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Heritability of brain volume change and its relation to intelligence

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ABSTRACT

Human brain volumes change throughout life, are highly heritable, and have been associated with general cognitive functioning. Cross-sectionally, this association between volume and cognition can largely be attributed to the same genes influencing both traits. We address the question whether longitudinal changes in brain volume or in surface area in young adults are under genetic control and whether these changes are also related to general cognitive functioning. We measured change in brain volume and surface area over a 5-year interval in 176 monozygotic and dizygotic twins and their non-twin siblings aged 19 to 56, using magnetic resonance imaging. Results show that changes in volumes of total brain (mean = −6.4 ml; 0.5% loss), cerebellum (1.4 ml, 1.0% increase), cerebral white matter (4.4 ml, 0.9% increase), lateral ventricles (0.6 ml; 4.8% increase) and in surface area (−19.7 cm^2,1.1% contraction) are heritable (h^2 = 43%; 52%; 29%; 31%; and 33%, respectively). An association between IQ (available for 91 participants) and brain volume change was observed, which was attributed to genes involved in both the variation in change in brain volume and in intelligence. Thus, dynamic changes in brain structure are heritable and may have cognitive significance in adulthood.

Introduction

Human brain volume is highly heritable in children (Lenroot et al., 2009; Peper et al., 2009; Wallace et al., 2006) and in adults (Baaré et al., 2001; Pfefferbaum et al., 2000; Thompson et al., 2001; Wright et al., 2002), with heritability estimates exceeding 90% (Peper et al., 2007). This suggests that genetic influences on overall brain size are present early in childhood and remain important in adulthood. However, it is well known that brain volume is far from static and changes throughout life. Having reached approximately 90% of its adult size around the age of six (Giedd et al., 1999), dynamic changes in brain structure continue to take place in children and adolescents (Giedd et al., 1999; Gogtay et al., 2004; Shaw et al, 2006; van Soelen et al., 2013), and on the other side of the age spectrum in older adults over 60 years of age (Bartzokis et al., 2001; Liu et al., 2003; Pfefferbaum et al., 2004; Raz et al., 2005; for review see Hedman et al., 2012). At both extremes of the age spectrum, changes in brain structure were found to be heritable (Pfefferbaum et al, 2004; van Soelen et al, 2012, 2013). In young adulthood, and particularly between 20 and 40 years of age, a period or relative stability in total brain volume is found (for review see Hedman et al., 2012), despite heritable focal changes in cortical thickness (Brans et al, 2010). At the individual level however, there is variation in the extent to which total brain volume and surface area changes in this period and it is not known whether genes are implicated in this process.

Several studies have shown that level of intelligence is positively correlated with total brain volume (Posthuma et al., 2002; Thompson et al., 2001), focal grey (Frangou et al., 2004; Haier et al., 2004; Hulshoff Pol et al., 2006; Thompson et al., 2001) and white (Hulshoff Pol et al., 2006) matter densities, and that these associations are mediated by common genetic factors (Hulshoff Pol et al., 2006; Posthuma et al., 2002; Toga and Thompson, 2005). Moreover, young adults with a higher intelligence show attenuated cortical thinning and more pronounced cortical thickening over time than subjects with average or below average intelligence (Brans et al., 2010). In adolescents, cortical maturation has been associated with intelligence (Brouwer et al., 2013; Shaw et al., 2006), as well as with changes in intelligence over time (Burgaleta et al., 2014; Ramsden et al., 2011). Thus, genes involved in individual variations in intelligence (Plomin and Spinath, 2004) overlap with those for individual variations in brain volume (Posthuma et al., 2002), and with local cortical thickness change (Brans et al, 2010).

However, it is unknown whether genes influence brain volume change in adulthood. Moreover, it is unclear whether brain volume change is associated with intelligence and if common genes are implicated in the association. Therefore, we examined whether changes in brain volume and surface area over time are related to intelligence

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and if so, whether genes common to both influence this relationship. This was investigated in a large longitudinal magnetic resonance imaging (MRI) study in 176 adult individuals from 86 twin families between 19-56 years of age, with a 5-year interval between scans.

Methods

Subjects

Twins and their siblings were from the twin-pair cohort at the University Medical Centre Utrecht and from the Netherlands Twin Registry, VU University Amsterdam, as described in Brans et al. (2010). At baseline assessment, a total of 242 participants from 106 twin families were assessed. Average age was 29 years. After 5-years 176 participants from 86 families (51 monozygotic (MZ) males, 41 dizygotic (DZ) males, 23 MZ females, 39 DZ females, and 22 siblings (11 males and 11 females)) participated again (Table 1; return rate 75%; 6 participants dropped out at follow-up due to poor scan quality). All participants gave written informed consent. DNA testing using polymorphic markers determined zygosity. Except for one twin pair, all twins and their siblings were reared together. Two twin pairs were born by caesarean section delivery. The study was carried out according to the directives of the "declaration of Helsinki" (amendment of Edinburg, 2000) and was approved by the medical ethics committee for research in humans (METC) of the University Medical Centre Utrecht, the Netherlands.

Brain imaging

Magnetic Resonance Imaging brain scans were acquired on a Philips NT (Best, the Netherlands) scanner on 1.5 T in all subjects. T1-weighted three-dimensional fast field echo (3D-FFE) scans with 160–180 contiguous coronal slices scans (TE = 4.6 ms, TR = 30 ms, flip angle = 30°, $1 \times 1 \times 1.2$ mm^3 voxels), and T2-weighted dual-echo turbo-spin-echo (DE-TSE) scans with 120 contiguous coronal slices (TE1 = 14 ms, TE2 = 80 ms, TR = 6350 ms, flip angle = 90°, $1 \times 1 \times 1.6$ mm^3 voxels) of the whole head were used for quantitative measurements. In addition, T2-weighted dual-echo turbo-spin-echo (DE-TSE) scans (TE1 = 9 ms, TE2 = 100 ms, flip angle = 90°, 0.98×0.98 mm^2) with 19 axial 5-mm slices and 1.2-mm gap of the whole head were used for clinical neurodiagnostic evaluation.

