





Genetic Influences on Individual Differences in Longitudinal Changes in Global and Subcortical Brain Volumes: Results of the ENIGMA Plasticity Working Group

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Additional Supporting Information may be found in the online version of this article.

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Abstract: Structural brain changes that occur during development and ageing are related to mental health and general cognitive functioning. Individuals differ in the extent to which their brain volumes change over time, but whether these differences can be attributed to differences in their genotypes has not been widely studied. Here we estimate heritability (h^2) of changes in global and subcortical brain volumes in five longitudinal twin cohorts from across the world and in different stages of the lifespan ($N = 861$). Heritability estimates of brain changes were significant and ranged from 16% (caudate) to 42% (cerebellar gray matter) for all global and most subcortical volumes (with the exception of thalamus and pallidum). Heritability estimates of change rates were generally higher in adults than in children suggesting an increasing influence of genetic factors explaining individual differences in brain structural changes with age. In children, environmental influences in part explained individual differences in developmental changes in brain structure. Multivariate genetic modeling showed that genetic influences of change rates and baseline volume significantly overlapped for many structures. The genetic influences explaining individual differences in the change rate for cerebellum, cerebellar gray matter and lateral ventricles were independent of the genetic influences explaining differences in their baseline volumes. These results imply the existence of genetic variants that are specific for brain plasticity, rather than brain volume itself. Identifying these genes may increase our understanding of brain development and ageing and possibly have implications for diseases that are characterized by deviant developmental trajectories of brain structure. *Hum Brain Mapp* 00:000–000, 2017. © 2017 Wiley Periodicals, Inc.

Key words: individual brain plasticity; heritability; longitudinal magnetic resonance imaging; twins; ENIGMA plasticity working group

INTRODUCTION

Global and subcortical brain volumes continue to change throughout life, from early development to old age [Dennison et al., 2013; Fjell et al., 2013; Gilmore et al., 2012; Hedman et al., 2012; Mills et al., 2016; Swagerman et al., 2014; Wierenga et al., 2014; Ziegler et al., 2012]. The extent to which brain structure changes with age is highly relevant, especially at both extremes of the lifespan. During childhood development, deviant developmental patterns of brain structure may be a better characterization of diseases such as childhood onset schizophrenia, autism, and attention deficit-hyperactivity disorder, than brain differences between health and disease at a fixed time point [Giedd et al., 2008; Rapoport and Gogtay, 2008; Shaw et al., 2010]. At the other end of the age spectrum, the extent of hippocampal volume decline has been related to memory performance [Kramer et al., 2007; Mungas et al., 2005; Stewart et al., 2011]. Schizophrenia has been associated with brain changes in young adulthood [for

reviews see Chiapponi et al., 2013; Hulshoff Pol and Kahn, 2008; van Haren et al., 2012]. In healthy individuals, structural changes (cortical thickness and surface) throughout the lifespan have been associated with intelligence [Schnack et al., 2015]. The speed at which the brain changes may, therefore, shed light on mental health, and may aid in prediction of mental health at the individual level.

Both global and subcortical brain volumes have been shown to be highly heritable [Baare et al., 2001; Batouli et al., 2014a; den Braber et al., 2013; Kremen et al., 2010; Renteria et al., 2014; Swagerman et al., 2014; Thompson et al., 2001; for reviews see Blokland et al., 2012; Peper et al., 2007]. The extent to which the longitudinal changes in these volumes in healthy development or ageing are driven by genes—based on longitudinal twin studies—has not been widely studied and are mostly based on the Dutch population (Supporting Information Table S1). These studies used a variety of modeling techniques to obtain heritability estimates of brain changes that may not

TABLE I. Cohort characteristics

Demographics	Brain SCALE	QTIM	Utwins1	VETSA	OATS
No. subjects in total 861	127	49	160	331	194
MZ/DZ complete pairs in total 203/169	25/27	10/12	36/37	75/53	57/40
Sex (M/F) in total 577/274	69/58	17/32	95/55	331/0	65/129
Mean age at baseline in yr (sd)	9.2 (0.1)	15.0 (2.0)	29.7 (7.8)	56.3 (2.6)	69.3 (4.7)
Mean scan intervals in yr (sd)	2.9 (0.2)	3.5 (0.4)	5.3 (0.7)	5.5 (0.5)	2.3 (0.7)

be directly comparable. The first longitudinal brain imaging study in twins addressed changes in ventricular volume in the elderly [Pfefferbaum et al., 2004], with a later report addressing changes in total brain volume and total cerebrospinal fluid [Lessov-Schlaggar et al., 2012]. They found stability of genetic factors over time and no significant heritability of univariate change rates in any brain structures that were measured. In young adulthood, changes in global brain volumes and cortical thickness were found to be heritable, and genetically associated with the level of intelligence [Brans et al., 2010; Brouwer et al., 2014], and the risk of schizophrenia [Brans et al., 2008]. Limited evidence of heritability of subcortical change was found in bipolar disorder [Bootsman et al., 2015]. In the period between childhood and adolescence, changes in global brain volumes and cortical thickness [van Soelen et al., 2012a, 2013] but not subcortical structures or white matter microstructure [Brouwer et al., 2012; Swagerman et al., 2014], were found to be heritable to some extent. Finding genes for these brain changes may aid in identifying genetic pathways to brain development in health and disease.

