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REVIEW

Genetics of intelligence

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This article provides an overview of the biometric and molecular genetic studies of human psychometric intelligence. In the biometric research, special attention is given to the environmental and genetic contributions to specific and general cognitive ability differences, and how these differ from early childhood to old age. Special mention is also made of multivariate studies that examine the genetic correlation between intelligence test scores and their correlates such as processing speed, birth weight and brain size. After an overview of candidate gene associations with intelligence test scores, there is a discussion of whole-genome linkage and association studies, the first of which have only recently appeared.
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The phenotype

Intelligence was described by 52 researchers in the field as follows,[1]

> Intelligence is a very general mental capability that, among other things, involves the ability to reason, plan, solve problems, think abstractly, comprehend complex ideas, learn quickly and learn from experience. It is not merely book learning, a narrow academic skill, or test-taking smarts. Rather, it reflects a broader and deeper capability for comprehending our surroundings – 'catching on,' 'making sense' of things, or 'figuring out' what to do.

The structure of intelligence differences

Despite over 100 years of concordant data, there is not widespread knowledge of the well-replicated psychometric structure of human cognitive ability differences. [2] The first formal mental test was devised by Binet in 1905, and there are now hundreds of them. One of the most widely used instruments is the Wechsler Adult Intelligence Scale III.[3] It has 13 individual tests (Table 1), which are administered by a trained tester to an individual subject. In the USA validation sample of 2450 adults, the mean correlation among these 13 tests was 0.49 (range 0.26–0.77): people who did well on any single subtest tended to do well on all of the others. A confirmatory factor analysis of these data found that there were four identifiable cognitive 'domains' underlying the tests: verbal comprehension, perceptual organisation, processing speed, and working memory.[2] Scores on the four domains show an average intercorrelation of 0.76 (range 0.63–0.83). That is, a single, general factor underlies performance on the cognitive domains, and heavily influences each of them. This general cognitive factor is sometimes referred to as just *g*, or 'general intelligence'. It was discovered by Charles Spearman in 1904 and is one of the most replicated findings in psychology, as demonstrated in a re-analysis of over 400 data sets collected during the 20th century.[4] It tends to account for about half the total variance when a heterogeneous set of mental tests is given to a normal adult sample. The general factors from different test batteries tend to correlate very highly with each other.[5]

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Table 1 A description of the 13 tests in the Wechsler Adult Intelligence Scale (version III) and the cognitive domain assessed by each test

Test name	*Test content*	*Cognitive domain*
Vocabulary	Explain to the tester what individual words mean	Verbal comprehension
Similarities	Explain what two words have in common. It starts with common, concrete words and the later, harder words are more abstract	Verbal comprehension
Information	General knowledge questions	Verbal comprehension
Comprehension	Questions about everyday life problems, aspects of society and proverbs	Verbal comprehension
Picture completion	Identify the missing element in a series colour drawings	Perceptual organisation
Block design	The testee is shown two-dimensional patterns made up of red and white squares and triangles. They try to reproduce these patterns using cubes with red faces, white faces and half-red/half-white faces	Perceptual organisation
Matrix reasoning	Find the missing element in a pattern that is built up in a logical manner	Perceptual organisation
Picture arrangement	Given a series of cartoon drawings, the testee puts them in an order that tells a logical story	Perceptual organisation
Arithmetic	Mental arithmetic problems	Working memory
Digit span	Repeat a sequence of numbers read aloud by the examiner. Sequences run from two to nine numbers in length. In the second part of this test, the sequences are repeated in reversed order	Working memory
Letter-number sequencing	The examiner reads aloud a series of alternate letters and numbers. The testee repeats them, putting the numbers first and in numerical order, followed by the letters in alphabetical order	Working memory
Digit symbol-coding	Write down the number that corresponds to a given symbol and do as many as possible in the time given	Processing speed
Symbol search	Indicate whether or not one of a pair of abstract symbols is contained in a list of abstract symbols. Do as many as possible in the time given	Processing speed

The stability and validity of intelligence differences

IQ test scores are life-long stable traits with important predictive validity. A 68-year follow-up of almost 500 people who took part in the Scottish Mental Survey of 1932 found a correlation (stability coefficient) of 0.66 between IQ scores on the same test taken at age 11 years and 79 years.[6] Intelligence test scores are strongly associated with academic success.[7] They are about the single best predictor of job success.[8] Childhood IQ is significantly related to how long people live.[9]

Univariate and multivariate analyses

Here, we discuss the heritability of and environmental contributions to single traits, such as general intelligence (*g*) and specific cognitive domains: these are *univariate* analyses. In twin studies, *multivariate* analysis involves the calculation of cross-trait cross-twin correlations; that is, the correlation between one twin's score on variable *X* with the co-twin's score on variable *Y*. Genetic mediation of the phenotypic covariance between *X* and *Y* is estimated by the extent to which this cross-trait cross-twin correlation is greater for monozygotic (MZ) than for dizygotic (DZ) twins. The extent to which genetic effects on one trait correlate with genetic effects on another trait independent of the heritability of the two traits is assessed by the *genetic correlation*. For example, in the case of specific cognitive abilities which are moderately heritable, multivariate genetic analyses have consistently found that genetic correlations are very high.[10] These multivariate genetic results predict that when genes are found that are associated with one specific cognitive ability, such as spatial ability, they will also be associated with other cognitive abilities such as verbal ability and memory.

