Heritability of neurocognitive functioning in the elderly: evidence from an Italian twin study

FRANCO GIUBILEI1*, EMANUELA MEDDA2*, CORRADO FAGNANI2, VALENTINA BIANCHI1, ANTONELLA DE CAROIS1, MARCO SALVETTI1, MICAELE SEPE-MONTI1, MARIA A. STAZI2

*Franco Giubilei and Emanuela Medda contributed equally to the work.

1Department of Neurological Sciences, Second Faculty of Medicine, University ‘La Sapienza’, Rome, Italy
2National Centre for Epidemiology, Surveillance and Health Promotion, Istituto Superiore di Sanità, Rome, Italy

Address correspondence to: Emanuela Medda. Tel: (+39) 06 4990 4153; Fax: (+39) 06 4990 4151. Email: emanuela.medda@iss.it

Abstract

Background: the genetic and environmental origins of individual differences in specific cognitive abilities in the elderly are poorly understood. One reason is the lack of studies performed in cohorts with normal cognitive functions.

Objective: to estimate the relative contributions of genetic and environmental factors in determining inter-individual variation in neurocognitive abilities in the Italian population.

Design: cross-sectional analysis of twin data.

Setting: a sample of older twins with normal cognition from the population-based Italian Twin Registry (ITR).

Subjects: twin pairs resident in Rome and born between 1926 and 1940, identified through the ITR in 2002. The final study population included 93 twin pairs.

Methods: subjects underwent neuropsychological tests providing information about different cognitive domains. The contributions of genetic and environmental effects were assessed using standard univariate twin modelling based on linear structural equations.

Results: the best-fitting model incorporated additive genetic (A) and unique environmental (E) sources of variance for the following tests: Mini-Mental State Examination (A = 55%), Raven (A = 56%), Attentional Matrices (A = 79%), Copying Drawings (A = 69%) and Story Recall (A = 54%).

For Phonological and Semantic Verbal Fluency, the best model included non-additive (D) and unique environmental influences (D = 62 and 54%, respectively). Cigarette smoking was estimated to be negatively associated with the score of Phonological Verbal Fluency. For Token test, the inter-individual variance was entirely due to environmental factors not shared by the twins.

Conclusion: our data showed that most of the specific cognitive abilities are moderately to highly heritable, and that the environmental factors of relevance for these abilities are those causing within-family differences.

Keywords: heritability, cognitive abilities, elderly, twins

Introduction

A particularly important feature of quality of life in the elderly is cognitive functioning, which includes general and specific cognitive ability. The diminution in cognitive ability that emerges with ageing has been extensively investigated, and has been associated with various determinants [1, 2]. This decline is a result of complex interactions of genetic and environmental factors, whose nature and mechanisms still remain largely unknown [3].

There is overwhelming evidence for the existence of genetic influences on individual general cognitive differences [4, 5, 6, 7]. However, the actual localisation and identification of genes underlying variation in general cognitive abilities has only recently begun. Success is currently limited to genetic mutations in neurodegenerative diseases causing severe cognitive effects. Less is known about the genetic and environmental origins of individual differences in specific cognitive abilities. In this regard, most studies have focused on children or young adult subjects [8, 9, 10].

In the elderly, studies on specific cognitive ability have investigated relatively few domains, such as executive functions and working memory, and have been performed in twin samples including subjects with cognitive deficit [11, 12, 13, 14]. Most of the data converge on the conclusion that genetic factors play a crucial role in specific
cognitive abilities [15, 16, 17, 18], but the real environmental influence on these cognitive abilities is not well quantified. Confounding factors might have influenced these conclusions as no previous studies have been performed using samples of old twins with normal cognitive functions.

Twins offer a unique and powerful method in genetic epidemiologic research. Considering the degree of phenotypic resemblance of monozygotic versus dizygotic twins with respect to a given trait, and assuming that relevant environmental exposures are shared by twins to the same extent regardless of zygosity (‘equal environments assumption’), it is possible to estimate the relative weight of genetic and environmental influences on the trait [19].

