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LETTER

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Genetic contributions to stability and change in intelligence from childhood to old age

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Understanding the determinants of healthy mental ageing is a priority for society today[1,2]. So far, we know that intelligence differences show high stability from childhood to old age[3,4] and there are estimates of the genetic contribution to intelligence at different ages[5,6]. However, attempts to discover whether genetic causes contribute to differences in cognitive ageing have been relatively uninformative[7–10]. Here we provide an estimate of the genetic and environmental contributions to stability and change in intelligence across most of the human lifetime. We used genome-wide single nucleotide polymorphism (SNP) data from 1,940 unrelated individuals whose intelligence was measured in childhood (age 11 years) and again in old age (age 65, 70 or 79 years)[11,12]. We use a statistical method that allows genetic (co)variance to be estimated from SNP data on unrelated individuals[13–17]. We estimate that causal genetic variants in linkage disequilibrium with common SNPs account for 0.24 of the variation in cognitive ability change from childhood to old age. Using bivariate analysis, we estimate a genetic correlation between intelligence at age 11 years and in old age of 0.62. These estimates, derived from rarely available data on lifetime cognitive measures, warrant the search for genetic causes of cognitive stability and change.

General cognitive ability (also known as general intelligence, or *g*[18]) is an important human trait. It shows consistent and strong associations with important life outcomes such as educational and occupational success, social mobility, health, illness and survival[18]. Maintaining good general cognitive ability in old age is associated with better physical health and the ability to carry out everyday tasks[19,20]. Intelligence differences are highly heritable from adolescence, and through adulthood to old age[5,6]. Long-term follow-up studies have shown that about half of the phenotypic variance in general intelligence in old age is accounted for by its measure in childhood[3,4]. The corollary of this is that there are systematic changes through the life course in the rank order of intelligence between people; that is, some people's intelligence ages better than others. The determinants of stability and change in intelligence across the human life course are being sought, and candidate determinants include a wide range of genetic and environmental factors[1,5,7,19,21,22]. There have been longitudinal studies within childhood/adolescence, middle adulthood and old age, but none that stretches from childhood to old age with the same individuals (to our knowledge). Until now, the proportion of the variance in lifetime cognitive stability and change explained by genetic and environmental causes has been almost unknown. Apart from a small contribution from variation in the *APOE* gene, suggested individual genetic contributions to stability and change in intelligence across the life course are largely unreplicated[22]. Therefore, an important novel contribution would be to partition the covariance between intelligence scores at either end of the human life course into genetic and environmental causes. To address this, the present study applies a new analytical method[13–17] to genome-wide association data from human participants with general cognitive ability test scores in childhood and again in old age.

Participants were members of the Aberdeen Birth Cohort 1936 (ABC1936) and the Lothian Birth Cohorts of 1921 and 1936 (LBC1921, LBC1936)[11,12,17]. They are community-dwelling, surviving members of the Scottish Mental Surveys of 1932 (the 1921-born individuals) and 1947 (the 1936-born individuals), in which they took a well-validated test of general intelligence (Moray House Test) at a mean age of 11 years. They were traced and re-tested again in old age on a large number of medical and psychosocial factors for studies of healthy mental and physical ageing. Here, we use cognitive ability test data from childhood and from the first occasion of testing in old age for each subject. For all three cohorts, cognitive ability in old age was measured using the first unrotated principal component from a number of diverse cognitive tests. Additionally, the LBC1921 and LBC1936 cohorts re-took the Moray House Test in old age. Thus, the present study partitions into genetic and environmental causes the variance in stability and change in general intelligence over a period of between 54 and 68 years. Testing for 599,011 SNPs was performed on the Illumina610-Quadv1 chip (Illumina); the genotyping of the samples in this study was described previously[17] and quality control is described in Methods Summary.

To estimate additive genetic and environmental contributions to variation in cognitive ageing we used genotype information from 536,295 genome-wide autosomal SNPs. The method used here is a multivariate extension of our recently developed method, which allows the estimation of distant relationships between conventionally unrelated individuals from the SNP data and correlates genome-wide SNP similarity with phenotypic similarity[13,15]. A detailed description of the overall approach and statistical methods is given in Supplementary Fig. 1 and the Supplementary Note. We used a linear mixed model to estimate variance components. The methodology for the estimation of genetic variation from population samples was described previously and has been applied to continuous traits, including height, body-mass index and cognitive ability[13,15–17], and to disease[23]. The method is analogous to a pedigree analysis, with the important difference that we estimate distant relatedness from SNP markers. Because the relationships are estimated from common SNP markers, phenotypic variance explained by such estimated relationships is due to linkage

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disequilibrium between the genotyped markers and unknown causal variants[13,14,21]. The method estimates genetic variation from SNPs that are in linkage disequilibrium with unknown causal variants, and so provides a lower limit of the total narrow sense heritability because additive variation due to variants that are not in linkage disequilibrium with the genotyped SNPs is not captured.

