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Analysis of genetic and environmental correlation between leisure activities and cognitive function in aging Chinese twins

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ABSTRACT

Objective: Leisure activity has been shown to be beneficial to mental health and cognitive aging. The biological basis of the correlation is, however, poorly understood. This study aimed at exploring the genetic and environmental impacts on correlation between leisure activities and cognitive function in the Chinese middle- and old-aged twins.
Methods: Cognition measured using a screening test (Montreal Cognitive Assessment, MoCA) and leisure activities including intellectual and social activity were investigated on 379 complete twin pairs of middle- and old-aged twins. Univariate and bivariate twin models were fitted to estimate the genetic and environmental components in their variance and covariance.
Results: Moderate heritability was estimated for leisure activities and cognition (0.44–0.53) but insignificant for social activity. Common environmental factors accounted for about 0.36 of the total variance to social activity with no significant contribution to leisure activity, intellectual activity and cognition. Unique environmental factors displayed moderate contributions (0.47–0.64) to leisure activities and cognition. Bivariate analysis showed highly and positively genetic correlations between leisure activities and cognition (r_G=0.80–0.96). Besides, intellectual activity and cognition presented low but significant unique environmental correlation (r_E=0.12).
Conclusions: Genetic factor had the moderate contribution to leisure activities and cognition. Cognitive function was highly genetically related to leisure activities. Intellectual activity and cognitive function may share some unique environmental basis.

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Classical twin method; genetic correlation; cognitive function; intellectual activity; social activity; leisure activities

Introduction

Human aging is accompanied by progressive declining in cognitive ability and reduced participation in various activities. Cognitive function and participating in leisure activity, such as intellectual and social activity are essential to guarantee the well-being, independent living and quality of life in the old population (Iizuka et al., 2019). Intellectual and social engagements are two representative domains of leisure activity, which are also important protective factors against cognitive decline (Bidzan, Bidzan, & Pąchalska, 2016). Actively taking part in all kinds of leisure activity can help to reduce the risk of cognitive impairment and maintain cognitive function (Iizuka et al., 2019).

The existing literature indicates that involvement in leisure activity may contribute to life satisfaction, happiness and successful aging in the old population (Cha, 2018; Hicks & Siedlecki, 2017). Leisure activity constitutes a major part of daily life and is considered as an important provider of cognitive stimulation at old ages. There is convincing evidence that involving in intellectual activity is associated with cognitive reserve in the old population (Ruthirakuhan et al., 2012). Higher level of intellectual activity participation can undoubtedly lead to better cognitive function and decelerated cognitive decline with aging. Engagement in social activities could decrease the risk of cognitive decline therefore maintaining or improving the resident quality of life (Su, Huang, Jin, Wan, & Han, 2018). A 12-year follow-up study in an old age population found that more social activity was associated with less rate of cognitive decline (James, Wilson, Barnes, & Bennett, 2011). Promoting social activity may help to maintain the cognitive function in middle- and old-aged population in Korea (Choi, Park, Cho, Chun, & Park, 2016). Published studies also confirmed that high level of social engagement was associated with good cognitive function and reduced rate of cognitive decline at old ages (Kelly et al., 2017). Increased engagement in social pursuits were related to a slowing rate of cognitive decline in a study of 20-year follow-up (Marioni et al., 2015). On the other hand, cognitive ability could in return affect social engagement within the ‘normal’ range of cognitive performance (Lifshitz-Vahav, Shrira, & Bodner, 2017).

It has been shown that frequent intellectual and social activity could help to improve the cognitive function in the general population. In fact, one study has revealed a reciprocal relationship between participating in leisure activity and cognitive function (Lifshitz-Vahav et al., 2017) emphasizing effect of leisure participation on cognitive improvement particularly in older adults with low basic cognitive

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level. Generally speaking, leisure activity may have a positive role in preserving or maintaining normal cognitive function even preventing or delaying cognitive decline with aging according to literature reviews (Fallahpour, Borell, Luborsky, & Nygard, 2016; Iizuka et al., 2019; Yates, Ziser, Spector, & Orrell, 2016). Participation in different type of leisure activities may be equally important in terms of maintaining cognitively intact.

