GENETIC INFLUENCES ON BRAIN STRUCTURE

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We report the first, detailed, 3-dimensional maps revealing how brain structure is influenced by individual genetic differences. A genetic continuum was detected, in which brain structure was increasingly similar in subjects with increasing genetic affinity. Genetic factors significantly influenced cortical structure in Broca's and Wernicke's language areas, as well as frontal brain regions ($r^2_{MZ} > 0.8$, $p<0.05$). Preliminary correlations were performed suggesting that frontal gray matter differences may be linked to Spearman's *g*, which measures successful test performance across multiple cognitive domains ($p<0.05$). These genetic brain maps reveal how genes determine individual differences, and may shed light on the heritability of cognitive and linguistic skills, as well as genetic liability for diseases that affect the human cortex.

Introduction

The degree to which genes and environment determine brain structure and function is of fundamental importance. Large-scale neuroimaging and genetic studies are beginning to uncover normal and disease-specific patterns of gene and brain function in large human populations[1,2]. Yet, little is known about the genetic control of human brain structure, and how much individual genotype accounts for the wide variations among individual brains. Recent reports show that many cognitive skills are surprisingly heritable, with strong genetic influences on IQ[3,4], verbal and spatial abilities, perceptual speed[5], and even some personality qualities, including emotional reactions to stress[6]. These genetic relationships persist even after statistical adjustments are made for shared family environments, which tend to make members of the same family more similar. Given that genetic and environmental factors, *in utero* and throughout lifetime, shape the physical development of the brain, we aimed to map patterns

of brain structure that are under significant genetic control, and determine whether these structural features are linked with measurable differences in cognitive function. The few existing studies of brain structure in twins suggest that the overall volume of the brain itself[7] and some brain structures, including the corpus callosum[8,9] and ventricles, are somewhat genetically influenced, while gyral patterns, observed qualitatively[10] or by comparing their 2D projections, are much less heritable[11]. To make the transition from volumes of structures to detailed maps of genetic influences, recent advances in brain mapping technology have allowed the detailed mapping of structural features of the human cortex, including gray matter distribution, gyral patterning, and brain asymmetry. These features each vary with age, gender, handedness, hemispheric dominance, and cognitive performance in both health and disease. Composite maps of these features, generated for large populations, can reveal patterns not observable in an individual[12]. Such patterns include statistical maps that show whether heredity and nongenetic factors are involved in determining specific aspects of brain structure.

Gray Matter Differences. Among the structural features that are genetically regulated and have implications for cortical function is the distribution of gray matter across the cortex. This varies widely across normal individuals, with developmental waves of gray matter gain and loss subsiding by adulthood[13], and complex deficit patterns observed in Alzheimer's disease, schizophrenia, and healthy subjects at genetic risk for these disorders. In this study, we began by comparing the average differences in gray matter (**Fig. 1**) in groups of unrelated subjects, dizygotic (DZ) and monozygotic (MZ) twins (*see Methods*). Although both types of twins share gestational and postgestational rearing environments, DZ twins share, on average, half their segregating genes, while MZ twins are normally genetically identical (with rare exceptions due to somatic mutations).

We found that brain structure is under significant genetic control, in a broad anatomical region that includes frontal and language-related cortices. The quantity of frontal gray matter, in particular, was most similar in individuals who were genetically alike; intriguingly, these individual differences in brain structure were tightly linked with individual differences in IQ. The resulting genetic brain maps reveal a strong relationship between genes, brain structure, and behavior, suggesting that highly heritable aspects of brain structure may also play a fundamental role in determining individual differences in cognition.

