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A genetic analysis of brain volumes and IQ in children

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ABSTRACT

In a population-based sample of 112 nine-year old twin pairs, we investigated the association among total brain volume, gray matter and white matter volume, intelligence as assessed by the Raven IQ test, verbal comprehension, perceptual organization and perceptual speed as assessed by the Wechsler Intelligence Scale for Children-III. Phenotypic correlations between the brain volumes and intelligence traits ranged between .20 and .33. Processing speed and brain volume did not correlate. The relation between brain volume and intelligence was entirely explained by a common set of genes influencing both sets of phenotypes.

1. A genetic analysis of brain volumes and IQ in children

Sir Francis Galton (Galton, 1869) was the first to systematically attempt to investigate the effect of heredity on intellectual abilities using normal distribution and pedigree analysis. Later Galton suggested the use of twin studies to disentangle nature from nurture and developed, based on his work on inheritance, regression and correlation coefficients. Like many of his contemporaries Galton thought that head circumference and intelligence are positively related. In 1901, with Pearson he used their newly developed correlational techniques to compute the correlation between head size and academic record. This correlation turned out to be low (.1; Fancher, 1983; Tredoux, 2007).

Since 1901, the relationship between total brain volume (TBV) and intelligence in adults (e.g. Andreasen et al., 1993; Egan et al., 1994; Thoma et al., 2005; Wickett, Vernon, & Lee, 2000; Witelson, Beresh, & Kigar, 2006) and children (e.g. Frangou, Chitins, & Williams, 2004; Reiss, Abrams, Singer, Ross, & Denckla, 1996) has been well established. In a review McDaniel (2005) estimated a population correlation between intelligence and TBV of .33. To study whether this relationship is a function of nerve conduction velocity or the number of neurons, a number of studies also examined the correlation between intelligence and *white matter volume* (WMV) and *gray matter volume* (GMV) separately. Gray matter consists of neural cell bodies, dendrites and synapses, whereas white matter consists of myelinated axons. The myelination hypothesis (Miller, 1994) states that thicker myelin sheaths will result in larger brain volume. Increased myelination in turn leads to increased speed of cortico-cortical connections, which is in concordance with research evidence showing that people with faster brains, as expressed by shorter reaction time and inspection time, are more intelligent (Posthuma, De Geus, & Boomsma, 2002). Nevertheless, the relation between WMV and intelligence is unclear. Andreasen et al. (1993) and Reiss et al. (1996) did not find a relation between intelligence and WMV in children and adults, while Posthuma et al. (2002) and Thoma et al. (2005) observed a significant positive relation in adults. One possible explanation for this discrepancy can lie in the subtle differences in WMV responsible for differences in cognitive function: Pujol et al.

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(2004) showed a significant difference of only 1.6% in WMV between a group of children (N=100) with cognitive decline and a group of controls (N=50). This observed difference was equivalent to a 3.2-year myelination delay. So, to detect the effect of WMV on intelligence in the normal population samples of sufficiently large size are required. In contrast, in both children and adults there is consistent evidence for a positive relation between GMV (Andreasen et al., 1993; Frangou et al., 2004; Posthuma et al., 2002; Reiss et al., 1996; Thoma et al., 2005; Wilke, Sohn, Byars, & Holland, 2003) and cortical thickness (Shaw et al., 2006) and intelligence.

These earlier studies on brain volume and intelligence often report on samples of above average IQ and/or range restricted samples (e.g. Egan et al., 1994; Frangou et al., 2004; Reiss et al., 1996; Wickett et al., 2000; Wilke et al., 2003; Witelson et al., 2006). The studies in children used groups of subjects which typically ranged from five to eighteen years (Frangou et al., 2004; Reiss et al., 1996; Wilke et al., 2003). Brain volumes are age dependent (Giedd et al., 1999; Lenroot et al., 2007). TBV peaks at age eleven for girls and age fifteen for boys, after which it slowly decreases (Giedd et al., 1999). GMV follows an inverted U-shaped developmental pattern which peaks between nine and fifteen years depending on brain area and sex. WMV on the other hand increases linearly with age (Lenroot et al., 2007; see also Lenroot & Giedd, 2006 for a review on brain development in children and adolescents). Therefore, the wide age range may blur the relation between brain volumes and intelligence. This may explain for instance the finding in the study of Wilke et al. (2003), where there was no relationship between WMV and IQ and where the relation between GMV and IQ was present in the older age group (mean age 15 years) only.

To disentangle the etiology of variation in brain volume and intelligence twin studies are useful. These studies can separate variation caused by differences in human DNA sequence and other genetic sources of variation and variation caused by differences in environment (Plomin & Kosslyn, 2001). The proportion of genetic variance over the total variance is defined as *heritability*. Environmental variance can be decomposed into variance shared by family members (*shared environment*) and variance which is unique for each individual (*unique environment*). Heritability estimates are obtained by comparing the resemblance between *monozygotic twins* (MZ) with the resemblance between *dizygotic twins* (DZ). When MZ twin correlations are higher than DZ twin correlations, part of the twin resemblance in the phenotype is caused by genetic effects. When DZ twin correlations are more than half the size of MZ correlations, the resemblance between twins is at least partly caused by shared environmental effects. The importance of unique environment is reflected by differences between MZ twins.

Using a multivariate genetic design one can establish the etiology of the relation between IQ and brain structure. The association may be caused by genetic factors which influence brain structure as well as IQ, and / or by environmental factors influencing both traits. These types of studies can lead to new insights not only about how genes affect intelligence, but also about how the brain works. As stated by Plomin and Kosslyn (2001) and Peper, Brouwer, Boomsma, Kahn, and Hulshoff Pol (2007) genetic studies on brain and intelligence will help dissecting pathways relating genes, brain and intelligence. Currently the nature of the genetic polymorphisms involved in intelligence and brain volume are unclear (Deary, Spinath, & Bates, 2006).