In the literature, multiple studies have reported the genetic effects on leisure participation (Aaltonen et al., 2017; Aaltonen, Kujala, & Kaprio, 2014; Haberstick, Zeiger, & Corley, 2014; van der Zee, Helmer, Boomsma, Dolan, & de Geus, 2020) and on cognition (Iacono et al., 2018; Xu, Sun, Duan, et al., 2015). Although the relationship between leisure activity and cognition has been intensively studied, the genetic and environmental impacts on the correlation have not been well documented. Understanding the genetic and environmental contributions to the observed correlation could provide clues for forming strategic measures to promote healthy cognitive aging through efficient management and intervention. We hypothesized the existence of genetic and environmental modulation on both leisure participation and cognition and aimed at assessing their common genetic and environmental components using the classical twin design. This article reports our findings on genetic and environmental correlations from applying bivariate twin models to a Chinese cohort of middle- and old-aged twins.

Materials and methods

Sample collection

Twin subjects were collected through the Qingdao Twin Registry (QTR) based at Qingdao Center for Disease Control and Prevention (Qingdao CDC), which was the first twin registry in China. Twin participants were recruited from local CDC institutions, communities and public media from 2012 to 2013. Twins unwilling or unable to take part in the project and the incomplete twin pairs were excluded from the sampling. The final sample constituted a total of 379 complete adult twin pairs, encompassing 240 pairs of monozygotic (MZ) twins (114 male or MZM, 126 female or MZF) and 139 pairs of dizygotic (DZ) twins (41 males or DZM, 39 females or DZF, 59 opposite sex or OSDZ) aged 51.8 ± 7.6 years (range: 40–80 years). Zygosity was identified by multiple DNA markers with 99.9% correct assignment (Becker et al., 1997; von Wurmb-Schwark, Schwark, Christiansen, Lorenz, & Oehmichen, 2004) at the laboratory of Qingdao Blood Center. The sample collection was described in detail elsewhere (Xu, Sun, Duan, et al., 2015; Xu, Sun, Ji, et al., 2015).

Institutional Review Board of Qingdao CDC approved the study. The project was conducted in accordance with the ethical principles of the Helsinki Declaration. All participants signed the informed consent and then completed the questionnaire of leisure activity and cognition together in the same survey with well-trained investigators.

Measurements of leisure activity

The checklist of leisure activity was adopted and modified from previously relevant studies (Gow, Avlund, & Mortensen, 2014; Jopp & Hertzog, 2010; Leung et al., 2011; Verghese et al., 2006) so as to comply with Chinese traditional socio-cultural context. Questionnaire of leisure activity, including the intellectual and social subscales reflected a wide range of activities. Intellectual activity was composed of the following 7 questions: (1) reading newspaper; (2) reading books or magazines; (3) writing or keeping a diary; (4) watching TV; (5) travelling; (6) going to theater, cinema or concert; and (7) using internet or library. Social activity consisted of the following seven terms: (1) participating in the social or community activities; (2) dining or attending parties (including playing chess, mahjong, and cards etc.); (3) communicating with friends by telephone or letter; (4) entertaining with friends at home; (5) visiting friends; (6) meeting with the co-twin; and (7) contacting co-twin by telephone.

Besides leisure activity, the subjects were questioned to evaluate the frequency or intensity of participation in the intellectual and social activities. Every item was assessed by the average involvement during the past 1 year period. Participants rated how often they took part in each activity based on a five-point scale: (1) never, (2) at least once a year, (3) at least once a month, (4) at least once a week, (5) everyday or frequent involvement. We quantified the intellectual and social activity with average scores of composite measurement of intellectual and social activity with higher score indicating more activity participation. The leisure activity was assessed by the sum of intellectual and social activity to evaluate the general level of leisure activity engagement, ranging from 2 to 10.

