Genetics of Brain Structure and Intelligence

Arthur W. Toga and Paul M. Thompson

Laboratory of Neuro Imaging, Department of Neurology, School of Medicine, University of California, Los Angeles, California 90095; email: toga@loni.ucla.edu, thompson@loni.ucla.edu

Annu. Rev. Neurosci.
2005. 28:1–23

doi: 10.1146/
annurev.neuro.28.061604.135655

First published online as a
Review in Advance on
January 14, 2005

0147-006X/05/0721-
0001$20.00

Key Words

heritability, IQ, brain mapping

Abstract

Genetic influences on brain morphology and IQ are well studied. A variety of sophisticated brain-mapping approaches relating genetic influences on brain structure and intelligence establishes a regional distribution for this relationship that is consistent with behavioral studies. We highlight those studies that illustrate the complex cortical patterns associated with measures of cognitive ability. A measure of cognitive ability, known as *g*, has been shown highly heritable across many studies. We argue that these genetic links are partly mediated by brain structure that is likewise under strong genetic control. Other factors, such as the environment, obviously play a role, but the predominant determinant appears to genetic.

Contents

INTRODUCTION

The relationship between genetics, brain structure, and intelligence is an age-old polemic evident in such diverse disciplines as phrenology, sociology, education, neuroscience, and politics. Measures of brain anatomy, inferred from cranial morphology (circa the 1800s) or made directly with imaging using magnetic resonance, have been correlated with a variety of cognitive assessments (see, e.g., Andreasen et al. 1993, McDaniel & Nguyen 2002). Numerous reviews of the literature (Herrnstein & Murray 1994, Jensen 1998)—in addition to personal experience—lead one to conclude, perhaps heretically, that we are not all created equal. But the question still deserves attention: What are the relative influences of nature (genetics) and nurture (environment) on the brain, and how do these affect intelligence?

Structural imaging of total brain gray and white matter volumes is perhaps the most obvious approach to correlate brain measures with general intelligence. Brain structure measured from MRI correlates with intelligence test scores as total brain volume (Gignac et al. 2003), as do the volumes of individual lobes and aggregate gray and white matter volumes (Posthuma et al. 2002). The quest for better specificity regarding regional correlations of brain structure with intelligence has required more sophisticated analytic techniques to achieve sufficient sensitivity. Voxel-based morphometry, where voxels belonging to an area in the brain are counted and analyzed (Ashburner & Friston 2000, Haier et al. 2004), and surface-based approaches, where three dimensional (3D) models of brain structures are compared across subjects (Thompson et al. 2001a), have each demonstrated regional differences in relationships to IQ.

That there is a clear relationship between intelligence and regional brain volumes does not shed light on why there are differences across individuals. Heritability of gray matter density (Thompson et al. 2001a) and familial contributions to brain morphology in general have been demonstrated repeatedly (Baaré et al. 2001a, Pfefferbaum et al. 2001). Studies of healthy twins (Posthuma et al. 2002) and cohorts of siblings discordant and concordant for a specific disease (Cannon et al. 2002, Narr et al. 2002) all provide evidence regarding the heritability of brain morphology. Finally, empirically we (Devlin et al. 1997) showed that monozygotic twins reared apart are more alike—for many cognitive measures including IQ—compared with fraternal twins raised together. This underscores the relevance of genetic factors in shaping intelligence and brain structure.

Interactions with the environment also contribute to differences in brain morphology. Several animal studies show that environmental stimulation can alter synaptic

densities in the cortex of rodents reared in impoverished versus enriched environments (Greenough et al. 1970, Diamond 1988). Furthermore, animals maintained in enriched environments were better problem solvers (but not in all tests) than those not maintained in enriched environments (Forgays & Forgays 1952). Thus it is clear that several, interrelated factors influence cognitive function in general, and intelligence specifically.

Here we examine the recent application of sophisticated brain-mapping approaches relating genetic influences on brain structure and intelligence. We highlight those studies that illustrate the complex cortical patterns associated with measures of cognitive ability. Drawing on work with cohorts of subjects at risk for several genetically linked diseases, twins, and observations during brain maturation and degeneration with age, we characterize this interesting and important basis for human diversity.

INTELLIGENCE

Intelligence has several meanings, largely based on the context in which the term is used. Generally referring to competence and accomplishment, in neuroscience intelligence is typically referred to as general cognitive ability and quantified as Spearman's *g*—after its first proponent, Charles Spearman (1927), the statistician who developed factor analysis. Many psychometric and twin studies have used this cognitive measure to quantify intellectual function.

Intelligence testing began in 1897 with the work of the French psychologist Alfred Binet, who, together with Theodore Simon, developed tests to identify children who needed special remedial teaching. By developing norms for mental ability at each age, Binet could quantify whether a child was ahead of or behind his peers, and by how many years. German psychologist Wilhelm Stern noted that being a year ahead at age 5 was more significant than at age ten, so he multiplied the ratio of mental age to chronological age by 100 to obtain an intelligence quotient (or IQ—a term coined by American scientist Lewis Terman), with scores over 100 being above average. IQ tests, among them the Army Alpha and Beta Tests, were subsequently adopted by the U.S. army to help assign jobs to vast numbers of recruits; nearly two million American men had taken these tests by 1919. Lewis Terman at Stanford University subsequently adapted the Binet-Simon tests for the American school curriculum and published the Revised Stanford-Binet Intelligence Tests in 1937, 1960, and 1985. IQ tests began to be widely used in schools after World War I, largely to predict academic potential and to assign children to suitable classes according to intellectual ability. Traditional intelligence tests and scholastic aptitude tests (SAT) remain a key part of college admissions to this day. Among the tests still in use is the Wechsler Adult Intelligence Scale (WAIS). On the basis of work by psychologist David Wechsler in the 1930s, the WAIS (and its counterpart for assessing children—the WISC) provides separate scales for verbal, performance, and total IQ. These scales are often used to assist with psychiatric diagnosis.

Spearman's *g*: quantified general cognitive ability (intelligence); basic general factor of mental ability

In psychometric research, statistical analysis can distill from multiple tests a measure of mental ability that is independent—as far as possible—of the subject matter of the tests. In computing the *g* factor, for example, factor analysis isolates a component of intellectual function that is common to multiple cognitive tests, but not specific to the task being performed. IQ tests come in different forms, but they typically assess visuospatial, deductive, semantic, and symbolic reasoning ability. Specific subtests may evaluate a subject's ability to perform inferences, to detect similarities and differences in geometrical patterns or word patterns, and to process complex information quickly and accurately.

People differ substantially in their performance on these tests, but those who do well on one test tend to do well on others. The high correlations among scores on tests of spatial relations, logic, vocabulary, picture

completion, and even reaction times support the notion that there may be an overarching skill that underlies intellectual ability, rather than many distinct and independent abilities. Scores on a range of tests can be factor analyzed to give *g*, a single summary measure of cognitive ability. *g* is composed of a small number of (non-independent) subfactors representing more specific abilities (Carroll 1993, Deary 2001), but each of these correlates closely with *g*. One of the best tests for measuring "pure *g*" is thought to be Raven's Progressive Matrices, a nonverbal test of inductive reasoning.

The validity of *g* as a single, unitary measure of intelligence has been hotly debated by its advocates and detractors (Jensen 1969, Brand 2001, in favor; see Gould 1996, Kamin 1997 for contrary views). Most psychometric researchers agree that the *g* factor is sensitive to individual differences in abilities to learn, reason, and solve problems. It predicts scholastic achievement, employment, lifetime income, and even health-related parameters such as life expectancy (Gottfredson 1997). The ethics and validity of using IQ tests to predict educational potential, and in college admissions and recruitment decisions, are still somewhat controversial. In the 1960s, many boards of education rejected IQ testing because of concerns about possible cultural biases in test questions, and there was a general backlash against psychometric testing in admissions and hiring decisions, a political trend that has been reversed somewhat today.

From a scientific standpoint, some argue that the basic general factor of mental ability (*g*) can explain performance variations on individual mental tests (Spearman 1927, Jensen 1998). Most mental ability tests correlate with *g*, and the degree to which they do has been termed their *g*-loading [analogous to an octane rating for gasoline (Jensen 1980)]. Performance variations on different tasks may therefore depend on how much each task draws on a general cognitive process underlying mental ability (the unitary intelligence theory). Advocates of unitary intelligence have typically pointed to physiological parameters in the brain that are correlated with *g*, including reaction times, nerve conduction velocity, or cerebral glucose metabolism during problem solving (Haier et al. 1988). Other brain-based correlates of *g* have been observed in recent MRI studies showing that differences in frontal gray matter volumes correlate with *g* ($p < 0.0044$; $p < 0.0176$ after correction for multiple tests; Thompson et al. 2001a; see also Haier et al. 2004).

A more modular view, to some extent implicit in brain-mapping studies, interprets intelligence as reflecting multiple abilities that may have anatomically distinct biological substrates in the brain. Functional MRI, for example, can be used to build a more mechanistic model of intelligence because it can localize brain systems involved during cognitive tasks. The activation of specific neural systems in the frontal and parietal lobes correlates with *g*, which suggests that these regions interact to contribute to *g* (Prabhakaran et al. 1997, 2001; Duncan et al. 2000; Gray et al. 2002).

A contrary view of intelligence holds that important intellectual abilities are poorly assessed or entirely missed by standardized intelligence tests. Sternberg (1999) proposed a triarchic theory of intelligence, in which practical and creative intelligence are regarded on par with analytic skills. For Sternberg, analytic intelligence denotes one of three primary intellectual skills, namely one that is similar to the *g* factor—the ability to recognize and apply logical relations. Equally fundamental, however, are practical intelligence, which denotes pragmatic and social skills, and creative intelligence, or the ability to come up with imaginative solutions to problems rather than applying familiar logical rules or book knowledge. Social or emotion-related abilities have also been argued to be essential ingredients in mental function (Salovey et al. 2002).