We first performed a univariate analysis of cognitive ageing (Supplementary Note), which we had defined previously as intelligence scores in old age phenotypically adjusted for intelligence at childhood, by fitting the Moray House Test of intelligence at age 11 as a linear covariate[24]. We estimated that 0.24 (standard error 0.20) of phenotypic variance in cognitive ageing was accounted for by the SNP-based similarity matrix. We next conducted a bivariate genetic analysis of intelligence scores early and later in life, to partition the observed phenotypic covariance in intelligence measured in childhood and old age into genetic and environmental sources of variation. Information on the environmental correlation comes from the comparison of the two phenotypes within individuals whereas the genetic correlation is inferred from between-individual comparisons of the two phenotypes (Supplementary Note). That is, the analysis can inform us about genetic and environmental contributions to stability and change in intelligence across the life course. The phenotypic correlation between Moray House Test intelligence at age 11 and the general intelligence component in old age was 0.63 (standard error 0.02) (Table 1). The bivariate analysis resulted in estimates of the proportion of phenotypic variation explained by all SNPs for cognition, as follows: 0.48 (standard error 0.18) at age 11; and 0.28 (standard error 0.18) at age 65, 70 or 79 (referred to hereafter as 65–79). The genetic correlation between these two traits was 0.62 (standard error 0.22), and the environmental correlation was 0.65 (standard error 0.12). From the results of the bivariate analyses we can make a prediction about the proportion of phenotypic variance explained by the SNPs for cognition at 65–79 years given the phenotype at age 11 years. This provided a prediction of 0.21 (standard error 0.20), which is consistent with the actual estimate of 0.24 (standard error 0.20) from the univariate analysis (Supplementary Table 1), suggesting that the bivariate normal distribution assumption underlying the bivariate analysis is reasonable. Hence, the results from the bivariate analysis contain the full description of the genetic and environmental relationships between cognition at childhood, cognition at old age, and cognitive change. We re-ran this model with different cut-offs for relatedness (Supplementary Table 2). The estimates are very similar but with, as expected, larger standard errors for more stringent cut-offs, which result in a smaller sample size. This shows that the results are not driven by unusually high correlations for a few close relatives.

In the present analyses we did not adopt the usual procedure of dividing the parameter estimates by the standard errors to obtain test statistics and accompanying *P* values, because the standard errors were derived from a first-order Taylor series of the logarithm of the likelihood about the parameter estimates[25] and these can be biased for modest sample sizes. A more appropriate procedure is to use the likelihood-ratio test statistic to test the hypotheses that the genetic correlation coefficient is zero (no genetic correlation) or 1 (perfect genetic correlation). When using a likelihood-ratio test, the estimated genetic correlation coefficient of 0.62 has a borderline significant difference from zero (likelihood-ratio test statistic = 2.56, $P = 0.055$, one-sided test) (Supplementary Fig. 2), and does not differ significantly from 1. This was tested by fitting a repeatability model (which implies a genetic correlation of 1.0 and the same heritability of repeat observations) that has three fewer parameters than the full bivariate model. It resulted in a very similar value of the maximum log-likelihood value; the likelihood-ratio test statistic was 5.6 ($P = 0.133$, 3 degrees of freedom) (Supplementary Table 3).

LBC1921 and LBC1936 had the same Moray House Test administered at age 11 and again in old age. The bivariate analyses were repeated, therefore, using the same test of intelligence in childhood and old age in this subsample of the cohorts. The phenotypic correlation between Moray House Test intelligence at age 11 and in old age was 0.68 (standard error 0.01) (Table 1). The bivariate analysis resulted in estimates of the proportion of phenotypic variation explained by all SNPs for the Moray House Test, as follows: 0.30 (standard error 0.23) at age 11; and 0.29 (standard error 0.22) at age 70–79. The genetic correlation between these two traits was 0.80 (standard error 0.27). When using a likelihood-ratio test, the estimated genetic correlation coefficient of 0.80 is not significantly different from zero (likelihood-ratio test statistic = 1.51, $P = 0.11$). The environmental correlation between these two traits was 0.63 (standard error 0.13). From the results of the bivariate analyses we can make a prediction of the proportion of phenotypic variance explained by the SNPs for the Moray House Test at 70–79 years conditional on the phenotype at age 11 years. This results in an estimate of 0.074 (standard error 0.24) (Supplementary Table 4). Although the standard errors of the estimates are larger because a smaller data set was used, the results are similar to those using the full data and it appears that the choice of phenotype at old age (Moray House Test or a linear combination of a number of tests) has not led to a bias in inference. The estimates suggest that cognition early and late in life are similar traits, with possibly some genetic variation for cognitive change.