Methods

Subjects. 40 healthy normal subjects, consisting of 10 monozygotic (MZ) and 10 dizygotic (DZ) twin pairs were drawn

from a twin cohort consisting of all the same-sex twins born in Finland between 1940 and 1957, inclusive, in which both members of each pair were alive and residing in Finland as of 1967 (*n*=9,562 pairs: 2,495 MZ, 5,378 DZ, and 1,689 of unknown zygosity[14]. Pairs were excluded if either member or any of their first-degree relatives had a history of hospitalization, medicine prescriptions, or work disability due to a psychiatric indication from 1969 to 1991. MZ pairs were matched with the DZ pairs for age (48.2±3.4 years), gender, handedness, duration of cohabitation, and parental social class. Each zygosity group included 5 male pairs and 5 female pairs. The study protocol was reviewed and approved by the institutional review boards (IRBs) of the University of California (Los Angeles), and the National Public Health Institute of Finland, and all subjects signed IRB-approved informed-consent forms.

Cognitive Testing

A neuropsychological test battery[15] was administered to each co-twin by a different examiner blind to zygosity. All subjects received the same test battery in a fixed order. 17 different cognitive domains were assessed, including verbal and spatial working memory, selective and divided attention, verbal knowledge, motor speed, and visuospatial ability. A measure of general cognitive ability, in the form of an overall intelligence quotient (IQ) was prorated from age-scaled scores on the Vocabulary, Similarities, Block Design, and Digit Symbol subtests of the Wechsler Adult Intelligence Scale – Revised (WAIS-R; D.Wechsler, *WAIS-R Manual*, Psychological Corporation, Cleveland). This measure exhibited 98% correlation with full-scale IQ based on all of the WAIS-R subtests.

Zygosity

For all pairs zygosity was determined by DNA analysis using the following markers: *DIS80* (20 alleles), *DI7S30* (13 alleles), *apoB* (20 alleles), *COL2A1* (10 alleles), *vWA* (9 alleles), and *HUMTH01* (6 alleles). Assuming an average heterozygosity rate of 70% per marker, this procedure will falsely classify a DZ pair as MZ in approximately 1/482 cases.

Magnetic Resonance Imaging

3D maps of gray matter and models of cortical surface anatomy were derived from high-resolution 3D ($256^2 \times 124$ resolution) T_1-weighted (MPRAGE) magnetic resonance images acquired from all 40 subjects on a 1.5 T Siemens scanner (Siemens Corporation, New York).

Image Processing and Analysis

A radio-frequency bias field correction algorithm eliminated intensity drifts due to scanner field inhomogeneity. A supervised tissue classifier generated detailed maps of gray matter, white matter, and cerebrospinal fluid (CSF). Briefly, 120 samples of each tissue class were interactively tagged to compute the parameters of a Gaussian mixture distribution that reflects statistical variability in the intensity of each tissue type[16,17]. A nearest-neighbor tissue classifier assigned each image voxel to a particular tissue class (gray, white or CSF), or to a background class. The inter/intra-rater reliability of this protocol, and its robustness to changes in image acquisition parameters, have been described previously[17]. The error variance, i.e. variation associated with map error and reproducibility, was further confirmed to be small by the extremely high intraclass correlations in the MZ pairs (around 1.0), which would not otherwise be obtainable (**Fig. 2**). Gray matter maps were retained for subsequent analysis.

3D Cortical Maps

To facilitate comparison and pooling of cortical data across subjects, a high-resolution surface model of the cortex was automatically extracted for each subject[18]. 38 gyral and sulcal boundaries, representing the primary gyral pattern of each subject, were digitized on the highly-magnified 3D surface models. Gyral patterns and cortical models were used to compute a 3D vector deformation field, which reconfigures each subject's anatomy to the average configuration of the entire group (n=40), matching landmark points, surfaces, and curved anatomic interfaces. Data was accordingly averaged or compared, to the maximum possible degree, across corresponding cortical regions[12]. Additional 3D vector deformation fields reconfigured one twin's anatomy into the shape of the other, matching landmark points, surfaces, and curved anatomic interfaces the pair of 3D image sets. Given that the deformation maps associate cortical locations with the same relation to the primary folding pattern across subjects, a local measurement of gray matter density was made in each subject and *averaged across equivalent cortical locations*.