Processing was done on the neuroimaging computer network of the Department of Psychiatry at the University Medical Center Utrecht. All images were coded to ensure blindness for subject identification and diagnoses, scans were manually put into Talairach frame (no scaling) for segmentation purposes, and corrected for inhomogeneities in the magnetic field (Sled et al., 1998). Our automatic processing pipeline was used for segmentation of total brain, grey (GM) and white matter (WM) of the cerebrum (Brouwer et al., 2010). In short, pure GM and WM intensities were directly estimated from the image. The amounts of pure and partial volume voxels were modeled in a non-uniform partial volume density, which is fitted to the intensity histogram. Expected tissue fractions, based on the pure intensities and the partial volume density, were subsequently computed in each voxel within the cerebrum. Intracranial, ventricle and cerebellum segmentations were checked after measurement and corrected manually if necessary (Schnack et al., 2001).

To estimate the cortical surface, we used the CLASP (Constrained Laplacian Anatomic Segmentation Using Proximity) algorithm designed at the McConnell Brain Imaging Centre of the Montréal Neurological Institute (Kabani et al., 2001; Kim et al., 2005; MacDonald et al., 2000). A 3-dimensional surface consisting of 81,920 polygons was fitted to the WM–GM interface. This defined the inner surface of the cortex, which was then expanded to fit the GM–cerebrospinal fluid interface, thereby creating the outer cortical surface (Kim et al., 2005; MacDonald et al., 2000). The surfaces of the participants were registered to an average surface created from 152 individuals (International Consortium for Brain Mapping: Lyttelton et al., 2007) allowing comparison of cortical surface locally between subjects both at baseline as well as follow-up measurement. The mid-areas between the white matter (i.e., inner surface) and the grey matter (i.e., outer surface) at baseline and follow-up measurement were used as a measure of cortical surface area. These were subtracted to obtain a measure of surface area change.

Cognitive assessment

Intelligence was estimated by the total Intelligence Quotient (IQ), verbal IQ and performance IQ, as based on the Dutch 1997 experimental version of the WAIS III. IQ was available at baseline for 119 participants of the original sample (41 MZ (20 complete pairs), 59 DZ (27 complete pairs), 19 siblings), of whom 91 had repeated MRI measurements (43 twin families (26 monozygotic (11 complete pairs), 48 dizygotic (21 complete pairs), 17 siblings)).

Statistical analyses

To estimate the relative contribution of genetic and common and unique environmental factors on the variation of brain volume change and surface area change, the extended twin-sibling model was applied. This model is based on the fact that MZ twins are genetically identical and DZ twins share on average 50% of their genes. Both types of twins share their familial environment. Therefore, if MZ twins resemble each other more than DZ twins, genetic factors are important for that trait. The presence of shared environmental factors is suggested when correlations in DZ twins are larger than half the MZ correlation. Unique

Table 1
Demographics of the twins and their siblings.

	MZ	DZ	Siblings
Sex, male/female	51/23	41/39	11/11
Age at time of the first scan, y[a] [range]	31.09 (9.02) [19.45 to 55.88]	28.21 (5.98) [19.07 to 51.58]	28.01 (3.07) [20.22 to 31.34]
Height, cm	177.12 (8.97)	177.14 (8.81)	174.32 (11.97)
Handedness, r/l/ambidextrous	57/15/2	67/7/6	17/4/1
Level of education, y	13.69 (12.90)	13.41 (2.56)	12.73 (3.18)
Parental level of education, y	12.22 (2.64)	12.08 (2.76)	12.05 (2.79)
Follow-up duration, y[a]	5.13 (0.56)	5.51 (0.69)	5.41 (0.55)
Full-scale IQ[b]	106.8 (15.3)	103.4 (8.3)	105.6 (12.3)
Verbal IQ[b]	107.2 (15.8)	104.0 (8.2)	108.9 (15.5)
Performance IQ[b]	103.1 (13.0)	101.7 (10.2)	98.9 (8.3)

Means and standard deviations (number of subjects for categorical variables).

[a] Age differed significantly between the groups (i.e., MZ, DZ and siblings); $F_{2,173} = 7.10$, $p = 0.001$, post-hoc analysis for multiple comparisons revealed that this was due to MZ twins having significantly higher age than DZ twins. F-u duration differed significantly between the groups: $F_{2,173} = 3.54$, $p = 0.031$, post hoc analysis for multiple comparisons revealed that this was due to DZ twins having significantly longer f-u duration than MZ twins.

[b] Full-scale, Verbal and Performance IQ were available in 91 participants that had repeated MRI scans.

environmental influences are present if the MZ correlation is less than 1 (Boomsma et al., 2002). By including siblings, the statistical power to detect the influences of common environmental factors shared by family members is enhanced, because, similar to DZ twins, a twin and its non-twin sibling also share 50% of their genes on average and share the familial environment (Posthuma et al., 2000).