Using population-based genetic analyses, we have quantified, for the first time, the genetic and environmental contribution to stability and change in intelligence differences for most of the human lifespan. Genetic factors seem to contribute much to the stability of intelligence differences across the majority of the human lifespan. We provide a lower limit of the narrow sense heritability of lifetime cognitive ageing. The point estimate using a general cognitive ability component in old age is 0.24, albeit with a large standard error (0.20). We describe the estimate as a lower limit because the methods used in the present study allow us only to estimate the proportion of the genetic variation contributing to cognitive ageing that is captured by genetic variants in linkage disequilibrium with common SNPs; this will be lower than the total narrow sense heritability. We do not have a good estimate of the total amount of additive genetic variation for cognitive ageing, and so we cannot easily quantify any heritability that is missing from our estimate. Some of the possible genetic contribution we have found to cognitive change might be attributable to developmental change between age 11 and young adulthood. However, the large phenotypic correlation between age 11 and old-age intelligence, and the fact that heritability estimates of general intelligence by age 11 are at about adult levels[5], lead us to posit that most of the genetic variation we have found is a contribution to ageing-related cognitive changes. The estimate of the genetic contribution to lifetime cognitive change was lower when, for a subsample, the same test was used in childhood and old age.

The bivariate analysis conducted here quantifies how differences in intelligence early and late in life are attributable to environmental

Table 1 | Bivariate analysis of intelligence at age 11 and at age 65–79

	Using general intelligence component in old age		Using Moray House Test in old age	
	Estimate	Standard error*	Estimate	Standard error*
h_1^2	0.478	0.177	0.298	0.229
h_2^2	0.280	0.177	0.289	0.221
r_G	0.623	0.218	0.798	0.266
r_e	0.652	0.125	0.630	0.132
r_P	0.627	0.015	0.680	0.014

Where h_1^2 and h_2^2 are variance explained by all SNPs for intelligence at age 11 and old age, respectively; r_G is genetic correlation; r_e is residual correlation; r_P is phenotypic correlation. A total of 1,940 unrelated individuals were included with the general intelligence component phenotype data at childhood (1,830) or old age (1,839) (1,729 individuals had both phenotypes). Of the 1,515 LBC1921 and LBC1936 individuals, there were 1,391 with genetic information and Moray House Test scores both at age 11 and in old age.

* The standard errors are estimated from a first-order Taylor series expansion about the estimated maximum likelihood values and may be biased downwards[25]. For testing hypotheses we have used the likelihood-ratio test statistic, which is more accurate.

or genetic factors. A genetic correlation of zero would imply that intelligence early and late in life are entirely separate traits genetically, and that variation in the change in intelligence from childhood to old age is partly genetic and a function of the heritability of intelligence early and late in life. At the other extreme, a genetic correlation of one implies that the two traits have the same genetic determinants, so that any variation in the change in intelligence between the two stages in life is purely environmental. At conventional levels of significance we could not rule out either a genetic correlation of zero or one; however, our estimates suggest that genetics and environment could each contribute substantially to the covariance between intelligence at age 11 and old age, and that genetic factors might have a role in cognitive change between the two stages of the life course.

