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# Patterns of cognitive function in aging: the Rotterdam Study

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**Abstract** Cognitive impairment is an important hallmark of dementia, but deterioration of cognition also occurs frequently in non-demented elderly individuals. In more than 3,000 non-demented persons, aged 45–99 years, from the population-based Rotterdam Study we studied cross-sectional age effects on cognitive function across various domains. All participants underwent an extensive cognitive test battery that tapped into processing speed, executive function, verbal fluency, verbal recall and recognition, visuospatial ability and fine motor skills. General cognitive function was assessed by the g-factor, which was derived from principal component analysis and captured 49.2 % of all variance in cognition. We found strongest associations for age with g-factor [difference in z-score −0.59 per 10 years; 95 % confidence interval (CI) −0.62 to −0.56], fine motor skill (−0.53 per 10 years; 95 % CI −0.56 to −0.50), processing speed (−0.49 per 10 years; 95 % CI −0.51 to −0.46), and visuospatial ability (−0.48 per 10 years; 95 % CI −0.51 to −0.45). In contrast, the effect size for the association between age and immediate recall was only −0.25 per 10 years (95 % CI −0.28 to −0.22), which was significantly smaller than the relation between age and fine motor skill ($P < 0.001$). In conclusion, in non-demented persons of 45 years and older, general cognition deteriorates with aging. More specifically, fine motor skill, processing speed and visuospatial ability, but not memory, are affected most by age.

**Keywords** Aging · Cognitive function · Cohort · G-factor · Population-based · Dementia

## Introduction

Normal aging, as well as various clinical diseases, such as for example dementia, are accompanied by a deterioration of cognitive function. Even though memory decline is a hallmark of dementia, other cognitive domains, like executive function and processing speed are also often affected [1]. Many studies focus on persons in pre-clinical stages of dementia, i.e. mild cognitive impairment, and therefore are not always generalizable to community-dwelling elderly [2–4]. Still, cognitive aging has also been investigated extensively outside the context of dementia. Age effects have been documented on several cognitive domains, such as spatial orientation, inductive reasoning, memory, verbal and number skills, and in a variety of populations [5, 6]. However, different rates of cognitive decline across cohorts have also been reported and age effects on cognition could be altered over time due to changes in a population with regard to, for example, education, environment, health

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**Table 1** Participation to the current study presented per cohort

| | RSIII-1 | RS-II-3 | RS-I-5 | Total |
|---|---|---|---|---|
| Time period of invitations for participation | Jan 2008–Feb 2012 | Dec 2008–Sep 2011 | Dec 2008–Nov 2010 | Jan 2008–Feb 2012 |
| Females (%) | 55.7 | 56.3 | 59.9 | 57.5 |
| Mean age in years (standard deviation) | 60.0 (8.1) | 72.4 (5.2) | 79.5 (4.8) | 71.9 (9.7) |
| Total number of living persons invited for the current study | 6,027 | 2,322 | 2,952 | 11,301 |
| Refusal | 1,074 | 344 | 597 | 2,015 |
| Incapable to participate | 10 | 38 | 92 | 140 |
| Incapable to participate due to self-reported dementia | 0 | 25 | 62 | 87 |
| Non-response | 1,017 | 23 | 56 | 1,096 |
| Total number of responders to invitation and interview | 3,926 | 1,892 | 2,145 | 7,963 |
| Number of participants to any cognitive test | 1,132 | 1,639 | 1,651 | 4,422 |
| Number of participants to all cognitive tests | 764 | 1,189 | 1,068 | 3,021 |

Note that for cohort RSIII-1 there is a remarkably large difference between the amount of persons that participated in the interview and the amount of persons that participated in any of the cognitive tests. This large difference can be explained by the fact that the included sample (n = 1,132) was selected from the point at which the design organization test was included in the study. This test was only fully introduced into the Rotterdam Study in January 2008. Sex and mean age are based on the number of participants to any cognitive test (n = 4,422)

factors, or employment [7–9]. Therefore, more contemporary data on aging effects on cognition are needed.

In order to gain a comprehensive understanding of cognitive function in non-demented elderly, it is essential to study a broad range of cognitive domains in unselected community-dwelling persons. Furthermore, in addition to studying separate domains, it is equally important to investigate global cognition. The rationale for this is that cognition consists of a general underlying construct that is domain-independent and reflects an individual's general cognitive function. This construct is linked to intelligence and can be quantified as a general cognitive factor, or g-factor. The g-factor is a stable concept, comprising the shared variance between cognitive tests, and can be interpreted as a common underlying factor to a variety of cognitive domains [10–12]. The g-factor has even been shown to be independent of cognitive test batteries used, and can therefore be easily generalized to other studies [13].