The relation between brain structure and cognition has been studied in genetic informative samples in adults (Carmelli, Swan, DeCarli, & Reed, 2002; Schoenemann, Budinger, Sarich, & Wang, 2000; Thompson et al., 2001; Tramo et al., 1998; Wickett et al., 2000). Posthuma et al. (2002), Hulshoff Pol et al. (2006) and Posthuma et al. (2003) showed in a sample of 135 individuals (existing of twins and siblings coming from 60 twin families) that the relationship between full scale IQ and WMV and GMV is completely mediated by genetic factors, as well as the relationship between verbal IQ and performal IQ and several focal GM and WM areas. A similar genetic origin was found for the association between working memory, GMV and WMV (Posthuma et al., 2003). In addition, for the other three dimensions of the Wechsler Adult Intelligence Scale-III (WAIS-III), it was found that processing speed was genetically related to WMV, whereas perceptual organization and verbal comprehension were neither related to WMV nor to GMV. In another study in young adults and adolescents, 80% of the correlation between TBV and IQ could be explained by genetic factors common to TBV and IQ (Pennington et al., 2000). However, roughly two third of the 66 twin pairs in this sample consisted of twin pairs with reading disabilities (DeFries, 1985). This may make it hard to generalize the findings of this study to the normal population. And since brain structure is known to change during adolescence (Giedd et al., 1999) it is possible that some of these genetic associations could have been partly mediated by age-related changes.

Here we report a genetic study in a population-based sample of 112 nine-year-old healthy twin pairs (Peper, Brouwer, et al., 2008; Peper, Schnack, et al., in press; Van Leeuwen, Van den Berg, & Boomsma, 2008). In this important period of cognitive development and (structural) brain maturation (Blakemore & Choudhury, 2006), we examine whether TBV, GMV, and WMV are associated with intelligence, verbal comprehension, perceptual organization and perceptual speed. If a significant association is found, we investigate whether genetic and/or environmental factors mediate the association.

2. Material and methods

2.1. Participants

The group of children participating in intelligence testing consisted of 112 nine-year-old twin pairs (M=9.1, SD=.10). There were 23 monozygotic male (MZM), 23 dizygotic male (DZM), 25 monozygotic female (MZF), 21 dizygotic female (DZF) and 20 dizygotic pairs of opposite sex (DOS). For the same sex twin pairs, zygosity determination was based on DNA polymorphisms (90 twin pairs), or on questionnaire items (2 pairs; (Rietveld et al., 2000). From the 112 families, 107 (N=214) underwent magnetic resonance (MR) scanning. This group consisted of 22 MZM, 22 DZM, 23 MZF, 21 DZF and 19 DOS twin pairs.

Average time between intelligence testing and magnetic resonance imaging (MRI) was 43 days (with psychological

testing before MRI; *SD*=35). The study was approved by the Central Committee on Research involving Human Subjects (CCMO). Parents signed informed consent statements for the children as well as themselves. Children also signed consent. Parents were financially compensated for their travel expenses and children received two presents worth €10, one after a testing day (see also Van Leeuwen et al., 2008).

2.2. Measurements

One day children were tested at the VU University (VU) in Amsterdam and one day a MRI scan was made at the University Medical Center in Utrecht (UMCU). At the VU all children underwent cognitive testing. After arriving between nine and eleven o'clock in the morning, children were individually tested in separate rooms by experienced test administrators. Children completed as part of a larger test battery the Wechsler Intelligence Scale for Children-III (WISC-III; Wechsler et al., 2002) and the Raven Standard Progressive Matrices (Raven, 1960). The whole protocol took approximately 5 h, including two short breaks and one long lunch break.

2.2.1. Intelligence testing

IQ scales were assessed with the Dutch adaptation of the WISC-III (Wechsler et al., 2002). For the analysis we used the three dimensions described in the WISC-III guidelines: Verbal Comprehension (VC; information, similarities, vocabulary, and comprehension), Perceptual Organization (PO; block design, picture completion, picture arrangement, and object assembly), and Perceptual Speed (PS; digit–symbol substitution and symbol search). Children also completed the Raven Standard Progressive Matrices (SPM; Raven, 1960) at their own pace after verbal instruction. The test consists of 60 problems divided into five sets of twelve, which become progressively more difficult. The test provides an index of general intelligence. For children, retest reliability is .88 (Raven, 1960). Raven-SPM scores were estimated based on the Rasch model (Rasch, 1966). In the Rasch model, every person is represented by a person parameter θ that reflects that person's ability. Every test item is represented by a difficulty parameter β. The probability that a person j answers item i correctly is parameterized by the logistic function $p(Y_{ij}=1)=\Psi(\theta_j-\beta_i)$, where θ_j is the person parameter, β_i is the difficulty parameter for that particular item, and $\Psi(x)=\exp(x)/(1+\exp(x))$ (see also Van den Berg, Glas, & Boomsma, 2006). Thus, for example, the probability that person j with ability θ_j answers item i with difficulty level β_i correctly, equals $e^{\theta j-\beta i}/[1+e^{\theta j-\beta i}]$. When $\theta_j-\beta_i=0$, the probability of a correct answer is exactly 50%, as $e^0=1$. When ability dominates the difficulty, $\theta_j>\beta_i$, then the probability is higher than 50%, becoming 100% when ability is infinitely higher than the difficulty. When ability is lower than the difficulty of the item, $\theta_j<\beta_i$, then the probability of a correct answer is lower than 50%, becoming 0% when the ability is infinitely lower than the difficulty. Note that the values for θ and β, the ability of a person and the difficulty of an item, are on the same scale. Rasch scores were estimated using the Gibbs sampler as implemented in the BUGS software (http://www.mrc-bsu.cam.ac.uk/bugs) by taking the mean of each individual's posterior distribution. The estimation procedure used no assumptions regarding the distribution of the intelligence scores or item difficulties. Extreme scores (like no item correct or all items correct) are inestimable in the Rasch model. Therefore, individuals who had extreme scores were assigned a value half a logit higher than the second highest scoring individuals (for further details see Van Leeuwen et al., 2008).

