MAPPING GENETIC INFLUENCES

ON HUMAN BRAIN STRUCTURE

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'The repeated identification of heritable aspects of brain structure suggests the notion of mapping differential genetic influences on different brain systems.' [from page 8].

'Genetic brain maps can be derived from population-based atlases, shedding light on familial risk for human brain disorders.' [from page 15].

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ABSTRACT

Recent advances in brain imaging and genetics have empowered the mapping of genetic and environmental influences on the human brain. These techniques shed light on the 'nature/nurture' debate, revealing how genes determine individual differences in intelligence quotient (IQ) or risk for disease. They visualize which aspects of brain structure and function are heritable, and to what degree, linking these features with behavioral or cognitive traits or disease phenotypes. In genetically transmitted disorders such as schizophrenia, patterns of brain structure can be associated with increased disease liability, and sites can be mapped where non-genetic triggers may initiate disease. We recently developed a large-scale computational brain atlas, including data components from the Finnish Twin registry, to store information on individual variations in brain structure and their heritability. Algorithms from random field theory, anatomical modeling, and population genetics were combined to detect a genetic continuum in which brain structure is heavily genetically determined in some areas but not others. These algorithmic advances motivate studies of disease in which the normative atlas acts as a quantitative reference for the heritability of structural differences and deficits in patient populations. The resulting genetic brain maps isolate biological markers for inherited traits and disease susceptibility, which may serve as targets for genetic linkage and association studies. Computational methods from brain imaging and genetics can be fruitfully merged, to shed light on the inheritance of personality differences and behavioral traits, and the genetic transmission of diseases that affect the human brain.

1. Introduction

The quest to understand the nature of genetic information and its impact on the brain and behavior have revolutionized

contemporary science. Large-scale genetic studies are now revealing the relative roles of genes and environment in shaping brain development and disease. They may also suggest steps towards preventive and therapeutic strategies for many inherited disorders (Collins and McCusick, 2001). A second revolution in our understanding of human genetics is likely to come from combining genetic techniques with large scale neuroimaging studies. Current brain mapping initiatives are charting brain structure and function in thousands of subjects (e.g. Mazziotta et al., 2001; *N*=7000, including 5800 genotyped subjects and 342 MZ (monozygotic) and DZ (dizygotic) twins). These techniques create detailed maps of functional and metabolic change, fine-scale anatomy and neurochemistry (Toga and Mazziotta, 2002). These maps are stored in a computational atlas that can be stratified by age, diagnosis, genotype, or other demographic or cognitive factors. Since the connection between genes and disease or behavior is often elusive, brain imaging data provides an intermediate phenotype that can quantitatively characterize disease, or cognitive processes (*cf.* Posthuma et al., 2000; de Geus et al., 2001). These data can then be linked with genetic variations that might underlie differences in brain function and behavior.

Inherited Behavior and Disease. A striking trend in behavioral genetics has been the finding that many cognitive skills are surprisingly heritable, with strong genetic influences on IQ (Bouchard and McGue, 1981; Plomin and Loehlin, 1989), verbal and spatial abilities, perceptual speed (Alarcón et al., 1998), and even some personality qualities, including extraversion and emotional reactions to stress (Eley and Plomin, 1997). 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. A heated debate has surrounded the role of genes in shaping human personality and IQ (e.g. Bouchard and McGue, 1981; Herrnstein and Murray, 1994; Gould, 1996; Carson and Rothstein, 1999; Kamin and Goldberger, 2002), in part due the perceived political and social implications, and ethical concerns over the misuse of information on individual differences. Nonetheless, genes and environment play crucial roles in the transmission and expression of disorders such as schizophrenia, autism, alcoholism, depression, as well as neurological conditions with known risk genes, such as Alzheimer's disease. Specialized methods have therefore been developed to assess how genes and environment affect brain function, typically with the goal of shedding light on the mechanism and transmission of disease.

Genetic Diversity. Heritable diseases and behavioral traits arise from DNA variations passed on from parents to their offspring. These genetic polymorphisms alter molecular function, and ultimately, behavior. If two randomly selected individuals' genomes were aligned, between 0.1 and 0.2 percent of the nucleotides would not match. About 85% of these

sequence variations are *single nucleotide polymorphisms* (SNPs). These are sites where at least 1% of the entire human population has a different base (Sherry et al., 2001), and they occur roughly every 350 to 1000 base pairs along the genome. About 200,000 of these SNPs, or about half of the total, occur in protein coding regions or upstream regulatory sites. These are likely to account for almost all human heritable variation, and contribute to common diseases such as Alzheimer's disease, arthritis and diabetes. By altering a protein's amino-acid sequence or expression pattern, these functional SNPs modify behavioral traits, disease susceptibility and treatment response. To find susceptibility genes and quantitative trait loci, association studies can now identify genetic variation by genotyping individuals at thousands of these loci, using high-throughput SNP detection chips (Wang et al., 1998).