Linear effects of sex and age on brain volume change/surface area change per year were tested using structural equation modeling (SEM), thereby corrected for familial dependencies. For genetic model fitting, SEM was performed to investigate the relative contributions of genetic and environmental factors of brain volume change and surface area change. SEM can estimate the contribution of additive genetic (A), common (or shared) environmental (C) and unique environmental (E) factors to the variance in one trait by maximizing the likelihood function, which is in part determined from comparing the observed covariance matrix to the covariance matrix predicted by the model. Because brain volumes/surface area and intelligence in adulthood show little evidence for influences of shared environment (C), analyses incorporating change measures and IQ were based on models containing additive genetic (A) and unique environmental (E) influences only. To determine whether change over time was significantly different from zero, we first computed change values per year, corrected for age and sex using a linear regression model, and then tested whether the mean was zero in a univariate model. Unstandardized residuals of these regressions were entered in a univariate model to establish heritability. All available data were entered in the model estimating heritability of brain volume change/surface area change, using raw data maximum likelihood estimation of parameters.

The bivariate genetic analysis yielded an estimate of the phenotypic correlations (r_{ph}) between brain volume change/surface area change and IQ, which can result from correlated genes or correlated environmental factors represented by genetic (r_g) and environmental correlations (r_e) respectively. Decomposition of the phenotypic correlations was based on the comparison of cross-trait/cross-twin correlations for MZ and DZ twins, i.e., the correlation between a trait (e.g., brain volume change) of twin 1 with another trait (e.g., IQ) of twin 2, where twin 1 and twin 2 represent the two twins from a pair. If the absolute value of the correlation between brain volume change of twin 1 and IQ of twin 2 is larger in MZ twins than in DZ twins, this indicates that genes influencing brain volume change (partly) overlap with genes that influence IQ. The extent of the overlap is reflected by the magnitude of the genetic correlation r_g. Likewise, r_e represents the extent of overlap of environmental factors influencing the traits. The extent, to which either of these correlations explains the observed correlation between two traits, also depends on the etiology of the traits. For example, a genetic correlation between two traits may exist, but when the traits themselves show a low heritability, this genetic correlation will only explain the observed correlation to a small extent. We therefore also computed the $r_{ph\text{-}a}$ and $r_{ph\text{-}e}$ (Toulopoulou et al., 2007), which is defined by the genetic (environmental, respectively) covariance, divided by the standard deviations of the two traits. These two can be interpreted as the phenotypic correlation that would be observed if only genetic factors (environmental factors, respectively) would be taken into account.

It was tested whether an AE model fits as well as an E model, taking the simplest model explaining the data best. A Chi-squared larger than $\chi^2 = 3.84$ (1 df) (Neale et al., 2003) indicates a significant difference at alpha = 0.05, which means that the reduced model provides a significantly worse fit to the data and indicates that the discarded effect (e.g. additive genetic influence) cannot be left out of the model without seriously deteriorating the goodness of fit. All analyses were performed using the OpenMX package (Boker et al., 2011).

As a post-hoc analysis, we investigated whether the influences of genes on brain changes were the same for males and females. We first tested for quantitative sex differences by allowing the correlation between additive genetic factors acting on members of opposite-sex twin pairs and opposite-sex sibling pairs to be smaller than 0.5. If this is the case, it can be concluded that different genetic factors act on brain volume change for males and females. In the second step, we tested for qualitative sex differences by constraining the correlation between males and females to be equal within zygosity.

Results

Changes in brain volumes and surface area

Over the 5-year interval, whole brain volume decreased [mean (sd) = −6.40 (19.97) ml; percent change = −0.51 (1.58)%], with 66% of the adult participants showing whole brain volume loss (See Table 2; Fig. 1). Cerebral volume decreased [−7.67 (18.79) ml; percent change = −0.70 (1.69)%] with 67% of the participants showing cerebral volume decrease. Cerebral white matter volume increased [4.38 (16.57) ml; percent change = 0.91 (3.27)%], with 64% of the participants showing cerebral white matter volume increase. Cerebral grey matter volume decreased [−12.05 (12.35) ml; percentage change = −1.97 (1.99)%], with 86% of the adult participants showing a decrease in grey matter volume over the 5-year interval. Cerebellum volume increased [1.43 (3.33) ml; percentage change = 1.04 (2.44)%], with 64% of adult participants having an increase. This was due to an increase in cerebellar white matter volume (2.97 ml (8.0%)) accompanied by a decrease in cerebellar grey matter volume (−1.55 ml (−1.47%)). Lateral ventricles increased [0.61 (1.23) ml;

Table 2
Heritability (percent additive genetic effects of total variance) of brain volume changes and surface area change. Third and fourth column show raw (uncorrected for age and sex) change during the 5 year interval in ml for brain volume and cm^2 for surface area. Heritability estimates of brain volume changes and surface area change were based on 176 subjects.