2.2.2. MR image acquisition and processing

A three-dimensional T1-weighted coronal spoiled-gradient echo scan of the whole head (256×256 matrix, TE=4.6 ms, TR=30 ms, flip angle=30°, 160–180 contiguous slices; 1×1×1.2 mm^3 voxels, Field-of-View=256 mm/70%) was acquired. Furthermore, a single-shot EPI (Echo Planar Imaging) scan was made as part of a diffusion tensor imaging (DTI)-series (SENSE factor 2.5; flip angle 90°; 60 transverse slices of 2.5 mm; no gap; 128×96 acquisition matrix; FOV 240 mm; TE=78 ms) together with a magnetization transfer imaging (MTI) scan (60 transverse slices of 2.5 mm; no gap;128×96 acquisition matrix; FOV 240 mm; flip angle 8°; TE=4.5 ms; TR=37.5 ms), which were used for segmentation of the intracranial volume (see Peper, Brouwer et al. (2008) for details on MR acquisition and processing).

The scans were coded to ensure blindness for subject and zygosity identification. The T1-weighted images were automatically put into Talairach orientation (Talairach & Tournoux, 1988) without scaling, by registering them to a model brain in Talairach orientation. The translation and rotation parameters of this registration were then applied to the images (Maes, Collignon, Vandermeulen, Marchal, & Suetens, 1997). After linear registration to the T1-weighted image, the intracranial segment served as a mask for all further segmentation steps. The T1-weighted images were corrected for field inhomogeneities using the N3 algorithm (Sled, Zijdenbos, & Evans, 1998). Our automatic image processing pipeline was used for segmentation of total brain volume, and gray and white matter of the cerebrum. The software included histogram analysis, mathematical morphology operations, and anatomical knowledge based rules to connect all voxels of interest, as was validated before (Schnack et al., 2001; Schnack, Hulshoff, Baare, Viergever, & Kahn, 2001). The intracranial and total brain segments were all visually checked and edited if necessary. Ten brains from the cohort were randomly selected and analyzed by two independent raters to estimate inter-rater reliability. Intra-class Correlation Coefficients (ICC) were above 0.97.

Four DZ individuals did not complete the MR scanning, leading to a total number of 210 children who successfully completed the protocol. Due to motion artifacts, separation of gray and white matter tissue was not possible in 14 subjects (6 MZ, 8 DZ). These subjects were included in the analyses of total brain volume. One outlier was excluded (DZ) since he had extremely large ventricles. Consequently, the total number of individuals included in total gray and white matter analyses was 195 (84 MZ, 111 DZ), whereas for total brain volume the number of subjects was 209 (90 MZ, 119 DZ).

2.3. Statistical analyses

All data analyses were performed using the software package Mx (Neale, Boker, Xie, & Maes, 2006). First, means and sex regressions on the means and general covariance matrices

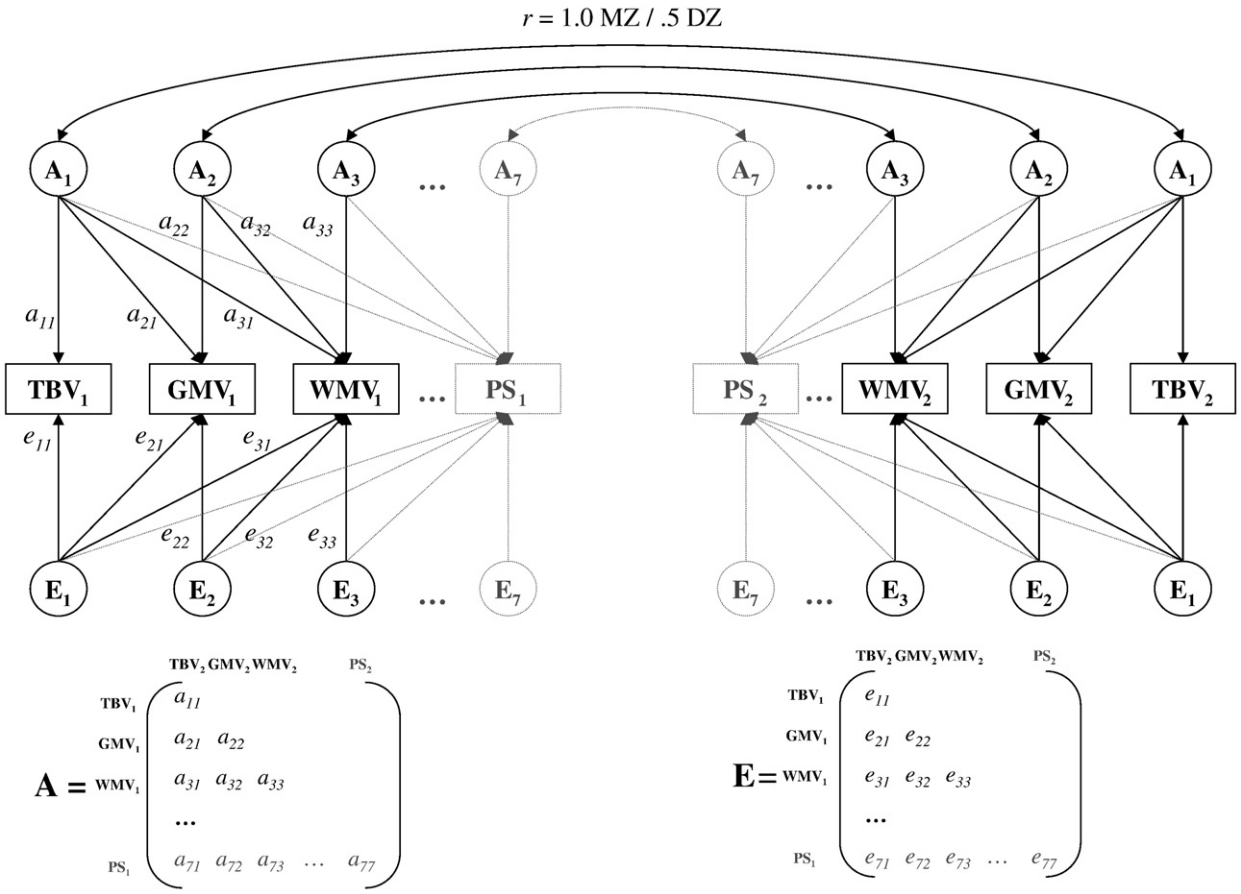


Fig. 1. Path model and matrices of the seven variate saturated AE model, with on the left side phenotypes measured in twin 1 and on the right side phenotypes in twin 2. For clarity reasons only total brain volume (TBV), white matter volume (WMV), gray matter volume (GMV), and processing speed (PS) are included (*A*=genetic factor, *E*=environmental factor, *a*=genetic factor loading, *e*=environmental factor loading).