Measurements of cognitive function

The Montreal Cognitive Assessment (MoCA, www.mocatest.org) was introduced to evaluate the cognitive function of the participants. MoCA, including several domains of cognition is a very good age-sensitive and effective tool for cognitive screening (Ciesielska et al., 2016; O'Driscoll & Shaikh, 2017). Each twin pair was interviewed face to face by the same well trained and experienced investigator. The total score of MoCA was adjusted by adding 1 if the participant got no more than 12 years of schooling according to the criteria of MoCA.

Statistical analysis

Basic analysis

Epidata3.1 (www.epidata.dk) was adopted to input data and conduct the quality control of the data. The Box-Cox transformation was applied to convert each indicator variable because of the skewed distribution of the raw data of leisure activities, intellectual activity, social activity and cognitive function of this twin sample. The Box-Cox transformation was done using the free R package *car* (http://cran.r-project.org/web/packages/car/index.html). Age, gender and their interaction and education (education was coded from 1 to 5, representing never attending school, primary school, middle school, high school, college degree and above, respectively) were considered as the covariates to adjust their influences on all indices in fitting the twin models. Twin correlation was measured by calculating the intra-pair correlation coefficients (ICCs). Comparison of ICCs between

MZ and DZ twins provided indication on genetic effect and on mode of genetic inheritance for heritability estimation using twin modeling described below. Likewise, twin correlation between two traits was assessed by calculating the cross-twin cross-trait correlation (CTCTC) estimated as the correlation between trait 1 on twin 1 and trait 2 on twin 2, separately for MZ and DZ twins. CTCTC was used for guiding the fitting of bivariate twin models (see below). Twin correlations were estimated using R and package *mets* (http://cran.r-project.org/web/packages/mets/index.html) adjusting the effects of age, sex and their interaction and education. The data analysis was described in detail elsewhere (Xu et al., 2018).

Classical twin modeling

The classical twin model quantifies the genetic contribution to a trait by relating the assumed difference in genetic similarity between groups of MZ and DZ twin pairs to the difference in trait correlations. The classical twin modeling begins with estimating the variance of a phenotype or trait from its observed variations in MZ and DZ twins, and then attempts to estimate how much of it is due to unobserved or latent genetic effects including additive (A), dominant (D) genetic effects, i.e. heritability; shared common environment (C) – events that happen to both twins, affecting them in the same way; nonshared or unique environment (E) – events that occur to one twin but not the other. Practically, the three components can be estimated by fitting the so-called full ACE model to include additive genetic, common and unique environmental effects if the ICC of MZ twins is less than two times that of DZ twin. A full ADE model including dominant genetic effect can fitted when the ICC of MZ twins is more than doubled that of DZ twins. Nested models of the full models, such as, AE, CE/DE and E can be fitted by dropping variance components. The full and its nested models can be compared using likelihood ratio test so that the best fitting model is chosen on the basis of the parsimonious principle and the Akaike's Information Criterion (AIC) (Huang, 2017; Shipley & Douma, 2020). In addition to the univariate twin modelling described above, we fitted bivariate twin models to assess the genetic and environmental correlations between leisure activity and cognitive function. CTCTC was estimated before fitting the bivariate model and compared across zygosities to provide indication of mode of inheritance for fitting bivariate ACE or ADE model. Twin models were fitted by the free R package *mets* and Mx (http://www.vcu.edu/mx). The twin modeling was described in detail elsewhere (Xu et al., 2018; Xu, Zhang, Tian, Duan, et al., 2017; Xu, Zhang, Tian, Wu, et al., 2017).