Genes and the hierarchy of intelligence through the ages

Heritability

'When data across all studies are collapsed, genetic influences [on intelligence differences] account for around 50% of the variance'.[11] Statements very similar to this may be found in many reviews, but the detail is more interesting.

More than 25 years ago there were already large reviews of the heritability of human cognitive ability differences, whose conclusions have not been overturned by more recent studies. In Nichols'[12] review, the mean difference in MZ–DZ correlations for 30 studies of general intelligence was 0.22, suggesting a broad heritability (h^2) of about 0.44. Nichols' own analysis was of almost 3000 sets of 11th grade, same-sex twins from the National Merit Twin Study from years 1962 and 1965. The MZ and DZ correlations for cognitive total score were 0.86 and 0.62, respectively, and for five special abilities were 0.74 and 0.52, respectively. With correction for unreliability of test measurement, an estimated 7% error rate in zygosity diagnosis, and

assortative mating, Nichols reckoned the broad heritability of general intelligence at about 0.7.

Bouchard and McGue[13] reviewed the world literature on IQ correlations between relatives with different degrees of genetic and family rearing overlap. They found 111 adequate studies, yielding 526 correlations based on 113 942 pairings. The results for 17 different types of family pairing are shown in Table 2. The results were compatible with the prediction that the correlations were higher among people who were genetically more similar. A few notable details are that: 79% of the MZ (reared together) correlations were greater than 0.80; and parent–child correlations often involve different cognitive tests (thus, probably making them underestimates of the true correlation). The greater correlations between the same pairings reared together suggests an influence of the rearing environment on intelligence similarity, although many of these studies were based on young children and we shall see later that this makes a difference.

More recent biometrical studies have been aimed at more specific questions, and have typically involved path analyses using structural equation modelling procedures to estimate genetic and environmental contributions.[14] Two of the principal questions are the age differences in these influences and whether the influences affect general and/or specific cognitive abilities.

From infancy to adulthood: twins An analysis of first to sixth grade twins (148 MZ, 135 same sex DZ) from the Western Reserve Twin Project suggested that, 'abilities may be differentially affected by genetic and environmental variation. However, these differential patterns may be simply reflecting the degree to which specific abilities measure general intelligence'.[15] Using 17 ability measures from the Wechsler Intelligence Scale for Children (WISC) and another test battery, they found that all the tests were influenced by genetic sources common to all tests: in other words, they found a genetic *g*. They also found some genetic effects that were specific to domains of cognitive functioning such as verbal, spatial, perceptual speed, and memory functions. Correlations between phenotypic *g* loadings and genetic *g* loadings were 0.88 and 0.76 for the two mental test batteries.

This was investigated further in a Dutch Twin Study in which 194 pairs took Raven's Progressive Matrices (a test of nonverbal reasoning with a high *g*-loading) at age 16.1 years and the WAIS at age 17.6 years.[16] The heritability estimates for Full Scale IQ, Verbal IQ and Performance IQ were 0.82, 0.84, and 0.68, respectively. There were no significant effects of shared environment. There were substantial unique environmental contributions, specific to each subtest. The principal interest from these data is the contribution to each subtest from genetic factors. This followed the hierarchical model of mental abilities and, thus, genetic contributions were divided into contributions shared by all tests, those shared by tests covering the same cognitive domain, and contributions to individual tests (Table 3). A general genetic factor contributed a mean of 30% of the variance to all tests (range 8–53%). Note, for example, that 48% of the variance in Raven scores comes from a genetic factor shared with all of the WAIS tests. There are modest contributions from genetic factors at the level of the cognitive domain and the individual test. The heritability of the individual tests ranges from 27 to 76%, with a mean of 56%. The contribution of unique environment to subtests ranges from 24 to 73% with a mean of 44%. The authors concluded: 'the factorial structure of the WAIS subtests is determined by individual differences in genetic structure (phenotypic *g* is strongly related to genetic *g*)' (p. 207); 'The covariation among the WAIS

Table 2 Summary of the review of the world literature on IQ correlations between relatives with different degrees of genetic and family rearing overlap (from Bouchard and McGue, 1981)[13]