The aim of this study was to investigate patterns of cognitive function in middle-aged and elderly community-dwelling persons. We specifically studied both general cognition, using the g-factor, as well as specific cognitive domains.

## Methods

### Setting

The study is embedded within the Rotterdam Study, a population-based cohort study in middle-aged and elderly participants that started in 1990 and aims to investigate frequency, causes and determinants of chronic diseases [14]. The initial cohort encompassed 7,983 persons and was expanded by 3,011 persons in 2000 and by 3,932 persons in 2005. In-persons examinations take place every 3–4 years and consists of home interview and three center visits. The institutional review board of Erasmus MC approved the study and participants gave written informed consent.

### Study population

Table 1 shows the number of participants from each cohort used in this study. Also, age at time of invitation to the study, sex and if available level of education are given for participants and non-participants to the study (Supplementary table 1). Additionally, we show age and sex of participants by year (Supplementary Table 2). The current cross-sectional study focuses on the period from January 1st 2008 onwards, because only then the full cognitive test battery in its current format was implemented. From the persons who responded to the invitation to participate in the study (n = 7,963), persons with a stroke (n = 325) or prevalent dementia (n = 73) were excluded from the sample used in this study. Sixteen persons had both a stroke and dementia and were excluded. For dementia, the assessment is based on a two-step procedure, which has been published before [15]. It involves screening by mini-mental state examination (MMSE), additional work-up by CAMDEX, informant interview, additional neuropsychological assessment, imaging, and final diagnosis in a consensus meeting led by a neurologist. For stroke, the

**Table 2** Description of cognitive tests

| Cognitive test | Test demand | Latent skills |
|---|---|---|
| Mini mental state examination [17] | 30 Item test (range 0–30) | Global cognitive function |
| Stroop task [18] | | |
| Reading subtask | Reading color names aloud (time taken) | Speed of reading |
| Color naming subtask | Naming colors (time taken) | Speed of color naming |
| Color-word interference subtask | Naming colors of color names printed in incongruous ink color (time taken) | Interference of automated processing and attention |
| Letter-digit substitution task [19] | Writing down numbers underneath corresponding letters (range 0–125) | Processing speed, executive function |
| Verbal fluency test [20] | Mentioning as many animals possible in 1 min | Efficiency of searching in long-term memory |
| 15-Word learning test [21] | | |
| Immediate recall | Immediate recall of 15 words directly after visual presentation (range 0–15) | Verbal learning |
| Delayed recall | Delayed recall of words 10 min after visual presentation (range 0–15) | Retrieval from verbal memory |
| Recognition | Correctly recognize words that were shown 10 min before (range 0–15) | Recognition of verbal memory |
| Design organization test [22] | Reproduce designs using a numerical code key (range 0–56) | Visuospatial ability |
| Purdue pegboard both hands [23] | In 30 s, place as many pins in parallel rows of holes using left and right hand simultaneously (range 0–25) | Dexterity and fine motor skill |

assessment is based on self-report, family doctor files, and files of medical specialists, which are all discussed in a consensus panel led by a neurologist [16]. Also, neuroimaging is used if required.

Until February 29th 2012, cognitive tests were performed in 3,706 up to 4,176 persons. In case of technical problems, refusal of participation, physical limitations, or deviation from instructions, test results were excluded. This explains the range in number of subjects that performed various cognitive tests. The number of persons in the study who completed a valid cognitive test result on any of the tests used was 4,422 (Table 1). The complete cognitive test battery was available in 3,021 persons.

## Cognitive test battery

During two separate center visits a cognitive test battery was administered, which included MMSE [17], Stroop test [18], letter-digit substitution task (LDST) [19], verbal fluency test [20], 15-word verbal learning test (15-WLT) [21], design organization test (DOT) [22] and Purdue pegboard test [23]. A description of the cognitive tests, test demands and latent skills measured is given in Table 2. Level of education was obtained and categorized into seven levels, ranging from primary to university education. Higher scores indicate a better performance on all cognitive tests, except for the Stroop task in which a higher score indicates a worse performance. Scores for the Stroop task were thus inverted for better comparison to other tests. The DOT is a test which is based on and highly correlated to WAIS-III block design, but is administered in two rather than 10 min and is less dependent on motor skills than the block design test [22]. Test score on the DOT has a range from 0 to 56 points for each subject.