Results

The descriptive statistics, including median, percentiles and results of the fitted linear models on each measurement for the effects of age, sex and the interaction and education were shown in Table 1. Detailed description analysis of cognitive function can be found elsewhere (Xu, Sun, Duan, et al., 2015). There was a strong pattern of decrease in leisure activities, intellectual and social activity and cognitive function with age, as indicated by the significantly negative regression coefficients ($P < 0.05$). Sex and age-sex interaction showed no significance for all the indicators ($P > 0.05$). All the indicators went up significantly with the level of education ($P < 0.05$).

The ICCs for all measurements of leisure activities and cognitive function for MZ and DZ twins were estimated separately. Overall, MZ twins had higher ICCs than DZ twins suggesting potential genetic influence although there were no statistical significance (Right side of Table 1). We first fitted a full univariate ACE model and its nested models to each indicator of the leisure activities and cognitive function. Leisure activities, intellectual activity and cognitive function were best fitted by the AE models, whereas social activity had the CE as its best fitting model after model selection. Both the full and the best fitting models were presented in Table 2. Moderate heritability (0.44–0.53) was estimated with 95% CIs well beyond zero again except social activity. Significant common environmental factor was found to account for about 0.36 of the total variance to social activity only. Unique environmental factors displayed moderate contributions (0.47–0.64) to leisure activities and cognitive function.

We found that CTCTCs for three phenotype combinations were higher in MZ than in DZ twins implying potential genetic involvement in the correlations between leisure activities and cognitive function although there were no statistical significance (Table 3). Hence, we additionally fitted bivariate twin models to estimate the genetic and environmental correlations for cognition with the leisure activities. Similar to the univariate analysis, both full and the nested models were fitted for best fitting model selection with the nested models fitted by dropping the genetic and environmental components in the covariance between leisure activities and cognitive function. In Table 4, we also presented the estimated genetic and environmental correlations in the full models and the best fitting models for the combination of cognitive function with every indicator of leisure activities. The correlations between leisure activities and cognitive function were all best fitted the AE model. Furthermore, the combinations between leisure activities and cognitive function presented highly, positively and significantly genetic correlations (r_G=0.80–0.96), all with 95% CIs far above 0. We only found one mild, positive but significant unique environmental correlation between cognition and intellectual activity (r_E=0.12, 95% CI: 0.01–0.23). The unique environmental correlations of the other combinations were all not different from zero. We also did not find any common environmental correlation between leisure activities and cognitive function.

Discussion

As an effort for deepening our understanding the biological mechanisms underlying the orchestration of leisure activities and cognition, this article presented novel findings on the genetic and environmental contributions to the observed individual variations in leisure activities and in cognitive function as well as their correlation, using classical twin method applied to Chinese middle- and old-aged twins.

Univariate analysis found moderate heritability estimates of cognitive function, leisure activities and intellectual

Table 1. Descriptive statistics, regression outputs and ICCs for the indicators.

Indicator	Median	95% Range	Age		Sex		Age × sex		Education		ICCs		
			Coefficients	*P*	Coefficients	*P*	Coefficients	*P*	Coefficients	*P*	MZ	DZ	*P*
Leisure activities	5.57	3.43-7.71	−0.0273	0.0057	−0.3758	0.2748	0.0097	0.1424	0.3836	$< 10^{-12}$	0.50	0.34	0.07
Intellectual activity	2.43	1.57-4.14	−0.0119	0.0051	−0.1402	0.3437	0.0032	0.2598	0.1976	$< 10^{-12}$	0.52	0.37	0.08
Social activity	3.00	2.00-4.14	−0.0232	0.0229	−0.4807	0.1776	0.0123	0.0716	0.1520	7.4680×10^{-9}	0.39	0.31	0.40
Cognitive function	22.0	8.2-28.0	−3.5718	0.0019	−28.6971	0.4766	0.6512	0.3997	36.3880	$< 10^{-12}$	0.42	0.30	0.20

Note: Sex, males coded 1 and females coded 2; Education, never attending school coded 1, primary school coded 2, middle school coded 3, high school coded 4, college degree and above coded 5; ICC, intra-class correlation coefficient; MZ, monozygotic; DZ, dizygotic.