Structure	h^2 of change (CI)[a]	Change[b]	Change %
Total brain	**0.43 [0.17 to 0.62]**	**−6.40 (19.97)**	−0.51 (1.58)
Cerebrum	**0.48 [0.22 to 0.67]**	**−7.67 (18.79)**	−0.70 (1.69)
Cerebrum GM	0.10 [0.00 to 0.35]	**−12.05 (12.35)**	−1.97 (1.99)
Cerebrum WM	**0.29 [0.02 to 0.52]**	**4.38 (16.57)**	0.91 (3.27)
Cerebellum	**0.52 [0.34 to 0.66]**	**1.43 (3.33)**	1.04 (2.44)
Cerebellum GM	**0.25 [0.02 to 0.46]**	**−1.55 (4.75)**	−1.47 (4.84)
Cerebellum WM	**0.42 [0.20 to 0.59]**	**2.97 (5.47)**	8.0 (16.10)
Lateral ventricles	**0.31 [0.09 to 0.51]**	**0.61 (1.23)**	4.76 (9.14)
Third ventricles	**0.29 [0.08 to 0.48]**	0.03 (0.15)	4.24 (17.80)
Surface	**0.33 [0.07 to 0.53]**	**−19.69 (25.84)**	−1.05 (1.37)
Left hemisphere	**h^2 of change (CI)[a]**	**Change[b]**	**Change %**
L brain	**0.45 [0.19 to 0.65]**	**−2.09 (11.77)**	−0.32 (1.87)
L cerebrum	**0.52 [0.24 to 0.70]**	**−3.01 (10.29)**	−0.54 (1.85)
L cerebrum GM	0.10 [0.00 to 0.36]	**−5.19 (7.32)**	−1.68 (2.36)
L cerebrum WM	0.23 [0.00 to 0.48]	**2.18 (8.62)**	0.91 (3.33)
L cerebellum	0.13 [0.00 to 0.35]	**0.90 (2.51)**	1.32 (3.62)
L lateral ventricles	**0.28 [0.04 to 0.50]**	**0.32 (0.66)**	4.77 (9.45)
L surface	**0.36 [0.11 to 0.54]**	**−9.21 (13.65)**	−0.98 (1.45)
Right hemisphere	**h^2 of change (CI)[a]**	**Change[b]**	**Change %**
R brain	0.14 [0.00 to 0.36]	**−4.31 (11.30)**	−0.69 (1.79)
R cerebrum	**0.31 [0.05 to 0.53]**	**−4.66 (10.05)**	−0.85 (1.80)
R cerebrum GM	0.16 [0.00 to 0.38]	**−6.86 (6.86)**	−2.26 (2.25)
R cerebrum WM	**0.28 [0.32 to 0.51]**	**2.19 (8.45)**	0.93 (3.42)
R cerebellum	0.00 [0.00 to 0.20]	**0.53 (2.67)**	0.80 (3.92)
R lateral ventricles	**0.30 [0.09 to 0.48]**	**0.28 (0.62)**	4.83 (9.76)
R surface	0.24 [0.00 to 0.46]	**−10.47 (13.93)**	−1.11 (1.48)

In bold = significant.
h^2 = heritability (the percentage additive genetic effect of the total variances).
Total brain = cerebrum + cerebellum + brain stem.
GM = Gray Matter.
WM = White Matter.
CI = Confidence Interval
[a] Univariate heritability estimates were based on the data corrected for age and sex. Performing the analysis on the uncorrected data showed similar results.
[b] Mean (SD) raw change in volumes (ml), surface area (cm^2) over a 5 year interval. Significance testing of change is based on values per year corrected for age and gender.

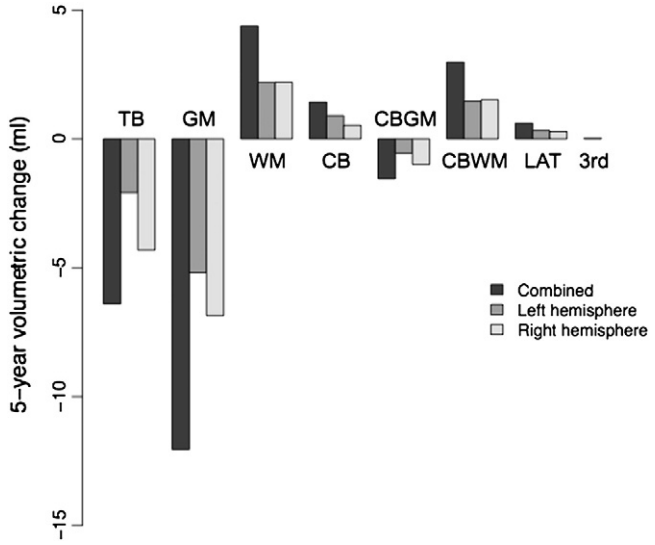

Fig. 1. Brain volume change over a five year interval (ml). Brain volume change in ml for total brain (TB); grey matter (GM); white matter (WM); cerebellum (CB); grey matter of the cerebellum (CBGM); white matter of the cerebellum (CBWM); lateral ventricles (LAT) and third ventricle (3rd), for the left hemisphere, right hemisphere and hemispheres combined in 176 subjects.

percent change = 4.76 (9.14)%] with 69% of the participants showing an increase in lateral ventricles over the 5-year interval. Surface contracted [−19.69 (25.84) cm^2; percentage change = −1.05 (1.37)%] with 78% of the participants showing surface contraction. Decreases and increases described above were also seen when considering left and right hemisphere separately (Table 2). We found no significant sex effects on change. A significant age effect on cerebral GM change (total; $p = 0.004$, right; $p = p < 0.001$) in that a higher age at baseline was associated with a smaller decrease for total and right cerebral GM. Cerebral WM change resulted in a significant age effect (total; $p = 0.001$, left; $p = 0.007$, right; $p < 0.001$) where those with a higher age at baseline had a larger decrease/smaller increase in cerebral WM. Furthermore, a significant age effect was found for change in the ventricles (total; $p < 0.001$, left; $p = 0.002$; right; $p < 0.001$) in that higher age at baseline was associated with larger increase in the ventricles. Despite the lack of significant effects of age and sex on several change measures, we chose to correct all variables for age at baseline and sex to exclude possible effects on heritability estimates. These corrected values were entered in the twin model.