The ENIGMA consortium [Thompson et al., 2014, 2017] provides an excellent platform to study genes implicated in brain structures [Hibar et al., 2015; Stein et al., 2012]. As part of the ENIGMA consortium, the ENIGMA Plasticity Working Group aims to identify genes involved in longitudinal brain changes. It is difficult to draw firm conclusions from the aforementioned studies on heritability of brain changes due to differences in methodologies and sample sizes. Therefore, as a first step, here we study generalizability and robustness of heritability of global and subcortical brain volume changes across multiple longitudinal twin cohorts from across the world and in different stages of the lifespan, in a meta-analysis. We further compare a variety of univariate and multivariate data analytic techniques to investigate whether different models to assess heritability of brain changes provide similar heritability estimates. Furthermore, we ask the question whether individual differences in changes in these volumes are explained by the same genetic factors as those that explain individual differences in the volumes themselves. At this point, it is an open question whether the recently found SNPs influencing total brain

volume and subcortical volumes [Bis et al., 2012; Hibar et al., 2015; Stein et al., 2012] are overlapping with those for volumetric change rate. If so, we may benefit from the existing literature on the genetics of brain volumes and possibly increase power, by investigating those genes that have been found to influence brain volumes. If not, we have the opportunity to search for additional genes unique to changes in the brain that could shed light on the biological pathways of development and healthy ageing.

METHODS

Participants and Protocols

Five longitudinal twin cohorts (BrainSCALE, QTIM, Utwins1, VETSA, OATS) were included in the present meta-analysis to estimate heritability of global and subcortical change rates across different cohorts and ages (Table I). These twin cohorts are all characterized by having two magnetic resonance imaging scans made at an interval of several years, in each subject.

MRI Processing

All MRI data were processed using the FreeSurfer segmentation pipeline [Fischl et al., 2002, 2004; Reuter et al., 2012]. Details on the cohort characteristics and image acquisition and processing can be found in the Supplementary Material. Quality checking for all sites was done according to the ENIGMA-2 protocols [Hibar et al., 2015; <http://enigma.ini.usc.edu>]. Left and right volumes of subcortical structures (thalamus, caudate nucleus, putamen, pallidum, hippocampus, amygdala, nucleus accumbens) and global structures [total brain volume (including cerebellum but excluding brainstem), cortical gray matter, cortical white matter, cerebellum gray matter, cerebellum white matter, lateral ventricles] were extracted for each cohort. Change rates per year were computed by subtracting baseline volume from follow-up volume, divided by the scanning interval in years.

It must be noted that some of our cohorts used a different scanner at baseline and follow-up. This could potentially

influence the results. However, if we assume the effect of scanner update to be linear, this may lead to a bias in the estimate of mean change, but maintains the individual differences between subjects, and hence still allows for estimating heritability. More generally, this also explains why heritability of brain volume changes may be detected in age ranges where there is little change observed *at a group level*, as long as there are intraindividual differences. In contrast, if brain changes are prominent but similar for all subjects in a certain period of life, heritability is expected to be low.

Whether a genetic component influencing a change rate can be detected directly strongly depends on the variance of the error compared to the variance of the change. Assuming that $V_{i,b}$ is the true volume of subject i at baseline, the measured volume at baseline is $W_{i,b} = V_{i,b} + \epsilon_{i,b}$, where the latter term is a measurement error. The measured volume at follow-up $W_{i,f}$ can be written as $W_{i,b} + (\Delta V)_i + \epsilon_{i,f} - \epsilon_{i,b}$, where $(\Delta V)_i$ is the true change of subject i over time, and $\epsilon_{i,f}$ is the measurement error at follow-up.

Hence, the variance of observed change can be written as

$$\begin{aligned} \text{Var}(W_f - W_b) &= \text{Var}(\Delta V) + \text{Var}(\epsilon_f) + \text{Var}(\epsilon_b) \text{ or} \\ &= \text{Var}(W_f) + \text{Var}(W_b) - 2\text{Cov}(W_f, W_b), \end{aligned} \quad (1)$$

assuming error terms are independent. To investigate whether the variance of the direct change is large enough compared to the measurement error, we first implemented a univariate model using the change rate only, to estimate heritability for change in global volumes in four cohorts, and change in subcortical volume in all five cohorts.

The Univariate Twin Model

Twin cohorts provide information on the heritability of traits, through the comparison of monozygotic (MZ) and dizygotic (DZ) twin pairs. MZ pairs generally share 100% of their genes, and DZ pairs share on average 50% of their segregating genes. Hence, if the volumetric change rates in MZ twins are more alike than in DZ twins, it can be concluded that genes contribute to the individual differences observed in a trait, under the equal environment assumption. The equal environment assumption states that MZ twins are not exposed to a more similar environment than DZ twins. If this assumption fails, the traditional twin model will overestimate variance attributed to genetic factors. If both MZ and DZ twins are alike to a similar extent, it can be concluded that common environmental effects influence the trait. The total variance of a trait was split in additive genetic variance (A), common or shared environmental variance (C) and environmental variance (E) unique to the individual. From these estimates, heritability was computed as the proportion of the variance that was attributed to additive genetic factors (Fig. 1, Supporting Information, Model 1). Significance of heritability of change rates in the individual cohorts was based on twice

the difference between the log-likelihoods of the full model, and the model in which the influence of additive genetic factors was set to zero. Minus twice the log-likelihood difference comparing a model in which a variance component is free to a model in which this component is set to zero is distributed as a 50:50 mixture of χ^2 distributions with 0 and 1 degrees of freedom, respectively [Dominicus et al., 2006]. The significance level was set to 0.05. Significance of the common environmental component was determined similarly. We fitted the ACE model and submodels (AE, CE, and E) for each structure and each cohort. When a variance component (A or C) could be dropped from the model without deteriorating the fit, the most parsimonious model was selected. If either A or C could be dropped but not both, the best fitting model (AE or CE) was selected based on the AIC criterion.