Paring	*Number of correlations*	*Number of pairings*	*Weighted average correlation*
Monozygotic (MZ) (together)	34	4672	0.86
MZ (apart)	3	65	0.72
Midparent–midoffspring together	3	410	0.72
Midparent–offspring together	8	992	0.50
Dizygotic (together)	41	5546	0.60
Siblings (together)	69	26473	0.47
Siblings (apart)	2	203	0.24
Single parent–offspring (together)	32	8433	0.42
Single parent–offspring (apart)	4	814	0.22
Half siblings	2	200	0.31
Cousins	4	1176	0.15
Nonbiological sibling pairs (adopted–natural pairings)	5	345	0.29
Nonbiological sibling pairs (adopted–adopted pairings)	6	369	0.34
Adopting midparent–offspring	6	758	0.24
Adopting parent–offspring	6	1397	0.19
Assortative mating	16	3817	0.33

Table 3 Additive (A) genetic contributions (percent of variance) to general mental ability (*g*), four specific cognitive domains (verbal comprehension (VC), freedom from distraction (FD), perceptual organisation (PO), Raven test), and to individual tests within domains (specific)

WAIS subtest or Raven test	*Cognitive domain*	A_g	A_{VC}	A_{FD}	A_{PO}	A_{Raven}	$A_{specific}$
Information	VC	44	14	—	—	—	17
Comprehension	VC	34	11	—	—	—	11
Arithmetic	FD	53	—	5	—	—	7
Similarities	VC	40	13	—	—	—	0
Digit span	FD	30	—	3	—	—	29
Vocabulary	VC	52	17	—	—	—	3
Coding	FD	10	—	1	—	—	38
Picture Completion	PO	8	—	—	8	—	11
Block design	PO	31	—	—	30	—	9
Picture arrangement	PO	11	—	—	10	—	14
Object assembly	PO	15	—	—	15	—	19
Raven's matrices	Raven	48	—	—	—	16	—

Results are from a Dutch Twin Study (Rijsdijk *et al*, 2002)[16].

subtests and the covariation between the subtests and the Raven in our data are predominantly influenced by a second-order genetic factor and thus strongly support the notion of a biological basis of *g*' (p. 209).

Analyses of a Dutch Twin Study have also addressed the changing genetic contribution with age. Twins ($N=209$ pairs) were assessed by the RAKIT test battery at ages 5, 7, and 10 years, and on the WISC-R at age 12 years.[17] For Full-scale IQ (general intelligence), the contributions (percent variance) were as follows at ages 5, 7, 10, and 12 years: genetics, 26, 39, 54, 64; shared environment, 50, 30, 25, 21 (for the latter three values, the 95% confidence interval includes zero); and unique environment, 24, 31, 21, 15. This decrease in the shared environmental contribution and increase in genetic influence with age from childhood to adolescence was congruent with previous studies.[14] The best-fitting model showed an additive genetic influence which was a common factor, but with age-specific factor loadings; thus, 'continuity in cognitive abilities is mainly due to additive genetic factors' (p. 245). Shared environment contributed to continuity and change in cognition, and unique environment contributed to change in development.

The relatively low heritability of mental ability in young children was replicated in the Twins Early Development Study.[18] The h^2 for verbal ability and parents' reports of children's nonverbal abilities in 6963 pairs of twins at ages 2, 3, and 4 years ranged from 0.25 to 0.30. The shared environmental estimates (c^2) on the other hand explained 0.61–0.65 of the variance. Parents' socio-economic status and chaos in the home accounted for about 10% or less of the total variance in test scores, indicating that they mediate some of the c^2 effect, but most of that variance remained unexplained.[19]

The increase in importance of genetic effects from infancy to childhood has also been demonstrated in longitudinal analyses of twin data from different research groups.[18,20] For example, in data from 2824 twins analysed using a genetic longitudinal latent *g* model, heritability increased from 0.17 for a composite score across ages 2, 3 and 4 years to 0.47 at age 7 years.[18] The same genes appeared to affect IQ across age. The term (genetic) 'amplification' has been used to describe this pattern of effects.[21]

An unusual twin analysis involved whole population cohorts of 11-year-old twins who took part in the Scottish Mental Surveys of 1932 (572 pairs) and 1947 (517 pairs).[22] Zygosity information was not available, and the authors used a novel application of a mixture distribution to estimate genetic and environmental contributions using information about whether the twins were same or opposite sex. Estimates were similar for both populations, born in 1921 and 1936, respectively, with h^2 about 0.70 and c^2 about 0.21.