## G-factor [12]

To calculate a general cognitive factor (g-factor) we performed a principal component analysis incorporating color-word interference subtask of the Stroop test, LDST, verbal fluency test, delayed recall score of the 15-WLT, DOT and Purdue pegboard test. For tests with multiple subtasks we chose only one subtask in order to prevent highly correlated tasks distorting the factor loadings. Principal component analysis was performed on complete case data of 3,021 persons. The g-factor was identified as the first

**Table 3** Characteristics of the study population

| | Men (n = 1,880) | Women (n = 2,542) | *P* value sex difference* |
|---|---|---|---|
| Age, years | 71.5 ± 9.5 | 72.2 ± 9.8 | 0.02 |
| Primary education only (%) | 9.5 | 16.8 | <0.01 |
| Cognitive tests | | | |
| Mini mental state examination, test score | 27.6 ± 2.3 | 27.6 ± 2.2 | 0.02 |
| Stroop reading subtask, seconds | 17.8 ± 3.7 | 18.0 ± 3.7 | 0.97 |
| Stroop color naming subtask, seconds | 24.8 ± 5.4 | 24.2 ± 4.9 | <0.01 |
| Stroop interference subtask, seconds | 54.3 ± 20.2 | 54.4 ± 21.3 | 0.11 |
| Letter digit substitution task, number of correct digits | 27.6 ± 6.8 | 27.7 ± 7.7 | <0.05 |
| Verbal fluency test, number of animals | 21.8 ± 5.7 | 21.2 ± 5.9 | 0.46 |
| 15-Word learning test immediate recall, number of correct answers | 20.8 ± 6.0 | 22.9 ± 6.3 | <0.01 |
| 15-Word learning test delayed recall, number of correct answers | 6.5 ± 2.7 | 7.5 ± 2.9 | <0.01 |
| 15-Word learning test recognition, number of correct answers | 13.0 ± 2.1 | 13.5 ± 1.9 | <0.01 |
| Design organization test, number of corrects | 25.6 ± 9.8 | 23.0 ± 10.3 | <0.05 |
| Purdue pegboard test, number of pins placed | 9.4 ± 1.8 | 9.9 ± 1.8 | <0.01 |

Values are unadjusted mean ± standard deviation

* *P* values for cognitive tests comparing values of men and women are adjusted for level of education

unrotated component of the principal component analysis and explained 49.2 % of all variance in the cognitive tests. This is a typical amount of variance accounted for by the g-factor [12].

### Statistical analysis

To aid comparison across cognitive tests we first calculated z-scores for cognitive test scores. The MMSE score was not standardized due to its skewed nature. We used analysis of covariance to compare scores between men and women, adjusting for level of education. We used linear regression models to investigate the continuous association between age and cognitive test score, corrected for level of education. In additional analyses we used subcohort as an extra covariate to the linear regression model to test for cohort effects. We used Z tests to formally test differences of age effects between cognitive tests. We tested interaction effects between age and sex and explored non-linear effects of age on cognition. All analyses were performed using the statistical software package SPSS version 20.0 for Windows. Results are presented with 95 % confidence intervals (CI).

## Results

Mean age was 71.9 years (SD = 9.7), with 57.5 % women (Table 3). Men scored better than women on the DOT, whereas women scored better on Stroop color naming, immediate recall, delayed recall and recognition parts of the 15-WLT, and Purdue pegboard test (Table 3). Pearson correlation coefficients between all cognitive test scores are shown in Supplementary table 3.

Figure 1 illustrates MMSE score and g-factor in 5-year strata of age. MMSE score stayed stable until age 70 and then showed a rapid decline. In contrast, the g-factor showed decline in scores already from age 45 onwards. The mean decline in g-factor per 10 year increase in age was −0.59 (95 % CI −0.62 to −0.56). For both MMSE score and g-factor we also found a quadratic effect of age (Table 4).