Measuring Heritability. Complementary to this approach, genetic influences on behavioral traits or disease expression can also be estimated without direct examination of DNA. In the simplest model, a heritability statistic (h^2) is computed expressing the percentage of the variation in a trait that is due to genetic differences in a population (as opposed to that due to environmental factors, such as nutrition, education, or experience). These statistics are estimated by measuring similarities among relatives with different degrees of genetic affinity. In the classical twin design, a feature is regarded as *heritable* if it shows a genetic cascade in which within-pair correlations (typically called intraclass correlations, or ICCs) are higher for pairs of MZ twins (who share all their genes, except for rare somatic mutations), and lower for same-sex DZ twin pairs (who on average share half their genes). Falconer's method (Falconer, 1989) computes heritability as twice the difference between these correlations. High values, near 1.0, are found for the most genetically determined traits, and near-zero values for traits that are unaffected by individual genetic differences. Twin-based estimates show extremely high heritability for some physical characteristics, such as finger-print ridge count (h^2=0.98), height (h^2=0.66-0.92) and, to a lesser degree, weight (h^2=0.42). Many studies point to a substantial genetic contribution in autism (h^2=0.90-0.95), bipolar disorder (h^2=0.6-0.8), schizophrenia (h^2=0.4-0.9) and depression (h^2=0.4-0.55; Peele and DeGrandpre, 1995). Being brought up in the same family environment tends to make family members more alike, so that MZ twin similarities cannot be attributed solely to genetics. The advantage of using DZ twins, when assessing genetic components of trait variance, is that they serve as a control for shared rearing environment. The adequacy of using DZ twins as a control has been debated (see e.g., Vogel and Motulsky, 1997, Kamin et al., 2000, for a discussion of the 'shared environment assumption').

In an alternative design, *adoption studies* consider intrapair correlations between MZ twins reared apart and reared together

(e.g. Bouchard et al., 1990). More complex statistical designs (e.g. Mx, LISREL; Neale and Cardon, 1992; Posthuma and Boomsma, 2000) use path analysis and structural equation modeling to capture trait covariances between other types of relatives. These measure goodness of fit for various genetic models and estimate various genetic and environmental parameters. Some include variance components due to dominance and epistasis (these are non-additive interactions between genes at the same, or different, loci). A popular model, the ACE model, derives path coefficients that represent the proportion of trait variance due to additive genetic (a^2), shared (or *common*) environment (c^2), and the unique environment (e^2) of each twin. In this model, a^2 is the heritability. Of particular interest is the understanding of gene x environment correlations and interactions (Rowe and Jacobson, 1999; Boomsma et al., 1999). These are posited to explain the paradox of high heritability but strong environmental effects on IQ (see Dickens and Flynn, 2001, and Garlick, 2002, for a discussion of the 'Flynn effect' and multiplier effects). Dickens and Flynn (2001), for example, suggested a genetic model in which individual IQ is affected by both environment and genes, but where individuals' environments are matched to their IQs. Such a model allows very large effects for environment on IQ, while incorporating the highest estimates of heritability. These gene x environment correlations can be *active* or *reactive*, occurring (1) when subjects actively select environments (e.g. more intellectual stimulation) in a way that depends on their genotype, or (2) when the environment reacts to individuals differently according to their genotype. Genetic models (e.g. Falconer and Mackay, 1996) typically include these gene x environment correlations as part of the genetic variance, as they do depend directly on genotype. Finally, *bivariate genetic models* correlate a trait in one relative with a different trait in another relative (i.e., a 'cross-trait covariance'). This procedure determines the proportion of the correlation between two measures (e.g. gray matter and IQ, or volumes of two different structures) that is attributable to genetic factors (Pfefferbaum et al, 2000; Posthuma et al., 2002), sometimes pointing to a common genetic basis. A key aspect of all these modeling approaches is that they produce a set of parameter estimates, or statistics, describing genetic influences on a particular trait, or phenotype. It is this feature of the behavioral genetics models that will be exploited to produce maps of genetic effects on brain structure.

2. Heritability of Brain Structure

Extending the heritability concept to brain images, the trait measured in a population might be a particular functional or metabolic signal (measured with functional magnetic resonance imaging (fMRI), positron emission tomography (PET), or electroencephalography (EEG)), or the shape or size of an anatomic structure, measured from an MRI scan. Given that

genetic and environmental factors, *in utero* and throughout lifetime, shape the physical development of the brain, a major goal is to determine which aspects of brain structure are under significant genetic control, and whether these structural features are linked with measurable differences in cognitive function (Thompson et al., 2001; Plomin and Kosslyn, 2001; Posthuma et al., 2002; Wright et al., 2002). The most heritable features can be exploited in discordance designs; these capitalize on the lack of genetic variation to aid detection of disease-specific differences.