As a post-hoc analysis, we measured the differences between the subjects that showed brain growth over time (33%), as compared to those that showed brain volume decrease (66%). There were no differences in age at baseline, sex, follow-up duration and zygosity between these groups. There were slightly more siblings than twins in the group that showed brain increases ($p = 0.04$). Subjects showing brain volume increases had significantly higher IQ ($p < 0.001$), VIQ ($p < 0.001$) but also PIQ ($p = 0.01$) compared to subjects showing brain decreases. The brain volume increase could mainly be attributed to white matter volume increase: At baseline, the two groups showed no difference in white matter and total brain volume. Subjects showing an increase in total brain volume showed an increase in white matter volume ($p < 0.001$), whereas subjects showing total brain volume decrease did not. Subjects showing brain volume increases, had larger ventricles at baseline ($p = 0.01$), but their ventricles did not increase

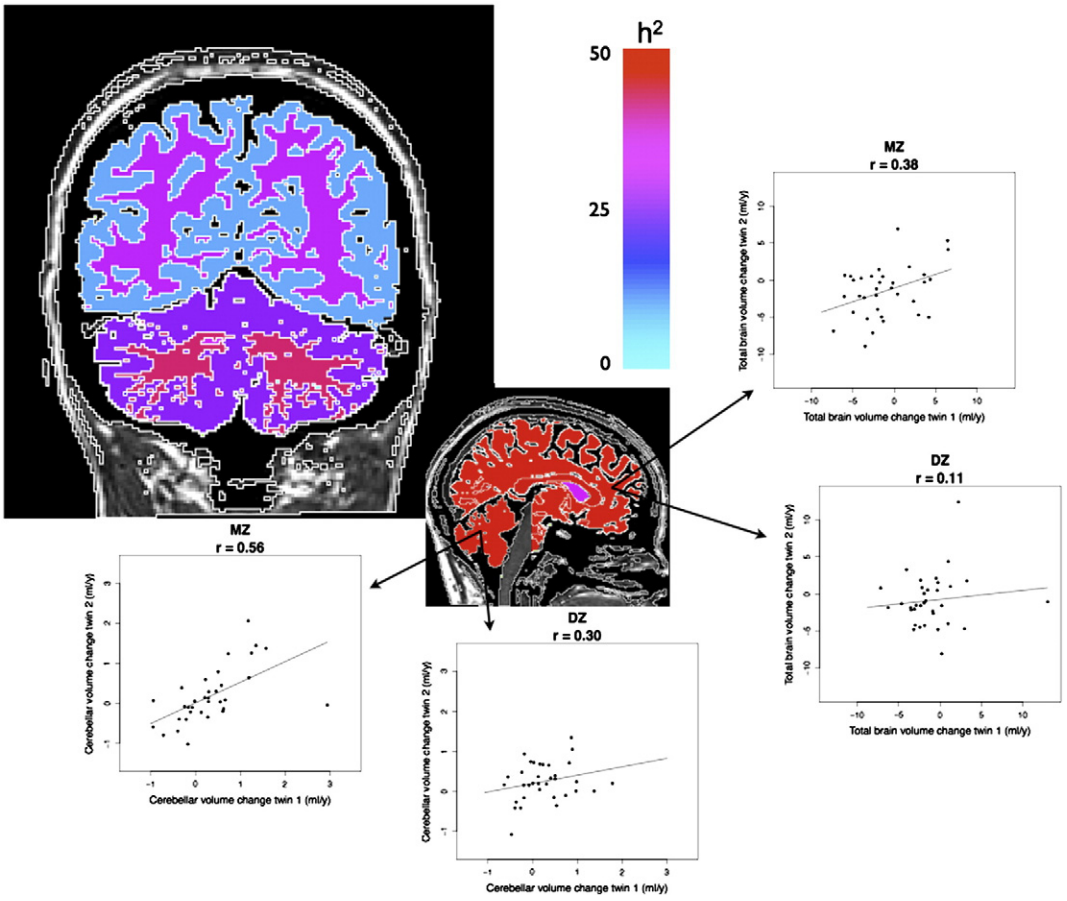

Fig. 2. Heritability of 5-year brain volume change. The color of brain regions represents the heritability estimate (h^2). Correlations for volume change in whole brain and cerebellum between monozygotic (MZ) twin pairs (34 complete pairs) and dizygotic (DZ) twin pairs (34 complete pairs) are shown. Regression lines are shown in black.

over the five year interval, compared to subjects showing brain volume decreases.

Heritability of brain volume and surface area change

Heritabilities of brain volume change and surface area change over time are listed in Table 2. (See Supplemental Table 1 for twin-correlations for changes in brain structure). Additive genetic effects accounted for 43% (CI: 17 to 62) of the variance in whole brain volume change (Fig. 2), and 48% (CI: 22 to 67) in cerebrum (whole brain excluding the cerebellum and brain stem) volume change. Cerebellum volume change showed significant heritability with additive genetic effects accounting for 52% (CI: 34 to 66) of the total variance (Fig. 2). Cerebellar white matter volume change and cerebellar grey matter volume change were heritable with additive genetic factors accounting for 42% (CI: 20 to 59) and 25% (CI: 2 to 46) of the variance, respectively. Cerebral GM volume change was not significantly influenced by genetic factors. In contrast, cerebral WM volume change showed a significant heritability of 29% (CI: 2 to 52). Change in lateral and third ventricle volumes showed significant heritabilities of 31% (CI: 9 to 51) and 29% (CI: 8 to 48) respectively. Total surface area change showed a significant heritability with genetic factors accounting for 33% (CI: 8 to 54) of the total variance. Overall, genetic influences reached somewhat higher estimates in the left as compared to the right hemisphere. Results were comparable computing heritabilities of change values uncorrected for age and sex.

The post-hoc analysis on the influence of sex on the heritability of brain volume change revealed no significant quantitative sex differences. There also were no significant qualitative sex-difference, but the difference between males (42%) and females (86%) reached borderline significance ($p = 0.052$). See Supplemental Table 2 for more details.