were estimated in a saturated model. Means, regressions and covariance matrices for the 14 traits (i.e. seven phenotypes (TBV, GMV, WMV, IQ, VC, PO and PS) in twin 1 and in twin 2) were estimated separately for MZ and DZ twin pairs. Sex effects (regressions) were modeled for the mean structure, but not separately for the covariance structure, the sample size does not permit testing for sex differences in variance components. Standardization of the covariance matrices for MZ and DZ twin pairs provides correlation matrices of MZ and DZ within-trait and cross-trait correlations. By fitting a series of nested models in which the means and variances between MZ and DZ twins were equated, several assumptions were tested such as equality of means and variances between MZ and DZ twins. These models were also used to test for sex effects on the means. We continued constraining parameters until the most parsimonious model with still acceptable fit was established. The choice for the best fitting model was based on likelihood-ratio tests. The difference between minus twice the log likelihoods (−2 *LL*) of two nested models, asymptotically follows a χ^2 distribution. The degrees of freedom are given by the difference in the number of parameters estimated in the two nested models. A high increase in χ^2 against a low gain of degrees of freedom denotes a worse fit of the sub model compared to the full model. All data were analyzed, including data from twin pairs with incomplete data using the raw data option in Mx.

2.3.1. Genetic modeling

2.3.1.1. Univariate analysis. In the classic twin design MZ and DZ twin correlations contain the information on the relative influence of genetic and environmental factors on the variability in traits. When MZ twin correlations are higher than DZ twin correlations, part of the twin resemblance in the phenotype is caused by genetic factors (comprising of *additive effects* of alleles at one or more loci (*A*) and *non-additive effects* of alleles (*D*)). When DZ twin correlations are more than half the size of MZ correlations, the resemblance between twins is at least partly caused by shared environmental factors (*C*; common environmental factors shared between siblings brought up in the same family). Differences between MZ twins reflect the importance of unique environment (*E*). Large sample sizes are required to have sufficient power to detect *D* or *C* (Boomsma, Busjahn, & Peltonen, 2002; Plomin, DeFries, McClearn, & McGuffin, 2001).

The phenotype for an individual can be represented as:

$$P_{ij} = a^*A_{ij} + c^*C_{ij} + d^*D_{ij} + e^*E_{ij},$$

where i=1,2, …or 112 (families) and j=1 or 2 (twin 1 and twin 2) and A, C, D and E are latent variables (factors) standardized to have unit variance. The variance in P due to A, C and E is given by the square of a, c and e, respectively, so that Var (P)=a^2+c^2+d^2+e^2. The observed variance in a population thus is attributed to variance caused by genes and variance caused by environment. Note that e^2 also contains variance due to measurement error. MZ twins have the same DNA sequence and therefore genetic factors are perfectly correlated in MZ twins. DZ twins share on average half of their segregating genes, so that the expected correlation between their additive genetic factors (A) is 1/2. The genetic correlation between the dominance deviations (D) is 1/4. By definition the correlation between common environmental factor (C) is one, and between unique environmental factors (E) is zero. Therefore the covariance within MZ twin pairs is: Cov (MZ)=a^2+c^2+d^2, and within DZ twin pairs: Cov (DZ)=1/2 a^2+1/4 d^2+c^2. When only data from twins reared together are available, it is only possible to estimate c under the assumption that d is zero or any other specified value, and vice versa, since a model including free parameters for both c and d is not identified.

2.3.1.2. Multivariate analysis. To determine to what extent the covariation between the seven measures was due to genetic and environmental effects, multivariate genetic factor analysis was applied. In a multivariate analysis the *cross twin–cross trait correlations* (e.g. the correlation between GMV in twin 1 and VO in twin 2) for MZ and DZ twins and siblings contain information on the etiology of the association between traits. If MZ cross correlations are larger than the DZ cross correlations, this indicates genetic factors play a role in the covariation between the two traits.

Based on the sample size and on inspection of the MZ and DZ correlations estimated in the saturated models a genetic model in which the relative contributions of A and E were estimated was fitted to the data. Fig. 1 represents the seven variate saturated AE model as applied in the multivariate genetic analyses. For clarity reasons only TBV, WMV, GMV, and PS are included in the figure. In a seven-variate saturated AE model the factor loadings of the A and E factors are modeled in lower triangular matrices of dimensions 7×7 (for seven variables: three brain measures and four intelligence measures), where matrix **A** contains the genetic factor loadings and **E** the unique environmental factor loadings. The model is than represented as follows:

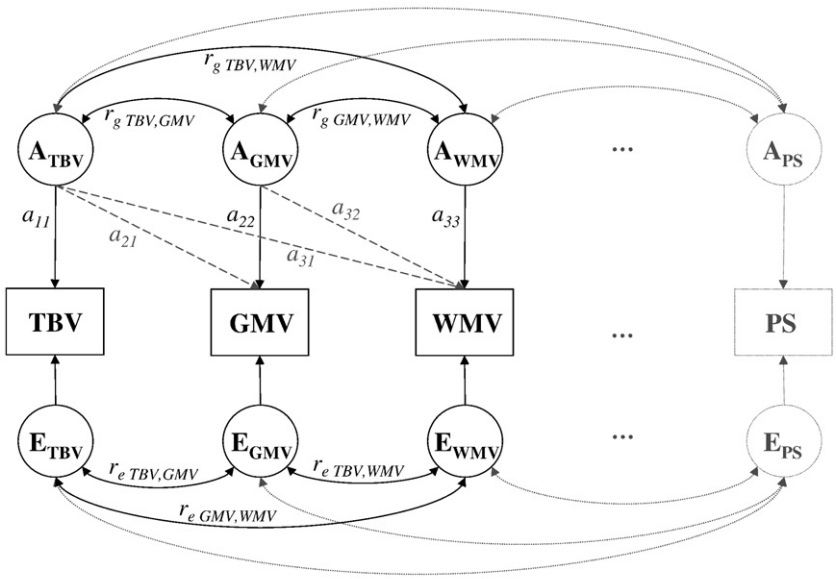
$$\boldsymbol{p}_{ij} = \mathbf{A}\times\boldsymbol{a}_{ij} + \mathbf{E}\times\boldsymbol{e}_{ij}$$