Most of the studies described above concern ages up to adolescence. A Dutch study with several hundred adult subjects from extended twin families contained two cohorts, aged around 26 and 50 years.[23,24] They were given a Dutch version of the Wechsler Adult Intelligence Scale III. Genetic factors accounted for 85% of the variation in Verbal IQ and 69% of Performance IQ.[23] The remainder was accounted for by nonshared environment. There were no significant effects of shared environment. The heritability estimates for the four Wechsler cognitive domains were: verbal comprehension = 0.84; working memory = 0.65; perceptual organisation = 0.68; and processing speed = 0.63.[24]

From infancy to adulthood: adoption studies The Colorado adoption project included adopted children and their adoptive parents, and also their biological mothers and some biological fathers, as well as control parents and their children. Parents undertook a 3-h test battery, with cognitive, personality, and other assessments. Children

were tested at ages 1, 2, 3, and 4 years in the home. At 7 and 12 years, they were seen in a lab. At 9, 10, and 11 years, they undertook a telephone interview. At age 4 years, the h^2 for specific cognitive abilities were: verbal = 0.12; spatial = 0.31; perceptual speed = 0.21; and visual memory = 0.06.[25] These were not significantly different. The heritability of general mental ability increased over time, with the 1, 2, 3, 4, and 7 year h^2 estimates of 0.09, 0.14, 0.10, 0.20, and 0.36, respectively.[26] A further report applied a Schmid–Leiman-type hierarchical model to the analysis of the genetic and environmental contributions to verbal, spatial, perceptual speed, and memory domains in the year 7 assessment data.[27] A genetic *g* factor influenced all four domains, with additional domain-specific genetic influences on verbal, spatial, and memory domains. There were no significant shared environment effects; the nonshared environment effects were principally domain-specific, with a shared effect between spatial and memory domains. By age 12 years, with 175 adoptive families and 209 control families, the h^2 for ability domains derived from a mixture of WISC and Educational Testing Service tests was as follows: verbal = 0.26, spatial = 0.35, perceptual speed = 0.38, memory = 0.53.[28] Genetic correlations between the ability domains ranged from 0.27 to 0.58. A simple model, which assumed that the genetic correlations among the four areas were identical, fitted well. Thus about half of the phenotypic association between the cognitive domains was caused by genetic factors and the authors concluded that, 'specific cognitive abilities appear to be influenced by a pervasive genetic factor whose contribution to each ability does not differ substantially' (p. 262). The effects of familial environment transmission were nonsignificant.

A more recent analysis of the Colorado Adoption Project asked, 'what is the pattern of genetic and environmental influence on the stability of cognitive skills from early childhood through late adolescence'.[11] There were 245 adoptive and matched control families. Children by that stage had taken cognitive tests at age 16 years (the WAIS). Phenotypic stability coefficients were moderate to high from age 2 years onwards. For example, the correlation between ages 7 and 16 years was 0.68, and between 12 and 16 years 0.80. At age 16 years, the mean correlation between adoptive siblings' intelligence test scores was 0.11, and between control siblings was 0.30. Genetic sources were responsible for stability of general cognitive ability from age 1 years to age 16 years. For nonshared environment, only age-specific effects were required, suggesting that they contribute mainly to age-to-age instability or test-error. The mean of the genetic correlations between all ages from 2 to 16 years was 0.78 (range 0.57–1.0).

The Texas Adoption Project involves about 300 families in Texas who adopted children through a church-related scheme for unwed mothers. Children went to adopted homes within a few days from birth and were adopted permanently. Birth and adoptive parents tended to be middle class. Children took Stanford-Binet or age-appropriate Wechsler tests at around age 7 years, at which time adults, excluding birth fathers, took the Adult Wechsler and/or the Revised Beta test. Children were tested on the adult tests at a 10-year follow-up.[29] The correlations of the Beta test between adopting fathers and mothers and their adopted children (with whom they had spent 17 years on average in the same home) were 0.08 and −0.02, respectively. Correlations between fathers and mothers and their biological children were 0.20 and 0.21, respectively. The correlation between the birth mothers and their adopted-away children was 0.33. Three of the six subscales of the Revised Beta exam had specific genetic contributions beyond a general genetic factor. A later analysis of the Texas Adoption Project examined both parent–offspring and sibling correlations.[30] Sibling correlations were higher for biologically related siblings than for adopted siblings, whose scores correlated near to zero. The estimated additive genetic effect on general intelligence was 0.78, for true scores in the population. The authors concluded that, 'The major contributor to familial resemblance is the genes. Shared family environment has an appreciable effect on IQ when children are small, but this becomes minor by the time they are late adolescents.'

From infancy to adulthood: other studies Combining adoption and twin study features, Bouchard[31] summarised the world literature on MZ twins reared apart, a powerful design to examine heritability. There are five studies, with *N*s of 12, 19, 38, 45, and 48. The weighted average intraclass correlation is 0.75, which is also an estimate of the heritability, given assumptions about lack of contact, and no bias in placement. This value is similar to the estimate from studies of adolescent adoptees. Bouchard *et al*.[32] had shown earlier, in the Minnesota Study of Twins Reared Apart, that amount of contact between separated twins was not correlated with their similarity on general intelligence.