A still broader view of intelligence has been popularized by Gardner (2000). Gardner posits at least seven types of intelligence (mathematical, spatial, musical, bodily-kinesthetic, intra-personal, and

interpersonal). The case for multiple intelligences has been supported by studies of brain lesions that cause very specific neurological deficits but leave many cognitive abilities intact (e.g., speech or visuospatial skills). Gardner considers that proponents of the *g* factor confuse intelligence with a highly specific type of scholastic performance.

The most negative view of IQ testing is that inherent biases make cognitive tests a poor measure of individual competence. Detractors of IQ tests say that the ability to answer some questions may depend on a person's upbringing or cultural background, and that the questions assume a familiarity or agreement with certain cultural norms. Situational factors may also impair performance (Steele & Aronson 1995; Gould 1996, p. 166; Baumeister et al. 2002; Schmader & Johns 2004).

Fluid and Crystallized Intelligence

Even among psychometric researchers who agree that there is a general factor in cognitive ability, crystallized and fluid intelligence are often distinguished (Cattell 1971). Crystallized intelligence refers to the large body of factual knowledge that an individual accumulates over his/her lifespan, including, for example, vocabulary. This ability to apply knowledge to solve problems is largely determined by education and experience, and increases with age. Fluid intelligence, however, refers to analytical reasoning ability, as well as memory and information processing speed, and it declines somewhat with age. The fluid component of intelligence is thought to be largely genetically determined, however. In addition, fluid intelligence is strongly associated with working memory (Prabhakaran et al. 2001) and is correlated with activation during cognitively demanding tasks observed with functional MRI (Gray et al. 2003).

BRAIN MAPPING

Because of its promise in localizing brain function, functional brain imaging has been widely applied to map brain activation in a variety of psychiatric and neurological disorders. Brain activation can be examined noninvasively while subjects perform specific tasks or cognitive assessments [see Cabeza & Nyberg 2000, for a review of studies using positron emission tomography (PET) and functional MRI (fMRI)]. However, the cause of individual differences in hemodynamic-based functional measures—their heritability, for example—is largely unknown. Although it is clear that functional imaging provides the link between the anatomic maps and cognitive measures, the present paucity of data using fMRI may be due to the vagaries of neurovascular coupling, the variability of the response or the limitations of instrumentation, and protocols to date. Numerous efforts are underway to collect sufficient baseline data to attempt to improve sensitivity. The International Consortium for Brain Mapping has developed a battery of fMRI tests (Mazziotta et al. 2001) that exhibit stable baseline across subjects. These ultimately can be used to normalize other more cognitively challenging behavioral tasks in much the same way as structural scans are normalized for placement into an atlas. Similarly, the Bioinformatics Research Network has developed a series of tasks (**http://www.nbirn.net**) specifically designed to normalize across populations of schizophrenic patients and their normal matched controls. Thus, it is likely that in the near future we will see many more studies examining genetic influences on brain function using fMRI.

Brain map: a relationship between points in a coordinate space and features or annotations describing brain structure and/or function

Structural brain mapping, in contrast, has already shown specific patterns related to intelligence (see above) and, as with other brain-mapping studies, can provide the anatomic framework to achieve improved sensitivity in functional studies. For this reason, we next review the steps required to create brain maps. These include maps of morphologic features, such as the 3D distribution of gray and white matter in the brain, and statistical maps that compile these maps from whole populations. To examine sources of morphological and

Cortical pattern matching: encoding both gyral patterning and gray matter variation

functional variability across subjects, we also review methods that combine imaging and genetic statistics to compute genetic influences on the brain (Thompson et al. 2001a, 2003). This combination as in correlation creates an important link between genetics, brain measures, and intelligence, shedding light on the systems involved in cognition and which factors affect their function.

Atlases to regionally chart the degree and extent of individual variations in brain structure require detailed descriptions of anatomy to achieve a morphometric comparison rather than the volumetric comparisons described above. To create atlases that contain detailed representations of anatomy, we have developed model-driven algorithms that use geometrical surfaces to represent structures in the brain, such as the cortex, hippocampus, ventricles, and corpus callosum (Thompson & Toga 1996, 2003). Anatomic models provide an explicit geometry for individual structures in each scan, such as landmark points, curves, or surfaces. These modeling approaches can also answer the following questions: How does anatomy differ across subjects and between groups? What is the degree of individual variability in anatomy, and how do these differences link with cognitive measures? What are the sources of these variations, and to what degree are they influenced by genes and environment? Brain mapping can provide answers to these and other questions; the answers are typically displayed in the form of a brain map.

Maps of Brain Structure

First we consider the analysis steps required to compute the patterns of genetic influences on brain structure, using a database of brain MRIs from twins (Thompson et al. 2001). The process can be conceived as shown in **Figure 1**, where a sequence of image analysis steps are applied to brain MRI scans from multiple subjects. The goal of such an analysis is typically to create color-coded maps of brain regions with structural differences between groups, or in this case to reveal where individual differences in brain structure depend on genetic factors.

Registration and Mapping

D MRI scans are first rotated and scaled to match a standardized brain template in stereotaxic space. This template may be either an average intensity brain dataset constructed from a population of young normal subjects (Mazziotta et al. 2001) or one specially constructed to reflect the average anatomy of a subgroup of defined homogeneous subjects (e.g., Mega et al. 2000, Thompson et al. 2000, Janke et al. 2001; see these papers for a discussion of disease-specific templates). Once aligned, a measure of the brain scaling imposed is retained as a covariate for statistical analysis. A tissue classification algorithm then segments the image data into regions representing gray matter, white matter, cerebrospinal fluid (CSF), and nonbrain tissues. Because the digital models reside in the same stereotaxic space as the atlas data, surface and volume models stored as lists of vector coordinates are amenable to digital transformation, as well as geometric and statistical measurement (Mega et al. 2000, Narr et al. 2003, Thompson et al. 2004, Zhou et al. 1999). The underlying 3D coordinate system is central to all atlas systems because it supports the linkage of structure models and associated image data with spatially indexed neuroanatomic labels.

Cortical Pattern Matching

MRI scans have sufficient resolution and tissue contrast, in principle, to track cortical gray and white matter differences in individual subjects. This affords the opportunity to measure regional degrees of heritability and establish structural and even gyral/sulcal relationships with specific cognitive measures. Even so, extreme variability in gyral patterns confounds efforts (*a*) to compare between groups and (*b*) to determine the average profile of patterns within a group. Cortical pattern matching

methods (detailed further in **Figure 2**) address these challenges. They encode both gyral patterning and gray matter variation. This can substantially improve the statistical power to localize effects of genes and environmental factors on the brain. These cortical analyses can also be used to measure cortical asymmetries (Narr et al. 2001, Sowell et al. 2001).

Briefly, a 3D geometric model of the cortical surface is extracted from the MRI scan and flattened to a two-dimensional planar format (to avoid making cuts, a spherical topology can be retained; Fischl et al. 2001; Thompson et al. 1997, 2002). A complex deformation, or warping transform, is then applied that aligns the sulcal anatomy of each subject with an average sulcal pattern derived for the group. To improve feature alignment across subjects, all sulci that occur consistently can be digitized and used to constrain this transformation. As far as possible, this procedure adjusts for differences in cortical patterning and