where i=1,2, …or 112 (families) and j=1 and 2 (twin 1 and twin 2), vector $\boldsymbol{p}$ denotes the 7 phenotypes and has the dimension 7×1. Vectors $\boldsymbol{a}_{ij}$ and $\boldsymbol{e}_{ij}$ have the dimensions 7×1 and contain the genetic and environmental factors. The random factors are standardized to have unit variance. The variance in $\boldsymbol{p}$ due to $\boldsymbol{a}$ and $\boldsymbol{e}$ is than given by:

$$\mathbf{V_P} = \mathbf{A}\times\mathbf{A}' + \mathbf{E}\times\mathbf{E}'$$

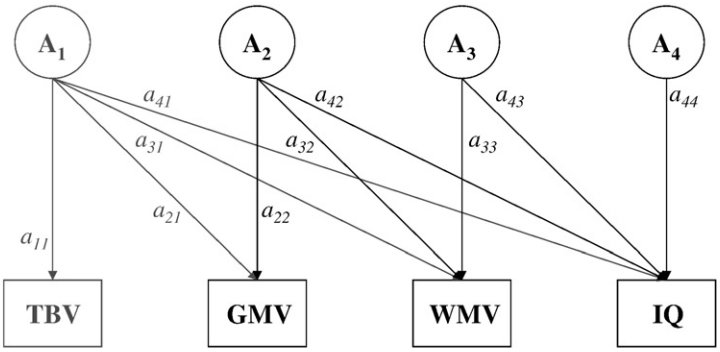
where matrix $\mathbf{V_P}$ is a symmetric matrix of 7×7, **A** and **E** are lower triangular matrices of 7×7, and ' indicates transposition. This seven-variate AE model is a completely saturated model; and was used to test whether variation in genes contributed significantly to the variability in brain volume and intelligence by assessing the deterioration in model fit after the A factors were dropped from the model.

The extent to which genetic factors on one trait correlate with the genetic factors on another trait is expressed in the genetic correlation (r_g; see also Fig. 2). The genetic correlation matrix is equal to the standardized genetic covariance matrix (**A**×**A**'). The size of the genetic correlations is independent of the influence of the genetic variance on the traits. Therefore,



$$r_{g\ \mathrm{WMV,\ GMV}} = (a_{31}{*}a_{21} + a_{32}{*}a_{22}) \,/\, \sqrt{((a_{22}{}^2 + a_{21}{}^2){*}\ (a_{33}{}^2 + a_{32}{}^2 + a_{31}{}^2))}$$

Fig. 2. Genetic correlation (r_g) between WMV and GMV. (TBV)=total brain volume, PS=processing speed, A=genetic factor, E=environmental factor, r_e=environmental correlation).



$$r_{g\ WMV,IQ} = (a_{41}{*}a_{31} + a_{42}{*}a_{32} + a_{43}{*}a_{33}) / \sqrt{((a_{33}{}^2 + a_{32}{}^2 + a_{31}{}^2){*}(a_{44}{}^2 + a_{43}{}^2 + a_{42}{}^2 + a_{41}{}^2))}$$

$$r_{g\ WMV,IQ-TB} = (a_{42}{*}a_{32} + a_{43}{*}a_{33}) / \sqrt{((a_{33}{}^2 + a_{32}{}^2){*}(a_{44}{}^2 + a_{43}{}^2 + a_{42}{}^2))}$$

Fig. 3. The genetic correlation between white matter volume (WMV) and IQ uncorrected and corrected for total brain volume (TBV; GMV = gray matter volume, *A* = genetic factor, *a* = genetic factor loading).

this correlation still can be high in case there is hardly any genetic variance. The same applies for the matrix of the environmental correlations (see Boomsma & Molenaar, 1986; Martin & Eaves, 1977; Neale & Cardon, 1992).

To determine whether differences in intelligence were driven by proportion WMV and GMV, we corrected in subsequent analyses the phenotypic (using partial correlation) and genetic correlations between GMV and WMV and the intelligence measures for TBV (Lenroot et al., 2007). The corrected genetic correlation was derived by estimating the covariances after correction for genetic effects of TBV. This is illustrated in Fig. 3, where the correlation between WMV and IQ serves as an example. Because GMV and WMV corrected for TBV are in fact the proportions GMV and WMV (i.e. when one proportion increases, the other decreases), the correlations between corrected GMV and WMV and intelligence have opposite signs.

3. Results

Maximum likelihood estimates of means and standard deviation are presented in Table 1. There were significant effects of sex on the means of TBV, GMV, WMV and PS; girls had smaller TBV, GMV, and WMV, and performed better on PS.

Table 1
Maximum likelihood estimates of means for girls and boys, and *SD* of the seven variables

Variable	*N*	Mean girls	Mean boys	*SD*
TBV	209	1291	1421	117
GMV	195	705	780	65
WMV	195	429	470	47
Raven	223	−1.30*	−1.30*	1.07
VC	224	100	100	15
PO	224	100	100	12
PS	223	105	95	14

Note. *based on Rasch score, the mean of total number correct items is 36.70. TBV = total brain volume, GMV = gray matter volume of the cerebrum, WMV = white matter volume of the cerebrum, VC = verbal comprehension, PO = perceptual organization, PS = processing speed.

Table 2 presents the phenotypic correlations between the seven variables. Most phenotypic correlations were significant, except for the correlation between WMV and IQ, between the three brain volumes and PS and between PS and VC. Phenotypic correlations amongst the brain measures ranged from .5 to .9, amongst intelligence measures from .1 to .5, and between the brain and intelligence measures from .1 to .3.