Table 2. The full and the best fitting model for the indicators.

Indicator	Model	A(95%CI)	C/D (95%CI)	E(95%CI)	−2LL	AIC	χ^2	Δdf	*P*
Full model									
Leisure activities	ACE	0.33(-0.01, 0.67)	0.18(-0.13, 0.49)	0.50(0.41, 0.59)	1282.239	1298.239	–	–	–
Intellectual activity	ACE	0.30(-0.03, 0.62)	0.22(-0.07, 0.52)	0.48(0.39, 0.57)	−7.191	8.808727	–	–	–
Social activity	ACE	0.15(-0.19, 0.50)	0.23(-0.06, 0.53)	0.61(0.50, 0.72)	1395.414	1411.414	–	–	–
Cognitive function	ACE	0.22(-0.13,0.57)	0.20(-0.11,0.51)	0.58(0.48,0.68)	8578.376	8592.377	–	–	–
Best fitting model									
Leisure activities	AE	0.51(0.43, 0.60) *	–	0.49(0.40, 0.57) *	1283.349	1297.349	1.110	1	0.2921
Intellectual activity	AE	0.53(0.45, 0.62) *	–	0.47(0.39,0.55) *	−5.287	8.713404	1.904	1	0.1676
Social activity	CE	–	0.36(0.27, 0.44) *	0.64(0.56, 0.73) *	1396.180	1410.180	0.766	1	0.3815
Cognitive function	AE	0.44(0.34,0.53) *	–	0.56(0.47,0.66) *	8579.842	8591.842	1.466	1	0.226

Note: A, Additive genetic influence; C, Common/Shared environmental influence; E, Unique/non-shared environment influence; –2LL, twice the negative log-likelihood; AIC, Akaike's information criterion;χ^2, difference of χ^2 value; Δdf, change in degree of freedom; P, χ^2 test in model fitting; AE or CE model is nested within the ACE model, the ACE model is the fully saturated model. The best fitting model was chosen on the basis of a change in χ^2 not representing a significant worsening of fit.
$^*P < 0.05$.

Table 3. Phenotypic correlation between leisure activities and cognitive function pair.

Leisure activities and cognitive function pair	CTCTC				
	MZ	n_{MZ}	DZ	n_{DZ}	*P*
Leisure activities-cognition	0.47	238	0.35	136	0.18
Intellectual activity-cognition	0.48	239	0.36	137	0.18
Social activity-cognition	0.33	239	0.20	138	0.19

Note: CTCTC, cross-twin cross-trait correlation; MZ, monozygotic; n_{MZ}, number of monozygotic twin pair; DZ, dizygotic; n_{DZ}, number of dizygotic twin pair.

Table 4. Estimated genetic and environmental correlation between leisure activities and cognitive function.

leisure activities and cognitive function pair	Model	Correlation coefficient			AIC	χ^2	Δdf	*P*
		r_G(95%CI)	r_C(95%CI)	r_E(95%CI)				
Full model								
Leisure activities-cognition	ACE	0.91(0.37, 1.00)	0.13(-1.00, 1.00)	0.05(-0.07, 0.17)	723.401	–	–	–
Intellectual activity-cognition	ACE	0.89(0.39, 1.00)	0.33(-1.00, 1.00)	0.13(0.01, 0.25)	649.400	–	–	–
Social activity-cognition	ACE	0.94(0.05, 1.00)	−0.21(-1.00, 1.00)	−0.05(-0.17, 0.07)	953.255	–	–	–
Best fitting model								
Leisure activities-cognition	AE	0.94(0.60, 1.00) *	–	0.04 (-0.07, 0.16)	721.466	0.065	1	0.799
Intellectual activity-cognition	AE	0.96(0.66, 1.00) *	–	0.12(0.01, 0.23) *	647.907	0.507	1	0.476
Social activity-cognition	AE	0.80(0.33, 1.00) *	–	−0.05(-0.16, 0.07)	951.407	0.152	1	0.696