Because of the highly skewed distributions of ventricular volumes, which could potentially influence the heritability results, a log transformation was applied to lateral ventricle volumes [Kremen et al., 2012]. The included phenotypes were corrected for age, sex, and scanner (where appropriate) beforehand, combining baseline and follow-up data in one linear model when both phenotypes were entered in the model, thereby accounting for individual differences in scanning interval.

Meta-Analysis of Heritability

Heritability estimates h_i^2 ($i = 1 \dots 5$) from the ACE model were pooled based on the cohort size N_i ($i = 1 \dots 5$, the number of twin pairs in study i), following [Batouli et al., 2014b; Blokland et al., 2012; Verweij et al., 2010]. Even though the ACE model was not the best fitting model in the individual cohorts, using the full model allowed us to combine the estimates from different cohorts and additionally had the potential to detect significant variance components that could not be detected in cohorts separately.

The meta-analytic heritability was defined as

$$h_M^2 = \sum_{i=1}^5 \left(\frac{N_i h_i^2}{N} \right),$$

where $N = N_1 + \dots + N_5$, the total number of twin pairs. Confidence intervals for these estimates were computed based on the variance of heritability estimates in the set of twin cohorts:

$$\sum_{i=1}^5 \frac{N_i (h_i^2 - h_M^2)^2}{N}.$$

Subsequently, because several of the structures we study here follow a developmental pattern of growth and subsequent volume loss, we split up the processes of development and ageing. Because of the large age gaps between our cohorts, our data is not best suited to determine the turning point between growth and decrease. Based on the

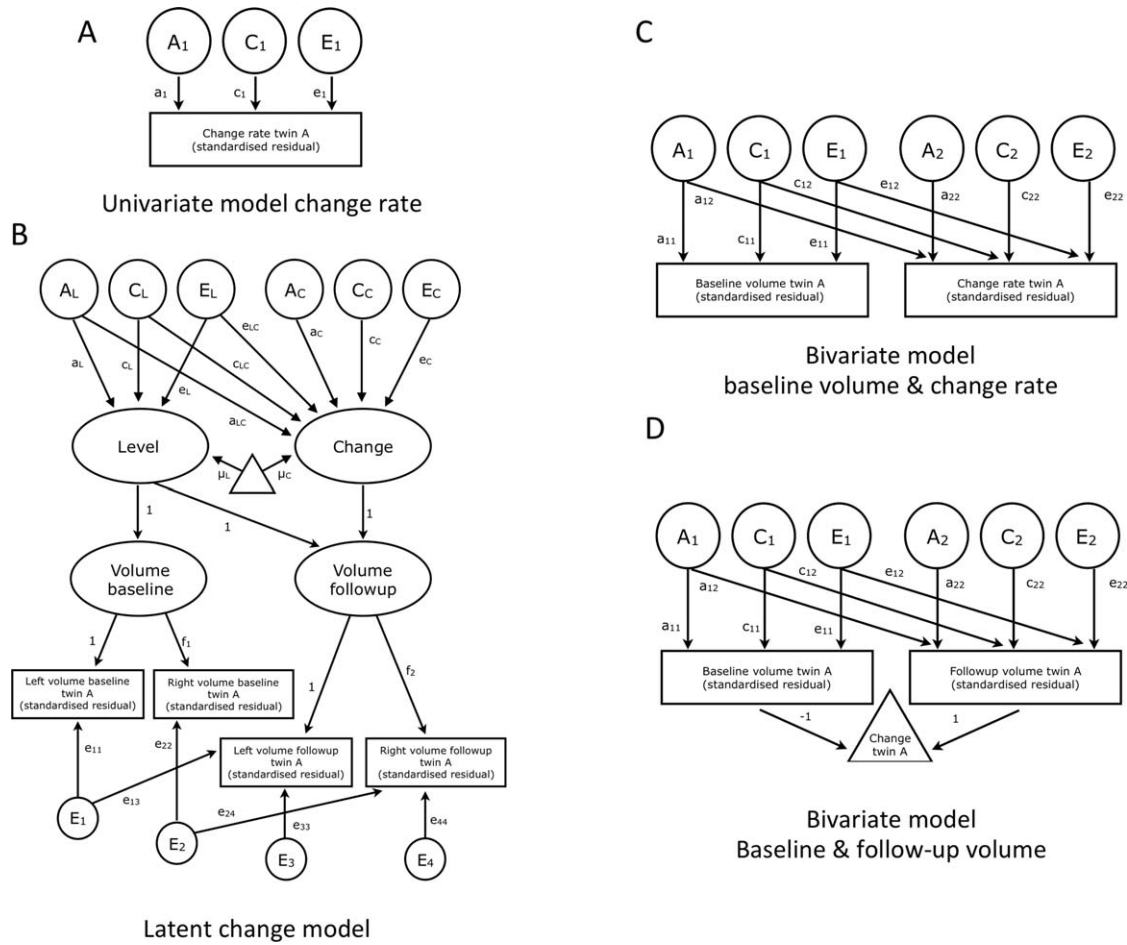


Figure 1.