Figure 2 shows mean test scores in 5-year strata of age. We found the strongest decline for Purdue pegboard, LDST, DOT and Stroop interference task (Table 5). In contrast, smaller effects of age were found for 15-WLT immediate recall (−0.25 per 10 years; 95 % CI −0.28 to −0.22), delayed recall (−0.23 per 10 years; 95 % CI −0.26 to −0.20) and recognition (−0.09 per 10 years; 95 % CI −0.12 to −0.05). These differences in age effects between the memory subtasks versus Purdue pegboard, LDST, DOT and Stroop were confirmed by formal statistical testing (Z tests). For example, the age effects on the Purdue pegboard test or DOT were both significantly larger than the effect on immediate recall ($P < 0.001$). Still, the strongest effects of age were on the g-factor, rather than any individual cognitive test.

Finally, we found that for the Purdue pegboard test and LDST, age effects were stronger in women than men. Also, quadratic effects of age on cognition were found for the Stroop tasks, the LDST, verbal fluency, and the Purdue pegboard test. Adding subcohort as an extra covariate to the model did not reduce the effects of age on cognitive scores.

## Discussion

In a large community-dwelling cohort of persons 45 years and older, we found that age strongly affects

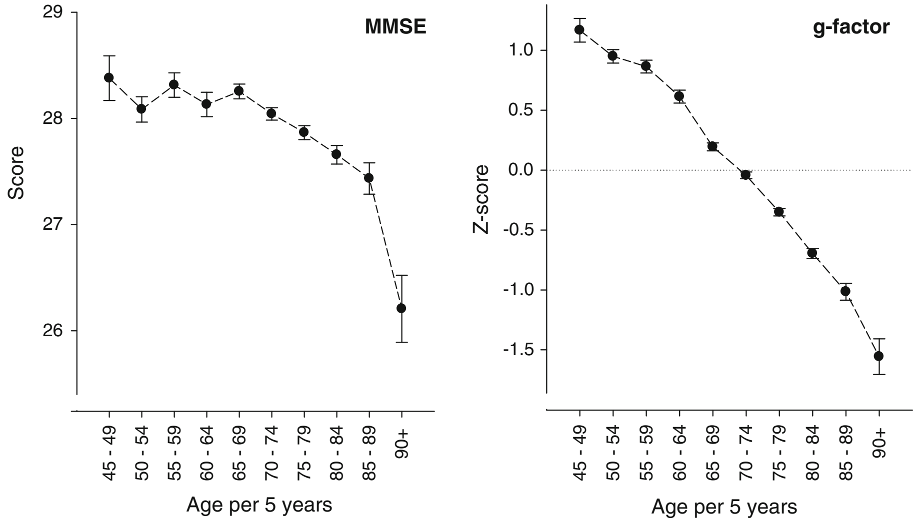

**Fig. 1** Age effects on global cognitive scores. The x-axis represents age per 5 years and the y-axis represents the MMSE-score or z-score of the g-factor. *Error bars* represent 95 % confidence intervals. Estimates are adjusted for level of education. *MMSE* mini mental state examination, *g-factor* general cognitive factor

**Table 4** Association of age with global cognitive function

| N = 3,021 | Total | Men | Women | $P_{\text{interaction}}$* | $P_{\text{quadratic}}$** |
|---|---|---|---|---|---|
| MMSE | −0.24 (−0.30; −0.18) | −0.30 (−0.39; −0.22) | −0.19 (−0.28; −0.10) | 0.11 | <0.01 |
| G-factor | −0.59 (−0.62; −0.56) | −0.60 (−0.64; −0.56) | −0.58 (−0.62; −0.54) | 0.73 | <0.01 |

Values represent differences in MMSE score and g-factor per 10 year increase, adjusted for level of education