Volume Studies. The few existing studies of brain structure in twins suggest that the overall volume of the brain itself (Bartley et al., 1997; Tramo et al., 1998) and some brain structures, including the corpus callosum (Oppenheim et al., 1998; Pfefferbaum et al., 2000) and ventricles, are highly genetically influenced. Gyral patterns, observed qualitatively (Biondi et al., 1998) or by comparing their 2D projections, are much less heritable (Bartley et al., 1997). Bartley et al. (1997) reported a 94% heritability for brain volume (MZ ICC=0.95, $p<0.00001$; DZ ICC=0.35, $p=0.09$), based on structural equation modeling in 10 MZ and 9 DZ pairs scanned with MRI. In elderly twins, Sullivan et al. (2001) found that the volume of the hippocampus was less heritable ($h^2=0.4$) than that of the adjacent temporal horns ($h^2=0.6$), corpus callosum ($h^2=0.8$) and intracranial volume ($h^2=0.8$). They suggested that environmental differences, perhaps interacting with genetic differences, may exert especially strong or prolonged influences on hippocampal size. A lower heritability figure for hippocampal size is consistent with its role in memory encoding, its vulnerability to plasma cortisol levels, and its plasticity in later life (Maguire et al., 2000; see also Lyons et al., 2001, for a related MRI study in monkeys). In a similar vein, Baaré and colleagues (2001) found that individual differences in lateral ventricle volume were best explained by a structural equation model containing common (58%) and unique (42%) environmental factors, indicating genes to be of little or no influence. The same authors found that genetic factors almost entirely accounted for individual differences in whole brain (90%), gray (82%) and white (88%) matter volume, in a study based on a sizeable sample of 54 MZ and 58 DZ twin pairs, and 34 of their full siblings. In their multivariate analysis of body height, and volumes of gray matter, white matter and the intracranial space, Baaré et al. noted that a large part of the genetic influences were common to the three brain measures, and a smaller part was shared with height. Some genes may therefore have a general effect on the brain, while other genes may affect specific volumes. More recently, Pfefferbaum et al. (2001) used diffusion imaging, which is sensitive to myelination levels and fiber orientation, to quantify the microstructure of the corpus callosum in 15 MZ and 18 DZ pairs. They found that anterior interhemispheric connecting pathways, in the callosal *genu*, were more susceptible than splenial pathways to environmental influences, perhaps reflecting the prolonged maturation of the frontal cortex well into adulthood (Sowell et al., 1999). Using bivariate

genetic modeling, these authors also noted that intracranial volume and corpus callosum area were tightly correlated, a correlation due entirely to shared genetic effects between these two brain structures.

Shape Studies. Several studies have set out to understand how genetic factors affect the shape of brain structures; shape can be a sensitive index of pathology in Alzheimer's disease (Thompson et al., 1997; Csernansky et al., 1999), fetal alcohol syndrome (Sowell et al., 2001; Bookstein et al., 2002), schizophrenia (Narr et al., 2002), and many other psychiatric disorders. Studies of anatomical shape have typically noted increased shape similarity in MZ twins rather than measuring heritability. Lohmann et al. (1999), for example, represented the sulci of the human brain as three-dimensional polygonal lines, and noted that deeper (ontogenetically early) sulci were more similar in shape, especially in MZ twins, than superficial sulci (N=19 MZ pairs). Anatomical shape variability can also be measured by principal component analysis of a set of shapes from multiple subjects, or alternatively by representing shapes as a linear combination of geometric functions (Gerig et al., 2001; Thompson and Toga, 2002 reviews these modeling approaches). Le Goualher et al. (2000) noted reduced variation in the shape parameters of the central sulcus in 10 MZ twin pairs (*left hemisphere*: z=-2.66, p<0.005; *right hem.*: z=-2.26, p<0.05), but not in 10 DZ twin pairs (p>0.05), relative to differences in random pairs. Performing a similar factor analysis to reduce the dimension of their volumetric data, Pennington et al. (2000) distilled the volumes of 13 individual brain structures in a large twin MRI cohort (N=132) into two main factors ('cortical' and 'subcortical') that accounted for 64% of the variance. For these two factor scores, and for left and right neocortex and total cerebral volume, all MZ intraclass correlations were significant and substantial (r=0.78-0.98), as well as being larger than the corresponding DZ correlations (r=0.32-0.65). Wright et al. (2002) extended this design to parcellate 92 regional gray matter volumes in 10 MZ and 9 DZ twin pairs, scanned with MRI. Inter-regional relationships were summarized by principal component analysis of the resulting *genetic correlation matrix.* This identified shared genetic effects on the frontal-parietal cortices and bilateral temporal cortex and insula. As the size and scope of these studies increases, decomposition of the genetic correlation matrix is likely to be a key exploratory tool to identify supraregional brain systems (Wright et al., 1999) which share common genetic influences, systems which may cut across conventional anatomic boundaries.

