Gene, environment and cognitive function: a Chinese twin ageing study

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Abstract

Background: the genetic and environmental contributions to cognitive function in the old people have been well addressed for the Western populations using twin modelling showing moderate to high heritability. No similar study has been conducted in the world largest and rapidly ageing Chinese population living under distinct environmental condition as the Western populations.

Objective: this study aims to explore the genetic and environmental impact on normal cognitive ageing in the Chinese twins.

Design/setting: cognitive function was measured on 384 complete twin pairs with median age of 50 years for seven cognitive measurements including visuospatial, linguistic skills, naming, memory, attention, abstraction and orientation abilities. Data were analysed by fitting univariate and bivariate twin models to estimate the genetic and environmental components in the variance and co-variance of the cognitive assessments.

Results: intra-pair correlation on cognitive measurements was low to moderate in monozygotic twins (0.23–0.41, overall 0.42) and low in dizygotic twins (0.05–0.30, overall 0.31) with the former higher than the latter for each item. Estimate for heritability was moderate for overall cognitive function (0.44, 95% CI: 0.34–0.53) and low to moderate for visuospatial, naming, attention and orientation abilities ranging from 0.28 to 0.38. No genetic contribution was estimated to linguistic skill, abstraction and memory which instead were under low to moderate control by shared environmental factors accounting for 23–33% of the total variances. In contrast, all cognitive performances showed moderate to high influences by the unique environmental factors.

Conclusions: genetic factor and common family environment have a limited contribution to cognitive function in the Chinese adults. Individual unique environment is likely to play a major role in determining the levels of cognitive performance.

Keywords: ageing, cognitive function, heritability, Chinese twins, older people

Introduction

The old-aged Chinese population has increased dramatically in recent decades. By end of 2013, the population aged over 60 had been ~200 million and accounted for 14.9% of the total population. This number is estimated to reach ~25% in 2030. It is expected that, by year 2050, there will have been 440 million of old people over 60 years accounting for 1/3 of the whole population. The rapidly ageing Chinese population is creating a growing burden to the society [1]. Studying and promoting healthy ageing for mid-life and older adults hold the key to improve public health in the fast ageing population.
Cognitive function is a strong determinant of self-care ability in the old people. The age-related declines in cognitive performances, e.g. memory and attention have been well documented and constituted one of the greatest threats to an individual’s ability to live independently [2]. It has been shown that, as a complex trait, cognitive function can be under control of both genetic and environmental factors. In the past decades, the classical twin method has been applied to estimate the genetic and environmental contributions to cognitive performances, e.g. the Swedish Adoption/Twin Study of Aging (SATSA) and the Minnesota Twin Study of Adult Development and Aging (TSADA) [3]. Heritability estimates of cognitive performance were 30% for the Iowa Screening score, 60% for the Mini-Mental State score and 67% for the Digit Symbol Substitution score [4]. Heritability of general cognitive ability (GCA) in SATSA was estimated to be 81% in the younger and middle-aged twins from 27 to 65 years, 54% at the age of 65–85 [5] and 62% at age of 80 and over [6]. The Older Australian Twin Study (OATS) reported a heritability estimate for GCA of 74% [7]. In the Longitudinal Study of Aging Danish Twins (LSADT), estimates of heritability of composite scores derived from three cognitive measures including digit span, word list recall and category fluency ranged from 0.39 to 0.76, and heritability estimates for digit span, word list recall and category fluency as individual measures were 0.26, 0.43 and 0.37 [8, 9], respectively.

Although the genetic and environmental aspects of cognitive function have been well studied in the Western populations, to our knowledge, no similar study has been conducted in the rapidly ageing Chinese population. This paper reports results from the first twin study on cognitive performance in Chinese middle-aged adult and old-aged twins as part of a comprehensive investigation on genetic and environmental regulation on ageing phenotypes or traits.