*MMSE* mini mental state examination, *g-factor* general cognitive factor

* *P* value for interaction between age and sex

** *P* value for quadratic effect of age on cognition for total sample

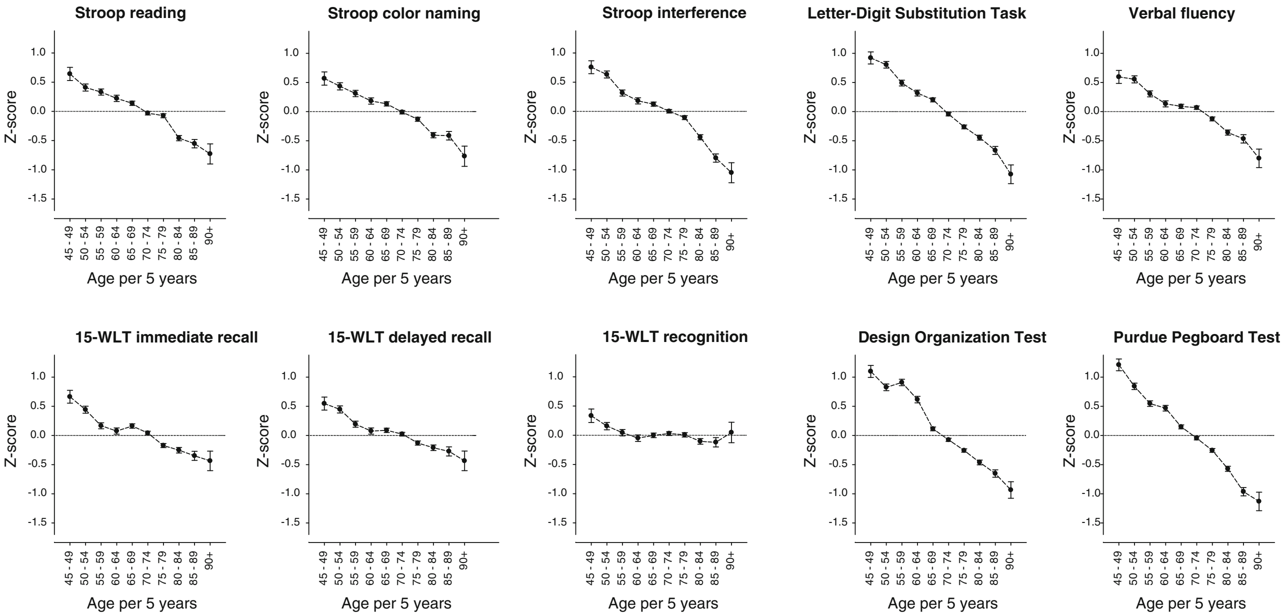

**Fig. 2** Cognitive function in 5-years bins. The *x-axis* represents age per 5 years and the *y-axis* represents the z-score on the test. *Error bars* represent 95 % confidence intervals. All estimates are adjusted for level of education. *15-WLT* 15-Word learning test

general cognitive function, measured by the g-factor. The effect of age on general cognitive function was already apparent from 45 years onwards. Investigating separate cognitive domains, we found strongest associations of age with fine motor skill, processing speed, and visuo-spatial ability.

**Table 5** Association of age with cognitive test scores

| | Total | Men | Women | $P_{\text{interaction}}$* | $P_{\text{quadratic}}$** |
|---|---|---|---|---|---|
| Stroop reading, n = 4,042 | −0.32 (−0.35; −0.29) | −0.31 (−0.35; −0.26) | −0.31 (−0.35; −0.27) | 0.43 | <0.01 |
| Stroop naming, n = 4,041 | −0.32 (−0.35; −0.29) | −0.34 (0.39; −0.29) | −0.30 (−0.33; −0.26) | 0.10 | <0.01 |
| Stroop interference, n = 4,030 | −0.41 (−0.44; −0.38) | −0.43 (−0.47; −0.38) | −0.40 (−0.44; −0.36) | 0.12 | <0.01 |
| Letter-digit substitution task, n = 4,074 | −0.49 (−0.51; −0.46) | −0.42 (−0.46; −0.38) | −0.53 (−0.56; −0.49) | 0.01 | <0.01 |
| Verbal fluency test, n = 4,176 | −0.32 (−0.35; −0.29) | −0.29 (−0.33; −0.24) | −0.34 (−0.38; −0.30) | 0.19 | <0.01 |
| 15-Word learning test immediate recall, n = 3,826 | −0.25 (−0.28; −0.22) | −0.25 (−0.30; −0.21) | −0.25 (−0.29; −0.21) | 0.77 | 0.25 |
| 15-Word learning test delayed recall, n = 3,825 | −0.23 (−0.26; −0.20) | −0.23 (−0.28; −0.18) | −0.23 (−0.28; −0.19) | 0.75 | 0.71 |
| 15-Word learning test recognition, n = 3,902 | −0.09 (−0.12; −0.05) | −0.09 (−0.15; −0.04) | −0.08 (−0.13; −0.04) | 0.75 | 0.39 |
| Design organization test, n = 3,706 | −0.48 (−0.51; −0.45) | −0.50 (−0.55; −0.46) | −0.46 (−0.50; −0.42) | 0.21 | 0.12 |
| Purdue pegboard test, n = 3,801 | −0.53 (−0.56; −0.50) | −0.48 (−0.53; −0.44) | −0.56 (−0.60; −0.53) | 0.02 | <0.01 |