The main purpose of the present study is to explore, in cognitively normal twins aged 62–80 years and belonging to the population-based Italian Twin Registry (ITR), the relative contributions of genetic and environmental factors in determining inter-individual variation of specific neurocognitive abilities.

Methods

Participants

The Italian twin registry

The ITR, a nationwide database of all ‘possible twins’ in the Italian general population, was set up in 2001 [20] using a personal identification number (fiscal code). Population-based twin registries such as the ITR [20, 21], as well as several other extant or emerging registries worldwide [22] are highly valuable for epidemiologic research due to the lack of ascertainment bias [23].

Subjects in the study

In 2002, the ITR identified 2,993 possible twin pairs resident in Rome and born between 1926 and 1940. A questionnaire for twin status ascertainment and a letter for the presentation of the Registry were sent to them. According to a previous estimate of an average 40% surplus of pseudo-twins in the ITR [20], around 1,200 subjects contacted were expected not to be twins. Among those who were expected to be real twins (∼1,800), 506 responded confirming their twin status and were, therefore, contacted by telephone. Out of these 506 twins, 265 (52.4%) agreed to undergo a neuropsychological assessment at the Department of Neurological Sciences of the University ‘La Sapienza’ of Rome. As 75 subjects were excluded from the study because one twin in a pair was dead or refused to participate, the final study population included 95 intact twin pairs (n = 190). Subjects signed an informed consent and underwent a battery of neuropsychological tests administered by the same trained physician. Data on socio-demographic characteristics and medical history were also collected (Table 1). These data did not reveal any significant differences between the twins participating in the study (190 subjects, 95 pairs) versus the remaining ones.

Two out of the 95 twin pairs [one monozygotic (MZ) male, one dizygotic (DZ) female] were also excluded because of cognitive deficit caused by cerebrovascular disease in a twin, leaving a total of 93 pairs for the data analysis. None had a medical history of brain disease nor were taking sedative or antidepressive therapies, and nobody lived in a sheltered accommodation.

Zygosity was determined by using a validated self-report questionnaire [24], which included questions on twins’ similarities during childhood. According to the answers, twin pairs were classified as MZ or DZ.

Measures

Cognitive performance was evaluated using a battery of neuropsychological tests largely employed in the clinical setting. The raw scores of each assessment instrument were