Heritability of intelligence might not be the same for all levels of social background. There is an apparent paradox between the low estimates of c^2 for intelligence in middle childhood and the fact that, when children are rescued from poverty, their IQ tends to become higher than other family members.[33] The hypothesis that there is a nonlinear association between heritability and shared environment and family background was tested in 114 MZ and 205 DZ pairs of 7-year-olds (54% black, 43% white) from the National Collaborative Perinatal Project.[34] This sample has a high proportion of impoverished families. One useful summary is an analysis in which families were dichotomised into high and low socio-economic status (SES). For high SES families, h^2 was 0.71 and c^2 was 0.15. For low SES families, h^2 was 0.10 and c^2 was 0.58.

Old age What happens to genetic and environmental contributions to intelligence in old age? Much information has come from various analyses of and subgroups within the Swedish Twin Registry, which has 25 000 same-sex twins born in Sweden between 1886 and 1958. In one such subdivision, the Swedish Adoption Twin Study of Ageing (SATSA), Pedersen *et al*[35] produced the 'first report of a quantitative investigation of cognitive abilities in the second half of the lifespan' (p. 346). The SATSA involves around 300 pairs of MZ and DZ twins reared apart (MZA, DZA) and together (MZT, DZT). The reared-apart twins were separated before age 11 years (52% at less than 1 year, and 69% by 2 years). Mean age for the whole sample was 65.6 years. The intraclass correlations for the first principal component from 11 cognitive tests (general intelligence) were as follows for the different groups: MZA = 0.78; MZT = 0.80; DZA = 0.32; DZT = 0.22. Broad heritability of general intelligence was estimated at about 0.80, with evidence of nonadditive effects. This is similar to the estimate for the MISTRA separated twins and to other estimates of the heritability in adulthood. Age at separation, degree of separation and numbers of years separated were not related to twins' similarity. The heritability of specific domains of ability was slightly lower, between 51 and 64%, for verbal-crystallised, nonverbal-fluid ability, perceptual speed, and memory. *g*-loadings of the individual tests correlated 0.77 with the heritability of the tests, which they concluded was evidence for shared genetic effects between cognitive domains. Memory tended to be less heritable than other ability domains. There was little contribution from shared environment. The genetic and nonshared environmental contributions (there were no significant shared environmental contributions) were largely stable after a 3-year follow-up.[36]

A later report of the SATSA sample used genetic analyses of latent growth curve models to address issues of the heritability of the mean level and slope (trajectory of decline) of cognitive ability during old age.[37] By this point, there were up to four cognitive assessments for each SATSA subject, at baseline ($N = 595$), 3 (560), 6 (539), and 13 (517) years. The intercept's (mean level of cognitive ability at 65 years) heritability was between 0.62 and 0.55 for single test domains, and 0.91 for *g*. This is higher than is found in other studies (the h^2 at age 80 years was reckoned to be 0.76), and is probably due to the fact that this study controlled for unreliability of measurement, thus modelling only systematic variance. Shared and common environment effects were very small, with unique environment accounting for most of the nongenetic variance. The slope (effectively, cognitive change in old age) had both linear and quadratic effects. The linear effect, by far the largest, showed almost no genetic influence, almost all of its variance being due to unique environment. The quadratic effect, the change in the change of cognition in old age, showed some genetic influence. The heritability of *g* showed a peak at 60–70 years, and a lower level at 80 years. For the individual cognitive domains (among which *g* accounted for 45% of the variance), the heritability decreased with age in processing speed and fluid/spatial ability while the heritability of memory appeared to increase with age, leading the authors to suggest that there might be genes specific for memory differences in old age. This is congruent with the finding that variation in the gene for apolipoprotein E, for example, is associated especially with memory in old age, but not with cognition in youth.[38–40] The clearest result was the general increase in the influence of the unique environment at older ages, for *g* and specific ability domains. Importantly, this study tells us that genetic influences are the main contributor to individual differences in cognition, but that unique environmental effects, although relatively small at any one age, have an increasing influence at older ages and appear more important for cognitive change. Added to the fact that, overall, there was more variability with old age, this supports Finch and Kirkwood's[41] ideas concerning the importance of stochastic effects on brain ageing. This SATSA analysis also reminds us that change in the absolute amount of variance with age is also important, and not just the genetic and environmental proportions of it.