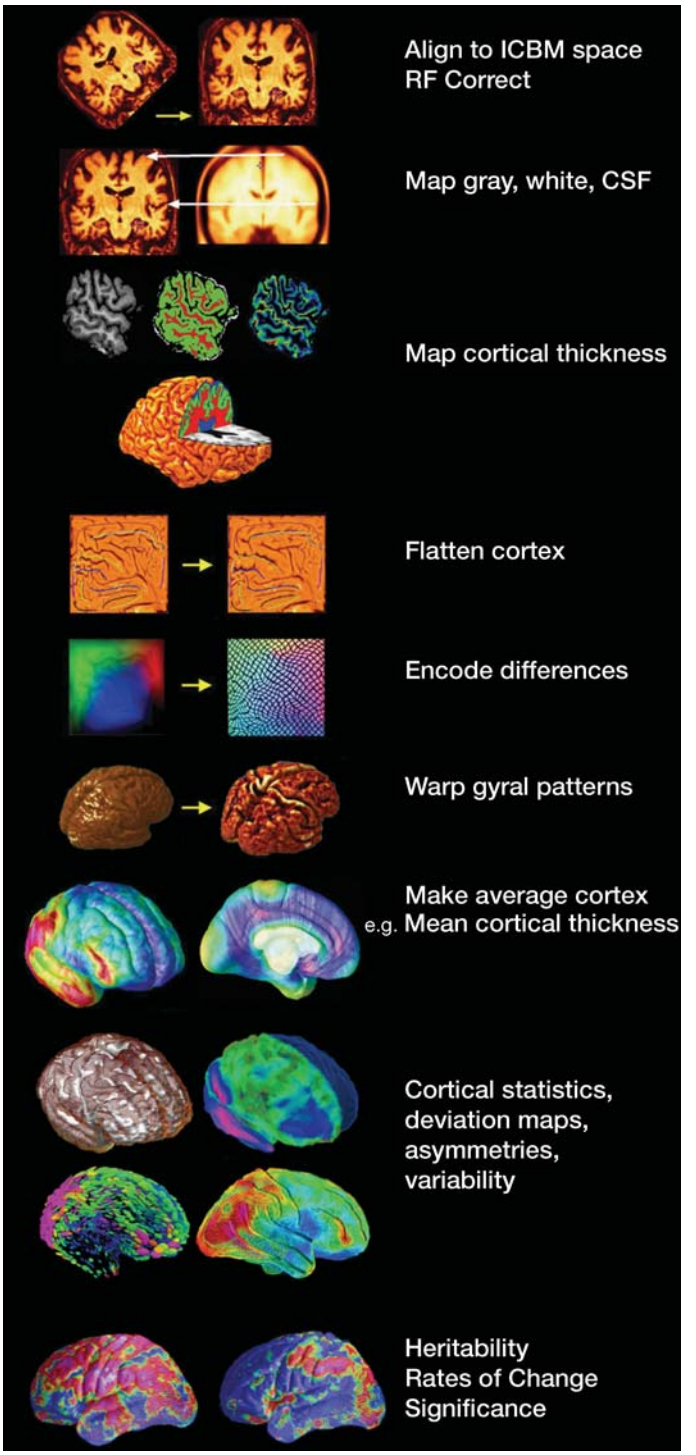

Figure 1

Analyzing cortical data. The schematic shows a sequence of image-processing steps that can be used to map how development and disease, or genetic factors, affect the cortex. Regions can also be identified where brain variation is linked with intelligence, specific cognitive measures, or clinical measures. The steps include aligning MRI data to a standard space, tissue classification, and cortical pattern matching, as well as averaging and comparing local measures of cortical gray matter volumes across subjects. (These procedures are detailed in the main text). To help compare cortical features of subjects whose anatomy differs, individual gyral patterns are flattened and aligned with a group average gyral pattern. Group variability and cortical asymmetry can also be computed. Correlations can be mapped between disease-related gray matter deficits and genetic risk factors. Maps may also be generated visualizing linkages between genes and morphology, cognitive scores, and other effects. The only steps here that are not currently automated are the tracing of sulci on the cortex. Some manual editing may also be required to assist algorithms that delete dura and scalp from images, especially if there is very little CSF in the subarachnoid space.

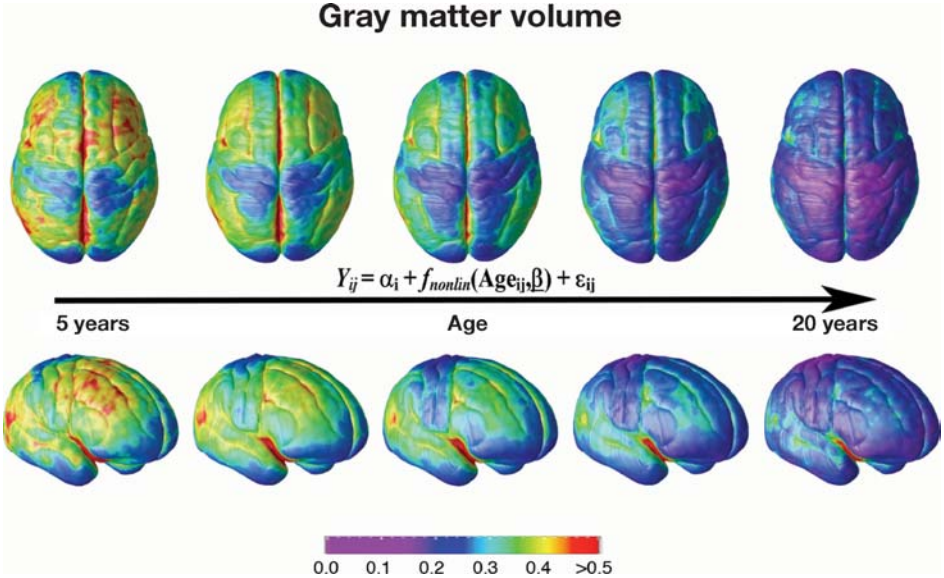

Figure 2

Right lateral and top views of the dynamic sequence of gray matter maturation over the cortical surface. The side bar shows a color representation in units of gray matter volume. Constructed from MRI scans of healthy children, these maps illustrate 15 years of brain development (ages 5–20; data from Gogtay et al. 2004). Red indicates more gray matter, blue less gray matter. Gray matter wanes in a back-to-front wave as the brain matures and neural connections are pruned. Areas performing more basic functions mature earlier; areas for higher-order functions (emotion, self-control) mature later. The prefrontal cortex, which handles reasoning and other executive functions, emerged late in evolution and is among the last to mature. Intriguingly, this sequence of brain changes is reversed in Alzheimer's disease (see **Figure 4**).

shape across subjects. Cortical measures can then be compared across subjects and groups.

Sulcal landmarks are used as anchors because homologous cortical regions are better aligned after matching sulci than by just averaging data at each point in stereotaxic space (see, e.g., fMRI studies by Rex et al. 2001; Zeineh et al. 2001, 2003; Rasser et al. 2004). 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 is made in each subject and averaged across equivalent cortical locations. To quantify local gray matter, gray matter density can be measured to compare the spatial distribution of gray matter across subjects. This gray matter density measures the proportion of gray matter in a small region of fixed radius (15 mm) around each cortical point (Wright et al. 1995; Bullmore et al. 1999; Sowell et al. 1999, 2003; Ashburner & Friston 2000; Mummery et al. 2000; Rombouts et al. 2000; Baron et al. 2001; Good et al. 2001; Thompson et al. 2001a,b). Given the large anatomic variability in some cortical regions, high-dimensional elastic matching of cortical patterns (Thompson et al. 2000, 2001b) is used to associate measures of gray matter density from homologous cortical regions first across time and then also across subjects. One advantage of cortical matching is that it localizes differences relative to gyral landmarks; it also averages data from corresponding gyri, which would be impossible if data were only linearly mapped into stereotaxic space. The effects of age, gender, zygosity, *g*, and other measures on gray matter can be assessed at each cortical point (see **Figure 3** for an example in twins).

Statistical Maps

An algorithm then fits a statistical model, such as the general linear model (GLM) (Friston et al. 1995), to the data at each cortical location. This model results in a variety of parameters that characterize how gray matter variation is linked with other variables. The significance of these links can be plotted as a significance map. A color code can highlight brain regions where linkages are found, allowing us to visualize the strength of these linkages. In addition, estimated parameters can be plotted, such as (*a*) the local rates of gray matter loss with aging (see **Figure 2** for example) at each cortical location (e.g., as a percentage change per year), (*b*) regression parameters that identify heritability, and even (*c*) nonlinearities in the rates of brain change over time (e.g., quadratic regression coefficients; Sowell et al. 2003). In principle, any statistical model can be fitted, including genetic models that estimate genetic or allelic influences on brain structure (Thompson et al. 2003). Finally, permutation testing is typically used to ascribe an overall significance value for the observed map. This adjusts for the fact that multiple statistical tests are performed when a whole map of statistics is visualized. Subjects are randomly assigned to groups, often many millions of times on a supercomputer. A null distribution is built to estimate the probability that the observed effects could have occurred by chance, and the result is reported as a significance value for the overall map.

GENETIC INFLUENCES ON BRAIN STRUCTURE

Statistical maps of cortical anatomy can also be used to reveal genetic influences on brain morphology. **Figure 3** shows intersubject variations in cortical gray matter distribution and their heritability. In a study of genetic influences on brain structure (Thompson et al. 2001a), we began by computing

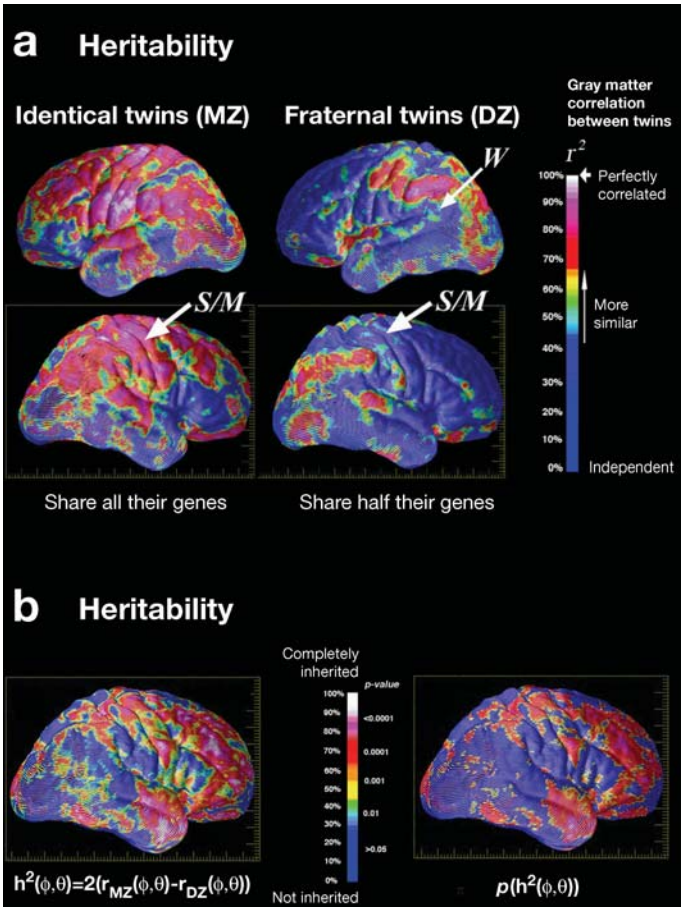

Figure 3

Heritability of gray matter. Intraclass correlation in gray matter density $g_{i,r}(\mathbf{x})$ for groups of identical and fraternal twins, after cortical pattern matching [giving maps $r_{MZ}(\phi, \theta)$ and $r_{DZ}(\phi, \theta)$, in **Figure 3*a***]. In behavioral genetics, a feature is heritable if r_{MZ} significantly exceeds r_{DZ}. An estimate of its heritability h^2 can be defined as $2(r_{MZ}\text{-}r_{DZ})$, with standard error $SE^2(h^2) = 4[((1 - r_{MZ}{}^2)^2/n_{MZ}) + ((1 - r_{DZ}{}^2)^2/n_{DZ})]$. **Figure 3*b*** shows a heritability map computed from the equation

$$h^2(\phi, \theta) = 2(r_{MZ}(\phi, \theta) - r_{DZ}(\phi, \theta)).$$

Regions in which significant genetic influences on brain structure are detected are shown in the significance map [**Figure 3*b*** (right)] $p[h^2(\phi, \theta)]$. Genetic influences on brain structure are pronounced in some frontal and temporal lobe regions, including the dorsolateral prefrontal cortex and temporal poles [denoted by *DLPFC* and *T* in **Figure 3*b*** (left)]. These effects were confirmed by assessing the significance of the effect size of h^2 by permutation (this involved repeated generation of null realizations of an h^2-distributed random field; for details of these permutation methods, see Thompson et al. 2004).

the intraclass correlations in gray matter (**Figure 3*a*,*b***) in groups of monozygotic (MZ) and dizygotic (DZ) twins. Forty 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 (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 $r \sim 0.9$ and higher, $p < 0.0001$ corrected; **Figure 3*a***) in a broad anatomical band encompassing frontal, sensorimotor, and linguistic cortices, including Broca's speech and Wernicke's language comprehension areas. MZ twins are genetically identical, so any regional differences must be attributed to environmental effects or gene-environment interactions. Meanwhile, sensorimotor and parietal occipital, but not frontal, territories were significantly more similar in DZ twins than random pairs. Affinity was greatest in the MZ pairs, suggesting a genetic continuum in the determination of brain structure. In behavioral genetics, a feature is heritable if the identical twin correlation exceeds the fraternal twin correlation. 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). Middle frontal regions, near 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, $p < 0.0001$; **Figure 3*b***). 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 ($h^2 = 0.57$).