(A) Univariate twin model. The path loadings a_1 , c_1 , and e_1 represent the genetic, common environmental influences and unique environmental influences on change rates, respectively. **(B)** Latent change model. The factors A_L , C_L , and E_L and corresponding factor loadings a_L , c_L , and e_L represent the influences of genetic, common environmental, and unique environmental influences on “level,” the non-changing component of the volumes. Likewise, A_C , C_C , and E_C and corresponding factor loadings a_C , c_C , and e_C reflect the influences that are unique to change. The contributions to level and change are allowed to be different for left and right, and baseline and follow-up, represented by the factor loadings f_1 and f_2 . The overlap between the factors for baseline and change are modelled by the paths a_{LC} , c_{LC} , and e_{LC} . Heritability of change in this model is computed as $(a_{LC}^2 + a_C^2) / (a_{LC}^2 + a_C^2 + c_{LC}^2 + c_C^2 + e_{LC}^2 + e_C^2)$. **(C)** Bivariate twin model including baseline volume and change rate. The path loadings a_{11} , a_{12} , and a_{22} represent the influences of genetic factors, the

path loadings c_{11} , c_{12} , and c_{22} represent common environmental influences and e_{11} , e_{12} , and e_{22} represent unique environmental influences. The factors A_1 , C_1 , and E_1 are shared between baseline volume and change rate, and A_2 , C_2 , and E_2 represent influences on change rate that are independent from the factors influencing baseline volume. **(D)** Bivariate twin model including baseline volume and volume at follow-up. The path loadings a_{11} , a_{12} , and a_{22} represent the influences of genetic factors, c_{11} , c_{12} , and c_{22} represent common environmental influences and e_{11} , e_{12} , and e_{22} represent unique environmental influences. The factors A_1 , C_1 , and E_1 are shared between baseline volume and followup, and A_2 , C_2 , and E_2 represent influences on follow-up volume that are independent from the factors influencing baseline volume. Heritability of change rate is derived from this model by computing $(a_{11}^2 + a_{12}^2 + a_{22}^2 - 2a_{11}a_{12}) / ((a_{11}^2 + c_{11}^2 + e_{11}^2) + (a_{12}^2 + a_{22}^2 + c_{12}^2 + c_{22}^2 + e_{12}^2 + e_{22}^2)) - 2[(a_{11}a_{12} + c_{11}c_{12} + e_{11}e_{12})]$.

longitudinal literature [e.g. Hedman et al., 2012; Mills et al., 2016; Vijayakumar et al., 2016; Wierenga et al., 2014], this point usually lies in the early to late teens for those structures that show nonlinear developmental patterns (total

brain, cerebral white matter, cerebellum, thalamus, pallidum, hippocampus, amygdala). We therefore chose to compute meta-heritability in the adolescent (BrainSCALE and QTIM) and adult cohorts separately.

Longitudinal Genetic Modeling

We first chose to apply the simplest genetic model to estimate heritability of change as change rates per year are the easiest phenotype to model and can easily be implemented when we search for genes involved in individual variation in brain plasticity. It is, however, not the optimal model for detecting heritability of a change measure. In addition, several models have been used to assess heritability of brain changes in the literature (Supporting Information Table S1). Hence, we apply three other models to compare approaches. Ideally, the genetic influences explaining individual differences in changes are estimated using a latent factor model [McArdle, 2009]. The latent change model makes optimal use of all available longitudinal data to estimate the heritability of volumetric measures at each time point, the heritability of change, and the relationship between baseline and change. In such a model, variables that represent baseline and follow-up volume—in this case left and right volume at baseline and follow-up—are entered directly. “Level” and “change” are included as latent factors in this model. These latent factors capture the shared variance of volume based on all four input variables and residual variance for follow-up measures. Genetic and environmental influences on these factors are estimated using family structure (model 2; Fig. 1B). Additionally, genetic overlap between baseline and change can be estimated. While the latent change model has been applied to brain structure [Raz et al., 2005], to our knowledge, the genetically informed variant [Panizzon et al., 2015] has not been applied to change in brain structure before. As a second longitudinal model, we estimated heritability of change in a bivariate twin model using baseline volume and change rate (model 3, Fig. 1C). Apart from estimating heritability of volumetric change, this model, like model 2, can also estimate the genetic overlap between baseline volume and change.

Finally, we implemented a bivariate twin model including baseline and follow-up volume. This model includes a genetic factor influencing both baseline and follow-up volumes and one genetic factor that is unique to the follow-up volume (model 4, Fig. 1D). This model is often used to study stability of the genetic factor acting on traits measured over time by testing whether the genetic correlation between the volumes over time is significantly different from 1. If so, this model shows the existence of a genetic factor explaining residual variance at follow-up. It must be noted that existence of a genetic factor influencing follow-up only is not the same as the existence of a genetic factor influencing change and in that aspect, model 4 is different from the ones described above. However, the existence of genetic variance of the difference between baseline and follow-up measures can be inferred using Eq. (1) above. All models were implemented using structural equation modeling contained in the OpenMx package [Boker et al., 2011] in R [R Developmental Core Team, 2008]. See Supporting Information for a more detailed description of the models.

The comparison of the four models estimating heritability of change was done in three of the cohorts that had sufficient

sample size and all structures available. In all four models, genetic influences on individual differences in change were estimated. From models 2 and 3, we estimated the genetic overlap individual variation between baseline volume and change rate.

RESULTS

Univariate Heritability of Change Rate—Meta-Analysis

Heritability estimates for change in global volumes for each cohort separately ranged from 0% to 72%. Fit statistics for the ACE model, submodels, and variance components for the best fitting model for each cohort and each structure separately can be found in Supporting Information Tables S3 and S4, see also Figure 2.