Another subsample of the Swedish Twin Registry is the OctoTwin project.[42] To be included in this project, twins had to be 80 years or older and alive in 1991–1993. The median age was 82 years (range 80 to >95); 89% lived independently. There were 110 MZ and 130 same sex DZ. They took a 1.5 h cognitive test battery, including Wechsler tests and some from a battery based on Thurstone's primary mental abilities; *g* accounted for 50% of the variance in the battery. In total, 52 MZ and 65 DZ pairs had full data. The heritability of the *g* factor was 0.62 (95% CI = 0.29–0.73), uncorrected for error of measurement. The heritability (95% CI) of the cognitive domains was: verbal = 0.55 (0.24–0.81); spatial = 0.32 (0.00–0.58); speed of processing = 0.62 (0.29–0.73); and memory = 0.52 (0.07–0.67). All of the significant environmental contribution was nonshared. Having estimated the h^2 in very old age, the OctoTwin data were used to answer the question, 'are different cognitive abilities influenced by the same genes and environments, or are independent genetic and environmental influences operating?'.[43] The heritability of *g* was 0.76 and all of the four cognitive domains had large loadings on *g*. The most substantial specific, non-*g*, genetic contribution was to memory. All of the specific (ie those not arising from *g*) genetic parameters could be dropped without significantly impairing the fit of the model, although this reflects the limited power of the study. The shared environment contribution could always be dropped without significantly affecting the fit of the model. They concluded that 'the same genetic influences were operating across different specific cognitive abilities' (p. 187). As with younger samples, genes tend to affect cognitive similarity

and the nonshared environment drives differences. A later analysis of the OctoTwin project included four cognitive assessments taken at 2-year intervals.[44] The idea was to examine whether proximity to death influences twin similarity. That is, given an occasion when one twin has died, were the twins becoming less similar in the testing occasion just prior to that? They did find evidence for such an effect. Thus, this is further evidence of stochastic influences of cognition in old age. The authors suggested that high cross-sectional heritability estimates in old age could be in part an artefact of selectivity.

Multivariate studies of *g* and its correlates

In this section, we shall address three areas of research in which multivariate modeling approaches have been used to decompose the covariance between general cognitive ability (*g*) and (a) speed of cognitive processing, (b) birth weight, and (c) brain volume.

g and speed of cognitive processing

Spinath and Borkenau[45] reviewed the behavior–genetic literature on *g* and speed of cognitive processing, typically measured via elementary cognitive tasks such as choice reaction time or speed of scanning in short-term memory. The consistent relation between shorter reaction times and higher intelligence mainly appeared to reflect genetic effects shared by both measures. Luciano *et al*[46] studied a wider range of information processing measures such as inspection time, choice reaction time, delayed response speed and accuracy with IQ in a sample of 245 MZ and 298 DZ twin pairs. Their results indicated the presence of a general genetic cognitive factor affecting both IQ and psychophysical phenotypes, as well as additional genetic factors explaining the additional test variance and covariance. Environmental sources of variance were nonshared and mostly test-specific. A further study investigated the association between inspection time and IQ using an even larger sample of Australian and Dutch participants in an extended twin family design, that is, MZ and DZ twins and one or more of their singleton siblings.[47] The IQ-inspection time covariation was best explained by pleiotropic genes influencing both inspection time and IQ, rather than affecting IQ via inspection time. Genetic modeling is thus providing new tests of cognitive science models in general and IQ-processing speed research in particular, suggesting that traditional directional models of causation (eg, 'bottom–up' *vs* 'top–down' processing dependencies) provide a poorer fit to the data than does a 'genetic *g*' model. Such a model was suggested by Plomin and Spinath,[48] and it involves the idea that genetic *g* might be assessed by psychometric tests of intelligence but also by reaction time, inspection time, and psychophysiological measures. Thus, it meets both the demand for a combined experimental-differential approach to human intelligence[49] and, in contrast to the modular view of cognitive differences, it suggests that, at a genetic level, individual differences in cognitive processes are nonspecific rather than independent.

g and birth weight

The negative effects of very low birth weight on intellectual development are well documented. There is an association between IQ and normal variance in birth weight.[50] Bivariate genetic analysis of this relationship in a longitudinal twin sample found a genetic mediation of birth weight and full IQ measured at ages 7 and 10 years, but not at ages 5 and 12 years.[51] At age 16 years, the genetic variance in birth weight completely overlapped with that in verbal IQ but not performance or full IQ.[52] However, genetic variance explained only a very modest proportion (roughly 4%) of individual differences in birth weight, whereas a substantially larger proportion of the variance in birth weight was explained by shared environmental factors. IQ showed a markedly different etiology, with genes explaining up to 72 per cent of IQ variance. Based on models incorporating a direction of causation parameter, the authors argued that these data might indicate that brighter mothers provide better prenatal environments for their children. Intrauterine environment might account for more of the variation in intelligence than is usually recognized, perhaps as much as 20% of the covariance between twins and 5% between non-twin siblings.[53]