Related MRI Studies

The high heritability of gray matter volumes, visualized in **Figure 3**, corroborates earlier studies that revealed strong genetic influences on brain structure. Studies of healthy twins suggest that overall brain volume is highly genetically influenced (Bartley et al. 1997, Tramo et al. 1998). Volumes of some brain structures are also under strong genetic control, including the corpus callosum (Oppenheim et al. 1989, Pfefferbaum et al. 2000) and ventricles, whereas gyral patterns are much less heritable (Bartley et al. 1997, Biondi et al. 1998). Bartley et al. (1997) reported a 94% heritability for brain volume (identical twin correlation = 0.95, $p <$ 0.00,001; fraternal twin correlation = 0.35, $p = 0.09$), on the basis of 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, consistent with its lifelong plasticity and fundamental role in learning and memory. 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 (2001b) 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. (2001b) 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, whereas 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, Gogtay et al. 2004). 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. 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. Interregional relationships were summarized by principal component analysis of the resulting genetic correlation matrix. This analysis 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 and which may cut across conventional anatomic boundaries.

Candidate Genes and Brain Function

Heritable aspects of brain structure are important to identify because they provide endophenotypes to guide the search for specific genes whose variations are linked with brain structure and function. For example, recent functional imaging work has shown that a polymorphism in the human brain-derived neurotrophic factor (BDNF) gene is associated with poor memory performance and with working memory activation mapped with fMRI (Egan et al. 2001, 2003). Diamond et al. (2004) have recently shown striking specificity of COMT (catechol-*o*-methyltransferase) polymorphisms to some but not other prefrontal cortex–dependent tasks in children (Diamond et al. 2004).

Heritability of cognitive function is certainly complex and difficult to dissociate from environmental factors, among other influences. A recent review of candidate genes contributing to human cognition lists more than 70 suspects (Morley & Montgomery 2001). However, examining this list and relating them to spatial patterns of gene expression or segmenting those that are related to neuroanatomical regions involved in cognition results in a far more tractable problem. For example, the prefrontal cortex, an area highly involved in cognition (see Winterer & Goldman 2003, among others), links only 3 of the 70 identified by Morley & Montgomery (2001).

Specific Genes and Brain Structure

With current databases of structural brain images, there is now significant power to assess the effects of specific candidate genes on brain structure. The easiest context for evaluating these genetic influences is to examine alleles overtransmitted to individuals with specific diseases such as dementia or schizophrenia. Using statistical maps to visualize brain systems that are at genetic risk, brain images can also provide a quantitative index of disease liability in individuals at increased genetic risk for disease (Cannon et al. 2002, Narr et al. 2002, Thompson et al. 2003).

For example, the apolipoprotein E4 (ApoE4) allele is found in 38% of all Alzheimer's disease patients, but in only 15% of

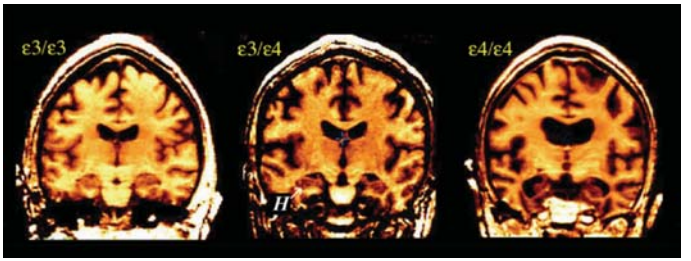

Figure 4

Patterns of brain structure associated with genetic risk for Alzheimer's disease. Brain structure is often significantly different from normal in subjects who are at genetic risk for a brain disorder but who are cognitively normal. Typical MRI scans are shown from healthy elderly subjects with zero, one, and two $\varepsilon 4$ alleles of the ApoE gene, each of which confers increased risk for late-onset Alzheimer's disease (data courtesy of G. Small, UCLA Center on Aging). Note the hippocampal atrophy and ventricular enlargement in those at risk. The $\varepsilon 3$ allele is most prevalent and is considered normal. Subjects at genetic risk may display metabolic and structural deficits before overt cognitive symptoms appear, which suggests that genetic and imaging information may identify candidates for early treatment in dementia (Small et al. 2000).

controls (Roses 1996). As shown in **Figure 4**, medial temporal brain structure shows profound atrophic changes in healthy ApoE4-positive individuals, and the ventricles expand, even before overt cognitive deficits can be detected. However, some brain regions are comparatively protected (e.g., frontal cortices in ApoE4 subjects with Alzheimer's disease; Geroldi et al. 1999, Hashimoto et al. 2001). Because neuroprotective drugs are effective in early dementia (Lehtovirta et al. 1995, 2000; Small et al. 2000) there is interest in associating patterns of brain change with specific genetic markers, especially if these patterns predict imminent disease onset among individuals at genetic risk.

Gray matter deficits are also found in healthy first-degree relatives of schizophrenia patients. Because these relatives are at increased genetic risk for developing the disorder themselves, there is great interest in understanding what factors promote or resist disease onset or progression (Weinberger et al. 1981, Suddath et al. 1990, Cannon et al. 2002, Thompson et al. 2003). **Figure 5** shows brain regions with significant reductions in gray matter density in healthy relatives of patients, relative to a population of normal controls who are not related to a schizophrenia patient (Cannon et al. 2002). This pattern of brain structure is intriguing because the observed deficit is associated with the degree of genetic risk (i.e., greater in MZ than DZ twins of a patient). There are also genetically mediated structural deficits in the hippocampus, and in the corpus callosum, in schizophrenic patients and in their healthy at-risk relatives (Narr et al. 2003). But, unlike the ApoE4 example, the specific genes involved in schizophrenia are currently unknown. By correlating alleles overtransmitted to patients with these structural variations, specific polymorphic genetic loci that mediate these deficits may be identified (Cannon et al. 2003). In this respect, brain mapping can assist in the search for genes involved in a disorder by generalizing genetic methods such as Haseman-Elston mapping to brain images.

Conversely, brain mapping may also help to establish the scope of brain abnormalities in diseases in which the genetic causes are already well understood. Williams syndrome, for example, results from a known genetic deletion in the 7q11.23 chromosomal region (Korenberg et al. 2000). The syndrome is associated with disrupted cortical development and mild-to-moderate mental retardation (Bellugi et al. 2000). By statistically averaging cortical thickness maps from 166 brain hemispheres and comparing Williams syndrome patients with healthy controls, we recently identified a sharply delimited region of language cortex with increased cortical thickness, revealing the cortical territory affected by the genetic deletion (Thompson et al. 2004). This selective augmentation of brain structure may underlie the relative strengths patients exhibit in language function. These maps also refine our knowledge of how the genetic deletion impacts the brain, providing new leads for molecular work on Williams syndrome and a link between genetic and behavioral findings in the disorder.