Heritability estimates for change in subcortical volumes for each cohort separately ranged from 0% to 58%. Fit statistics for the ACE model, submodels and variance components for the best fitting model for each cohort and each structure separately can be found in Supporting Information Tables S3 and S4, see also Figure 3.

Variance components for the meta-analysis in the full group and in the child and adult cohorts can be found in Table II, see also Figures 2 and 3. The change rate for all global volumes was significantly heritable in the full group analysis, with estimates ranging between ~20% for both white matter of the cerebrum and cerebellum, up to ~40% for change rate in total brain, gray matter of the cerebellum, cerebellum and lateral ventricles. These findings were mostly driven by the adult population [heritability estimates ~45% to ~55% with the exception of change rate in white matter volume (17%)]. Heritability estimates in children were low, with the exception of change in white matter volume (26%). In the child cohorts, a significant contribution of common environment could be detected for change in cerebellum volumes (total, gray, and white matter) and for total brain volume (~15% to ~35%). The change rate for caudate, hippocampus, amygdala, nucleus accumbens, and putamen were significantly heritable in the full group analysis, with heritability estimates ranging from 16% to 31%. Similar to the change rates in global volumes, these findings seemed to be driven by the adult cohorts. Individual differences in the change rate of the thalamus were significantly influenced by common environmental influences (15%) in the full group, but in children genetic influences significantly explained part of the variance.

Comparison of Longitudinal Genetic Models

Using four different modeling approaches (Supporting Information Fig. 1), we found that heritability estimates were very similar for most brain structures, using either a direct change rate in a univariate or bivariate model (models 1 and 3), or by computing the variance of change

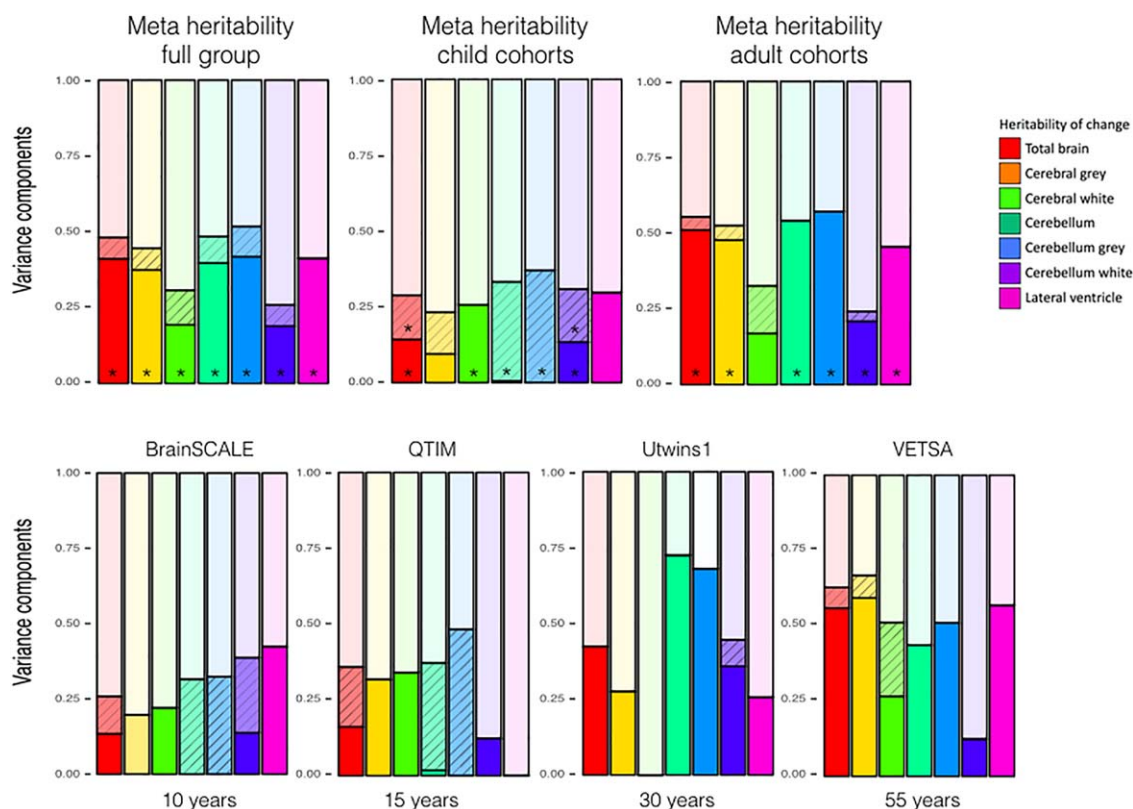


Figure 2.

Variance components of global change rate per year for four cohorts. The upper panel displays variance components for the meta-analyses in the full group, and child/adult cohorts separately. The lower panel shows results for the individual cohorts. The colours of the bars represent the different structures.

Heritability estimates (bottom) are displayed in the darkest, solid colour. Common environmental influences (middle) are displayed with diagonal shading. Unique environmental influences are displayed in the lightest colour. Significant h^2 and c^2 estimates in the meta-analyses are marked with a star.

from the variances and the covariance (model 4) in all cohorts. The latent factor model (model 2) was slightly more sensitive in detecting genetic or common environmental variance for most structures (Supporting Information Tables S2a,b,c). It must be noted that structures showing higher heritability estimates were more robust when comparing the four models, probably due to better signal to noise for that structure (global volumes more stable than subcortical volumes) or cohort (older cohorts more stable than younger cohort).