<p>| Table 1. Socio-demographic characteristics and relevant diseases of twins |
|---------------------------------|----------------|----------------|---------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>MZ twinsa (%)</th>
<th>DZ twinsb (%)</th>
<th>Total samplec (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Zygosity and gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24 (34.3%)</td>
<td>49 (42.2%)</td>
<td>73 (39.2%)</td>
</tr>
<tr>
<td>Female</td>
<td>46 (65.7%)</td>
<td>67 (57.8%)</td>
<td>113 (60.7%)</td>
</tr>
<tr>
<td>Twins from DZ male pairs</td>
<td></td>
<td></td>
<td>22 (11.8%)</td>
</tr>
<tr>
<td>Twins from DZ female pairs</td>
<td></td>
<td></td>
<td>40 (21.5%)</td>
</tr>
<tr>
<td>Twins from DZ opposite-sex pairs</td>
<td></td>
<td></td>
<td>54 (29.0%)</td>
</tr>
<tr>
<td><strong>Martial statusd</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unmarried</td>
<td>9 (13.0%)</td>
<td>12 (11.0%)</td>
<td>21 (11.8%)</td>
</tr>
<tr>
<td>Married/cohabitant</td>
<td>47 (68.1%)</td>
<td>75 (68.8%)</td>
<td>122 (68.5%)</td>
</tr>
<tr>
<td>Divorced</td>
<td>1 (1.4%)</td>
<td>6 (5.5%)</td>
<td>7 (3.9%)</td>
</tr>
<tr>
<td>Widowed</td>
<td>12 (17.4%)</td>
<td>16 (14.7%)</td>
<td>28 (15.7%)</td>
</tr>
<tr>
<td><strong>Children</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>53 (76.8%)</td>
<td>87 (72.1%)</td>
<td>140 (78.0%)</td>
</tr>
<tr>
<td>No</td>
<td>16 (23.2%)</td>
<td>23 (20.5%)</td>
<td>39 (20.0%)</td>
</tr>
<tr>
<td><strong>Smoking habits</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No smokers</td>
<td>41 (58.6%)</td>
<td>68 (58.6%)</td>
<td>109 (58.6%)</td>
</tr>
<tr>
<td>1–300 packs/year of cigarettes</td>
<td>12 (17.1%)</td>
<td>11 (9.5%)</td>
<td>23 (12.4%)</td>
</tr>
<tr>
<td>301–600 packs/year of cigarettes</td>
<td>7 (10.0%)</td>
<td>24 (20.7%)</td>
<td>31 (16.7%)</td>
</tr>
<tr>
<td>&gt;600 packs/year of cigarettes</td>
<td>10 (14.3%)</td>
<td>13 (11.2%)</td>
<td>23 (12.4%)</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>25 (38.5%)</td>
<td>39 (37.1%)</td>
<td>64 (37.6%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8 (11.9%)</td>
<td>5 (4.7%)</td>
<td>13 (7.5%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3 (4.5%)</td>
<td>6 (5.7%)</td>
<td>9 (5.3%)</td>
</tr>
<tr>
<td>Age at interview (mean ± SD)</td>
<td>67.9 ± 4.8</td>
<td>67.5 ± 4.7</td>
<td>67.6 ± 4.7</td>
</tr>
<tr>
<td><strong>Number of children (mean ± SD)</strong></td>
<td>1.74 ± 1.3</td>
<td>1.84 ± 1.1</td>
<td>1.80 ± 1.2</td>
</tr>
<tr>
<td><strong>Years of education (mean ± SD)</strong></td>
<td>11.8 ± 4.2</td>
<td>10.9 ± 4.5</td>
<td>11.2 ± 4.4</td>
</tr>
</tbody>
</table>

a MZ, monozygotic; DZ, dizygotic.

b n, number of individuals.

c SD, standard deviation.
d Numbers do not add up due to missing values.
adjusted for age and education according to the distribution of normative data for the Italian population.

The tests were selected to provide information about different areas of cognition: orientation and global assessment [Mini-Mental State Examination (MMSE)] [25, 26], selective attention (Attentional Matrices) [27], episodic long-term memory (Story Recall test) [28], non-verbal logical reasoning and problem-solving ability [Raven’s Coloured Progressive Matrices (PM 36)] [29, 30], word generation by phonological and semantic cues [Phonological (F-P-L) and Semantic (animals) Verbal Fluency test] [31, 32], auditory comprehension of complex sentences (Token test) [33], spatial abilities and constructional praxis (Copying Drawings) [34]. The diagnosis of dementia was made according to DSM IV criteria [35].

**Statistical analysis**

Twin intra-class correlations with their 95% confidence intervals for each cognitive scale were calculated for MZ and DZ twin pairs, separately. In the classical twin study, such correlations are informative in relation to the importance of genes and environment in explaining the total phenotypic variance in a trait. A substantially higher correlation in MZ twins, genetically identical, compared with DZ twins, who share on average 50% of their segregating genes, indicates that genetic factors play a role [36].

Standard univariate twin modelling based on linear structural equations was used [19]. The model allows for separation of the total phenotypic variance into the following components: (i) additive genetic variance (A), due to additive effects of alleles at each contributing genetic locus; (ii) non-additive genetic variance (D), determined by intra-locus (dominant) or inter-locus (epistatic) allelic interaction; (iii) common (shared) environmental variance (C), attributable to environmental events common to both members of a twin pair; (iv) unique (unshared) environmental variance (E), that results from environmental effects not shared by members of a twin pair, including measurement error. Model fitting was done with the statistical software Mx [37]. Parameters were estimated by the maximum likelihood method, where the models were fitted to the raw data on MZ and DZ pairs. Parameter estimates were reported under the best model; the latter was selected on the basis of the Akaike Information Criterion (AIC): the model with the lowest AIC value reflects a balance between goodness of fit and parsimony. (For more information about Statistical analysis, see the supplementary data, Appendix 1, on *Age and Aging* online.)