Table 3 displays the correlations in MZ twins (first figure on diagonal), and in DZ twins (second figure on diagonal). For all measures MZ correlations were higher than DZ correlations, indicating genetic influence on the variance of the seven traits. For the majority of the twin cross-correlations (off-diagonal of Table 3), the MZ correlations are larger than the DZ correlations, suggesting that the covariance between the measures is influenced by genetic factors. Table 4 presents the estimates of heritability (proportion of variance explained by genetic factors), and the proportions of variance explained by *D* or *C* and *E*, based on univariate genetic analyses of the 7 phenotypes. Based on these results, we decided to limit the multivariate model analyses on an AE model.

The first impression that genetic factors influence the variance and covariance between the seven phenotypes was confirmed in the seven-variate analysis: dropping the *A* component in the saturated AE model led to a significant deterioration of fit ($\Delta\chi^2 = 388.547$, $\Delta df = 28$, $p < .01$). Therefore it can be concluded that additive genetic factors contribute

Table 2
Phenotypic correlations between the seven variables corrected for sex

Variable	TBV	GMV	WMV	Raven	VC	PO
GMV	.89*					
WMV	.85*	.54*				
Raven	.20*	.22*	.13			
VC	.33*	.27*	.32*	.53*		
PO	.28*	.25*	.24*	.52*	.52*	
PS	.12	.06	.14	.16*	.12	.28*

Note. TBV = total brain volume, GMV = gray matter volume of the cerebrum, WMV = white matter volume of the cerebrum, VC = verbal comprehension, PO = perceptual organization, PS = processing speed, *significant $\alpha = .05$

Table 3
MZ and DZ correlations

Variable	TBV	GMV	WMV	Raven	VC	PO	PS
TBV	.94/.47	0.43	.38	.10	.30	.18	.01
GMV	.83	.84/.49	.29	.18	.24	.17	.00
WMV	.81	.62	.82/.40	.00	.31	.13	−.01
Raven	.21	.24	.12	.61/.33	.40	.30	.16
VC	.33	.28	.29	.51	.78/.64	.36	.11
PO	.25	.21	.23	.41	.37	.60/.22	.11
PS	.13	.04	.17	.15	.12	.22	.62/.21

Note. On the diagonal on the left side the MZ correlations and on the right the DZ correlations, below the diagonal MZ cross correlations and above the diagonal DZ cross correlations. TBV=total brain volume, GMV=gray matter volume of the cerebrum, WMV=white matter volume of the cerebrum, VC=verbal comprehension, PO=perceptual organization, PS=processing speed.

significantly to the variance and covariance in the three brain measures and the four intelligence measures.

The unstandardised genetic and environmental (co)variances which contribute to the phenotypic variance in and covariances between the three brain measures and the four intelligence measures are presented in Table 5. On the diagonal on the left the genetic variances, and on the right the environmental variances are presented. Genetic variances are larger than environmental variances, indicating that variance in genotype is more important than variance in environment to explain differences between children in brain volume and intelligence. On the lower off-diagonal the genetic covariances and on the upper off-diagonal the environmental covariances are displayed. The genetic covariances are larger than environmental covariances. Thus, the relationship between brain volumes and amongst brain and intelligence measures is mainly explained by genetic factors. In Table 6 the heritabilities (percentage of total variation explained by genetic variation) of the seven traits are presented. The traits were moderately to highly heritable. The heritabilities of the brain measures and IQ will not be thoroughly discussed, since they are discussed elsewhere (Peper, Schnack et al., in press; Van Leeuwen et al., 2008).

Table 7 shows the genetic and environmental correlations, below and above the diagonal, respectively. Amongst brain measures the genetic as well as the environmental correlations are significant, showing that correlations between genetic and environmental factors both contribute to the phenotypic correlations amongst the three brain measures. The same applies for the phenotypic correlations between PO and *g*, and PO and VC; common genetic as well environmental factors contribute to the phenotypic correlations between these intelligence measures. In contrast, the phenotypic correlations between brain and intelligence measures and among intelligence measures are explained by correlations between genetic factors only.

The phenotypic and genetic correlations between WMV and GMV and the intelligence measures corrected for TBV are shown in Table 8. The table shows that when corrected for TBV the correlation between GMV and WMV and the intelligence measures disappears. However, these genetic correlations should be interpreted with caution, since there are no phenotypic correlations. As follows from Tables 7 and 8 a large part of the genetic correlation between WMV and GM, and VC and PO was explained by genetic factors WMV and GMV have in common with TB. For example, the genetic correlation between WMV and VC is .35 (see Table 7). This genetic correlation is partly mediated by genes which have WMV and VC in common with TBV. In Table 8 the genetic factor which is common to TBV, WMV and VC is removed (see factor A_1, Fig. 3 which lowers the correlation between WMV and VC to .08. In the case of the relation between proportion GMV/WMV and Raven, this relation appears also to be

Table 4
Univariate analyses: variance component estimates

Variable	a^2	d^2	c^2	e^2
TBV	.94 (.62–.96)	–	.00 (.00–32)	.06 (.04–.09)
GMV	.77 (.40–.90)	–	.07 (.00–.43)	.15 (.09–.25)
WMV	.84 (.50–.90)	–	.00 (.00–.32)	.16 (.10–.27)
Raven	.50 (.00–.73)	–	.10 (.00–.52)	.40 (.27–.58)
VC	.28 (.00–.63)	–	.51 (.17–.74)	.21(.14–.33)
PO	.25 (.00–.72)	.35 (.00–.73)	–	.40 (.27–.58)
PS	.26 (.00–.72)	.34 (.00–.74)	–	.40 (.26–.62)

Note. TBV=total brain volume, GMV=gray matter volume of the cerebrum, WMV=white matter volume of the cerebrum, VC=verbal comprehension, PO=perceptual organization, PS=processing speed.

Table 5
Unstandardised estimates of the genetic and environmental (co)variances that contribute to the variance and covariances in and between the seven phenotypes

Variable	TBV	GMV	WMV	Raven	VC	PO	PS
TBV	60.39/3.58	3.94	4.51	.02	.60	2.63	−.16
GMV	56.52	61.19/10.95	−8.2	−3.61	.01	3.89	1.34
WMV	89.38	71.95	158.04/32.44	5.81	3.09	1.28	−3.61
Raven	16.11	22.32	11.33	64.53/48.11	2.27	14.97	−1.33
VC	35.81	30.04	58.34	79.61	175.36/47.18	27.99	.23
PO	25.17	21.91	39.79	52.32	65.64	87.21/68.39	7.43
PS	13.69	6.75	29.16	22.97	21.32	38.93	100.11/71.53

Note. On the diagonal on the left the genetic variances, and on the right the environmental variances. Below the diagonal the genetic covariances and above the environmental covariances. TBV=total brain volume, GMV=gray matter volume of the cerebrum, WMV=white matter volume of the cerebrum, VC=verbal comprehension, PO=perceptual organization, PS=processing speed.