Genetic Overlap Between Baseline Volume and Change Rate

From models 2 and 3, the overlap between the genetic factors explaining individual differences in baseline volume and change rate could be estimated. Phenotypic correlations were generally negative, indicating that greater baseline

volume was associated with greater negative change (i.e., greater volume reduction). This pattern may partially indicate regression to the mean. Positive phenotypic and genetic correlations were found for total brain and gray matter volume change in the oldest cohort and for total white matter volume in the youngest cohort. Genetic correlations were significantly different from zero for cerebellar gray matter volume, lateral ventricle volume and putamen, amygdala and nucleus accumbens in the VETSA cohort, and white matter volume in the BrainSCALE cohort, indicating overlap in the genetic factors influencing volume and volume change. The genetic correlation was significantly different from -1 and 1 for cerebellum, and gray matter of the cerebellum in both adult cohorts, and lateral ventricle in the VETSA cohort, implying the existence of a genetic factor unique to the change rate, i.e. not shared with baseline volume. It must be noted that change in cerebellar gray matter volume correlated highly with change in cerebellum volume so these are probably representing the same phenotype.

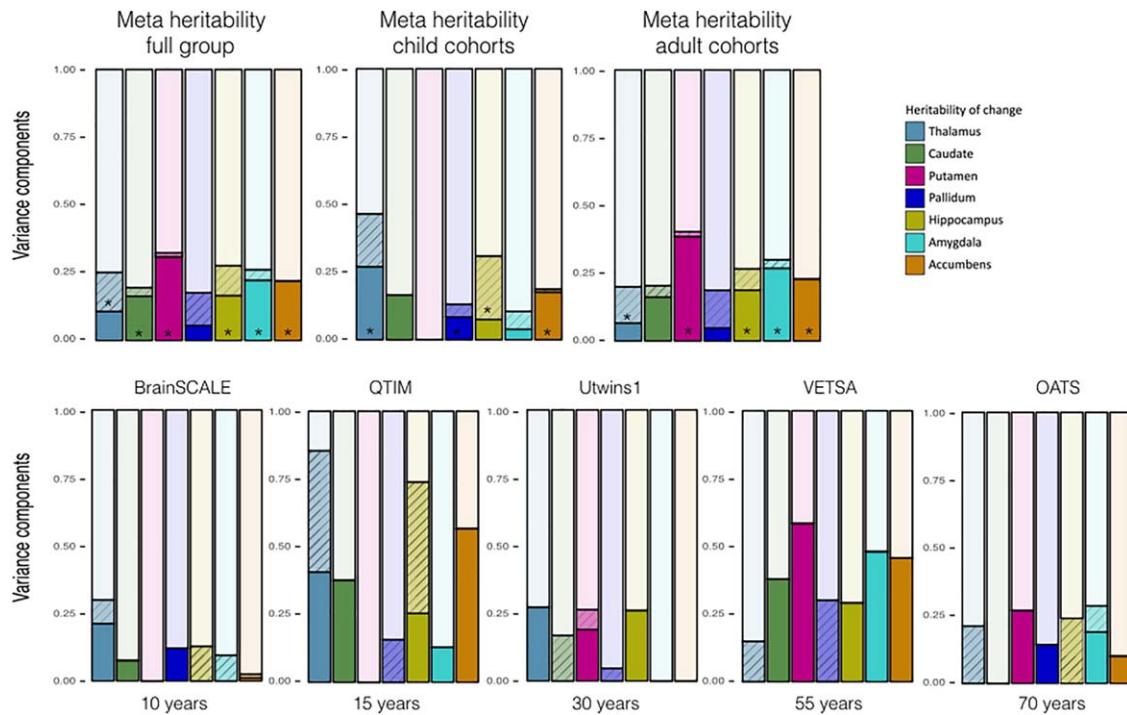


Figure 3.

Heritability of subcortical change rates per year for the five cohorts. The upper panel displays variance components for the meta-analyses in the full group, and child/adult cohorts separately. The lower panel shows results for the individual cohorts. The colours of the bars represent the different structures.

Heritability estimates (bottom) are displayed in the darkest, solid colour. Common environmental influences (middle) are displayed with diagonal shading. Unique environmental influences are displayed in the lightest colour. Significant h^2 and c^2 estimates in the meta-analyses are marked with a star.

DISCUSSION

Based on a meta-analysis of longitudinal twin cohorts, we find that change in several global and subcortical volumes in the human brain is heritable: genes play a significant role in the extent to which the brain changes over time between individuals. Heritability estimates of change rates in our meta-analysis ranged from 5% (pallidum, n.s.) to 42% (cerebellar gray matter) and were larger for the older cohorts than for the child cohorts. Individual differences in change rates of cerebellum volume, cerebellum gray matter volume change, and lateral ventricle volume were explained by genetic influences that were independent of the genetic influences of individual differences in baseline volume. An important finding is that longitudinal MRI is sensitive enough to detect influences of genes on individual variation in volumetric change of global and subcortical brain structures across multiple studies and age ranges.

Heritabilities for change rates in the meta-analysis were as high as 42%, but not as high as the heritability estimates that are generally reported for global and subcortical volumes themselves [Blokland et al., 2012; Peper et al., 2007; Verweij et al., 2010]. These lower estimates may be explained, in

part, by the observation that quantifying individual brain volume changes is harder than measuring a volume at one time point: assuming the volumes are obtained with similar measurement error, the part of the variance due to measurement error is about twice as large for a change measure compared with the error variance for the volume itself, and this puts an a priori upper bound on the heritability of change rates. The fact that the subcortical change rates seem less heritable than the change rates of the global volumes seems to underline this reasoning. A more interesting possibility is that environmental effects such as life experiences, play a greater role in the heritability of developmental and ageing trajectories than they do in determining brain structure volumes at a single point in time. At this point, we cannot distinguish between the two, but considering that we find genetic influences in this unique meta-analysis of longitudinal twin cohorts, we may conclude that genes are to some extent implicated in individual variation in several global and subcortical brain volumes changes. Of particular importance, these findings imply that it is relevant to search for genes involved in brain volume change such as undertaking a genome-wide analysis within the ENIGMA consortium [Thompson et al., 2014, 2017].