g and brain volume

Brain volume, assessed *in vivo* using magnetic resonance imaging correlates 0.33 (estimated population correlation) with psychometric intelligence.[54] Brain volume is highly heritable and substantially intercorrelated across brain regions.[55,56] These findings were extended using a multivariate genetic analysis.[57] They showed that whole-brain white matter and whole-brain gray matter were equally heritable, and that the correlation of gray and white matter volume with full-scale IQ and working memory from the WAIS-III were completely mediated by genetic factors. A follow-up study that examined genetic correlations between the WAIS III dimensions of verbal comprehension, perceptual organization, and processing speed and gray and white matter volumes, as well as cerebellar volume yielded a more complex pattern of results; for example all three brain volumes were related to working memory capacity, yet verbal comprehension was not related to any of the three.[24] A multivariate genetic analysis of body height and volumes of gray matter, white matter, and the intracranial space in a sample of 54 MZ and 58 DZ twin pairs and 34 of their full siblings indicated that a large part of the genetic influence on volume measures was shared, whereas the genetic influence shared with height was smaller.[58]

Molecular genetics and intelligence

Candidate gene studies

A sizeable proportion of the present article could be taken up with association studies, but most have yet to be replicated.[59] Various strategies exist for the selection of possible candidates genes relevant to the normal variation in cognition. For example, one source of candidates is genes associated with mental retardation. A review identified 282 molecularly identified mental retardation-associated genes, classified many of them in terms of function, and found that there were fruit fly homologs in the majority.[60] More specifically, some of the genes associated with nonspecific mental retardation code for proteins that interact with Rho GTPases, which are thought to be fundamental for efficient neural connectivity.[61] Possible genes related to cognitive ageing include genes associated with dementia, memory, cardiovascular disease, and oxidative stress.[62] As examples, we now emphasise two of the better-replicated cognition-genotype associations.

A meta-analysis of 38 studies (more than 20 000 subjects) found that possession of the E4 allele of *APOE* was associated in older people with poorer performance on tests of global cognitive function, episodic memory, and executive function.[40] The E2 allele appeared to be protective. The effect size was small, at about one-tenth of a standard deviation unit. This is an interesting case of variation in a gene that is related to cognition in old age but not in youth.[38] The mechanisms whereby the variations are detrimental and protective to cognition are not understood, although there are various suggestions.[63] The follow-up studies of the Scottish Mental Survey 1932 reported that variation in the genes for klotho[64] and nicastrin[65] might be associated with general intelligence at both ages 11 and 79 years, but these are, as yet, unreplicated. Other genes with variations related to intelligence are the cholinergic muscarinic 2 receptor[66] and cathepsin D.[67] Although it was originally associated specifically with memory, the gene for brain-derived neurotrophic factor has been associated with intelligence in healthy subjects.[68] Variation in the succinate-semialdehyde dehydrogenase gene has been associated with IQ.[69] All of these have small effects, consistent with a polygenic view of the heritability of intelligence.

There is growing evidence for an association between variation in the gene for catechol-*O*-methyl transferase and prefrontal/executive cognitive abilities.[70] COMT is a six-exon gene on chromosome 22 coding for catechol *O*-methyltransferase, an enzyme which inactivates the neurotransmitter dopamine (DA) and other catecholamines. A common functional polymorphism results in a VAL->MET substitution, such that the VAL variant is 3–400% more active.[71] Experimental studies using the CNS-penetrant COMT inhibitor Tolcapone indicate that COMT functional variants exert their effect via alterations in DA levels in prefrontal cortex.[72] Whereas sustained interest and research on a possible association of the VAL->MET polymorphism with schizophrenia has produced mixed results,[73] much clearer support has been found for an association of the VAL allele with improved executive function.[74] For example, the Met allele is associated with fewer preservative errors on the Wisconsin Card Sort test.[75] Interpretation of the data is complicated by the fact that Val^{158}Met is not the only mutation affecting COMT and that COMT is not the sole determinant of the effective level of prefrontal DA. Moreover, behavioral efficiency is related in an inverse U fashion to DA levels. These levels of complexity are exemplified in a study in which Stroop reaction time was low in VAL/VAL homozygotes who also carried the A1-DRD2 allele.[76] This pattern reversed in A1+ carriers, where VAL alleles now had a deleterious effect on Stroop performance. Whereas there were no main effects of COMT or DRD2, the COMT*DRD2 interaction predicted 13% of Stroop task variance. As COMT catabolises DA and DRD2 affects receptor density, these allele types jointly determine (in part) the functional levels of cortical DA, and the functional level of DA in turn exerts an inverse-U effect on attentional focus. In terms of the relationship of COMT to general cognitive ability, Val^{158}Met status is unrelated to childhood IQ, but is related to logical memory in old age, with heterozygotes ageing best.[77]

