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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., 2001), 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 (Boomsma et al., 2002; Hulshoff Pol et al., 2006; Posthuma et al., 2002; Toga and Thompson, 2005; Wright et al., 2001). 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 IIII. 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). Q4

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.

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