TABLE II. Meta-heritability estimates in the full group, and child and adult cohorts separately

Change rate	Full group meta-analysis, variance components			Child cohorts meta-analysis, variance components			Adult cohorts meta-analysis, variance components		
	h^2	c^2	e^2	h^2	c^2	e^2	h^2	c^2	e^2
Total brain	0.41	0.07	0.52	0.14	0.15	0.71	0.51	0.04	0.45
Cerebral gray	0.37	0.07	0.55	0.09	0.14	0.77	0.48	0.04	0.48
Cerebral white	0.19	0.11	0.69	0.26	0.00	0.74	0.17	0.16	0.67
Cerebellum	0.40	0.09	0.51	0.01	0.33	0.67	0.54	0.00	0.46
Cerebellar gray	0.42	0.10	0.48	0.00	0.37	0.63	0.57	0.00	0.43
Cerebellar white	0.19	0.07	0.74	0.13	0.18	0.69	0.21	0.03	0.75
Lateral Ventricles	0.41	0.00	0.59	0.30	0.00	0.70	0.45	0.00	0.54
Thalamus	0.11	0.14	0.75	0.27	0.19	0.54	0.07	0.13	0.80
Caudate	0.16	0.03	0.80	0.16	0.00	0.84	0.16	0.04	0.80
Putamen	0.31	0.01	0.68	0.00	0.00	1.00	0.38	0.02	0.60
Pallidum	0.05	0.12	0.82	0.08	0.05	0.87	0.05	0.14	0.81
Hippocampus	0.17	0.11	0.73	0.08	0.23	0.69	0.19	0.08	0.73
Amygdala	0.22	0.04	0.74	0.04	0.07	0.89	0.27	0.03	0.70
Nucleus Accumbens	0.22	0.00	0.78	0.18	0.01	0.81	0.23	0.00	0.77

h^2 , heritability, proportion of variance attributed to additive genetic factors; c^2 , proportion of variance attributed common environmental factors; e^2 , proportion of variance attributed to unique environmental factors. Significant h^2 and c^2 components are displayed in bold.

We find moderate heritability estimates for change in several brain structures in the combined analysis. However, there were substantial differences in heritability at the site level, with estimates ranging from 0 to 72% and sometimes wide confidence intervals due to sample size. This stressed the importance of combining information from several cohorts, but we should not ignore true differences that may exist. One of the obvious explanations for the differences in heritability estimates between our cohorts is the difference in age. The youngest cohorts showed very little evidence for heritability of change rates. Individual differences in the extent to which the brain changes in the youngest cohorts seemed to a large extent to be driven by shared and/or unique environmental influences. In adults, the heritability estimates of change rates seemed to increase and possibly decrease again in old age. It is important to realise that a heritability estimate is the proportion of variance that can be attributed to genetic sources, and therefore, is also sensitive to changes in both genetic and environmental variance. Based on a largely cross-sectional cohort, heritability increased for white matter volume and decreased for gray matter volume during development, mainly as a result of changes in the size of the environmental variance [Wallace et al., 2006]. The heritability of cortical thickness has been found to increase as well in this cohort [Lenroot et al., 2009; Schmitt et al. 2014]. Reviews of cross-sectional heritability studies on brain volumes showed that heritability tends to increase during development, but decreases in older ages [Batouli et al., 2014b; Jansen et al., 2015]. In contrast, a cross-sectional comparison of five studies with average ages ranging from childhood to late life showed that the heritability of ventricular volume increased substantially with age [Kremen et al., 2013], due to an increase in absolute genetic

variance. Longitudinally, we find heritability of change in ventricular volume to be present already at a young age. One might expect the heritability of change in brain structure to be paralleled by heritable changes in general cognitive ability. Cross-sectional data on children and young adults seem to suggest such change because they show increases in genetic influences explaining individual differences with increased age [Haworth et al., 2010]. However, a longitudinal study over 35 years from young adulthood to middle age showed no genetic influences on individual differences of change in general cognitive ability [Lyons et al., 2009]. To conclude, the seeming inconsistencies between cross-sectional and longitudinal studies serve to highlight the fact that a change in heritability of volumes and in the heritability of change rates is not the same.

Apart from age, other differences between cohorts can create differences in heritability, especially since the cohorts have different size, scanners, scanning intervals, imaging protocols, and segmentation techniques. For example, the two oldest cohorts showing on average the highest heritability estimates of change rates, are also the largest. It is possible that sample size, in combination with a large follow-up duration for one of these cohorts, may have increased the power to detect heritability of change measures. Finally, we should be aware that even if the heritability estimates are similar in the different cohorts, it is not guaranteed that the same genes play a role at all ages. As an example, a recent study using family data from several generations showed indeed that different sets of genetic factors contribute to heritability of cortical thickness over healthy ageing [Chouinard-Decorte et al., 2014]. This results fits with the finding that a different set of genes influence baseline thickness and thickness change [Brans et al., 2010; van