Genome-wide linkage and association for intelligence

When, as in the case of cognitive ability, few candidate genes have been described, and almost none reliably, the most rational approach to identifying genes is to undertake a genome-wide search. Ideally, each subject would be typed at each DNA base pair (BP). However, genotyping thousands of individuals at each of 3 billion loci is prohibitive. Researchers therefore adopt strategies of linkage and association analysis, exploiting long- and short-range correlations, respectively, within the genome to localise QTLs using markers, which, because of shared ancestry, are transmitted alongside the QTL.[78]

Linkage Two (related) genome-wide family linkage studies of intelligence have been published.[79,80] These reported data from Australian twins assessed using subtests from the Multidimensional Aptitude Battery (a group-administered test battery modelled on WAIS subtests) and a pooled sample of Dutch twins assessed with the WAIS-III, showing heritability of ability between 0.59 (for Australian Performance IQ) to 0.86 (Dutch Full Scale IQ). Significant linkage was found at chromosome 2q and 6p. The linkage at 2q was specific for performance IQ, with negligible linkage for verbal IQ, suggesting that it may reflect not *g*, but a more specific, spatial processing ability. It was also linked to the Cambridge Contextual Reading Test, which correlates with intelligence. The 6p linkage was significant for full-scale-IQ, and showed suggestive linkage for performance and verbal IQ, suggesting that this locus affects

general ability. A number of candidate genes are present in these regions, several involved in fast, short-range glutamatergic neural transmission which is theorised to influence prefrontal cortex functioning.[81] The linkage of full-scale IQ lies close to Neuritin1, a gene involved in nervous system development and long-term plasticity,[82] and to succinate-semialdehyde dehydrogenase.[69]

These first genome-wide linkages of normal ability in unselected samples show convergence with linkage in clinical disorder. For instance, 2q21-33 holds a gene related to autism[83] and has been linked to cognitive deficits in childhood-onset schizophrenia,[84] while the 6p region has been associated with dyslexia, especially speeded reading measures.[84] It might be more generally the case that small mutations or slightly inefficient variants of genes detected in linkage analyses affect normal ability, while more severe mutants which greatly alter gene function or expression result in disorders such as Autism, ADHD, and William's syndrome.

The high heritability of *g* and specific abilities implies that more genes must exist than those lying within 2q and 6p. Indeed, the Australian study provided evidence for suggestive (rather than significant) support for a verbal latent factor relating information, vocabulary, and knowledge of rare words and linked to chromosome 7, as well as linkages specific to subtests such as digit symbol, supporting genetic control even at this level of specificity.[79]

Association No genome-wide direct association study for IQ has yet appeared. A variant of direct association, allelic or 'pooled' association, has been used. In allelic association, pools of DNA are formed by combining samples from individuals differing in mean score on the trait. The two or more pools are then typed, and a comparison is made of the frequency of alleles for each marker between the comparison groups. False positives are controlled by generating candidates from one sample and then examining these in additional samples to ensure that they replicate. Over the last decade, this method has been championed by Plomin and co-workers, beginning with an association analysis of 100 markers close to candidate genes in high and low IQ groups. Extensions of this approach lead to the report of a functional polymorphism in ALDH5A1 (MIM 271980) with cognitive ability.[69] Recently, this group reported the first genome-wide level allelic association study for cognition.[85] This study took advantage of a recent innovation in SNP testing which, instead of creating individual primers specific for each SNP, uses the pattern of binding to a common group of primers to individuate a panel of 10 000 or more SNPs. They reported association for a composite of cognitive measures (a *g*-factor) taken at age 7 years in a sample of 7000 twins. Five of the 10 000 SNPs showed replicable association. These lay on chromosomes 2, 6, 7, 11, and 18, and together accounted for less than 1% of ability variance. The genes or functions associated within these SNPs are unknown. One (rs1136141) lies within a noncoding region of heat-shock protein 'HSPA8' on chromosome 11. Several others do not lie in known genes. It is possible, therefore, that the SNPs are simply in linkage disequilibrium (LD) with the functional genes or, if they do mark the critical coding variations, that they affect gene regulation. The chromosomes 6 association lies close to but upstream of the chromosome 6 linkage report.[79]

Conclusion

Whereas the high heritability of intelligence differences has been made increasingly clear, the nature of the genetic polymorphisms implied by this heritability is unclear. The genes for individual differences in ability are often general in their effects: that is, just as *g* is associated with diverse cognitive and biological functions, the genes underlying differences in *g* themselves might affect many brain systems, rather than being specific for one or just a few cognitive modules. The evidence summarised above suggests that a maximum rate of progress in understanding the biology of a diverse range of cognitive differences would be achieved in the first instance by large-scale studies of general ability.[86]

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