Heritability of intelligence

Within twin-pair correlations for monozygotic twins were 0.81 (CI: 0.65 to 0.90), 0.79 (CI: 0.61 to 0.89) and 0.72 (CI: 0.49 to 0.85) for full-scale, verbal and performance IQ respectively.

Dizygotic/twin-sib correlations were 0.46 (CI: 0.17 to 0.67), 0.52 (CI: 0.26 to 0.70) and 0.24 (CI: −0.07 to 0.51) for full-scale, verbal and performance IQ respectively. Heritability of full-scale, verbal and performance IQ were estimated at 0.81 (CI: 0.69 to 0.89), 0.79 (CI: 0.66 to 0.87) and 0.71 (CI: 0.51 to 0.83), respectively.

Associations between brain volume change/surface area change and intelligence

Significant phenotypic correlations (r_{ph}) were found between full scale IQ and volume change in total, left and right whole brain change ($r_{ph} = 0.40$, $r_{ph} = 0.27$, and $r_{ph} = 0.37$) total, left and right cerebrum change ($r_{ph} = 0.41$, $r_{ph} = 0.36$, and $r_{ph} = 0.32$) and right cerebellum change ($r_{ph} = 0.34$) (Table 3 and Fig. 3). For whole brain and cerebrum, which decrease over time on a group level, this indicates that a higher IQ is associated with smaller brain volume loss, or even brain volume increase. For cerebellar volume, which increases over time, a higher IQ is associated with larger growth. Genes influencing both IQ and brain volume change drove most of these correlations (r_g around 0.7, see Table 3).

Significant phenotypic associations (r_{ph}) were found between verbal IQ and change in total, left and right whole brain change ($r_{ph} = 0.44$, $r_{ph} = 0.31$, and $r_{ph} = 0.37$), total, left, and right cerebrum ($r_{ph} = 0.46$, $r_{ph} = 0.40$, and $r_{ph} = 0.39$), total, left and right white matter change ($r_{ph} = 0.30$; $r_{ph} = 0.29$ and $r_{ph} = 0.27$) and right cerebellum change ($r_{ph} = 0.28$). Genes implicated in both verbal IQ and brain volume change explained all these associations to a large extent with significant r_g above 0.54 (see Table 3 and Fig. 2), except for the association between right cerebellum volume change and verbal IQ, for which the influences of genetic and environmental factors could not be disentangled.

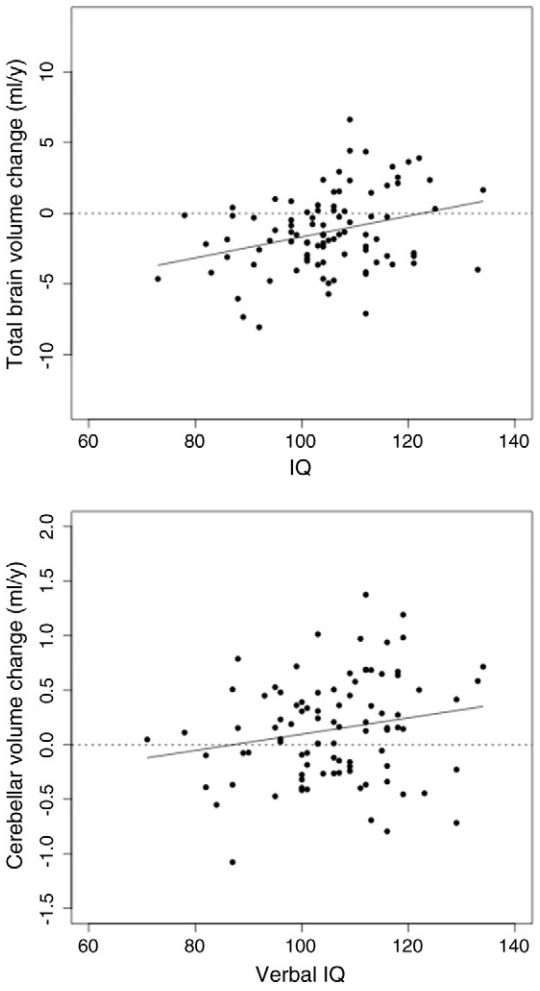

Fig. 3. Associations between change in brain volume and full scale IQ (top) and between right cerebellar change and verbal IQ (bottom) in individual twins and siblings (N = 91). Regression lines are shown as unbroken black lines and the black dashed lines in the middle show zero change.

Performance IQ was not significantly associated with brain volume change or surface area change. However, associations between performance IQ and brain volume change and surface area change largely followed the same pattern as that for IQ and verbal IQ (Supplemental Fig. 1).

Discussion

Here we report that dynamic changes in total brain volume and cortical surface area take place in young adulthood and that these changes are heritable. Moreover, brain volume changes in the young adult brain are positively related to intelligence and this association is mediated through genes common to both intelligence and brain volume change.

Specifically, we found significant heritability estimates for changes in total brain, cerebrum, cerebellum, cerebral white matter, grey and white matter of the cerebellum, and lateral and third ventricle volumes in young adults that were considerable, with values of h^2 equal to 43%, 48%, 52%, 29%, 25%, 42%, 31% and 29%. Also, for the first time we found evidence for significant change in surface area, with additive genetic effects accounting for 33% of the total variance. Heritability for brain volume changes did not differ significantly between the sexes, with the possible exception of cerebellum volume change, which seemed to

be more heritable in females (86%) than in males (42%; p = 0.052). We found little evidence of quantitative sex differences in the heritability of brain changes, but considering the wide ranges of confidence intervals around the opposite sex twin/sibling pair correlations we may conclude that the power was insufficient to detect these.