3. Mapping Genetic Influences

The repeated identification of heritable aspects of brain structure suggests the notion of mapping differential genetic

influences on different brain systems. To 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 (Thompson et al., 2001). 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 (Thompson et al., 2001a,b, 2002; Cannon et al., 2002). To see how individual variations in brain structure can be encoded, we first review the construction of population-based brain atlases. These atlases store information on individual differences, in a computational format that reveals where variation is greatest and what factors contribute to it.

3.1. Construction of Population-Based Brain Atlases. Brain structures vary from one individual to another in every metric: shape, size, complexity, and orientations relative to one another. The complexity and variability of brain structure, especially in the gyral patterns of the human cortex, make it difficult to compare and integrate brain imaging data across subjects. Two major challenges in population-based brain mapping are (1) identifying consistent patterns of brain structure that are systematically altered in disease (e.g. Alzheimer's, schizophrenia), and (2) detecting abnormal deviations in anatomy, relative to a statistical encoding of brain variation in a group. Probabilistic brain atlases (Mazziotta et al., 1995, 2001; Evans et al., 1996; Dinov et al., 2001; Thompson et al., 1996, 2002; Fischl et al., 2002) address these problems by storing brain maps and 3D anatomical models from multiple individuals in a standardized, 3D coordinate space. Mathematical strategies are then developed to create average models of brain structure and probabilistic measures of anatomic variation (see Miller et al., 2002, and Thompson and Toga, 2002, for mathematical reviews).

(i) Brain Averaging. The first step in a brain mapping study is typically to align 3D brain scans from multiple individuals into a standardized 3D coordinate space, so that every subject's anatomy can be referenced using stereotaxic (x,y,z) coordinates. Nonetheless, it is difficult to create a typical, or 'average', model of brain structure, relative to which individual differences can be assessed. If the image intensities of the subjects' scans are averaged together, pixel-by-pixel, features are washed away due to anatomical variability in the population (Fig. 1(a)). Fig. 1 illustrates a more sophisticated method to create a well-resolved, average template of anatomy (Fig. 1(b) and (c) shows an average template based on N=9 Alzheimer's patients). Here group features reinforced in their mean anatomic locations (Thompson et al., 2000; Fig. 1, *panel 6*). This method, based on *cortical pattern matching* (Thompson et al., 1996, 2002; cf. Davatzikos, 1996; Fischl et al., 1999), can

also generate average maps of gyral pattern asymmetry, and cortical gray matter distribution a group, resolving disease-specific patterns (Fig. 3). The detailed information that is retained on individual variability (Fig. 2(c),(d)) is useful for understanding genetic influences on brain structure, so we describe the measurement of these individual differences next.

(ii) Cortical Pattern Matching and Anatomical Averaging. Briefly, a 3D cortical surface model (Fig. 1(e),(f)) is extracted from each individual subject's scan (Fig. 1(d)). This represents their cortical surface anatomy in detail (Fig. 1(g); *triangulated mesh*). A set of 38 sulcal curves (Fig. 1(e),(f)) is then manually traced, representing each subject's primary gyral pattern. These curves are used as anchors to create a deformation mapping (Fig. 1, *panel 2*), which distorts the anatomy of one subject onto another, matching sulcal features exactly. To compute this mapping, cortical models and curves are first flattened (Fig. 1, *panel 1*), and a flow field is computed in the flattened space, to drive individual sulcal features onto an average set of curves (*panel 2*). Using a mathematical trick, a color code representing 3D locations of cortical points in each subject (*panel 3*) is convected along with this flow (*panel 4*). Then these warped color images are averaged across subjects and decoded to produce a crisp average cortical model for the group (*panel 6*).

(iii) Measuring Individual Differences. These deformation maps represent the complex distortion required to match one cortex to a group average (Fig. 2(b)). They also store local information on individual differences in gyral patterning. In a normal population, variability can be mapped by converting these differences into local measures of variance (3D r.m.s. deviation from the average anatomy). Gyral pattern variation is found to be greatest in perisylvian language-related cortices (*red colors*, Fig. 2(c)). Directional biases in gyral pattern variation can also be mapped (*elongated ellipsoids*, Fig. 2(d)). Group features of anatomy also emerge that are not apparent in individual subjects. The atlas localizes a prominent asymmetry in perisylvian cortices: right hemisphere structures are, on average, torqued forward relative to their counterparts on the left (Geschwind and Levitsky, 1968).