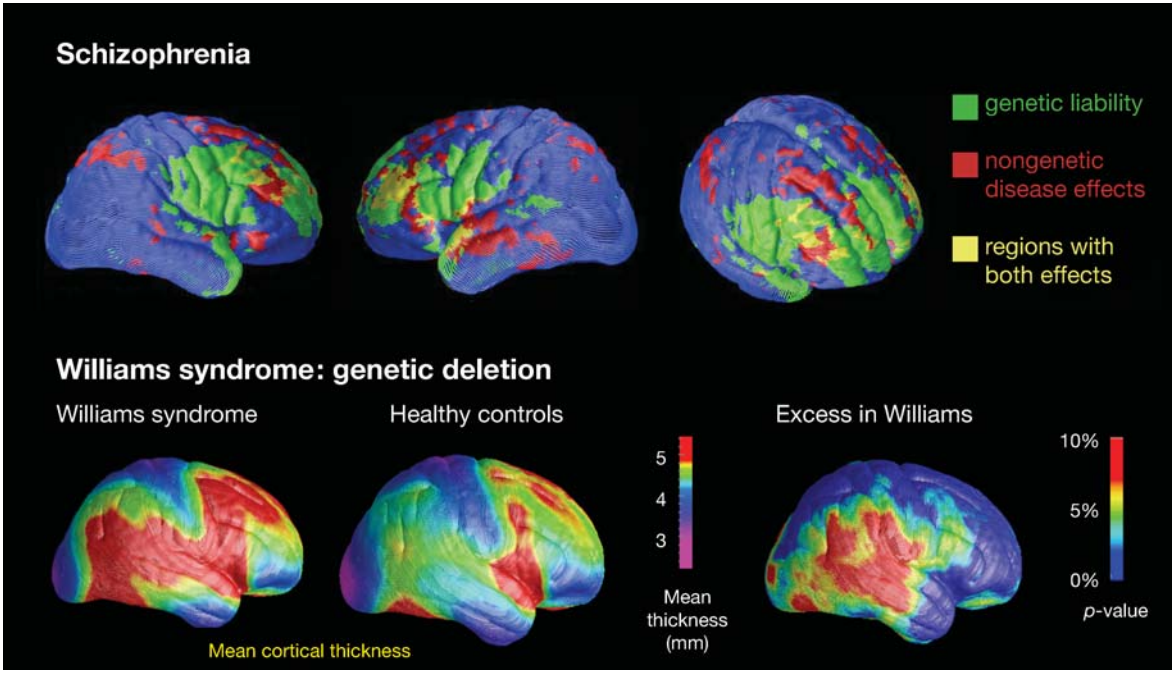

Figure 5

Patterns of brain structure associated with genetic risk for schizophrenia and with genetic deletion in Williams syndrome. Top row, last panel: Statistical combinations of brain scans from at-risk relatives of schizophrenia patients show that relatives have abnormally reduced gray matter density in the frontal cortex (*green*; data adapted from Cannon et al. 2002). In a twin design, statistical comparison of schizophrenia patients with their healthy identical twins reveals regions (*red*) in parietal and frontal cortices that have reduced gray matter density in disease. The source of these differences must be environmental in origin because the differences are based on averages of maps that subtract data from genetically identical twins. Bottom Row: Finally, group average maps of cortical thickness are shown for 43 subjects with Williams syndrome (*a*), and 40 matched healthy controls (*b*), which revealed that perisylvian language cortex is 10% thicker in the patients. Williams syndrome results from a known genetic deletion on chromosome 23q11. Composite brain maps such as these can help identify circumscribed cortical regions whose formation or maturation is influenced by the genetic lesion, perhaps during gyrogenesis.

HERITABILITY OF INTELLIGENCE

Before reviewing some of the brain substrates that correlate with intelligence, it is worth examining the evidence that there are genetic influences on intelligence; we argue that these genetic links are partly mediated by brain structure that is under strong genetic control. We review this literature only briefly because it has been examined thoroughly elsewhere (Herrnstein & Murray 1994, Gould 1996, Jensen 1998, Pinker 2002). In 1969, the debate regarding genetic influences on IQ became increasingly vitriolic after an article argued that there are racial differences in intelligence that may be genetic in origin (Jensen 1969). Most behavioral geneticists now agree that heredity plays a role in individual differences in intelligence, but some have argued that group differences in IQ include environmental influences or cultural biases in the tests (Lewontin 1975; see Jensen & Miele 2002, Gray & Thompson 2004, for reviews of arguments on this topic).

Correlations between related individuals show that both nature and nurture influence intelligence. Adopted MZ twins—raised apart—still correlate 0.72 for intelligence, i.e., one twin's intelligence strongly predicts the other's, despite their different rearing environments. This suggests an undeniable genetic component to intelligence. A popular line of attack against this argument states that several nongenetic factors could confound this association by making MZ twins more similar. For example, identical twins might be adopted into similar homes (selective placement). Sharing the same fetal environment might also make identical twins more alike cognitively or perhaps even less alike (via twin-twin competition for nutrition, transfusion effects, and so on). Also, fraternal twins may inadequately control for the effects of shared family environments (see Vogel & Motulsky 1997, Kamin & Goldberger 2002).

Nonetheless, adoption and family studies using sophisticated genetic model-fitting have shown *g* to be highly heritable across many studies, even more so than specific cognitive abilities [$h^2 = 0.62$, McClearn et al. (1997), Feldman & Otto (1997); $h^2 = 0.48$, Devlin et al. (1997); $h^2 = 0.6$–0.8, Finkel et al. (1998), Swan et al. (1990), Loehlin (1989), Chipuer et al. (1990), Plomin & Petrill (1997)]. The heritability of intelligence also increases with age: As we grow older, phenotype reflects genotype more closely. A strictly environmental theory would predict the opposite. Some IQ-related genes may not be switched on until adolescence or adulthood, but a more plausible explanation may be the existence of a gene by environment interaction (Boomsma et al. 1999, Rowe & Jacobson 1999). As individuals select or create environments that foster their genetic propensities throughout life, the genetic differences in cognition are greatly amplified (Plomin 1999). Jensen (1998) hypothesized that the more a mental test score correlates with general intelligence, or *g*, the higher its heritability is. If true, this hypothesis supports a biological rather than purely statistical basis for *g*.

Environmental Influences on Intelligence

Many environmental factors are known to influence intelligence favorably or adversely (Ceci & Williams 1997, Neisser 1998). By comparing identical twins reared apart and reared together, effects of different rearing environments can be established. Bouchard et al. (1990) found that growing up in the same family increased the IQ similarities for all types of relatives: Individual IQs correlated more highly with their MZ twins, siblings, and parents (0.86, 0.47, 0.42) if they grew up together than if they did not (0.72, 0.24, 0.22). Adopted children's IQs also correlate with their siblings (0.34) and adoptive parents (0.19), so 20%–35% of the observed population differences in IQ are thought to be due to differences in family environments. Intriguingly, these shared family environmental influences on IQ dissipate once young children leave home: As adults, adoptive relatives only correlated –0.01 for IQ (McGue et al. 1993), showing no lasting influence of shared upbringing on IQ. Those environmental influences on IQ that do last are thought to be experiences that an individual does not share with others, interpreted broadly to include the chemical environment in the womb and the multitude of random events in human experience that are hard to quantify or control.

Heritability does not imply inevitability because the environment can determine the relative impact of genetic variation (gene x environment interaction). For example, in a recent study of 320 pairs of twins who were born in the 1960s and given IQ tests at age 7, Turkheimer et al. (2003) found that environmental factors made a much bigger difference in the determination of childhood IQ in impoverished families relative to those with higher socioeconomic status. The heritability of IQ at the low end of the wealth spectrum was just 0.10 on a scale of zero to one,

but it was 0.72 for families of high socioeconomic status. The importance of environmental influences on IQ was four times stronger in the poorest families than in the higher status families, which suggests that nature matters more on the high end of socioeconomic status and nurture matters more on the low end. The genetic contribution to intelligence therefore differs in different environments—a caveat against general inferences based on heritability data. The same could be said of certain physical attributes such as height, which is heritable when nutrition is not limiting.

Population-level increases in intelligence test scores have also been observed in recent decades. Dutch 18-year-old men tested in 1982 scored 20 IQ points (standard deviation = 15) higher than did 18-year-old men tested in 1952 (Dickens & Flynn 2001). This widely replicated population-level increase in intelligence is known as the Flynn Effect. Because genetic variation remained fairly stable over such a short time frame, these relatively rapid increases are attributed to nongenetic factors such as improved schooling and technology, better access to education, and improved nutrition. There has also been a reduction in some environmental toxins (such as lead) and hazards that are detrimental to IQ. Dickens & Flynn (2001) also proposed powerful gene-environment interactions to reconcile the paradox that IQ is highly heritable even though average scores have increased significantly in recent decades.

Positive environmental influences on intelligence are hard to identify, in part, because of the inevitable confounding of variables in large-scale epidemiological studies of cognition. For example, duration of breastfeeding during infancy has been associated with higher IQ in a group of more than 2000 children assessed at age 6 (Oddy et al. 2003). However, this association has been contested because it is confounded by maternal age, intelligence, and education, as well as smoking during pregnancy. After adjusting for these confounding factors, breastfeeding during infancy is still associated with enhanced childhood cognitive development (by 2–5 IQ points for full-term infants and 8 points for those with low birth weight; Drane & Logemann 2000).

Gene x Environment Correlations

The significant influence of heredity on IQ has been misinterpreted to imply that there is little point trying to educate or be educated, or that IQ is somehow impervious to change. This is a fallacy because many environmental factors, including family rearing environments, socioeconomic status, diet, and schooling, influence IQ. As noted elsewhere (Plomin & Kosslyn 2001), gray matter volume may be correlated with intelligence partly because more intelligent individuals seek out mentally challenging activities that increase the volume of their gray matter. Such strong gene x environment correlations may draw individuals with higher genetic potential into learning environments more conducive to intellectual advancement. Gifted individuals might either create or evoke situations that further promote their intellectual ability (termed active and reactive genotype-environment (GE) correlation, respectively; Plomin et al. 1977). These correlations make it impossible to conceptually differentiate effects of nature and nurture (Ridley 2003).

If environments are not randomly assigned to each individual but are, in part, individually selected on the basis of genetically influenced preferences (GE autocorrelation), it becomes impossible to discern which genetic effects act directly on intellectual function and which result from the action of environmental variation causally linked with genetic differences (Block 1995). One form of GE correlation can be estimated explicitly in adoption designs: the environment that parents provide their offspring (Neale 1997). Active and reactive correlations are more difficult to estimate, leading to suggestions that the notion of heritability conflicts with common sense (Sesardic 2002).

ApoE4: apolipoprotein E4

BDNF: brain-derived neurotrophic factor

COMT: catechol-*o*-methyltransferase

CSF: cerebrospinal fluid

DZ: dizygotic

fMRI: functional magnetic resonance imaging

***g*:** a measure of cognitive ability

GLM: general linear model

MZ: monozygotic

PET: positron emission tomography

SAT: scholastic aptitude test

WAIS: Wechsler Adult Intelligence Scale

WISC: Wechsler Intelligence Scale for Children

BRAIN STRUCTURE AND INTELLIGENCE

If specific features of brain structure are under strong genetic control, investigators should determine whether any of these features are correlated with intelligence. If so, this correlation may not only reveal why IQ has repeatedly been found to be highly heritable, but also yield insight into possible neural mechanisms. To help understand this approach, we first review evidence that brain structure and intelligence are correlated before discussing evidence for the existence of genetic correlations between brain structure and intelligence (which means that the same sets of genes are implicated in determining both; Posthuma et al. 2002).