Thus, genes are not only involved in the absolute brain volume (Baaré et al., 2001; Pfefferbaum et al., 2000; Thompson et al., 2001; Wright et al., 2002), surface area (Eyler et al., 2011; Panizzon et al., 2009; Winkler et al., 2010), and total brain volume change on the verge of adolescence (Van Soelen et al, 2013), but genes are also involved in total brain volume change and surface area change in young adulthood. The extent to which genes explain individual differences in brain changes ranges from 28 to 52%. This leaves room for environmental influences also shaping these changes in brain structure. Thus, changes in brain volume may represent (plastic) changes as a result of an interaction between genetic background and environmental influences. Future studies on gene by environmental interactions may reveal how these factors may help shape individual brains over time. This may have implications, not only for physiological pathways leading to brain volume change, but also to cognitive functioning (Brans et al, 2010; Ramsden et al, 2011; Shaw et al, 2006). Therefore, we also measured whether there was a significant (genetic) association between brain volume change and cortical surface change with intelligence.

We found that intelligence is positively associated with change in global brain volume and that this association may be in part driven by genes in young adulthood. In particular, we report for the first time that a higher IQ is significantly associated with higher total brain volume increase or attenuated decrease. Our data suggest that common genes may be in part be implicated in this association. When separating out verbal and performance IQ in these twins, a higher verbal IQ was significantly associated with more increase or attenuated decrease in brain volume, specifically white matter, and this association was due to genes common to both. Performance IQ showed the comparable associations as verbal and total IQ, albeit to a lesser extent.

Previously, level of intelligence has been associated with thickness in particular areas of the cortex in childhood and adolescence (Shaw et al., 2006) and in adulthood (Brans et al., 2010). The change rates of cortical thickness and cortical surface over the lifespan are dependent on intelligence level (Schnack et al., 2014). Also, change in intelligence has been associated with changes in local cortical volume (Ramsden et al., 2011) and thickness (Burgaleta et al., 2014) in adolescents and genetic associations between intelligence and cortical thickness arise early in

Table 3
Brain volume change and IQ (full scale and verbal IQ) with significant phenotypic (r_{ph}) correlations and 95% intervals. Structures with a non-significant r_{ph} are excluded from the table. Correlation estimates and genetic decompositions were based on 91 subjects for which IQ and repeated MRI measurements were available.

Change in structure	r_{ph}	r_g	r_e	$r_{ph\text{-}a}$	$r_{ph\text{-}e}$
Full scale IQ					
Whole brain	**0.40** (0.14 to 0.59)	**0.67** (0.20 to 1.00)	−0.10 (−0.66 to 0.52)	**0.43** (0.12 to 0.64)	−0.03 (−0.22 to 0.20)
Cerebrum	**0.41** (0.15 to 0.60)	**0.68** (0.24 to 1.00)	−0.16 (−0.67 to 0.47)	**0.46** (0.15 to 0.65)	−0.04 (−0.21 to 0.17)
L whole brain	**0.27** (0.01 to 0.48)	0.50 (−0.02 to 0.91)	−0.17 (−0.64 to 0.42	0.32 (−0.01 to 0.55)	−0.05 (−0.21 to 0.15)
L cerebrum	**0.36** (0.10 to 0.56)	**0.59** (0.15 to 0.95)	−0.14 (−0.59 to 0.40)	**0.40** (0.10 to 0.61)	−0.04 (−0.18 to 0.14)
R whole brain	**0.37** (0.10 to 0.56)	0.91 (−1.00 to 1.00)	0.12 (−0.72 to 0.69)	0.32 (−0.01 to 0.57)	0.04 (−0.28 to 0.36)
R cerebrum	**0.32** (0.06 to 0.55)	**0.80** (0.09 to 1.00)	−0.36 (−0.82 to 0.61)	**0.44** (0.04 to 0.64)	−0.12 (−0.33 to 0.27)
R cerebellum	**0.34** (0.10 to 0.52)	1.00 (−0.24 to 1.00)	0.45 (−0.31 to 0.82)	0.14 (−0.16 to 0.41)	0.19 (−0.13 to 0.43)
Verbal IQ					
Whole brain	**0.44** (0.20 to 0.61)	**0.72** (0.30 to 1.00)	−0.08 (−0.61 to 0.47)	**0.46** (0.17 to 0.66)	−0.02 (−0.20 to 0.19)
Cerebrum	**0.46** (0.22 to 0.63)	**0.73** (0.34 to 1.00)	−0.11 (−0.61 to 0.45)	**0.49** (0.21 to 0.67)	−0.03 (−0.19 to 0.17)
Cerebrum WM	**0.30** (0.06 to 0.49)	**0.90** (0.34 to 1.00)	−0.38 (−0.70 to 0.13)	**0.44** (0.17 to 0.61)	−0.14 (−0.29 to 0.05)
L whole brain	**0.31** (0.06 to 0.51)	**0.54** (0.06 to 0.91)	−0.12 (−0.58 to 0.40)	**0.35** (0.03 to 0.57)	−0.04 (−0.19 to 0.15)
L cerebrum	**0.40** (0.16 to 0.58)	**0.65** (0.25 to 0.96)	−0.13 (−0.56 to 0.36)	**0.44** (0.16 to 0.63)	−0.04 (−0.17 to 0.13)
L cerebrum WM	**0.29** (0.04 to 0.48)	**1.00** (0.37 to 1.00)	−0.41 (−0.70 to 0.08)	**0.44** (0.17 to 0.60)	−0.16 (−0.30 to 0.04)
R whole brain	**0.37** (0.14 to 0.56)	**0.99** (0.16 to 1.00)	0.00 (−0.65 to 0.60)	**0.37** (0.05 to 0.58)	0.00 (−0.25 to 0.31)
R cerebrum	**0.39** (0.15 to 0.58)	**0.75** (0.18 to 1.00)	−0.04 (−0.71 to 0.59)	**0.41** (0.08 to 0.64)	−0.01 (−0.27 to 0.28)
R cerebrum WM	**0.27** (0.05 to 0.46)	**0.80** (0.27 to 1.00)	−0.32 (−0.67 to 0.22)	**0.39** (0.13 to 0.58)	−0.12 (−0.29 to 0.09)
R cerebellum	**0.28** (0.05 to 0.48)	1.00 (−1.00 to 1.00)	0.14 (−0.44 to 0.64)	0.22 (−0.07 to 0.44)	0.06 (−0.19 to 0.33)