Two measured covariates (number of children and number of packs of cigarettes smoked per year) were included in the models.

**Results**

Socio-demographic characteristics and relevant medical history of MZ and DZ twins are provided in Table 1. There were 35 MZ pairs (12 males, 23 females) and 58 DZ pairs (11 males, 20 females, 27 opposite sex). The MZ/DZ same-sex/DZ opposite-sex ratio was 1.1/1.0/0.9, and it did not deviate substantially from the expected 1/1/1 population distribution. No statistically significant differences between MZ and DZ twins were observed in the means for age, number of children and years of education, or in the distributions of gender, marital status, having children, and smoking habits. Furthermore, no differences between the two zygosity groups were detected for any relevant clinical conditions and diseases potentially related to cognitive performance. The proportions of twins with hypertension and diabetes mellitus were 37.6 and 7.5%, respectively, and myocardial infarction was reported in about 5% of the total sample.

Results from the neuropsychological examination indicated that none of the subjects satisfied the diagnosis of dementia according to DSM IV criteria nor had a MMSE score ≤ 24, confirming normal cognition in our twin sample.

Table 2 shows mean values and standard deviations of the neuropsychological tests in twins considered as individuals, as well as within-pair intra-class correlations. As regards the means and the variances of the cognitive test scores— with the exception of the variance of Copying Drawings—we did not find statistically significant differences between MZ and DZ twins. While for the Token test the correlation was rather weak in both zygosity groups, all the other cognitive scales showed a substantially higher correlation in MZ than in DZ pairs, suggesting the presence of moderate to high genetic influences. The estimates ranged from 0.51 (MMSE) to 0.84 (Attentional Matrices) in MZ twins, and from 0 (Semantic Verbal Fluency) to 0.51 (Attentional Matrices) in DZ twins. In the case of Phonological and Semantic Verbal Fluency, the MZ correlation largely exceeded the DZ correlation, and this pointed to non-additive genetic effects.

The results of univariate twin modelling are shown in Table 3. The best-fitting model was an AE model incorporating additive genetic and unique environmental sources of variance for the following tests: MMSE (A = 55%), Raven (A = 56%), Attentional Matrices (A = 79%), Copying Drawings (A = 69%) and Story Recall (A = 54%). In the Attentional Matrices scale, where the correlations were consistent with possible shared environmental effects, the point estimate of these effects from the full ACE model was 0.23, but it did not reach the significance level (data not shown). For Phonological and Semantic Verbal Fluency, the best explanation of the data was obtained under a DE model, which provided estimates for non-additive genetic effects of 62 and 54%, respectively. Furthermore, number of packs of cigarettes smoked per year was estimated to be negatively associated (coefficient = −0.0041) with the score of the Phonological Verbal Fluency test.

With respect to the Token test, the best-fitting model was one in which the inter-individual variance was entirely due...
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Table 2. Mean values and twin intra-class correlations for the cognitive tests by zygosity group