(iv) 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 (Sowell et al., 1999; Giedd et al., 1999). Complex deficit patterns are observed in Alzheimer's disease, schizophrenia (Thompson et al., 1998, 2001), and healthy subjects at genetic risk for these disorders (Cannon et al., 2002). Figure 3 shows the average profile of gray matter deficits in early

Alzheimer's disease, based on MRI data from 26 AD patients and 20 healthy controls. To produce these maps, a tissue classifier creates maps of gray matter (*green colors*, Fig. 3(a)) in each subject. Rather than compute cortical thickness, which is extremely difficult in MRI data, a related measure, termed 'gray matter density' is more commonly used (Wright et al., 1995; Thompson et al., 1998; Ashburner and Friston, 2000). This describes the proportion of pixels segmenting as gray matter in a small spherical region around each cortical point. By storing individual variations in gray matter density at each cortical point, differences between the diseased group and the healthy control group can be expressed as a percentage, or as a significance map (Fig. 3(c)). Significance maps report the results of a statistical test, assessing the evidence for a group difference, at each cortical point; they plot these results in color as a color-coded map. An advantage of this approach relative to volumetric studies is the ability to localize effects on brain structure in the form of a map. Cortical pattern matching also increases signal to noise by associating gray matter measures from corresponding cortical regions; this also adjusts for shape changes in longitudinal studies (Fig. 3(d),(e)). In the resulting maps, regions of comparatively spared tissue may appear sharply delimited from regions with significant loss (Fig. 3(b)) or progressive loss (Fig. 3(d),(e)).

(v) Twin Differences. Brain mapping methods to assess individual differences can also be applied to assess behavioral genetic models of individual variation. Estimated model parameters (e.g., a^2, c^2, e^2), their error variance, and their goodness of fit (e.g. χ^2) may also be displayed as color-coded maps, as well as simpler measures of intraclass correlations and heritability coefficients.

(vi) Permutation Testing. The significance of these statistical genetic brain maps can be assessed using parametric or nonparametric methods. In each case appropriate adjustments must be made for multiple comparisons, as is conventional in functional brain imaging (see Thompson et al., 2000 for current approaches). These adjustments note that although thousands of statistical tests are performed at different points on the brain surface, their results are highly spatially correlated. Typically, to assess whether an observed pattern of correlations or significance values could have occurred by accident, a Monte Carlo simulation is run in which subjects are randomly assigned to groups and a null distribution is assessed for the statistic of interest. The development of analytical null distributions for statistics on manifolds is a topic of active research, and is likely to empower future genetic brain mapping designs (Thompson et al., 2000; Taylor and Adler, 2002).

3.2. Genetic Brain Maps. In a recent study of genetic influences on brain structure (Thompson et al., 2001), we began by

computing the intraclass correlations in gray matter (Fig. 4, *left columns*) in groups of MZ and DZ twins. 40 healthy normal subjects, consisting of 10 MZ and 10 age- (48.2±3.4 years) and gender-matched 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*=9562 pairs: 2495 MZ, 5378 DZ, and 1689 of unknown zygosity; Kaprio et al., 1990). Consistent with earlier studies reporting the high heritability of brain volume (Bartley et al., 1997), MZ within-pair gray matter differences were almost zero (*intraclass r*~0.9 and higher, $p<0.0001$ *corrected*; Fig. 4, *left 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 are attributed 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. Affinity was greatest in the MZ pairs, suggesting a genetic continuum in the determination of structure. With a sample size of 40, heritability coefficients and their differences across cortex cannot be estimated precisely. Nonetheless, initial 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, 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. 4; *right column*). Heritability estimates were comparable with twin-based estimates for the most highly genetically-determined human traits, including fingerprint ridge count ($h^2=0.98$), height ($h^2=0.66$-0.92), and systolic blood pressure ($h^2=0.57$).