In bold = significant correlations.
L = left.
R = right
CI = Confidence Interval.
WM = white matter.
r_g = genetic correlation.
r_e = environmental correlation.
r_{ph} = phenotypic correlation.
$r_{ph\text{-}a}$ = genetic covariance divided by sd(IQ) and sd(change): correlation that would be observed if only genetic factors were taken into account.
$r_{ph\text{-}e}$ = environmental covariance divided by sd(IQ) and sd(change): correlation that would be observed if only environmental factors were taken into account.

adolescence (Brouwer et al., 2013). Here, we add that total brain volume change in adulthood is positively associated with intelligence, and that this association could be in part heritable.

Thus, there is increasing evidence that the association between intelligence and the brain is not limited to the phenotype per se, but in addition is also related to the developmental course of the brain throughout life. Interestingly, there is a relationship between intelligence and brain networks, with higher efficiency of structural (Chiang et al., 2009) and functional (van den Heuvel et al, 2009) connectivity being positively associated with intelligence. Future studies may reveal to what extent intelligence is associated with dynamic changes in brain networks.

We found that genes for intelligence are overlapping with genes for total brain volume change. It must be noted that the genetic correlation between the two traits does however not imply causality, since the existence of the genetic correlation can indicate causality in one direction or the other.

The overlapping genes may directly influence both intelligence and brain volume change, and/or be represented through even more complicated pathways in which more intelligent people seek out mentally challenging activities that may increase their brain volume (Plomin and Kosslyn, 2001). There is evidence for changes in volume in particular areas of the brain after training on difficult tasks such as juggling (Draganski et al., 2004).

Finding genes and environmental influences implicated in brain volume change and IQ will ultimately help to unravel the relationship between cognition and brain structure. Identification of genes implicated in brain volume change seems one of the logical next steps to obtain this goal. Importantly, in a genome-wide meta-analysis a significant association with hippocampus volume and intracranial volume were recently revealed, as well as a suggestive association with total brain volume within DDR2, which encodes a receptor tyrosine kinase involved in cell growth and differentiation (Stein et al, 2012). With combined efforts to combine imaging and genetics data, such as is evidenced from the ENIGMA consortium (Stein et al, 2012), we may be able to identify genes for brain volume change. Finding genes implicated in brain volume change may be important for brain plasticity, not only in healthy adults but also for patients with schizophrenia or depression, diseases that are accompanied by (heritable) progressive brain tissue loss (Brans et al, 2008; Frodl et al, 2008) or lack of growth (Gogtay et al., 2008).

We found that cerebellar white matter volume increases over the five-year interval (2.97 ml) while cerebellar grey matter volume decreased (−1.55 ml), resulting in a net cerebellum volume increase (1.43 ml) in young adulthood. During childhood and adolescence, white matter volume of the brain increases at a faster rate than grey matter volume decreases, resulting in a net increase of total brain volume (e.g. Giedd et al., 1999; van Soelen et al., 2013). Possibly, a similar process holds for the cerebellum, albeit at a later age. A large cross-sectional study recently showed increases in cerebellar white matter volume at least up to 40 years old (Fjell et al., 2013). Longitudinal studies into cerebellar volume in healthy young adulthood are rare and small, and mixed results have been reported thus far: both decreases (Ho et al., 2003, 23 healthy subjects; Raz et al., 2005, subset of sample, < 20 subjects below 40 years of age) and stable volumes (Liu et al, 2003; 44 healthy subjects) and some evidence for increases (Tiemeier et al., 2010, subset of sample, 5 subjects over 20 years of age) have been reported. Here, we find an increase which may reflect prolonged maturation of the cerebellum.

This study has several limitations that have to be taken into consideration when interpreting its findings. One, while considerable in size, considering the inclusion of 176 individuals from 86 twin families with follow-up MRI brain scans, the number of inclusions is of limited statistical power when concerning changes in brain volumes with lower heritability. However, we did find significant and considerable heritability for total brain volume change as well as for several of its sub-structures. Two, we did not measure change in intelligence and could therefore not associate this with brain volume changes in adulthood. Three, our data allowed for application of the additive genetic model, but not for modeling of possible gene-by-environment interactions. Four, by estimating correlations between brain volume change and intelligence, we assume a linear association between the two. This may explain why young adults with a higher IQ showed a more pronounced increase in brain volume or attenuated decrease in brain (white matter) volume over time while a higher IQ was not reflected in cortical surface area change. Dynamic change in surface area is non-linear and depends strongly on intelligence (Schnack et al., 2014). We may not have had enough power to detect (subtle) differences in change rates depending on intelligence in a period of five years with the large majority of our sample ranging between 25 and 35 years of age at baseline.

In conclusion, we find that brain volume changes and surface area change in the healthy human brain are heritable. Moreover, individuals with a higher intelligence show continued brain expansion or attenuated decrease of brain tissue, but not surface area change, in adulthood, and genes are implicated in this process.

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