Gray Matter Mapping

To quantify local gray matter, we used a measure termed 'gray matter density' which has been used in prior studies to compare the spatial distribution of gray matter across subjects[19,20,12]. This measures the proportion of tissue that segments as gray matter in a small region of fixed radius (15 mm) around each cortical point. Given the large anatomic variability in some cortical regions, high-dimensional elastic matching of cortical patterns[21], constrained by all 1520 (=40×38) 3D sulcal models, associated measures of gray matter density from homologous cortical regions across subjects. Maps of intrapair gray matter differences,

generated within each MZ and DZ pair, were subsequently elastically realigned for averaging across the 10 pairs within each group, prior to intergroup comparisons.

Mapping Genetic Correlations and Asymmetry

Intraclass correlation between pairs of each zygosity was computed at each cortical point, after testing for heteroscedastic variance across each group. First, to assess whether it was significantly non-zero, broad-sense heritability was computed using Falconer's method[22] to determine all genic influences on the phenotype (with heritability, h^2, defined as twice the difference between MZ and DZ intraclass correlation coefficients). Since nongenetic familial effects contribute to the resemblance between relatives, such effects were accommodated, if not entirely eliminated, by assuming the same common environmental variance for MZ and DZ pairs (*cf*. [ref. 4]). Random field models were preferred, for this study, to a full structural equation model (e.g. [23]) given the low degrees of freedom per point available to estimate dominance and epistatic variance terms and reject simpler models based on the available database of 40 scans. Interaction and gene-environment covariance terms, as well as unique and shared environment factors, may be estimable with a more general familial design, an adoption design, or by using sample sizes much larger than available in the present study ([23], cf. [24]). The significance of genetic effects was computed pointwise both by reference to an analytical null distribution (*F*-test) and confirmed separately by assembling an empirical null distribution using 1,000,000 random pairings to avoid assuming bivariate normality. All map-based inferences were corrected for multiple comparisons by permutation. We used permutations to make statistical inferences that were not based on any assumptions about the error co-variances. To correct for the multiple comparisons implicit in our brain maps we established the null distribution of the largest statistic over the voxels analyzed. By adopting the critical threshold of this largest statistic, we could then maintain both strong and weak control over false-positive rates over the voxels analyzed.

Asymmetric heritability was tested by computing a set of 40 flows driving each subject's left hemisphere model onto the right, matching gyral patterns, and computing a field of heritability differences. This field was compared with its standard error (pooled across contralateral cortical points, after testing equality of variance across hemispheres, *cf*. [25]. Regions of asymmetric heritability were detected and their significance assessed by permuting the covariate vector coding for hemisphere. Maps of MZ intrapair gray matter differences associated with intrapair differences in the cognitive measure, Spearman's *g*, were generated by elastically realigning 3D maps for averaging across all MZ twin pairs and modeling *g* as a continuous covariate for linkage with local gray matter distribution. Maps identifying these linkages were computed pointwise across the cortex and assessed

statistically by permutation by computing the area of the average cortex with statistics above a fixed threshold in the significance maps ($p < 0.01$). Null distributions were assembled from random pairings of unrelated subjects. We preferred this to an analytical null distribution to avoid assuming that the smoothness tensor of the residuals of the statistical model were stationary across the cortical surface[26]. In each case, the covariate vector was permuted 1,000,000 times on an SGI RealityMonster supercomputer with 32 internal R10000 processors. An algorithm was then developed to report the significance probability for each map as a whole[12], so the significance of intrapair variance reduction by zygosity, heritability, asymmetry, and cognitively-linked patterns of gray matter distribution could be assessed after the appropriate correction for multiple comparisons.

Results

MZ within-pair gray matter differences were almost zero (*intraclass r*~0.9 and higher, $p<0.0001$ *corrected*; **Fig. 1**, *right column*) in a broad anatomical band encompassing frontal, sensorimotor and linguistic cortices, including Broca's speech and Wernicke's language comprehension areas. Since MZ twins are genetically identical, any regional differences would be interpreted as being attributable to environmental effects or gene-environment interactions. Meanwhile, sensorimotor and parietal occipital, but not frontal, territory was significantly more similar in DZ twins than random pairs (**Figs. 1** and **2**). Affinity was greatest in the MZ pairs, suggesting a genetic continuum in the determination of structure.