Table 6
Heritabilities of the seven variables

Variable	Heritability
TBV	.94 (.91–.96)
GMV	.85 (.76–.90)
WMV	.83 (.73–.89)
Raven	.57 (.40–.70)
VC	.79 (.69–.86)
PO	.56 (37–.70)
PS	.58 (.37–.73)

Note. Between brackets 95% confidence intervals. TBV=total brain volume, GMV=gray matter volume of the cerebrum, WMV=white matter volume of the cerebrum, VC=verbal comprehension, PO=perceptual organization, PS=processing speed.

Table 7
Genetic and environmental correlations between the seven variables

Variable	TBV	GMV	WMV	IQ	VC	PO	PS
TBV		**.63 (.42–.78)**	**.42 (.15–.63)**	.00 (−.28–.28)	.05 (−.22–.31)	.17 (−.14–.44)	−.01 (−.30–.29)
GMV	**.93 (.89–.96)**		**−.44 (−64–.17)**	−0.16 (−.40-.11)	.00 (−.28–.28)	.14 (−.15–.41)	.05 (−.24–.32)
WMV	**.92 (.86–.96)**	**.73 (.59–.87)**		.15 (−.13–.40)	.08 (−.21–.35)	.03 (−.26–.31)	−.07 (−.34–21)
Raven	**.26 (.05–.45)**	**.36 (.13–.56)**	.11 (−.12–.34)		.05 (−.20–.29)	**.26 (.02–.47)**	−.02 (−.27–.23)
VC	**.35 (.18–.50)**	**.29 (.10–.46)**	**.35 (.16–.52)**	**.75 (.58–.90)**		**.49 (.26–.67)**	.00 (−.26–.26)
PO	**.35 (.14–.54)**	**.30 (.07–.52)**	**.34 (.11–.56)**	**.70 (.49–.87)**	**.53 (.34–.69)**		.11 (−.17–.37)
PS	.18 (−.04–.38)	.09 (−.15–.31)	.23 (−.01–.45)	**.29 (.00–.57)**	.16 (−.07–.39)	**.42 (.12–.71)**	

Note. Genetic and environmental correlations are presented below and above the diagonal respectively (In bold significant correlations and heritabilities). TBV = total brain volume, GMV = gray matter volume of the cerebrum, WMV = white matter volume of the cerebrum, VC = verbal comprehension, PO = perceptual organization, PS = processing speed.

explained by genetic factors specific for the proportion GMV/WMV. A higher proportion GMV is related to better performance on the Raven, and this relation seems to be mediated by genes.

4. Discussion

We analyzed in 9-year old children the relation between brain volume and intelligence. We showed that there is a significant association among measures of brain volume as assessed by sMRI and cognitive traits and also showed that the relation among brain volumes and intelligence measures is entirely explained by a set of genes common to both sets of variables. Correlations between the different measures of brain volume and intelligence ranged between .20 and .33 (the non-significant correlation between IQ and WMV excluded). Processing speed and the brain volumes did not correlate. There was no indication that IQ, PO and VC correlated differently to each of the brain volumes.

Several features distinguish this study from the other studies on the relation between brain volume and intelligence done in children. First of all, all children were the same age, and therefore the reported relation between brain volumes and intelligence was relatively unaffected by age-related changes in brain structure demonstrated earlier (Giedd et al., 1999; Lenroot et al., 2007; Paus et al., 1999; Sowell, Trauner, Gamst, & Jernigan, 2002). Moreover, this is the largest study until now on the relation between brain volumes and intelligence in a group of children that is representative for the general population.

The correlation between TBV and VC and PO ranged between .28 and .33 replicating previous research on the relation between intelligence and TBV (McDaniel, 2005). We also reproduced the relation between GMV and intelligence (Andreasen et al., 1993; Frangou et al., 2004; Posthuma et al., 2002; Reiss et al., 1996; Thoma et al., 2005). In contrast to Wilke et al. (2003) we found a correlation between GMV and TBV and IQ in nine-year-olds. Possibly this can be explained by smaller sample size and wider age range in the study of Wilke et al. (1 year in the subgroups vs. 1 month in our sample).

We also reported partial correlations, which indicated that intelligence was not related to proportion WMV/GMV. The association between intelligence and WMV and GMV disappears once corrected for TBV (consisting of WMV, GMV, cerebellum volume and stem volume), since TBV and WMV and GMV are highly correlated. Nevertheless, we cannot merely conclude from the partial correlation analyses, that intelligence is only influenced by TBV and that WMV and GMV separately do not influence intelligence.

Our study is in agreement with previous studies in children showing that variance in IQ test performance is for 25 to 70% accounted for by genetic variation between individuals (Bartels, Rietveld, Van Baal, & Boomsma, 2002; Hoekstra, Bartels, & Boomsma, 2007; Jacobs et al., 2001; Plomin, 2003; Rietveld, Dolan, Van Baal, & Boomsma, 2003; Turkheimer, Haley, Waldron, D'Onofrio, & Gottesman, 2003). Genetic factors entirely explain the significant phenotypic correlations between the three brain volumes and IQ, PO and PS. This finding is in concordance with the findings by Posthuma et al. (2002) in adults. Possibly, these genetic factors come into play already early in development. Gale, O'Callaghan, Bredow, and Martyn (2006) and Gale, O'Callaghan, Godfrey, Law, and Martyn (2004) showed – measuring head circumference – that brain growth during infancy predicts intelligence in eight- and nine-years-olds, while brain size at birth and brain growth later in life is not associated with intelligence in both these age groups. After infancy children could not compensate for poor brain growth earlier in life. This shows that the relation between brain volume and intelligence already is established between birth and one year of age.