The samples studied here comprise the birth cohorts' survivors, those healthy enough to take part in the studies, and people with less cognitive decline. Therefore, we considered whether our estimate of genetic variation at older ages may be biased downwards because of censoring. From life tables officially published by the Scottish Government based on census data, we estimate that the individuals in our oldest sample who were born in 1921 and alive at age 11 are among the ~50% that were still alive at the time of sample collection. We know that lower childhood cognitive ability per se is associated with premature mortality[26], which, of course, our analyses adjust for, as specified in the models. However, because there is a paucity of data about genetic influences on lifetime cognitive change, we have limited information with regard to how these might affect life expectancy. The only way to know across the lifespan would have been if all children (that is, the ones who survived to older ages—whom we know about—and the ones who did not) had been genotyped in 1947. For non-normative (that is, pathological) cognitive change, there are genetic risk factors associated with younger-onset Alzheimer's disease that result in premature mortality, but such strongly heritable disease is rare and the genes do not seem to affect normative cognitive ageing in those aged 70 years and over[22]. Hence, this is not a concern with regard to our analyses. *APOE* ε4 is a well-known risk factor for non-normative cognitive decline, but any differential effect on survival occurs later in life, and is thus unlikely to have resulted in attrition in our cohort. Moreover, *APOE* is in Hardy–Weinberg equilibrium in even our oldest samples[24], supporting this inference. Other known genetic risk factors for Alzheimer's disease have a very small effect on the risk of disease[27]. Hence, a priori, we have nothing to suggest anything but a largely neutral effect of genes that influence cognitive ageing on survival. However, if there is an effect, the example of cognition[26] (by contrast with cognitive change) would suggest that this would be negative, which would somewhat reduce genetic variation in cognitive change across the lifespan among the survivors.

Until now, studies aimed at finding genetic contributions to cognitive ageing have offered little information. They use too-short follow-up periods, thereby providing too small an amount of cognitive change[7,22]. Cognitive assessments tend to be made only within old age, even though cognitive ageing occurs from young adulthood onwards. They are largely based on behavioural data in twin samples rather than information on DNA variation. The present study is unusual and valuable in capturing over half a century of cognitive stability and change and examining its causes. The results here provide estimates for the genetic and environmental contributions to cognitive stability and change across most of the human lifespan. Even with almost 2,000 individuals, the study's power was insufficient to achieve conventional levels of significance for the estimates. Our emphasis here has not been on the traditional significance thresholds for *P* values per se, but in trying to partition variance in cognitive ability into environmental and genetic causes. The phenotypes available here are rare, and so these point estimates are useful to guide future research. The present findings render attractive a search for genetic mechanisms of cognitive change across the life course. They also suggest the importance of environmental contributions to lifetime cognitive change.

METHODS SUMMARY

Subjects. Recruitment, phenotyping and genotyping of the samples were described previously[11,12,17]. The mental test at age 11 was a Moray House Test[11,12]. In old age, general intelligence was derived using principal components analysis of a number of mental tests and saving scores on the first unrotated principal component (Supplementary Note). In old age, the assessments of general intelligence were made at ages as follows: ABC1936, 64.6 years (standard deviation 0.9); LBC1936, 69.5 (standard deviation 0.8); LBC1921, 79.1 (standard deviation 0.6). The LBC1921 and LBC1936 samples, but not the ABC1936, had repeat testing of the Moray House Test (already taken at age 11 years) at 79.1 and 69.5 years, respectively. After applying the genome-wide complex trait analysis method[13,15], the distribution of inferred relationships in the samples was as shown in Supplementary Fig. 3. We removed one of each pair of individuals whose estimated genetic relatedness was >0.2. We retained 1,940 individuals with childhood or old-age phenotype data (1,729 individuals had both): ABC1936, 425; LBC1921, 512; and LBC1936, 1,003. Of the 1,515 LBC1921 and LBC1936 individuals, there were 1,391 with genetic information and Moray House Test scores at age 11 and in old age.

Genotyping quality control. Quality control procedures were performed per SNP and per sample. Individuals were excluded from further analysis if genetic and reported gender did not agree. Samples with a call rate ≤ 0.95, and those showing evidence of non-European descent by multidimensional scaling, were removed[17]. SNPs were included in the analyses if they met the following conditions: call rate ≥ 0.98, minor allele frequency ≥ 0.01, and Hardy–Weinberg equilibrium test with $P \geq 0.001$. After these quality control stages, 1,948 samples remained (ABC1936, $N = 426$; LBC1921, $N = 517$; LBC1936, $N = 1{,}005$), and 536,295 autosomal SNPs were included in the analysis.

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Supplementary Information is linked to the online version of the paper at www.nature.com/nature.

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Author Contributions I.J.D. and P.M.V. designed the study. J.Y. and P.M.V. performed statistical analyses, with I.J.D., M.E.G., A.T. and S.J.R. contributing to discussions regarding analyses. G.D., S.E.H., D.L., A.T., M.L. and L.M.L. performed quality control analyses and prepared data. S.E.H., M.L., L.M.L., A.J.G., J.C., P.R., H.C.F., S.J.R., P.H., L.J.W., G.M., D.J.P., J.M.S. and I.J.D. contributed genotype and phenotype data. I.J.D., P.M.V. and J.Y. contributed to writing the paper and Supplementary Information. All authors contributed to revising the paper and Supplementary Information.

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