A Genetic Continuum. In population genetics, a feature is *heritable* if it shows a genetic cascade in which within-pair correlations (**Fig. 2**) are highest for MZ twins, lower for DZ twin pairs, and lowest of all for unrelated subjects. Since we expected specific regions of cortex to be more heritable than others, we plotted these correlations across the cortex (**Fig. 2**) and assessed their statistical significance (*see Methods*). This uncovered a successively increasing influence of common genetics. A 95-100% correlation was revealed between MZ twins in frontal, linguistic and parieto-occipital association cortices, suggesting individual differences in these regions can be largely attributed to genetic factors. DZ twins, who share half their genes on average, were still near-identical in the supramarginal component of Wernicke's language area (r^2=0.7-0.8; $p<0.0001$) and highly similar in parieto-occipital association areas (60-70% correlation; $p<0.001$). They also showed significantly less affinity ($p<0.05$) in a sharply defined region that included the frontal cortices ($p>0.05$). The resulting pattern of twin correlations suggests substantial genetic influences in this region.

Mapping Genetic Correlations. With a sample size of only 40 twins, heritability coefficients cannot be estimated precisely, and limited statistical power precludes the detection of differences in heritability between individual regions of cortex. Preliminary comparisons of MZ and DZ correlations suggested that frontal, sensorimotor, and anterior temporal cortices were under significant genetic control *($p<0.05$, rejecting the hypothesis that $h^2=0$; one-tailed).* Preliminary estimates suggested that discrete middle frontal regions, in the vicinity of Brodmann areas 9 and 46[27] displayed a 90-95% genetic determination of structure (*i.e.*, $h^2 \sim 0.90$-0.95). Many regions are under tight genetic control (bilateral frontal and sensorimotor regions, $p<0.0001$; **Fig. 3**). Due to small sample sizes, any provisional heritability estimates should be interpreted with caution, but were comparable with twin-based estimates for the most highly genetically-determined human traits, including fingerprint ridge count ($h^2=0.98$), height ($h^2=0.66$), and systolic blood pressure ($h^2=0.57$)[28]. Genetic influences here are far higher than for the most environmentally influenced characters (*e.g.*, social maturity, for which $h^2=0.16$; [29]).

Language Asymmetry. Given the high heritability of reading skills and performance on linguistic tasks[30], we were interested in whether the structure of language cortices would also be heritable, and if so whether heritability would be higher in the left hemisphere, which is dominant for language in most (right-handed) subjects. The heritability of brain size does not vary markedly by hemisphere[31], but one MZ twin study of cortical surface areas[32] suggested the possibility of differing left/right genetic influences. Intriguingly, when a 3D map was made subtracting the heritability of the structures in one hemisphere from their counterparts in the other, differences in Wernicke's language area were highly significant, even after hemispheric differences in gyral patterning were directly accommodated. Heritability was significantly greater on the left ($p<0.05$, *corrected*). Although no other regions displayed this lateralized effect, we cannot infer that there are no such asymmetries elsewhere, as we were underpowered, in a sample of 40, to make general comparisons of heritability among cortical regions. Nonetheless, the asymmetry in language-related cortex was significant, and was corroborated by the genetic correlation maps as well (**Figs. 2** and **3**) in that Wernicke's and Broca's speech area displayed highly significant heritability on the left ($p<0.0001$) but not on the right ($p>0.05$).