3.3. Genes, Brain, and Cognition. Many psychometric and twin studies have used a cognitive measure termed *Spearman's g* or *'general cognitive ability'* to assess intellectual function and its heritability. In computing *g*, factor analysis is used to isolate a component of intellectual function common to multiple cognitive tests. The construct validity of the measure has been widely debated by its advocates and detractors (Jensen, 1969; Brand, 2001; see Kamin, 1997 for a contrary view). Nonetheless, like IQ, Spearman's *g* has been shown to be highly heritable across many studies, even more so than specific cognitive abilities ($h^2=0.62$, McClearn et al., 1997; cf. Feldman and Otto, 1997; $h^2=0.48$, Devlin et al., 1997; $h^2=0.6$-0.8, Finkel et al., 1998; *cf.* Swan et al., 1990; Loehlin et al., 1989; Chipuer et al., 1990; Plomin and Petrill, 1997). In Thompson et al. (2001), we recently found that differences in frontal gray matter were significantly linked with differences in intellectual function ($p<0.0044$; $p<0.0176$ after correction for multiple tests) as quantified by *g*, which was itself also

highly heritable (h^2=0.70±0.17). Moderate correlations between IQ and gray matter volume or total brain volume have been widely replicated in MRI studies, to the extent that IQ is now commonly used as a potentially confounding variable in morphometric studies of disease. Most MRI-based studies estimate a moderate brain-size/IQ correlation of around 0.40 to 0.51 (Andreasen et al., 1993; see Peters, 1995 on issues in interpreting this correlation).

Duncan et al. (2000) also found a regionally-specific linkage between *g* and frontal metabolic activity measured by positron emission tomography (PET). Frontal brain regions typically show task-dependent activity in tests of working (short-term) memory, divided and sustained attention, and response selection.. In a large independent sample of twins, Posthuma et al. (2002a,b) also found high heritability for gray matter volumes. However, using a cross-twin cross-trait (bivariate genetic) analysis to compute genetic correlations, they demonstrated that the linkage between gray matter and *g* is highly genetic, in other words it is strongly mediated by common genetic differences. Genetic factors may therefore contribute to structural differences in the brain that are linked with cognitive differences. Cognitive performance appears to be linked with brain structure in the very regions where structure is under greatest genetic control, suggesting that genetic variations contribute profoundly to brain function in the frontal cortex. The direction of causation is less clear. Logically, genetic factors may influence brain volume which in turn influences cognition. In practice, each factor is likely to influence the others. Genes with pleiotropic effects may influence both brain volume and cognition, without there necessarily being a direct effect of brain volume on cognition. In addition, individuals with higher IQ may also seek more intellectual stimulation, develop more synapses, and seek environments correlated with their genotypes (Dickens and Flynn, 2001). This supports of the notion of cognition having a causal effect on brain structure. Because the brain remains plastic throughout life, systematic differences in behavior are likely to exert their own reciprocal effects on gene expression and the physical structure of the brain.

3.4. Disease Liability. The tight genetic control of brain structure, particularly in frontal brain regions, may also contribute to disease susceptibility. Frontal gray matter deficits are found in schizophrenia patients and their healthy first degree relatives (Weinberger et al., 1981; Suddath et al., 1990; Cannon et al., 1998). There is also a strong familial risk for many neurodegenerative diseases that affect 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 highly heritable brain structure may increase familial liability to cortical degenerative disease, specifically in frontal regions.

Recently, major susceptibility genes have been identified for both early- and late-onset Alzheimer's disease (AD), in which gray matter deficits progress rapidly across the cortex in concert with symptoms (Thompson et al., 2002). Risk genes include a mutated β-amyloid precursor protein gene on chromosome 21q (Goate et al., 1991), the presenilin-1 and -2 genes on chromosomes 14q and 1q (St. George-Hyslop, 2000), and the apolipoprotein E epsilon 4 allele (ApoEε4), which is found in 38% of all Alzheimer's disease patients, but only 15% of controls (Roses, 1996). Medial temporal brain structure shows profound atrophic changes in healthy ApoEε4 positive individuals even before cognitive deficits emerge (Fig. 5). At the same time, some brain regions may be comparatively protected (e.g. frontal cortices in ApoEε4 subjects with AD; Geroldi et al., 1999; Hashimoto et al., 2001). Structural and metabolic imaging are often helpful for early detection of dementia, at a time when neuroprotective drugs may be most effective (Lehtovirta et al., 1995, 2000; Small et al., 2000). In future, distinct patterns of atrophy may be associated with specific genetic markers, shedding light on the expected course of disease for individual patients. As yet, genetic testing is not recommended for clinical diagnosis of dementia, except as an adjunct to other diagnostic procedures (Relkin et al., 1996). Rather than analyzing data from individual patients, currently the most fruitful combination of genetics and imaging is perhaps their application to large patient populations. This shows great promise for identifying genetically mediated deficits, and for seeking out genetic markers and susceptibility loci that are linked with them.