Materials and methods

Sample collection

The study was based on the Qingdao Twin Registry (QTR) established in 1998 at the Qingdao Center for Disease Control and Prevention (Qingdao CDC) [10, 11], the first population-based twins registry in China [12, 13]. Twins were recruited through the network of Qingdao CDC in residential communities in the municipality of Qingdao through residence registry, medical records and media announcements. Complete pairs of middle-aged and old-aged twins were recruited in 2012 and 2013. Twins unconscious, unable or unwilling to co-operate and incomplete twin pairs were excluded from sampling. The final sample consisted of 384 twin pairs including 244 monozygotic (MZ) and 140 dizygotic (DZ) twin pairs aged from 33 to 80 years with a median age of 50. Venous blood was drawn for zygosity determination for like-sex twin pairs using 16 multiple STR (Short Tandem Repeat) DNA markers [14, 15] at the central laboratory of Qingdao Blood Center with correct zygosity assignment ascertained to be 99.9%.

The study was approved by Regional Ethics Committee at Qingdao CDC Institutional Review Boards (QDCDC-IRB) and conducted according to the principles of the Helsinki Declaration. All participants signed consent form and completed questionnaire and health examination in the local service centre of Qingdao CDC or community hospital/clinics.

Measurements of cognitive function

For each twin pair, face-to-face interview with each twin was performed by the same well-trained and experienced interviewer. We used the MoCA (Montreal Cognitive Assessment, www.mocatest.org, (4 November 2014, date last accessed) Beijing version) scale to test the general cognitive performance of the participants. MoCA is the most age-sensitive and effective test for assessing cognitive function of healthy ageing [16–20]. The MoCA scale includes several cognitive domains including visuospatial/executive (score 0–5), naming (score 0–3), attention (score 0–6), language (score 0–3), abstraction (score 0–2), delayed recall (score 0–5) and orientation (score 0–6). Educational level was quantified by totalling the number of years to complete the participant’s highest of schooling, adding 1 score if it is <12 years of education. So the MoCA is a brief 0–30 point assessment of global cognition that evaluates a broad array of cognitive domains.

Data analysis

Data were entered and corrected by Epidata3.1 (www.epidata.dk 4 November 2014, date last accessed). Considering the skewed distribution of cognitive function, all seven cognitive measurements were transformed by Box–Cox power transformation to ensure approximately normal distribution using the free R package car. Data were first analysed to estimate the intra-class or intra-pair correlation coefficients (ICCs). In the model fitting, age, sex and education were included as co-variates to adjust for their effects on cognitive performance [21]. For each measurements, we estimated ICC and tested statistical significance for the effects of age, sex and education using \textit{twinslm} function in the free R package \textit{mets} by setting type =’u’.

Twin modelling

For each of the seven cognitive measurements, the classical twin model decomposes total variance into additive genetic (A), dominant genetic (D)/shared family environment (C) and unique environmental (E) components by fitting the models encompassing the A, C and E components (the full ACE model) or the A, D and E components (the full ADE model) with the ADE model only considered when phenotype correlation in MZ twins is over two times that in the DZ twins. By dropping each variance components from the full model in turn, the nested models (AE, CE, DE, E) can be fitted and statistical significance of corresponding removed variance component can be tested using the likelihood ratio test. Comparison between the full and the nested models enables
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selection of the best performance model based on the principle of model parsimony as indicated by the Akaike's Information Criterion (AIC) [22]. Besides univariate twin modelling, we also fitted bivariate models with aim at assessing the genetic and environmental components in the co-variance between two cognitive assessments. Twin models were fitted using the free R package mets and the free software package Mx (http://www.vcu.edu/mx 4 November 2014, date last accessed).

Results

In Table 1, we showed the descriptive statistics (median, percentiles) together with results from fitting linear models for twins to each measurement for the effects of age, sex and education. There was a strong pattern of declining in cognitive function with increasing age and decreasing birth-cohort as indicated by the highly significant negative regression coefficients. On the contrary, cognitive function went up significantly with level of education. For sex, naming and attention were lower in females than in males while females had higher level of delayed recall. Table 1 also had ICCs for all measurements for MZ and DZ twins estimated separately. Overall, MZ twins had higher ICCs than those for DZ twins for all items except language, an indication of genetic influence in most of the cognitive measurements. However, only orientation had significantly higher ICC for MZ than for DZ twins with \( P < 0.001 \). Similar pattern was applied to visuospatial skill and attention but at borderline significance.

