that in all age groups the proportion of patients receiving antihypertensive treatment was negatively correlated with educational level [7]. Moreover, in accordance with Stamler we found that education was negatively related to blood pressure [25].

The preparatory phase of the trial had not been designed in view of this special study. Thus, no data were collected on duration of hypertension, smoking and alcohol consumption, or existence of minor psychopathological symptoms. Statistical analysis and discussion are limited because of this lack of information. Many pharmacological studies focused on the relation between psychotropic drug use and cognitive functions [4, 15], but there is very little published epidemiological data. Despite extensive research we found only two epidemiological studies that addressed this question. In a sample of 1026 Danes 20–70 year old Laursen did not find differences in cognitive functioning in relation to consumption of drugs affecting the central nervous system [16]. A large variety of drugs, including analgesics, were considered, which could explain the lack of association. Hayward examined the relation between use of hypnotics and cognitive performance in 124 elderly people aged 70–85 years and did not find any difference between users and nonusers [12]. We report here a significant association between low cognitive performances and psychotropic drug use in general practice. The relation was found in both genders, whatever the motive for consulting the GP, and in all age groups. Our data suggest that cognitive performance differences between users of psychotropic drugs and nonusers increased with age. This finding is consistent with the great sensitivity of elderly people to psychotropic drugs [11, 18]. The interpretation of the relation between psychotropic drugs and cognitive functioning is limited by the absence of precise data on potential confounders, especially depressive symptomatology.

Interrelations between cognitive performance, blood pressure and antihypertensive medication have been examined in several recent studies [1, 5, 6, 7, 8, 23, 27], but there is no definitive consensus on an independent association of hypertensive medication and/or blood pressure with cognitive performance. In this study we found a negative association between blood pressure and cognitive performance adjusted on age and education level, in treated and nontreated individuals. Conversely, when we

stratified our sample according to blood pressure level we observed a negative association between antihypertensive medication and test scores in all strata.

Whether cognitive impairment in hypertensive individuals is due to white-matter lesions remains to be answered [24, 26]. However, there are other possible explanations, including that of the behavioural effects of antihypertensive medication [19] and the fact that hypertensive individuals have particular psychological profiles that might correspond to a particular neuropsychological pattern [17]. Another explanation is proposed by Farmer, taken from longitudinal measure of blood pressure, suggesting that cognitively impaired patients have reduced their adherence to antihypertensive treatment regimens [8].

Consumers of either psychotropic drugs or antihypertensive medications had approximately 30% increased risk of low cognitive performance compared to nonconsumers. This increase in the risk of scoring poorly was similar to that associated with 10 years of ageing. Medication seems to be an important covariate to consider in longitudinal studies of cognitive decline in ageing.

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