Soelen et al., 2012b] but does not necessarily extrapolate to different sets of genetic factors contributing to change rates at different periods of life. In our full meta-analysis, we combined estimates from structures that at a group level show growth in development and loss in ageing. At this point, it is not clear that the biology underlying individual differences in change rates is the same or different for these two periods: it is possible that variants that code for efficient growth, may also cause more efficient brain stability, or slower decay at later ages. It is also possible that these processes are driven by different genetic factors. Separating our analyses into a younger and older age group, did show however that heritability was more robust in ageing than in development. This is potentially an interesting finding as it suggests that during development environmental influences may play a substantial role. In adults, activities ranging from physical exercise to learning a new skill have shown to cause changes in the brain [Valkanova et al., 2014]. This may suggest that in childhood and adolescence, a period in which the brain acquires many new skills, offering the right environment could cause the brain to develop in an optimal manner. We have to be careful interpreting our data as such, because the younger cohorts are relatively small and were measured with a short age interval. Indeed, preliminary data from third wave of the BrainSCALE study shows that heritability measured between the ages of 9 and 17 compared to the age range from 9 to 12, increased from 0 to 32% and from 22% to 54% for annual gray and white matter volume change, respectively. One way to further investigate the question of the same genetic factors influence brain changes throughout the lifespan would be to examine longitudinal family studies spanning several generations. Alternatively, we plan to investigate the role of age when doing a genome-wide association (GWA) study on volumetric changes in global and subcortical volumes.

The finding that an individual's genotype influences the rate of his/her brain changes, particularly in the adult and elderly populations, can be interpreted as the existence of genes that influence individual differences in the speed of brain ageing. Indeed, many genetic pathways that regulate ageing have been identified in animal studies [Kenyon, 2010] and it is possible that some of these could be involved in the longitudinal changes we observe. Additionally, accelerated brain ageing has been observed in diseases such as schizophrenia [Koutsouleris et al., 2014; Schnack et al., 2016], bipolar disorder and depression [Koutsouleris et al., 2014], and mild cognitive impairment and Alzheimer's disease [Gaser et al., 2013; Lowe et al., 2016]. Genetic vulnerability for disease could be related to individual differences in the rate of brain changes. As many psychiatric disorders are thought to be developmental diseases, it is possible that these genes also influence individual variation in the rate of brain development.

It is an important question whether the genetic factors influencing brain volumes themselves are the same as the genetic factors influencing brain change rates. One could

speculate that a brain volume is the sum of the brain changes that occur up to that time. In that case, the genetic factors that influence the volume and change rate may be expected to overlap and indeed we found this at least partly to be the case for several structures. It must be noted that these incremental volumes could be influenced by different genes acting explaining individual differences in brain changes at different ages, so that full genetic overlap between volume and change rate is probably not expected if such epigenetic effects are present. At this moment, it is not known whether the effects of individual genes will be easier to detect from the volumes or the change measure. If these genetic factors are different, gathering longitudinal rather than cross-sectional data in imaging genetics studies is worth the additional effort because it could lead to finding genomic variants that influence plasticity directly. For the cerebellum, cerebellar gray matter and lateral ventricle volumes, we found evidence that part of the genetic variance involved in adult change rate is indeed independent of the genetic sources that influence baseline volume. One interpretation of this finding would be that plasticity of these structures as a reaction to environmental sources is dependent on the genetic profile. Another explanation would be that developmental and ageing trajectories of brain structure are not only phenotypically different [Fjell et al., 2013; Tamnes et al., 2013], but also driven by genetically different processes. In both cases, the genes that influence the susceptibility for environmental sources or ageing are considered to be independent from the genes that code for the "innate" volume.

This study has several limitations to take into account. One, the meta-heritability is based on the assumption that the genetic factors explaining individual differences of change are the same throughout the lifespan. Considering the highly nonlinear developmental and ageing patterns of the brain and the fact that gene-expression in the brain varies with age [Berchtold et al., 2008; Colantuoni et al., 2011; Kumar et al., 2013], it is possible that this assumption is not valid. There was little evidence of heterogeneity in our meta-analysis (data not shown) but this might be an effect of the low number of studies included rather than true homogeneity. The estimates we provide here should therefore be considered an average over the lifespan, rather than a constant value. Two, there are differences between the cohorts that are intertwined with age, sex and methodology. It is therefore not possible to draw definite conclusions about the possibility that different genes play a different role at different ages, or that the influence of genes on individual differences in brain changes may differ between the sexes. Three, the balance of the variance of the change rate and the variance of measurement error may be cohort and age dependent and data quality and quality control procedures will still be an important factor when performing genetic studies. Four, the twin model presumes that the equal environment assumption holds, which we could not test for our data. Five, there were changes in scanning methods over time in the two oldest cohorts. We assume that possible effects of a

scanner change are linear but we cannot rule out that this is not the case. However, both members of all twin pairs were scanned on the same scanner. As we may expect that a scanner update has the same effect on a subject regardless his/her zygosity, any scanner-related variance would be labeled as common environment in the twin model. Given that the estimated C components are rather small in both the VETSA and OATS cohort, we can argue that scanner updates did not strongly influence our results.

To conclude, this study shows that annual change rates of global and subcortical volumes are heritable, especially in adulthood. This implies that the individual's genetic profile contributes to the rate of brain changes, specifically in older age. Identifying those genes may help us understand the genetics of ageing and brain diseases that are characterized by accelerated brain ageing. Finally, this study shows that measuring brain changes using volumetric MRI carries enough genetic signal to attempt a GWA study and this will be the next goal of the ENIGMA plasticity group.

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