Note: A, Additive genetic influence; C, Common/Shared environmental influence; E, Unique/non-shared environment influence r_G, genetic correlation between traits; r_C, common/shared environmental correlation between traits; r_E, unique/non-shared environmental correlation between traits; AIC, Akaike's information criterion; χ^2, difference of χ^2 value; Δdf, change in degree of freedom; P, χ^2 test in model fitting. The best fitting model was chosen on the basis of a change in χ^2 not representing a significant worsening of fit.
$^*P < 0.05$.

activity. The genetic and environmental analysis of cognitive function was detailed elsewhere (Xu, Sun, Duan, et al., 2015). The present study indicated for the first time that genetic factor significantly contributed to both leisure activities and intellectual activity, whereas, we did not observe significant genetic contribution to social activity although social activity is one component of leisure activities. This does not however mean that there is no additive genetic effect in social activity, just our sample size does not give sufficient power to get it significant by dissecting it from the common environment. As a result, heritability estimate for the composite leisure activities is slightly reduced as compared with intellectual activity (both the mean and 95% CI). On the other hand, the significant early-life environmental effect (comment environmental component C) could have cultivated a twin pair's active lifestyle in engaging in social activities maintained to their adult-age (through epigenetics). We think that this phenomenon serves as a good example of early-life environment in modulating adult-age behavior.

The genetic correlation expresses the extent to which two measurements reflect the same set of genes. Study on genetic correlation can facilitate to explore the pleiotropic genetic variants. This study exhibited that the relatedness between leisure activities and cognitive function stemmed predominantly from genetic rather than the environmental causes, implying that the underlying genes may have pleiotropic effects on leisure activities and cognition. The bivariate genetic analysis showed that the significantly genetic correlation between leisure activities and cognition was high and in the positive direction which was in line with the corresponding CTCTC estimate, suggesting that leisure activities and cognitive function may share some similar genetic background.

We found only intellectual activity and cognitive function presented mild and positive unique environmental correlation. In contrast, we did not observe any significant unique environmental correlation between leisure/social activity and cognitive function. The significant unique environmental correlation between intellectual activity and cognitive function could contribute to the establishment of health and lifestyle habits that would be beneficial to maintain both normally intellectual activity and cognitive functions with aging. Furthermore, we also failed to show the common environmental correlation between all kinds of leisure activities and cognitive function.

In Table 4, the magnitudes of the estimated significant genetic correlation for cognitive function with leisure activities (0.94), intellectual activity (0.96) as well as social activity (0.80) were all very high. This could be explained by the big difference in CTCTCs across zygosities. Our novel findings can be instructive for designing molecular genetic studies to identify pleiotropic genes that regulate both leisure activities and cognitive function. Note that high genetic correlation does not necessarily mean high genetic contribution (heritability) to the co-variation between two traits when the effect from these pleiotropic genes is limited on each trait. This is the case for leisure activity and cognition. The estimated heritability for both traits are actually moderate suggesting that considerable proportions of phenotype variation are due to common (especially social activity) and individual unique environments. The latter is actually highly valuable because the environmental factors can be modified to promote leisure activities with aim to improve cognitive performance and postpone cognitive aging.

In this study, MoCA as a screening instrument may not be optimal to assess the subjects' cognitive function, particularly for the younger half of the sample. Also, the intellectual and social activity was assessed by self-report, which may lead to recall bias, especially for participants with cognitive difficulties. These points may help to partially explain the low heritability of cognition. Moreover, our sample size is still relatively small considering the fact that multiple covariates were included for adjustment. We hope that future studies with well-designed, standardized or validated instruments could help to validate our findings.

Disclosure statement

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