We fitted both full ACE and ADE models and their nested models to each of the seven cognitive measurements and to cognitive score. After model selection, five of them had the AE model while language, abstraction and delayed recall had the CE model as their best fitting model (Table 2). In all the AE models, only low to moderate heritability (0.28–0.44) was estimated with 95% CIs well beyond zero. The highest heritability (0.44) was obtained by cognitive score. Likewise, the CE models had low to moderate C components (0.23–0.33) with all 95% CIs above zero.

Considering the large age range of our sample, we stratified all the participants into two age groups, the young group (<50 years, 177 pairs) and the old group (≥50 years, 207 pairs) and fitted twin models to see whether the heritability estimates differed by age group. Only the heritability of ‘attention’ decreased significantly from young to old groups with heritability going down from 0.5427 (95% CI: 0.4048–0.6807) in the young to 0.2587 (95% CI: 0.1164–0.4011) in the old groups. No statistically significant age group difference in heritability estimates was observed on the other traits.

For each combination of the seven items of cognitive function, we additionally fitted bivariate models to examine the genetic and environmental components in their phenotype correlation. Similar to the univariate analysis, both full and nested models were fitted by dropping the genetic and environmental components in the co-variance of two cognitive assessments. In Table 3, we showed the estimated proportion of genetic and environmental co-variance (left side of table)
and corresponding genetic and environmental correlation (right side of table) for each combination of measurement pairs. Similar to the univariate analysis, the best fitting models were either AE or CE models. Different from the univariate analysis, the co-variance for some of the measurement pairs exhibited high genetic and low unique environmental contributions (e.g. 0.91 and 0.09 for visuospatial skill and naming; 0.83 and 0.17 for attention and language) while for some others low genetic and high unique environmental contribution (e.g. 0.2 and 0.8 for abstraction and orientation; 0.32 and 0.68 for naming and attention). In general, the estimated coefficients for unique environmental correlation were very

<table>
<thead>
<tr>
<th>Subphenotype pair</th>
<th>Co-variance</th>
<th>Correlation coefficient</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>A (95% CI)</td>
<td>C (95% CI)</td>
<td>E (95% CI)</td>
</tr>
<tr>
<td>Visuospatial/Executive—Naming</td>
<td>0.91</td>
<td>–</td>
<td>0.09</td>
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<tr>
<td>Visuospatial/Executive—Attention</td>
<td>0.54</td>
<td>–</td>
<td>0.46</td>
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<tr>
<td>Visuospatial/Executive—Language</td>
<td>–</td>
<td>0.34</td>
<td>0.66</td>
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<tr>
<td>Visuospatial/Executive—Abstraction</td>
<td>–</td>
<td>0.33</td>
<td>0.67</td>
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<td>Visuospatial/Executive—Delayed recall</td>
<td>–</td>
<td>0.26</td>
<td>0.74</td>
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<tr>
<td>Visuospatial/Executive—Orientation</td>
<td>0.38</td>
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<td>0.62</td>
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<td>Naming—Attention</td>
<td>0.32</td>
<td>–</td>
<td>0.68</td>
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<tr>
<td>Naming—Language</td>
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<td>Naming—Abstraction</td>
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<td>0.51</td>
<td>0.49</td>
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<td>Naming—Delayed recall</td>
<td>0.76</td>
<td>–</td>
<td>0.24</td>
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<tr>
<td>Naming—Orientation</td>
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<td>0.50</td>
<td>0.50</td>
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<td>Attention—Language</td>
<td>0.83</td>
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<td>0.51</td>
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<td>Language—Orientation</td>
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<td>Abstraction—Orientation</td>
<td>0.20</td>
<td>–</td>
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<tr>
<td>Delayed recall—Orientation</td>
<td>0.61</td>
<td>–</td>
<td>0.39</td>
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A, genetic co-variance between traits; C, shared environmental co-variance between traits; E, non-shared environmental co-variance between traits; \( \tau_a \), genetic correlation between traits; \( \tau_c \), shared environmental correlation between traits; \( \tau_e \), non-shared environmental correlation between traits.

*P < 0.05.
low and for some of the phenotype pairs, the coefficients were not different from zero, an indication that the random error in one measurement had nothing to do with that in the other.