A recent meta-analysis (including a total of 1375 subjects) found that total brain volume and IQ were correlated significantly in all but 1 of 28 MRI studies, with an estimated correlation of 0.33 (McDaniel & Nguyen 2002). This finding implies that ~10% of the population variability in IQ can be predicted from brain volume measures alone. Some studies have quoted slightly higher figures for these correlations (e.g., 0.41; Andreasen et al. 1993), and the exact value obtained will depend on the measurement error of the technique because measurement errors will tend to diminish any observed correlation (relative to the true correlation).

Linkages between brain structure and IQ also can be further localized by parcellating the brain into subregions or by creating maps of the correlations between gray matter and IQ. Recently, we found that intellectual function (*g*) was significantly linked with differences in frontal gray matter volumes, which were determined primarily by genetic factors (Thompson et al. 2001a). Posthuma et al. (2002) extended these findings using a cross-twin cross-trait (bivariate genetic) analysis to compute genetic correlations. They demonstrated that the linkage between gray matter volumes and *g* is mediated by a common set of genes. Haier et al. (2004) used voxel-based morphometry in two independent samples to identify substantial gray matter correlates of IQ. More gray matter was associated with higher IQ in all lobes, underscoring a distributed model of the neural basis of intelligence. Intriguingly, the strongest correlations are typically found between IQ and frontal gray matter volumes (Thompson et al. 2001a, Haier et al. 2004), the same brain regions that are under greatest genetic control. Frontal brain regions play a key role in working memory, executive function, and attentional processes, and their structure has rapidly expanded in recent primate evolution, consistent with their role in reasoning and intellectual function.

Environmental Influences on Brain Structure

Neural plasticity in humans may also lead to use-dependent structural adaptation in cerebral gray matter in response to environmental demands. At the gross level observable with MRI, there is already evidence that the human brain may adapt dynamically to reflect the cognitive demands of the environment. Neuroimaging studies have observed structural plasticity after training on difficult motor tasks such as juggling (Draganski et al. 2004). Increased hippocampal volumes have also been found in taxi drivers with enhanced spatial navigation skills (Maguire et al. 2000). Gaser & Schlaug (2003) also found gray matter increases in motor, auditory, and visual-spatial brain regions when comparing professional musicians (keyboard players) with a matched group of amateur musicians and nonmusicians. Brain structure is by no means unchanging even in health. Dynamic regional changes over the entire life span can be mapped (**Figure 2**), showing a progressive change in cortical volume. The heritability of brain structure, although certain, is neither final nor static. However, without genetic brain-mapping techniques (described in this review), strictly speaking it is

not certain whether these brain differences are attributable to innate predisposition or due to adaptations in response to skill acquisition and repetitive rehearsal of those skills.

Intelligence therefore depends, to some extent, on structural differences in the brain that are under very strong genetic control. This indicates a partly neuroanatomical (structural) explanation for the high heritability of intelligence. These methods are currently being applied to large databases that assess the impact of candidate genes on brain structure, which allows causal pathways between genes, brain, and behavior to be pursued at the allelic level.

CONCLUSION

Currently, the most fruitful combination of genetics and imaging is perhaps their application to large patient populations. This shows great promise for seeking out genetic markers that are linked with brain structure, as well as intellectual function and cognition, more generally. Brain mapping can provide some of the hard data to establish a basis for why people vary in their general mental capacity. This review illustrates the bridge afforded by structural imaging between genetics and behavior.

Nature is not democratic. Individuals' IQs vary, but the data presented in this review and elsewhere do not lead us to conclude that our intelligence is dictated solely by genes. Instead genetic interactions with the environment suggest that enriched environments will help everyone achieve their potential, but not to equality. Our potential seems largely predetermined.

That our interpretation of intelligence, the brain, and heritability has succumbed to a variety of political and social pressures is undeniable. How the public chooses to use scientific findings in the establishment of policy, particularly in regards to education and law, however, is not the stuff of a chapter in *Annual Review of Neuroscience*. As our understanding of the complex relationships between genes, brain, and intelligence improves, what becomes of this knowledge remains to be seen.

ACKNOWLEDGMENTS

Funding support for this work was provided by grant P41 RR13642 from the National Center for Research Resources, the Center for Computational Biology, U54 RR21813, and a Human Brain Project grant and the International Consortium for Brain Mapping, funded by the National Institute of Mental Health and the National Institute on Drug Abuse (P20 MH/DA52176). Additional support was provided by grants from the National Institute for Biomedical Imaging and Bioengineering and the National Center for Research Resources (R21 EB01651, R21 RR019771; to P.T.).

LITERATURE CITED

Andreasen NC, Flaum M, Swayze V 2nd, O'Leary DS, Alliger R, et al. 1993. Intelligence and brain structure in normal individuals. *Am. J. Psychiatry* 150:130–34

Ashburner J, Friston KJ. 2000. Voxel-based morphometry—the methods. *NeuroImage* 11(6):805–21

Baare WF, Hulshoff Pol HE, Boomsma DI, Posthuma D, de Geus EJ, et al. 2001a. Quantitative genetic modeling of variation in human brain morphology. *Cereb. Cortex* 11:816–24

Baare WF, van Oel CJ, Hulshoff Pol HE, Schnack HG, Durston S, et al. 2001b. Volumes of brain structures in twins discordant for schizophrenia. *Arch. Gen. Psychiatry* 58(1):33–40

Baron JC, Chetelat G, Desgranges B, Perchey G, Landeau B, et al. 2001. In vivo mapping of gray matter loss with voxel-based morphometry in mild Alzheimer's disease. *NeuroImage* 14:298–309

Bartley AJ, Jones DW, Weinberger DR. 1997. Genetic variability of human brain size and cortical gyral patterns. *Brain* 120(2):257–69

Baumeister RF, Twenge J, Nuss CK. 2002. Effects of social exclusion on cognitive processes: Anticipated aloneness reduces intelligent thought. *J. Pers. Soc. Psychol.* 83:817–27

Bellugi U, Lichtenberger L, Jones W, Lai Z, St. George M. 2000. I. The neurocognitive profile of Williams Syndrome: a complex pattern of strengths and weakenesses. *J. Cogn. Neurosci.* 12(Suppl. 1):7–29

Biondi A, Nogueira H, Dormont D, Duyme M, Hasbon D, et al. 1998. Are the brains of monozygotic twins similar? A three-dimensional MR study. *Am. J. Neuroradiol.* 19(7):1361–67

Block N. 1995. How heritability misleads about race. *Cognition* 56:99–128

Boomsma DI, de Geus EJ, van Baal GC, Koopmans JR. 1999. A religious upbringing reduces the influence of genetic factors on disinhibition: evidence for interaction between genotype and environment on personality. *Twin Res.* 2:115–25

Bouchard TJ Jr, Lykken DT, McGue M, Segal NL, Tellegen A. 1990. Sources of human psychological differences: the Minnesota Study of Twins Reared Apart. *Science* 250:223–28

Brand C. 2001. *The G factor*. **http://www.douance.org/qi/brandtgf.htm**

Bullmore ET, Suckling J, Overmeyer S, Rabe-Hesketh S, Taylor E, Brammer MJ. 1999. Global, voxel, and cluster tests, by theory and permutation, for a difference between two groups of structural MR images of the brain. *IEEE Trans. Med. Imag.* 18:32–42

Cabeza R, Nyberg L. 2000. Imaging cognition II: an empirical review of 275 PET and fMRI studies. *J. Cogn. Neurosci.* 12(1):1–47

Cannon TD, Thompson PM, van Erp TGM, Toga AW, Poutanen V-P, et al. 2002. Cortex mapping reveals regionally specific patterns of genetic and disease-specific gray-matter deficits in twins discordant for schizophrenia. *Proc. Natl. Acad. Sci. USA* 99(5):3228–33

Cannon TD, van Erp TG, Bearden CE, Loewy R, Thompson P, et al. 2003. Early and late neurodevelopmental influences in the prodrome to schizophrenia: contributions of genes, environment, and their interactions. *Schizophr. Bull.* 29(4):653–69

Carroll J. 1993. *Human Cognitive Abilities: A Survey of Factor-Analytic Studies*. Cambridge, UK: Cambridge Univ. Press

Cattell RB. 1971. *Abilities: Their Structure, Growth, and Action*. Boston: Houghton Mifflin

Ceci SJ, Williams WM. 1997. Schooling, intelligence, and income. *Am. Psychol.* 52:1051–58

Chipuer HM, Rovine MJ, Plomin R. 1990. LISREL modeling: genetic and environmental influences on IQ revisited. *Intelligence* 14:11–29

Deary IJ. 2001. Human intelligence differences: a recent history. *Trends Cogn. Sci.* 5:127–30

Devlin B, Daniels M, Roeder K. 1997. The heritability of IQ. *Nature* 388(6641):468–71

Diamond A, Briand L, Fossella J, Gehlbach L. 2004. Genetic and neurochemical modulation of prefrontal cognitive functions in children. *Am. J. Psychiatry* 161:125–32

Diamond MC. 1988. *Enriching Heredity*. New York: Free Press

Dickens WT, Flynn JR. 2001. Heritability estimates versus large environmental effects: the IQ paradox resolved. *Psychol. Rev.* 108:346–69

Draganski B, Gaser C, Busch V, Schuierer G, Bogdahn U, May A. 2004. Neuroplasticity: changes in grey matter induced by training. *Nature* 427(6972):311–12

Drane DL, Logemann JA. 2000. A critical evaluation of the evidence on the association between type of infant feeding and cognitive development. *Paediatr. Perinat. Epidemiol.* 14:349–56

Duncan J, Seitz RJ, Kolodny J, Bor D, Herzog H, et al. 2000. A neural basis for general intelligence. *Science* 289(5478):457–60

Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, et al. 2001. Effect of COMT Val 108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proc. Natl. Acad. Sci. USA* 98:6917–22

Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, et al. 2003. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell* 112:257–69

Feldman MW, Otto SP. 1997. Twin studies, heritability, and intelligence. *Science* 278:1383–84

Finkel D, Pedersen NL, Plomin R, McClearn GE. 1998. Longitudinal and cross-sectional twin data on cognitive abilities in adulthood: the Swedish Adoption/Twin Study of Aging. *Dev. Psychol.* 34:1400–13

Fischl B, Liu A, Dale AM. 2001. Automated manifold surgery: constructing geometrically accurate and topologically correct models of the human cerebral cortex. *IEEE Trans Med. Imag*. 20(1):70–80

Forgays DG, Forgays JW. 1952. The nature of the effect of free-environmental experience in the rat. *J. Comp. Physiol. Psychol.* 45:322–28

Friston KJ, Frith CD, Frackowiack RS, Turner R. 1995. Characterizing dynamic brain responses with fMRI: a multivariate approach. *NeuroImage* 2(2):166–72

Gardner H. 2000. *Intelligence Reframed*. New York: Basic Books

Gaser C, Schlaug G. 2003. Gray matter differences between musicians and nonmusicians. *Ann. N. Y. Acad. Sci.* 999:514–17

Geroldi C, Pihlajamaki M, Laakso MP, DeCarli C, Beltramello A, et al. 1999. APOE-epislon4 is associated with less frontal and more medial temporal lobe atrophy in AD. *Neurology* 53(8):1825–32

Gignac G, Vernon PA, Wickett JC. 2003. Factors influencing the relationship between brain size and intelligence. In *The Scientific Study of General Intelligence*, ed. H Nyborg, pp. 93–106. Amsterdam: Pergamon

Gogtay N, Lusk L, Hayashi KM, Giedd JN, Greenstein D, et al. 2004. Dymanic mapping of human cortical development during childhood and adolescence. *Proc. Natl. Acad. Sci. USA* 101(21):8174–79

Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. 2001. A voxel-based morphometric study of ageing in 465 normal adult human brains. *NeuroImage* 14(1 Pt. 1):21–36

Gottfredson LS. 1997. Why *g* matters: the complexity of everyday life. *Intelligence* 24:79–132

Gould SJ. 1996 [1981]. *The Mismeasure of Man*. New York: Norton

Gray JR, Braver TS, Raichle ME. 2002. Integration of emotion and cognition in the lateral prefrontal cortex. *Proc. Natl. Acad. Sci. USA* 99:4115–20

Gray JR, Chabris CF, Braver TS. 2003. Neural mechanisms of general fluid intelligence. *Nat. Neurosci.* 6:316–22

Gray JR, Thompson PM. 2004. Neurobiology of intelligence: science and ethics. *Nat. Rev. Neurosci*. 5:471–82

Greenough WT, Fulcher JK, Yuwiler A, Geller E. 1970. Enriched rearing and chronic electroshock: effects on brain and behavior in mice. *Physiol. Behav.* 5(3):371–73

Haier RJ, Jung RE, Yeo RA, Head K, Alkire MT. 2004. Structural brain variation and general intelligence. *NeuroImage* 23(1):425–33

Haier RJ, Siegel BV, MacLachlan A, Soderling E, Lottenberg S, Buchsbaum MS. 1992. Regional glucose metabolic changes after learning a complex visuospatial/motor task: a positron emission tomography study. *Brain Res.* 570:134–43

Haier RJ, Siegel BV, Nuechterlein KH, Hazlett E, Wu JC, et al. 1998. Cortical glucose metabolic-rate correlates of abstract reasoning and attention studied with positron emission tomography. *Intelligence* 12:199–217

Haier RJ, Siegel B, Tang C, Abel L, Buchsbaum MS. 1992. Intelligence and changes in regional cerebral glucose metabolic-rate following learning. *Intelligence* 16:415–26

Haier RJ, White NS, Alkire MT. 2003. Individual differences in general intelligence correlate with brain function during nonreasoning tasks. *Intelligence* 31:429–41

Hashimoto M, Yasuda M, Tanimukai S, Matsui M, Hirono N, et al. 2001. Apolipoprotein E epsilon 4 and the pattern of regional brain atrophy in Alzheimer's disease. *Neurology* 57(8):1461–66

Herrnstein RJ, Murray C. 1994. *The Bell Curve*. New York: Free Press

Janke AL, de Zubicaray GI, Rose SE, Griffin M, Chalk JB, Galloway GJ. 2001. 4D deformation modeling of cortical disease progression in Alzheimer's dementia. *Magn. Reson. Med.* 46:661–66

Jensen AR. 1969. How much can we boost I.Q. and scholastic achievement? *Harvard Educ. Rev.* 39(1):1–123

Jensen AR. 1980. *Bias in Mental Testing*. New York: Free Press

Jensen AR. 1998. *The G Factor: The Science of Mental Ability*. Westport, CT: Praeger

Jensen AR, Miele F. 2002. *Intelligence, Race, and Genetics: Conversations with Arthur R. Jensen*. Boulder, CO: Westview

Kamin LJ. 1997. Twin studies, heritability, and intelligence. *Science* 278:1385

Kamin LJ, Goldberger AS. 2002. Twin studies in behavioral research: a skeptical view. *Theor. Popul. Biol.* 61(1):83–95

Kaprio J, Koskenvuo M, Rose RJ. 1990. Population-based twin registries: illustrative applications in genetic epidemiology and behavioral genetics from the Finnish Twin Cohort Study. *Acta Genet. Med. Gemellol.* 39(4):427–39

Korenberg JR, Chen XN, Hirota H, Lai Z, Bellugi U, et al. 2000. VI. Genome structure and cognitive map of Williams Syndrome. *J. Cogn. Neurosci.* 12(Suppl. 1):89–107

Lehtovirta M, Helisalmi S, Mannermaa A, Soininen H, Koivisto K, et al. 1995. Apoliopoprotein E polymorphism and Alzheimer's disease in eastern Finland. *Neurosci Lett.* 185(1):13–15

Lehtovirta M, Partanen J, Konomen M, Hiltunen J, Helisalmi S, et al. 2000. A longitudinal quantitative EEG study of Alzheimer's disease: relation to apolioprotein E polymorphism. *Dement. Geriatr. Cogn. Disord.* 11(1):29–35

Lewontin RC. 1975. Genetic aspects of intelligence. *Annu. Rev. Genet.* 9:387–405

Loehlin JC. 1989. Partitioning environmental and genetic contributions to behavioral development. *Am. Psychol.* 44:1285–92

Lyons DM, Yang C, Sawyer-Glover AM, Moseley ME, Schatzberg AF. 2001. Early life stress and inherited variation in monkey hippocampal volumes. *Arch. Gen. Psychiatry* 58(12):1145–51

Maguire EA, Gadian DG, Johnsrude IS, Good CD, Asburner J, et al. 2000. Navigation-related structural change in the hippocampi of taxi drivers. *Proc. Natl. Acad. Sci. USA* 97(8):4398–403

Mazziotta J, Toga AW, Evans A, Fox P, Lancaster J, et al. 2001. A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM). *Phil. Trans. R. Soc. Lond. (R. Soc.)* 356:1293–322

McClearn GE, Johansson B, Berg S, Pedersen NL, Ahren F, et al. 1997. Substantial genetic influence on cognitive abilities in twins 80 or more years old. *Science* 276:1560–63

McDaniel MA, Nguyen NT. 2002. *A meta-analysis of the relationship between MRI-assessed brain volume and intelligence*. Presented at Proc. Int. Soc. Intel. Res., Nashville, TN

McGue M, Bouchard TJ Jr, Iacono WG, Lykken DT. 1993. Behavioral genetics of congnitive ability: a life-span perspective. In *Nature, Nurture and Psychology*, ed. R Plomin, GE McClearn, pp. 59–76. Washington, DC: Am. Psychol. Assoc.

Mega MS, Dinov ID, Lee L, Masterman DM, O'Connor SM, et al. 2000. Orbital and dorsolateral frontal perfusion defect associated with behavioral response to cholinesterase inhibitor therapy in Alzheimer's Disease. *J. Neuropsychiatr. Clin. Neurosci.* 12:209–18

Morley KI, Montgomery GW. 2001. The genetics of cognitive processes: candidate genes in humans and animals. *Behav. Genet*. 31(6):511–31

Mummery CJ, Patterson K, Price CJ, Asburner J, Frackowiack RS, Hodges JR. 2000. A voxel-based morphometry study of semantic dementia: relationship between temporal lobe atrophy and semantic memory. *Ann. Neurol*. 47(1):36–45

Narr KL, Cannon TD, Woods RP, Thompson PM, Kim S, et al. 2002. Genetic contributions to altered callosal morphology in schizophrenia. *J. Neurosci*. 22(9):3720–29

Narr KL, Thompson PM, Sharma T, Moussai J, Zoumalon C, et al. 2001. Three-dimensional mapping of gyral shape and cortical surface asymmetries in schizophrenia: gender effects. *Am. J. Psychiatry* 158(2):244–55

Narr KL, Thompson PM, Szeszko P, Robinson D, Jang S, et al. 2003. Regional specificity of hippocampal volume reductions in first-episode schizophrenia. *NeuroImage* 21(4):1563–75

Neale MC. 1997. *Mx: Statistical Modeling*. Richmond: Va. Commonwealth Univ., Dep. Psychiatry

Neisser U, ed. 1998. *The Rising Curve: Long-Term Gains in IQ and Related Measures*. Washington, DC: Am. Psychol. Assoc.