(i). Discordance Designs. *Discordant twin designs* offer unique advantages in isolating disease-specific differences. If only one of two twins possesses a given trait, intrapair differences can be averaged against a backdrop of extremely similar characteristics, to isolate new features of a trait. This procedure isolates disease effects that would be difficult to detect in the context of normal genetic variation. The design has greatest statistical power, relative to the standard case-control design, in the most highly heritable brain regions. In a recent schizophrenia study (Cannon et al., 2002), a map encoding the average differences in gray matter density between schizophrenia patients and their unaffected MZ co-twins revealed deficits primarily in dorsolateral prefrontal cortex, superior temporal gyrus, and superior parietal lobule. A map encoding variation associated with genetic proximity to a patient (MZ co-twins > DZ co-twins > control twins) isolated deficits primarily in polar and dorsolateral prefrontal cortex. We also found that deficits correlated with symptom severity and cognitive dysfunction but not with duration of illness or antipsychotic drug treatment. The ability to isolate phenotypes in unaffected relatives is important for assessing genetic risk for psychiatric disorders (De Geus and Boomsma, 2001; Baaré et al., 2001). Genes related to illness or phenotypic variation can be identified by analyzing polymorphic variation and transmission

patterns in affected families, and their relationship to the observed phenotype (Cardno and Gottesman, 2000; Gelernter and Goldman, 2000).

4. QTLs and Risk Alleles

Perhaps the most adventurous method for assessing genetic effects on brain structure and behavior is to explicitly search for associations with polymorphisms at broadly defined 'candidate genes' expressed in the brain (Gottesman, 1997; McGuffin et al., 2001). Chorney et al. (1998), for example, reported the discovery of a gene variation in chromosome 6 that is statistically linked with high intelligence. The gene codes for a growth factor receptor (IGF2R) which might conceivably affect brain structure or metabolism, and indirectly, cognition. This result, however, was not replicated when more stringent criteria were applied (Plomin et al., 2001a,b; cf. Hill et al., 1999, de Geus et al., 2001). Of special note in these studies is the ability to screen the entire genome to detect quantitative trait loci (QTLs) by linkage disequilibrium, followed by individual genotyping at promising markers (Plomin et al., 2001). A second approach is the individual typing of single nucleotide polymorphisms (SNPs) using microarrays (McGuffin et al., 2001). Complications arise because many psychiatric disorders and all known behavioral traits are polygenic. They result from the interaction of many genes with small effects as well as epigenetic factors. Data mining algorithms, based on machine learning and self-organizing maps (Tamayo et al., 1999), are breaking new ground in identifying gene sets that influence complex traits. Their successes in medicine include the identification of disease subtypes (e.g. in leukemia; Golub et al., 1999) and prognostic categories (in lymphoma; Alizadeh et al., 2000). These methods may in the future detect associations between genotype and brain structure, producing more specific information on the particular genes involved.

5. Conclusion

We have described a range of techniques for assessing genetic influences on brain structure. They represent an exciting new area of exploration in neuroscience. Genetic brain maps can be derived from population-based atlases, shedding light on familial liability for human brain disorders (Cannon et al., 2002). The correlational models of genetic determination, which we have focused on here, are among the simplest. We include them as a first step, as they illustrate the possibility of combining methods from genetics and brain image analysis. They can be extended to path analyses and structural equation

models used more widely in population genetics, in cases where sample sizes are large enough to reliably estimate their parameters.

A key advantage of using brain atlases for population-based medical and genetic research is that they can be stratified, according to genetic, demographic, or therapeutic criteria, to reflect a more constrained subset of the population. Differences in a diseased population, or one with known genetic risk, can be visualized by reference to a normative standard. Individual variation can also be mapped. Normative atlases based on young normals can store a rich variety of structural and functional data (Mazziotta et al., 1995, 2001), for multi-modality correlations. These atlases have recently been expanded to incorporate data from elderly and developing populations (Paus et al., 1999; Thompson et al., 2000, 2001), as well as data from the whole gamut of imaging devices (Toga and Mazziotta, 1996; Roland and Zilles, 1996).

Brain data is so complex and variable that it is advantageous to develop brain atlases, templates, and statistical models for large-scale investigations. Probabilistic atlases, for example, warehouse population-based data in a common 3D reference frame. They capture anatomic variability and individual differences using a variety of mathematical approaches. The interest in cortical anatomy, in particular, has motivated specialized approaches to analyze its structure. The resulting maps reveal how diseases progress, how they vary in different clinical populations, and how genes affect complex patterns of brain structure. This growing armory of tools shows enormous promise in shedding light on the genetic transmission of disease, and the structural and functional organization of the human brain.