Cognitive Linkages. To make a preliminary assessment of whether gray matter differences between subjects were significantly linked with differences in cognitive function, a cognitive measure termed *Spearman's g* was assessed for all 40 MZ twins. Like IQ, this widely-used measure isolates a component of intellectual function common to multiple cognitive tests, and has been shown to be highly heritable across many studies, even more so than specific cognitive abilities ($h^2=0.62$ [ref. 4]; *cf.* [24];

h^2=0.48 [ref. 33]; h^2=0.6-0.8 [ref. 34; cf. 35-38]). We found that differences in frontal gray matter were significantly linked with differences in intellectual function (*Table 1; p*<0.0044; *p*<0.0176 after correction for multiple tests) as quantified by *g*, which was itself also highly heritable (h^2=0.70±0.17 in this study). While these preliminary correlations should be evaluated in a larger sample, a recent abstract also observed that differences in regional gray matter volume were significantly correlated with differences in IQ, in a sample of 28 pediatric MZ twin pairs (mean age: 12.1 years) studied volumetrically (E. Molloy *et al.*, Abstract #447, 7th Annual Meeting of the Organization for Human Brain Mapping, Brighton, England, 2001).

In frontal brain regions, a regionally-specific linkage has previously been found[39] between *g* and metabolic activity measured by positron emission tomography (PET) suggesting that general cognitive ability may in part derive from a specific frontal system important in controlling diverse forms of behavior. Frontal regions also show task-dependent activity in tests involving working (short-term) memory, divided and sustained attention, and response selection[40]. Genetic factors may therefore contribute to structural differences in the brain that are statistically linked with cognitive differences. This is especially noteworthy since cognitive performance appears to be linked with brain structure in the very regions where structure is under greatest genetic control (**Figs. 2** and **3**). This emphasizes the pronounced contribution of genetic factors to structural and functional differences across individuals, as detected here in frontal brain regions.

Discussion

Genetic Brain Mapping. Influences of nature and nurture in the determination of individual brain structure are not independent; genes necessarily operate through the environment, particularly if they concern susceptibilities to environmental stressors or hazards[41]. Nonetheless, twin designs can reveal the degree to which heredity is involved, and the extent to which individual differences can be attributed to genetic and environmental factors. While genetic influences strongly determine aspects of intellect and its closely related traits, the extent to which genes shape brain structure is heterogeneous, displaying asymmetries that mirror asymmetries in its functional organization, and strongly controlling a broad anatomical band encompassing frontal, linguistic and sensorimotor cortex. As with any polygenic trait, multiple genes are likely to combine additively or interact at the same or different loci (dominance or epistasis) to structure the adult brain. Future studies mapping quantitative trait loci are likely to provide insight into the genes that determine brain structure[42], and neurocognitive skills that in some cases depend on it[43].

The tight coupling of brain structure and genetics, particularly in frontal brain regions, may contribute to the genetic liability for diseases that affect the integrity of the cortex. Frontal gray matter deficits are found in both schizophrenia patients and their healthy first degree relatives[44-46], and there is a strong familial risk for many neurodegenerative diseases that affect the frontal cortex, including frontotemporal dementia and primary progressive aphasia. The genetic cascades implicated in these diseases may or may not overlap with those involved in cortical determination, but the genetic coupling of brain structure we report here may result in increased familial liability to cortical degenerative disease, specifically in highly genetically-determined frontal regions. By controlling for nongenetic factors, twin studies may offer unique advantages in isolating disease-specific differences in these highly heritable brain regions.

Genetic brain maps, such as those introduced in this study, may reveal how genes determine individual differences in brain structure and function. Additional linkages were observed between cortical differences and intellectual function, suggesting that genetic brain mapping may shed light on the heritability of cognitive and linguistic skills, as well as familial liability for diseases that affect the human cortex.

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Figure Legends

Fig. 1. Genetic Continuum of Similarity in Brain Structure. Differences in the quantity of gray matter at each region of cortex were computed for identical and fraternal twins, averaged, and compared with the average differences that would be found between pairs of randomly selected, unrelated individuals (*blue colors, left column*). Color-coded maps show the percentage reduction in intrapair variance for each cortical region. Fraternal twins exhibit only 30% of the normal intersubject differences (*red colors, middle column*), and these affinities are largely restricted to perisylvian language and spatial association cortices. Genetically identical twins display only 10-30% of normal differences (*red and pink colors*) in a large anatomical band spanning frontal (F), sensorimotor (S/M), and Wernicke's (W) language cortices, suggesting strong genetic control of brain structure in these regions, but not others (*blue colors*; the significance of these effects is shown on the same color scale).