Genetic and environmental correlations can give an indication for the direction of causation for the association between intelligence and brain volume (De Moor, Boomsma, Stubbe, Willemsen, & De Geus, 2008). If intelligence causally influences brain volume, all genetic and environmental factors that influence intelligence will also, through the causal chain, influence brain volume. Under the causal hypothesis both genetic and environmental correlations should be significant, whereas a significant genetic correlation in the absence of an environmental correlation falsifies the hypothesized causal

Table 8
Phenotypic and genetic correlations between gray matter volume (GMV) and white matter volume (WMV) and intelligence measures corrected for total brain volume

	Phenotypic correlation		Genotypic correlation	
Variable	GMV	WMV	GMV	WMV
Raven	.09	−.08	.32	−.32
VC	−.06	.08	−.10	.08
PO	.00	.00	−.07	.06
PS	−.10	.07	−.21	.18

Note. VC = verbal comprehension, PO = perceptual organization, PS = processing speed; *significant $\alpha = .05$.

effect of intelligence. However, when traits are highly heritable (in the range of 90–100%), as is the case in brain volumes, causality (brain volume causes intelligence) cannot be distinguished from pleiotropy (the same set of genes affects brain volume as well as intelligence).

The heritability estimates for the brain volumes are around 90%. In contrast, variability in intelligence is for about 60% caused by differences in genotypes. If intelligence causally influences brain volumes, this would also be reflected in the genetic and environmental correlations: all genetic and environmental factors that influence intelligence would, through the causal chain, influence brain volume. However, our study shows that only the genetic correlations are significant. In fact 85% to 100% of the covariation between brain volume and intelligence are caused by shared genetic factors. This leaves two options: 1) the relation between brain volume and intelligence is caused by a set of genes which influences variation in brain volume and this variation in turn leads to variation in intelligence 2) pleiotropy: there is a set of genes which influence brain volume as well as intelligence.

Future studies should aim to dissect the pathways relating genes, brain and intelligence (Plomin & Kosslyn, 2001), using genome wide association (Kruglyak, 2008), gene expression (DeRisi, Iyer, & Brown, 1997; Tang, 2006), proteomics and metabolomics approaches (Petrella, Mattay, & Doraiswamy, 2008). We can speculate about the nature of the genes involved in the association between intelligence and brain volume. As mentioned before the association between brain volume and intelligence is established between birth and one year of age. Moreover, genes which influence brain volume, influence intelligence via a causal pathway or pleiotropy. Therefore, genes responsible for myelination and the proliferation and organization of synapses could possibly explain the relation between intelligence and brain volume, since both these processes predominantly occur before birth until early childhood (Lenroot & Giedd, 2006).

Based on linkage studies probable candidate genes for the association between brain volume and intelligence are the genes for prion protein (PrP; Rujescu, Hartmann, Gonnermann, Moller, & Giegling, 2003), brain-derived neurotrophic factor (BDNF; Miyajima et al., 2008; Savitz, Solms, & Ramesar, 2006; Tsai, Hong, Yu, & Chen, 2004) and the synaptosomal associated protein of 25 kD (SNAP-25; Gosso et al., 2006, 2008): A mutation in the PrP gene has been implied in white matter reduction and a decline in intelligence (Rujescu et al., 2003). BDNF exerts amongst others long-term effects on neuronal survival, migration, and dendritic and axonal growth (Pang & Lu, 2004) and intelligence (Miyajima et al., 2008; Tsai et al., 2004). Finally, SNAP-25 is amongst others implicated in axonal growth and IQ, and most strongly performal IQ (Gosso et al., 2006, 2008).

5. Limitations of the current research and directions for future research

One limitation of this study is that, in spite of the large sample size, we did not have sufficient power to test for sex differences in the relation between brain volumes and intelligence. The study of Lenroot et al. (2007) showed different trajectories of brain development between boys and girls for TBV, GMV, and WMV. We applied a linear correction for sex differences in brain volume and PS, which seems plausible since we did not measure a developmental curve. And declines in TBV and GMV only start after age nine in boys as well as girls (Lenroot et al., 2007). However, to test whether genetic and/or environmental factors have different effects in boys than in girls or some factors have an effect on one sex and not on the other, one should evaluate scalar and non-scalar sex limitation models in sufficiently large samples and take into account potential problems with fitting these models (see Neale, Roysamb, & Jacobson, 2006).

We only looked at gross brain volumes. A next step should be to investigate whether specific brain areas contribute to the relationship between brain volumes and intelligence. Voxel-based morphometry (VBM) analyses in adolescents and young adults showed positive correlations between IQ and gray matter density in the orbifrontal cortex and cingulated gyrus, the cerebellum, and thalamus and negative correlations in caudate nucleus; areas known to be involved in executive control (Frangou et al., 2004). In an adult sample Haier, Jung, Yeo, Head, and Alkire (2004) found a positive correlation between intelligence and gray matter density within all four lobes of the cerebrum (i.e. frontal (Brodmann areas (BA) 10, 46, 9), temporal (BA 21, 37, 22, 42), parietal (BA 43 and 3) and occipital (BA 19) lobe), and with white matter density in the right parietal area near BA 39. In adults, Hulshoff Pol et al. (2006) showed that the phenotypic correlation (up to .35) between intelligence and white matter of the superior occipitofrontal, callosal, and left optical radiation and gray matter of the frontal and occipital lobes and the parahippocampal gyrus could be explained by a common set of genes. Future studies should investigate if in children the same brain areas contribute to the relation between intelligence and brain structure and if the relation between these areas and intelligence stems from common genetic and/or environmental factors. Moreover, it would be interesting to follow the developmental trajectories between intelligence and brain structure, as Shaw et al. (2006) showed that more intelligent children follow a different developmental trajectory than less intelligent children. We intend to follow the children who were tested at age 9 years in the upcoming years, so as to be able to track these trajectories and elucidate the mechanisms underlying these trajectories.

To summarize, at 9 years of age, variation in brain structure is associated with individual differences in intelligence measures. This relation is entirely explained by genetic factors common to both sets of traits. The genes which influence brain volume, probably influence intelligence via a causal pathway or via pleiotropy. A causal chain from genes, to IQ to brain size is less likely.

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