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Figure Legends

Fig. 1. *Creating 3D Average Brain Templates for a Population*. Before computing individual anatomical differences, it is useful to create an average model of anatomy for a specific population. If MRI scans are mutually aligned and their intensities are averaged together pixel-by-pixel [(a); Evans et al., 1994], cortical features are washed away. To retain these features in the group average [(b),(c)], a procedure called cortical pattern matching can be

used (see Thompson et al., 2000 for details). From each individual's MRI scan (d) a cortical model [(e),(f)] consisting of discrete triangular elements (g) is created and flattened (*panel 1*), along with digital models of cortical sulci traced on the brain surface. A warping field drives the flat map (1), and a color code indexing corresponding 3D cortical positions (3),(4), to match an average set of flat 2D sulcal curves (2). If these color images are averaged across subjects and decoded before cortical pattern matching (3), a smooth average cortex (5) is produced. If they are warped first (5), averaged, and decoded, a crisp average cortex appears in which anatomical features are reinforced and appear in their mean stereotaxic locations (6). Such cortical averages provide a standard template relative to which individual differences may be measured (Fig. 2). Using warping (4), cortical data can be transferred, from individuals whose anatomy is different, onto a common anatomic template for comparison and integration.

Fig. 2. *Measuring Individual Brain Differences and Population Variability*. When a individual brain (*brown mesh*, (a)) is globally aligned and scaled to match a group average cortical model (*white surface*), a 3D deformation is computed to match its gyral anatomy with the group average (*pink colors: large deformations*, (b)). The 3D root mean square magnitude of these deformation vectors (*variability map*, (c)) shows that gyral pattern variability is greatest in perisylvian language areas (*red colors*). 3D confidence regions for gyral variations can be also stored locally to detect cortical abnormalities ((d), Thompson et al., 1997). Ellipsoids, (d), are elongated along directions in which normal variation is greatest; pink colors denote greatest anatomic variation. Deformations that match the gyral anatomy of one hemisphere with a reflected version of the opposite hemisphere can be averaged across subjects to detect anatomic asymmetries. These are greatest in perisylvian cortices (*red colors*, (e),(f); Thompson et al., 2001; Geschwind and Levitsky, 1968, first observed this feature in a volumetric study). Anatomic asymmetry is under greater genetic control in right-handers, suggesting a loss of a genetically programmed 'right-shift' phenotype in left-handers (Geschwind et al., 2002). All these maps provide detailed structural phenotypes that can be mined for genetic influences (Fig. 4). The maps shown here are based on a group of 20 healthy elderly subjects, but can be recomputed for any population.

Fig. 3. *Mapping Gray Matter Deficits in a Population*. Measures of gray matter (a) can be computed from MRI scans and compared across individuals and groups. Data from corresponding cortical regions are compared using cortical pattern matching (Fig. 1). Patients with mild to moderate Alzheimer's disease show a severe loss of gray matter [(b),(c)] relative to matched healthy controls, especially in temporal cortices (where deficits approach 30% locally – *red colors*). Patients with childhood onset schizophrenia show a progressive loss of gray matter, especially in temporal and superior frontal cortices [(d),(e)]. These structural measures are tightly correlated with worsening symptoms (Thompson et al., 2001, 2002), offering a promising endophenotype (biological marker) for genetic studies. These biological markers are likely to be more directly influenced by genes coding for structural proteins, regulatory elements, and signaling molecules, than clinical symptoms, such as hallucinations or disordered thinking.

Fig. 4. *Mapping Genetic Influences on Brain Structure: Heritability Maps*. Color-coded maps (*left columns*) show local gray matter correlations

between MZ and DZ twins. Falconer's heritability formula (Falconer, 1989) is applied to data from corresponding cortical regions (within and across twin pairs). The resulting value of h^2, and its significance (*lower right panel*) is plotted at each cortical point. Note the significant genetic control in an anatomical band encompassing parietal, sensorimotor, and frontal cortices. Computationally, cortical points are indexed in spherical coordinates, as an initially spherical surface mesh is deformed into the shape of each subject's cortex (Fig. 1(d)), and the angular parameters are used subsequently for computations. These mapping methods extend to other genetic designs, in which parameters denoting goodness of fit and coefficients describing genetic and environmental effects could each be plotted on the cortex to reveal the spatial patterns of genetic influences.

Fig. 5. *Risk Genes and Brain Structure*. Typical MRI scans are shown from healthy elderly subjects with zero, one, and two ε4 alleles of ApoE gene, which confers increased risk for late-onset Alzheimer's disease (data courtesy of Gary Small, M.D., UCLA Center on Aging). The ε3 allele is more prevalent, and considered normal. Patients at genetic risk may display metabolic and structural deficits before overt symptoms appear, suggesting that genetic and imaging information may identify candidates for early treatment in dementia (Small et al., 2000). Note the hippocampal atrophy (*H*) and ventricular enlargement (*V*) in those at risk.

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