Oddy WH, Kendall GE, Blair E, De Klerk NH, Stanley FJ, et al. 2003. Breast feeding and cognitive development in childhood: a prospective birth cohort study. *Paediatr. Perinat. Epidemiol.* 17:81–90

Oppenheim JS, Skerry JE, Tramo MJ, Gazzaniga MS. 1989. Magnetic resonance imaging morphology of the corpus callosum in monozygotic twins. *Ann. Neurol*. 26:100–4

Pfefferbaum A, Sullivan EV, Carmelli D. 2001. Genetic regulation of regional microstructure of the corpus callosum in late life. *Neuroreport* 12(8):1677–81

Pfefferbaum A, Sullivan EV, Swan GE, Carmelli D. 2000. Brain structure in men remains highly heritable in the seventh and eighth decades of life. *Neurobiol. Aging* 21:63–74

Pinker S. 2002. *The Blank Slate*. New York: Viking

Plomin R. 1999. Genetics of childhood disorders. III. Genetics and intelligence. *J. Am. Acad. Child Adolesc. Psychiatry* 38(6):786–88

Plomin R, DeFries JC, Loehlin JC. 1977. Genotype-environment interaction and correlation in the analysis of human behavior. *Psychol. Bull.* 84:309–22

Plomin R, Kosslyn SM. 2001. Genes, brain and cognition. *Nat. Neurosci.* 4:1153–54

Plomin R, Petrill SA. 1997. Genetics and intelligence: What's new? *Intelligence* 24:53–78

Posthuma D, De Geus EJ, Baare WF, Hulshoff Pol HE, Kahn RS, Boomsma DI. 2002. The association between brain volume and intelligence is of genetic origin. *Nat. Neurosci*. 5:83–84

Prabhakaran V, Rypma B, Gabrieli JDE. 2001. Neural substrates of mathematical reasoning: a functional magnetic resonance imaging study of neocortical activation during performance of the Necessary Arithmetic Operations Test. *Neuropsychology* 15:115–27

Prabhakaran V, Smith JAL, Desmond JE, Glover GH, Gabrieli JDE. 1997. Neuronal substrates of fluid reasoning: an fMRI study of neocortical activation during performance of the Raven's Progressive Matrices Test. *Cogn. Psychol.* 33:43–63

Rasser PE, Johnston PJ, Lagopoulos J, Ward PB, Schall U, et al. 2005. Analysis of fMRI BOLD activation during the Tower of London Task using Gyral Patter and Intensity Averaging Models of Cerebral Cortex. *NeuroImage*. In press

Rex A, Pfeifer L, Fink H. 2001. Determination of NADH in frozen rat brain sections by laser-induced fluorescence. *Biol. Chem*. 382(12):1727–32

Ridley M. 2003. *Nature via Nurture: Genes, Experience, and What Makes Us Human*. New York: Harper Collins

Rombouts SA, Barkhof F, Witter MP, Schettens P. 2000. Unbiased whole-brain analysis of gray matter loss in Alzheimer's disease. *Neurosci. Lett*. 285(3):231–33

Roses AD. 1996. Apolipoprotein E and Alzheimer's disease. A rapidly expanding field with medical and epidemiological consequences. *Ann. N. Y. Acad. Sci.* 802:50–57

Rowe DC, Jacobson KC. 1999. Mainstream: research in behavioral genetics. In *Behavioral Genetics: The Clash of Culture and Biology*, ed. RA Carson, MA Rothstein, pp. 12–34. Baltimore/London: Johns Hopkins Univ. Press

Salovey P, Mayer JD, Caruso D. 2002. The positive psychology of emotional intelligence. In *The Handbook of Positive Psychology*, ed. CR Snyder, SJ Lopez, pp. 159–71. New York: Oxford Univ. Press

Schmader T, Johns M. 2004. Converging evidence that stereotype threat reduces working memory capacity. *J. Pers. Soc. Psychol.* 85:440–52

Sesardic N. 2002. Heritability and indirect causation. *Proc. Philos. Sci. Assoc.* 70:1002–14

Small GW, Ercoli LM, Silverman DH, Huang SC, Komo S, et al. 2000. Cerebral metabolic and cognitive decline in person at genetic risk for Alzheimer's disease. *Proc. Natl. Acad. Sci. USA* 97(11):6037–42

Sowell ER, Mattson SN, Thompson PM, Jernigan TL, Riley EP, Toga AW. 2001. Mapping callosal morphology and cognitive correlates: effects of heavy prenatal alcohol exposure. *Neurology* 57:235–44

Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AW. 2003. Mapping cortical change across the human life span. *Nat. Neurosci*. 6(3):309–15

Sowell ER, Thompson PM, Holmes CJ, Batth R, Travner DA, et al. 1999. Localizing age-related changes in brain structure between childhood and adolescence using statistical parametric mapping. *NeuroImage* 9:587–97

Spearman C. 1927. *The Nature of "Intelligence" and the Principles of Cognition*. London, UK: Macmillan

Steele CM, Aronson J. 1995. Stereotype threat and the intellectual test performance of African Americans. *J. Pers. Soc. Psychol.* 69:797–811

Sternberg RJ. 1999. The theory of successful intelligence. *Rev. Gen. Psychol.* 3:292–16

Suddarth RI, Christison GW, Torrey EF, Casanova MF, Weinberger DR. 1990. Anatomical abnormalities in the brains of monozygotic twins discordant for schizophrenia. *N. Engl. J. Med*. 322(12):789–94

Sullivan EV, Pfefferbaum A, Swan GE, Carmelli D. 2001. Heritability of hippocampal size in elderly twin men: equivalent influence from genes and environment. *Hippocampus* 11(6):754–62

Swan GE, Carmelli D, Reed T, Harshfield GA, Fabsitz RR, Eslinger PJ. 1990. Heritability of cognitive performance in ageing twins. The National Heart, Lung, and Blood Institute Twin Study. *Arch. Neurol*. 47(3):259–62

Thompson P, Hayashi KM, de Zubicaray G, Janke AL, Rose SE, et al. 2003. Dynamics of gray matter loss in Alzheimer's disease. *J. Neurosci.* 23(3):994–1005

Thompson P, Hayashi KM, de Zubicaray G, Janke AL, Rose SE, et al. 2004. Mapping hippocampal and ventricular change in Alzheimer's disease. *NeuroImage* 22(4):1754–66

Thompson P, Toga AW. 1996. A surface-based technique for warping three-dimensional images of the brain. *IEEE Trans. Med. Imag.* 15(4):402–17

Thompson PM, Cannon TD, Narr KL, van Erp T, Poutanen V-P, et al. 2001a. Genetic influences on brain structure. *Nat. Neurosci.* 4(12):1253–58

Thompson PM, Cannon TD, Toga AW. 2002. Mapping genetic influences on human brain structure. *Ann. Med.* 24:523–36

Thompson PM, MacDonald D, Mega MS, Holmes CJ, Evans AC, Toga AW. 1997. Detection and mapping of abnormal brain structure with a probabilistic atlas of cortical surfaces. *J. Comp. Assist. Tomogr.* 21(4):567–81

Thompson PM, Toga AW. 2005. Cortical disease and cortical localization. *Nat. Encycl. Life Sci.* In press

Thompson PM, Vidal C, Giedd JN, Gochman P, Blumenthal J, et al. 2001b. Mapping adolescent brain change reveals dynamic wave of accelerated gray matter loss in very early-onset schizophrenia. *Proc. Natl. Acad. Sci. USA* 98(20):11650–55

Thompson PM, Woods RP, Mega MS, Toga AW. 2000. Mathematical/computational challenges in creating deformable and probabilistic atlases of the human brain. *Hum. Brain Mapp.* 9:81–92

Tramo MJ, Loftus WC, Stukel TA, Green RL, Weaver JB, Gazzaniga MS. 1998. Brain size, head size, and intelligence quotient in monozygotic twins. *Neurology* 50(5):1246–52

Turkheimer E, Haley A, Waldron M, D'Onofrio B, Gottesman II. 2003. Socioeconomic status modifies heritability of IQ in young children. *Psychol. Sci.* 14:623–28

Vogel F, Motulsky AG. 1997. *Human Genetics*. New York: Springer-Verlag

Weinberger DR, Delisi LE, Neophytides AN, Wyatt RJ. 1981. Familial aspects of CT scan abnormalities in chronic schizophrenic patients. *Psychiatry Res.* 4:65–71

Winterer G, Goldman D. 2003. Genetics of human prefrontal function. *Brain Res. Brain Res. Rev.* 43(1):134–63

Wright IC, McGuire PK, Poline JB, Travere JM, Murray RM, et al. 1995. A voxel-based method for the statistical analysis of gray and white matter density applied to schizophrenia. *NeuroImage* 2(4):244–52

Wright IC, Sham P, Murray RM, Weinberger DR, Bullmore ET. 2002. Genetic contributions to regional human brain variability estimated in a twin study by path analysis of parcellated grey matter maps. *NeuroImage* 17:256–71

Wright IC, Sharma T, Ellison ZR, McGuire PK, Fiston KJ, et al. 1999. Supra-regional brain systems and the neuropathology of schizophrenia. *Cereb. Cortex* 9(4):366–78

Zeineh MM, Engel SA, Thompson PM, Bookheimer SY. 2001. Unfolding the human hippocampus with high resolution structural and functional MRI. *Anat. Rec.* 265(2):111–20

Zeineh MM, Engel SA, Thompson PM, Bookheimer SY. 2003. Dynamics of the hippocampus during encoding and retrieval of face-name pairs. *Science* 299(5606):577–80

Zhou Y, Cheshire A, Howell CA, Ryan DH, Harris RB. 1999. Neuroautoantibody immunoreactivity in relation to aging and stress in apolipoprotein E-deficient mice. *Brain Res. Bull.* 49(3):173–79

Annual Review of Neuroscience

Volume 28, 2005

Contents

INDEXES

ERRATA

An online log of corrections to *Annual Review of Neuroscience* chapters may be found at http://neuro.annualreviews.org/