Fig. 2. Correlation between Twins in Gray Matter Distribution. Genetically identical twins are almost perfectly correlated in their gray matter distribution, with near-identity in frontal (F), sensorimotor (S/M) and perisylvian language cortices. Fraternal twins are significantly less alike in frontal cortices, but are 90-100% correlated for gray matter in perisylvian language-related cortex, including supramarginal and angular territories and Wernicke's language area (W). The significance of these increased similarities, visualized in color, is related to the local intraclass correlation coefficents (r).

Fig. 3. Significance of Genetic Control of Gray Matter Distribution. Brain regions for which cortical gray matter distribution is under significant genetic control are shown in *red*. Frontal (F) and lateral temporal (T) regions show significant heritability, consistent with their near-identity in identical twins (**Fig. 2**) and the weaker patterns of correlations observed in fraternal twins, who have less similar

genotypes. Wernicke's area shows significantly higher heritability in the left hemisphere (W_{left}), which is generally dominant for language function ($p<0.05$ for asymmetry).

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Table 1. *Random Effects Analysis Regressing Individual Regional Gray Matter Measures on the IQ measure, Spearman's g (n=40 subjects).* This table shows a highly significant relationship ($p<0.0044$) between gray matter volume in the frontal cortex**, and Spearman's *g*, a measure of IQ evaluated in all 40 subjects. The random effects analysis (I) is most powerful[47-50]. It uses all 40 subjects' data and it explicitly models, and controls for, correlations between twins in both measures[47-50]. The first columns show regression coefficients, effect sizes (*t*) and significance values for each regional brain measure, in a step-wise regression where only the predictive effects of overall gray matter volume ($t=1.73$, $p<0.046$) on IQ are factored out. In the final two columns, a Type III (simultaneous) regression model[49] was used, meaning that each predictor is tested controlling for all other model terms simultaneously. In this second analysis, correlations between brain regions are accounted for in assessing the significance of each regional effect. An *F* statistic and a significance value are shown assessing the fit of each model parameter. Although the power is substantially less, correlations were also significant if analyses were restricted to independent samples including one twin from each pair. In (II), correlations are measured in 20 twins (arbitrarily termed 'twin 1') selected randomly, one from each of the 20 twin pairs ($n=20$). Correlations are repeated in 'twin 2' ($n=20$; using the other subject from each of the 20 twin pairs). Pearson partial correlation coefficients (*R*), and their significance levels (one-tailed) are shown, suggesting in each independent sample a positive relationship between (greater) frontal gray matter and better cognitive performance. Although this analysis is slightly less powerful[48] due to splitting the sample into halves, the cognitive relationship appears at trend level in one sample ($p<0.0574$*) and significantly in the other ($p<0.0256$**).

I. *Random Effects Analysis*	Controlling for overall gray matter only			After controlling for other predictors	
Measure	Regression Coefficient (β)	Effect size (*t*)	Significance	$F_{1,33}$	Significance
Whole brain gray matter volume	0.0037	1.73	0.046	3.92	0.0561
Frontal gray matter volume	0.072	1.95	0.029**	9.37	0.0044**
Temporal gray matter volume	0.039	0.23	0.411	3.77	0.0607
Parietal gray matter volume	0.055	0.41	0.343	0.54	0.4690
Occipital gray matter volume	0.033	0.15	0.439	0.04	0.8376

II. *Correlation Analyses in Independent Samples*

First Sample using Twin 1; *n*=20	*R* (Twin 1)	Significance
Frontal gray matter volume	0.45343	0.0256**
Independent Sample using Twin 2; *n*=20	*R* (Twin 2)	Significance
Frontal gray matter volume	0.37392	0.0574*

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