Values represent differences in cognitive test scores per 10-year increase, adjusted for level of education. All cognitive scores are expressed as z-scores

* *P* value for interaction between age and sex

** *P* value for quadratic effect of age on cognition for total sample

Strengths of this study include the large community-dwelling study sample and availability of multiple cognitive tests. An important limitation to the interpretation of our results is the cross-sectional design. Also, relations between age and cognition could partly be influenced by cohort effects. However, differences in age effects across cognitive tests are comparable since all analyses were performed on the same group of persons. Another problem is that not all cognitive tests were completed by all participants to our study and that participants are younger and usually in better health compared to non-participants [24]. Therefore, in our g-factor analyses, we selected a sample with fully available cognitive data. We should keep in mind that this may have introduced some selection bias and has may reduce the generalizability of the results. We also note that in order to summarize the different cognitive tests into one g-factor, we selected six cognitive test variables under the assumption that these are representatives of various cognitive domains (executive function, processing speed, verbal fluency, memory, visuospatial ability, and fine motor skill), which are frequently used in cognitive aging research. Other studies may select different tests to construct a g-factor and will possibly get a slightly different outcome. However, it was previously found that g-factors constructed from variable test batteries result in factors that are highly correlated [13]. Thus, the g-factor is likely to be a stable concept. It is comprised of shared variance between tests, and can be interpreted as a factor which is common to a variety of cognitive domains.

In this study sample, we showed that the g-factor is affected already from age 45 onwards. Also, compared to the other cognitive tests in our battery, the g-factor was most strongly related to age. The strength of relation between age and cognition was consistent with those found by others [25, 26]. MMSE score only showed a decline from age 70 onwards. The MMSE is often used to test global cognitive function in older adults, yet it has frequently been criticised for its ceiling effect [27, 28]. In agreement with a large study of healthy elderly, we did not find strong effects of age on MMSE score [29].

Among our other cognitive tests, we found that fine motor skill, processing speed and visuospatial ability were most affected by age. In agreement with the observed relation between age and visuospatial ability, WAIS-III block design performance starts to decline from the mid-forties onward [12]. Other studies have also suggested a more prominent role for decline in visuospatial ability in aging research [30, 31]. One study reported a composite score of visuospatial ability to be a significant predictor of developing cognitive decline [2]. However, another large cohort study reported relatively small effects of age on visuospatial ability [4]. Already in the youngest age groups we found an effect of age on performance on the Purdue pegboard test. Population studies in the healthy elderly that looked into age effects on fine motor skills are scarce. The relatively large age effects on the LDST are in line with previous studies showing strong age effects on processing speed [9, 32]. Interestingly, these findings are supported by indirect evidence from neuroimaging studies which found that white matter declined faster than grey matter and white matter deterioration was associated with decline in motor skill and tasks of processing speed [33–35]. However, others concluded there is a relative stability of white matter volume in aging [36, 37]. The effect size we found relating age to memory was small compared to age effects on other cognitive scores. Again, this is in line with evidence showing that memory function is more dependent on grey matter which decreases gradually with aging [38, 39]. Furthermore, we found that women scored better on memory tests than men, which is in accordance with previous findings that women have better verbal memory than men [40, 41]. No difference in age effects on memory was found between men and women. It is expected that memory would be more strongly affected in dementia rather than normal aging. The exclusion of prevalent dementia cases from our study possibly contributed to the small negative effects of age on memory. However, there is a continuum between normal cognitive aging and dementia, and persons in the preclinical stages of dementia were not excluded from the study population. Normal cognitive aging research has often found that the more frontal brain functions such as attention and executive function are affected earlier than memory [42–44]. The relatively smaller effect on the verbal fluency test may reflect the fact that we used a category fluency test rather than a phonemic fluency test. Category fluency places a larger demand on memory performance rather than frontal lobe function [45, 46]. Furthermore, we found a stronger effect on the color-word interference subtask of the Stroop, compared to the reading and naming subtasks. The Stroop color-word interference task requires more cognitive control than the first two subtasks and is more dependent on executive function, specifically on attention and inhibition [19].

In conclusion, in persons of 45 years and older, age is most strongly related general cognitive function. Our findings also suggest that not memory, but fine motor skill, processing speed, and visuospatial ability are affected most by advancing age.

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**Conflict of interest** The authors declare that they have no conflict of interest.

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