<table>
<thead>
<tr>
<th>Test</th>
<th>Zygosity</th>
<th>N pairs</th>
<th>Mean ± SD</th>
<th>Correlation (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini-Mental State Examination</td>
<td>MZ</td>
<td>35</td>
<td>29.1 ± 1.1</td>
<td>0.51 (0.26–0.75)</td>
</tr>
<tr>
<td></td>
<td>DZ</td>
<td>58</td>
<td>29.2 ± 1.4</td>
<td>0.21 (0.00–0.46)</td>
</tr>
<tr>
<td>Token</td>
<td>MZ</td>
<td>35</td>
<td>31.5 ± 1.8</td>
<td>0.14 (0.00–0.47)</td>
</tr>
<tr>
<td></td>
<td>DZ</td>
<td>58</td>
<td>31.8 ± 1.9</td>
<td>0.06 (0.00–0.32)</td>
</tr>
<tr>
<td>Raven’s Coloured Progressive Matrices</td>
<td>MZ</td>
<td>35</td>
<td>29.0 ± 4.9</td>
<td>0.60 (0.38–0.81)</td>
</tr>
<tr>
<td></td>
<td>DZ</td>
<td>58</td>
<td>29.9 ± 4.0</td>
<td>0.33 (0.10–0.56)</td>
</tr>
<tr>
<td>Phonological Verbal Fluency</td>
<td>MZ</td>
<td>35</td>
<td>32.3 ± 9.2</td>
<td>0.69 (0.52–0.86)</td>
</tr>
<tr>
<td></td>
<td>DZ</td>
<td>58</td>
<td>31.9 ± 8.2</td>
<td>0.14 (0.00–0.39)</td>
</tr>
<tr>
<td>Semantic Verbal Fluency</td>
<td>MZ</td>
<td>35</td>
<td>18.6 ± 3.3</td>
<td>0.56 (0.33–0.79)</td>
</tr>
<tr>
<td></td>
<td>DZ</td>
<td>58</td>
<td>18.6 ± 3.6</td>
<td>0.00 (0.00–0.26)</td>
</tr>
<tr>
<td>Attentional Matrices</td>
<td>MZ</td>
<td>34</td>
<td>60.9 ± 10.4</td>
<td>0.84 (0.75–0.94)</td>
</tr>
<tr>
<td></td>
<td>DZ</td>
<td>56</td>
<td>62.4 ± 8.4</td>
<td>0.51 (0.31–0.70)</td>
</tr>
<tr>
<td>Copying Drawings</td>
<td>MZ</td>
<td>35</td>
<td>12.8 ± 0.7</td>
<td>0.52 (0.27–0.76)</td>
</tr>
<tr>
<td></td>
<td>DZ</td>
<td>58</td>
<td>12.7 ± 1.0</td>
<td>0.28 (0.04–0.52)</td>
</tr>
<tr>
<td>Story Recall</td>
<td>MZ</td>
<td>35</td>
<td>13.1 ± 3.9</td>
<td>0.59 (0.38–0.81)</td>
</tr>
<tr>
<td></td>
<td>DZ</td>
<td>58</td>
<td>13.8 ± 3.4</td>
<td>0.25 (0.01–0.49)</td>
</tr>
</tbody>
</table>

a MZ, monozygotic; DZ, dizygotic.
b Means and standard Deviations (SD) refer to single individuals.
c 95% CI = 95% confidence interval.
d Three pairs (1 MZ and 2 DZ) in which one of the twins had an outlier value on the scale were excluded.

Discussion

This study represents the first attempt to explore, in a sample of cognitively normal older twins belonging to the population-based ITR, the genetic and environmental contributions to inter-individual variability of specific cognitive abilities as evaluated by an extensive neuropsychological battery. With the exception of the Token test, we found that the best-fitting models implicated both genetic (additive or non-additive) and unique (unshared) environmental influences. In other words, our data indicated that the observed within-family resemblance in each of the tests was basically due to genetic effects common to relatives, and that the relevant environmental factors were those creating differences rather than similarities among relatives. Overall the heritability estimates were moderate to high, ranging from 0.54 (Semantic Verbal Fluency and Story Recall) to 0.79 (Attentional Matrices). The genetic factors were more likely to act in a non-additive (dominant or epistatic) manner for the Verbal Fluency abilities and in an additive manner for the remaining abilities. These results are in agreement with previous reports that highlighted the role of genetic factors in specific cognitive abilities such as memory and verbal fluency [12, 38]. We emphasise, however, the high genetic contribution observed in attentional (Attentional Matrices) and praxic (Copying Drawing) abilities, which has not been reported previously.