Discussion

To our knowledge, we have conducted the first twin study on cognitive function in the adult Chinese population. We observed low to moderate heritability with the highest of 0.44 obtained by cognitive score. Our heritability estimates were considerably lower than the 0.6 for the Mini-Mental State score and 0.67 for the Digit Symbol Substitution score reported by Swan GE [4], or 0.54–0.81 for GCA in SATSA [6], or 0.74 for GCA in OATS [7], or 0.54–0.79 from an Italian twin study [23], or 0.57 for cognitive function in the UK [24]. Our estimates seemed to be in agreement with results from a Danish twin study which reported low to moderate heritability estimates for digit span (0.26), word list recall (0.43) and category fluency (0.37) in the Longitudinal Study of Aging Danish Twins (LSADT) [8, 9]. In general, our heritability estimates for cognitive performances were lower than most of the Western countries. One reason for the disparity could be the different instruments used for measuring cognitive function. Here, we wanted to emphasise the importance of the unique environmental factors in explaining the differences. As a developing country, living standard or quality of life, family environment and working condition can be very different for the Chinese. These non-genetic factors could have profound influences in the development of cognitive impairment during ageing and introduce large proportion of variation in cognitive performance measured as the E components in our models. This is in contrast to the developed countries in the Western world where basic or standard living environments (e.g. education, health care) are well maintained. In fact, it has been found that genetic influences on cognition can be suppressed by social economic disadvantages [25], a situation that fits our study population. Another possible contributor to the differences could be ethnicity. As a result of adaptation to different environmental conditions, the Eastern and Western populations could have developed different schemes for maintaining cognitive function in response to gene–environment interactions. Well-designed twin studies in China and in the West using similar battery of cognitive measurements are needed to confirm our hypotheses and to provide replication to our results as well.

As the Chinese society becomes more and more knowledgeable as a result of economic transition, cognitive health will serve as an increasingly important determinant of well-being in the ageing population. The high contribution to cognitive function by unique environment in the Chinese twins suggested high importance of individual non-genetic factors such as quality of life, education, social environment in shaping cognitive function. In this sense, our results could impact the strategies for promoting cognitive health and healthy ageing in the Chinese population.

It is not surprising that our bivariate models reported moderate to high or even very high genetic or shared environmental component/correlation in the co-variation of the seven cognitive measurements as they encompass different domains of cognitive function. Taking attention-language for example, the shared genetic basis for the two measurements accounted for 83% of their co-variance (Table 3). The complete genetic correlation of 1 implied that the two items were genetically identical. In fact, the two measurements both represented ability in acquisition and analysis of linguistic information perceived. Similar perfect genetic correlation was estimated for delayed recall with naming, attention, language, abstraction and orientation. We assumed that, as a measurement for memory, the delayed recall share similar biological traits (e.g. genetic variants) with these abilities which can be modified by exogenous environmental factors for and during the development of various profiles of cognitive skills. Note that a strong genetic correlation did not necessarily translate to a high proportion of genetic co-variance as the latter was merely a relative measurement. Attention and delayed recall had perfect genetic correlation which accounted for only 54% of their co-variance due to influences from random factors including measurement error that explained for the rest of the co-variance with $r_e = 0.18$ (95% CI: 0.07–0.29).

It is necessary to point out the limitations of our study. Compared with published studies in the Western countries, our sample size was very small, a reason that could explain the large estimates of 95% CIs especially for the estimated genetic and environmental correlations as shown in Table 3. Another limitation is the relatively young age of our twin samples and the large span of age covered (47 years). Although age had been adjusted in the twin modelling, the non-linear pattern, if any, of age-dependent change in cognition could have been averaged out and which could also serve to reduce power of the study. Finally, our twins had overall low education level compared with twins from the developed countries. However, our questionnaire was copied from the Western design which could create difficulty in communication and understanding during the interview. Proper modification to the standard cognitive assessment system to avoid measurement error due to cultural and language issues can be necessary for future Chinese studies.

Key points

- Genetic factors have low to moderate contribution to the variation of cognitive measurements in Chinese twins.
- Cognitive performances in adult Chinese are mainly influenced by individual unique environments.
- The different domains for measuring cognitive function display moderate to high genetic or common environmental correlation.

Authors’ contributions

All authors contributed significantly to the study with C.X., Z.P., D.Z., Q.T: experiment design, conduct of project, data

Conflicts of interest
None declared.

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