The association between brain volume and intelligence is of genetic origin

TO THE EDITOR—The recent study by Thompson and colleagues[1] reported high heritability of gray-matter volume in several cortical regions using voxel-based MRI techniques. Gray matter substantially correlated with general intelligence, or '*g*'. These findings prompt three major questions: (i) is the high heritability specific to gray-matter volume, (ii) is the correlation with *g* specific to gray-matter volume and (iii) is the correlation between gray-matter volume and *g* of genetic or environmental origin?

We addressed the first question in a large Dutch sample of twins and their siblings (258 Dutch adults from 112 extended twin families)[2]. We found high heritability for total brain gray-matter volume (**Table 1**), comparable to the estimate reported by Thompson and colleagues[1]. In addition, we found high heritability for total brain white-matter volume.

As stated in a commentary[3] on the recent report in *Nature Neuroscience*[1], high heritability of gray matter implies that interindividual variation in cell-body volume is not modified by experience. Because white matter reflects the degree of interconnection between different neurons, interindividual variance in white-matter volume might be expected to be more under the influence of experience and less under genetic control. Our results clearly suggest otherwise. Either environmental experience barely contributes to interindividual variation in white-matter volume or, alternatively,

exposure to relevant environmental experience is under strong genetic control.

The subjects for whom MRI scans were available partly overlapped with a sample of extended twin families from a large study on cognition[4]. In the latter study, we found a heritability of *g* of 0.86, which is consistent with previous reports[5]. We have now confirmed a correlation between gray-matter volume and *g* (0.25; *p* < 0.05) and, in addition, have found a significant correlation between white-matter volume and *g* (0.24; *p* < 0.05). Thus, regarding the first two questions, we conclude that white-matter volume is also highly heritable and that *g* is related to the volumes of both gray and white matter.

In twin samples of sufficient size, the correlation between brain volume and *g* can be decomposed into genetic and environmental components[6]. Such analysis is based on the comparison of cross-trait/cross-twin correlations for monozygotic (MZ) and dizygotic (DZ) twins (or sibling pairs). If the correlation between brain volume of a twin and *g* in the co-twin is larger in MZ than in DZ twins, this indicates that the genes influencing brain volume partly overlap

with the genes that influence *g*. The extent of the overlap is reflected by the magnitude of the genetic correlation. When the cross-trait/cross-twin correlations are similar for MZ and DZ twins, this suggests that environmental factors contribute to the observed phenotypic correlation between brain volume and *g*. Given a heritability of 0.85 for brain volume[2], a heritability of 0.80 for *g* (ref. 5) and a correlation between brain volume and *g* of 0.40 (ref. 7), at least 17 MZ and 17 DZ pairs are needed to detect a genetic correlation with 80% power (and α = 0.05) that explains the observed correlation.

In 24 MZ pairs, 31 DZ pairs and 25 additional siblings, we decomposed the correlation between brain volumes and *g* into genetic and environmental components by using structural equation modeling for a multivariate genetic design (gray matter, white matter and g)[6]. This showed that the correlation between gray-matter volume and *g* was due completely to genetic factors and not to environmental factors. We obtained the same result for the correlation between white-matter volume and *g*. Thus, the answer to the third question is

Table 1. Heritability estimates from multivariate genetic analyses

	Heritability
Whole-brain gray matter	0.82
Whole-brain white matter	0.87
General intelligence (*g*)[a]	0.86
Working memory[a]	0.67

[a]WAIS-IIIR IQ test.
Details of brain imaging methods and subject characteristics of the MRI sample (258 subjects from 112 extended twin families) have been described previously[2], as have detailed characteristics of the WAIS-IIIR sample (688 subjects from 271 extended twin families)[4]. The overlapping dataset consisted of 135 subjects from 60 extended twin families (24 MZ pairs, 31 DZ pairs and 25 additional siblings).

Table 2. Observed (phenotypic) correlations, cross-trait/cross-twin correlations, genetic correlations and environmental correlations

	Correlation			
	Observed	MZ cross-trait/ cross-twin	DZ cross-trait/ cross-twin	Genetic
Whole-brain gray matter–*g*	0.25*	0.26*	0.14	0.29*
Whole-brain gray matter– Working memory	0.29*	0.32*	0.20*	0.38*
Whole-brain white matter–*g*	0.24*	0.22*	0.19	0.24*
Whole-brain white matter– Working memory	0.29*	0.27*	0.19	0.35*

*Significantly different from zero at the α = 0.05 level.
MZ, monozygotic twins; DZ, dizygotic twins, including sibling pairs. The cross-trait/cross-twin correlations in MZ pairs showed evidence for a genetic mediation between brain volumes and *g* (and its working-memory component); the cross-trait/cross-twin correlation for MZ pairs was as high as the correlation between brain volume and *g* (or working memory) within the same person. In other words, the IQ of MZ twins was predicted equally well from the size of the brain of their co-twins as from the size of their own brain. All analyses were carried out using maximum likelihood estimation implemented in Mx software[11]. Mx is especially suited to handle incomplete data structures, as is the case when not all variables have been measured in all subjects. Effects of sex and age have been regressed out on the observed scores. Observed correlations and cross-trait/cross-twin correlations were estimated from a saturated model in which the (co-) variances are not decomposed, whereas the genetic and environmental correlations were estimated from a multivariate genetic design in which the (co-) variances are decomposed into genetic and environmental components. The 'genetic correlation' reflects the correlation between the set of genes that influences brain volume and the set of genes that influences intelligence. The 'genetic contribution to the observed correlation' can be derived as the product of the genetic correlation and the square roots of the heritabilities of the two phenotypes.

that the correlation between brain volumes and *g* is, as anticipated[8], mediated entirely by genetic factors (**Table 2**).

As our measure of *g* consisted of the IQ score on the WAIS-IIIR IQ test, we were also interested in whether a particular dimension of *g* correlated more highly with gray- and white-matter volume than any other dimension. The four standard WAIS-IIIR dimensions are Verbal Comprehension, Perceptual Organization, Processing Speed, and Working Memory. We found that the Working Memory dimension had the highest phenotypic and highest genetic correlation with brain volumes. This is perhaps not surprising, because working memory is considered a major component of *g* (ref. 9). Also, working memory is often 'localized' in the frontal lobes[10], which provides further convergence between our findings and those of Thompson and colleagues[1].

Establishing that the correlation between brain volumes and *g* is mediated by common genetic factors is only the first step in unveiling the relation between them. The next step will be to identify specific genes that influence both brain volume and *g*.

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