For the Token test, no family resemblance was detected, and thus the inter-individual variance resulted in being exclusively accounted for by idiosyncratic environmental factors. This result is not easily explicable. Although the subjects were not taking sedative or antidepressive therapies, we speculate that mood might have influenced the auditory comprehension performance. This hypothesis is supported by the fact that having children was estimated to be associated with a better Token test performance in this study. In this respect, it is not possible to know how much of the individual-specific environmental influence on each of the tests is due to measurement error. A prospective design based on repeated measures would be needed to separate the contribution of measurement error from that of unshared environmental factors.

MMSE scores in our subjects clearly suggest normal cognitive function. This contrasts with previous studies that reported low MMSE scores, suggesting the presence of subjects affected by dementia or cognitive deficit [4, 11, 39]. We can thus hypothesise that factors other than genetic and environmental factors are likely to act in a non-additive (dominant or epistatic) manner for the Verbal Fluency abilities and in an additive manner for the remaining abilities. These results are in agreement with
environmental, such as anatomical and neurotransmitter damages connected to dementia, may influence the heritability estimates in those twin studies.

With respect to the measured environmental covariates that were introduced in the models, smoking appeared to have a negative impact on the Phonological Verbal Fluency performance. Relatedly, Fried et al. [40] recently found that current regular smokers performed significantly worse than non-smokers in a variety of cognitive areas predicated upon verbal/auditory competence. The mechanisms by which smoking affects cognitive performance are not clear. It has been proposed that smoking may increase oxidative stress through generation of free radicals, thereby affecting the inflammatory-immune systems, or that it may damage the cerebral arteries [41, 42].

In accordance with previous results [11, 12], no shared environmental influences on the variation of the cognitive scales emerged, confirming that the relevant environmental factors do not relate to childhood family background nor can they be ascribed to experiences shared by relatives in adulthood. However, in the Attentional Matrices scale the correlations were suggestive of possible effects of common environment. The point estimate of these effects from the full ACE model was appreciable in magnitude (0.23), but it was not significant. Clearly, issues of statistical power, which may have affected the model selection, should be considered here.

The limited sample size also prevented us from addressing other important issues, such as testing whether the magnitude of genetic effects on the scales varies according to gender or determining if the same set of genes influence the scales in males and females. Although gender-specific genetic processes have been suggested for dementia and cognitive dys-function in older twins [43], some twin studies on cognitive abilities in large elderly twin samples did not find any evidence of different genetic effects for men and women [44, 45].

The finding that unshared environmental factors play a substantial role in determining individual differences in neuropsychological performance suggests that the study of elderly MZ twins discordant for neurocognitive functioning, supplemented with neuroimaging and neurochemistry evaluations, would be of help to elucidate the specific environmental factors involved. However, to reduce the number of confounding factors, MZ twins affected by dementia or cognitive deficit should be excluded from these future studies.

As a neuropsychological evaluation is the best tool to define and monitor the cognitive deficits in old people, the identification of environmental factors that influence the performance on specific cognitive domains is crucial. This information is most likely to be elucidated by the neuropsychological tests employed in a clinical setting.

In conclusion, our results suggest that individual differences in specific cognitive abilities in older people with normal cognitive function are explained by both genetic and
environmental factors. The genetic contribution is moderate to high, as shown by heritability estimates between 0.54 and 0.79. The only exception is in auditory comprehension ability, for which no genetic effects are detected. The environmental factors that are relevant for these abilities appear to be those causing within-family differences. Further twin studies, possibly including neuroimaging and neurochemistry evaluations, are warranted to better understand the sources of inter-individual variation in specific cognitive abilities in the elderly. This knowledge might have an important role in the early diagnosis of cognitive impairments.

Key points
- Specific cognitive abilities were evaluated by a battery of neuropsychological tests in a sample of older Italian twins with normal cognitive function.
- Heritability estimates of cognitive abilities were moderate to high (range: 54–79%).
- Relevant environmental factors were those creating within-family differences.

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Conflict of interest
There are no conflicts of interest.

Supplementary data
Supplementary data for this article are available on Age and Ageing online.

References
The very long list of references supporting this article has meant that only the most important are listed here and are represented by bold type throughout the text. The full list of references is available on Age and Ageing online as Appendix 2.

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