Neuroimaging Endophenotypes: Strategies for Finding Genes Influencing Brain Structure and Function

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Abstract: It is vitally important to identify the genetic determinants of complex brain-related disorders such as autism, dementia, mood disorders, and schizophrenia. However, the search for genes predisposing individuals to these illnesses has been hampered by their genetic and phenotypic complexity and by reliance upon phenomenologically based qualitative diagnostic systems. Neuroimaging endophenotypes are quantitative indicators of brain structure or function that index genetic liability for an illness. These indices will significantly improve gene discovery and help us to understand the functional consequences of specific genes at the level of systems neuroscience. Here, we review the feasibility of using neuroanatomic and neuropsychological measures as endophenotypes for brain-related disorders. Specifically, we examine specific indices of brain structure or function that are genetically influenced and associated with neurological and psychiatric illness. In addition, we review genetic approaches that capitalize on the use of quantitative traits, including those derived from brain images. *Hum Brain Mapp 28:488–501, 2007.* © 2007 Wiley-Liss, Inc.

Key words: genetics; neuroimaging; endophenotype; MRI; PET; anatomy; functional MRI; fMRI

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INTRODUCTION

Identification of the genetic determinants of complex brain-related disorders such as autism, dementia, mood disorders, and schizophrenia is of paramount importance. These neurological and psychiatric illnesses represent a significant economic burden [Uhl and Grow, 2004] and are associated with substantial morbidity and mortality, but their underlying pathologies are poorly understood. Identifying the specific genes that contribute to risk for these illnesses should provide critical information on the causes of these diseases that may lead to the development of novel diagnostic and therapeutic strategies. Genetic studies of brain-related mental diseases have made some recent progress, but the field as a whole lags behind other complex diseases in the identification of disease-related genes and the

subsequent biological inferences that result from discovering a causal component of the pathological chain. There are many possible reasons for this, including a historical over-dependence on underpowered genetic study designs. However, a major reason for the slower progress in the genetics of mental illness is the relative lack of emphasis on quantitative endophenotypes that index disease risk [Gershon and Goldin, 1986; Gottesman and Gould, 2003]. Endophenotypes are markers that are genetically correlated with disease liability, and can be measured in all individuals (both affected and unaffected). They may also provide much greater power to localize and identify disease-related quantitative trait loci (QTLs) than does affection status alone [Blangero et al., 2003]. Biological endophenotypes are measurable intermediate phenotypes that are generally closer to the action of the gene and thus exhibit higher genetic signal-to-noise ratios [Gottesman and Gould, 2003].

Imaging methods are being successfully applied in a wide range of neurological and psychiatric disorders, providing important insights in the pathophysiology of these illnesses and clues for the development of novel treatments. Indeed, there is growing evidence that a host of common brain disorders, including addictions [Thompson et al., 2004], attention deficit hyperactivity disorder [Sowell et al., 2003b], dementia [Thompson et al., 2006], anxiety disorders, mood disorders [Bearden et al., in press], seizure disorders [Lin et al., in press], and schizophrenia [Cannon et al., 2002], are associated with alterations in brain structure and function. Although early large-scale brain-imaging research focused young, healthy, normal adult subjects [Mazziotta et al., 2001], in the past decade, normative studies of brain structure and function have been extended to the entire human lifespan, from childhood through extreme old age [Gogtay et al., 2004; Sowell et al., 2003a; Thompson et al., 2006]. Together these streams of research, which delineate the normal variation in brain structure and function as well as the pathological extremes of this variation, provide a backdrop for understanding genetic influences on neruoanatomy and neurophysiology. Since in vivo brain imaging methods are typically repeatable, provide quantitative data, and are often far more sensitive than behavioral observations to subtle brain changes, such markers have the potential to be endophenotypic markers [Hariri and Weinberger, 2003]. In this manuscript, we review current data suggesting that neuroanatomic and functional neuroimaging measures can be valid endophenotypes for a host of neurological and psychiatric illnesses. In addition, we will outline genetic methods that should capitalize on the complexity of imaging data and facilitate novel gene discovery, as well as test hypotheses about the action of specific, known genes.

DEFINING AN ENDOPHENOTYPE

Although twin, family and adoption studies have demonstrated that most neurological and psychiatric illnesses are substantially heritable (Table II gives heritability estimates for various illnesses), with a few notable exceptions, the molecular genetic origins of these illnesses remain elusive. Undoubtedly, the search for genetic loci involved in these disorders has been hampered by the genetic complexity of these illnesses, heterogeneity of disease expression (e.g., variable symptom presentation), and comorbidity with other disorders that may distort clinical presentation (e.g., substance abuse). Because genes predisposing to neurological or psychiatric illnesses may be transmitted without expression of the clinical phenotype (formal diagnosis), interest has arisen in developing endophenotypes, indicators of processes mediating between genotype and phenotype. Using endophenotypic markers may be advantageous, since they are generally less complex than their associated phenotype and thus may be more readily linked to a specific genetic locus [Gershon and Goldin, 1986; Glahn et al., 2004; Gottesman and Gould, 2003; Leboyer et al., 1998; Lenox et al., 2002]. In addition, endophenotypes for complex human psychiatric and neurological disorders could potentially be extended to animal models [Gottesman and Gould, 2003], advancing our understanding of the neurobiology of psychiatric disorders, and furthering the development of novel medications [Nestler et al., 2002]. Furthermore, endophenotypes may be necessary to resolve the status of family members in genetic studies of neurological and psychiatric disorders.

For a marker to be considered an endophenotype, it must be shown to (1) be highly heritable, (2) be associated with the phenotype (formal diagnosis), (3) be independent of clinical state, and (4) impairment must cosegregate with the illness within a family, with nonaffected family members showing impairment relative to the general population [Gershon and Goldin, 1986; Glahn et al., 2004; Gottesman and Gould, 2003; Leboyer et al., 1998; Lenox et al., 2002]. In the current review, we focus on the heritability of neuroanatomic and functional neuroimaging measurements. We also briefly describe how brain anatomy and physiology are altered in individuals with neurological and psychiatric illnesses and their relatives.

HERITABILITY OF NEUROANATOMY

The size, shape, and complexity of the primate brain vary considerably between individuals and a significant portion of this variability is influenced by genetic factors. While very early stages of primate brain development are predominantly mediated by genetic programs [Rubenstein and Rakic, 1999; Rubenstein et al., 1999], later stages of development, organization, and brain maturation result from a complex interaction of genetic and environmental influences [Rakic, 1988]. Genetic influence is typically expressed as a heritability statistic (denoted h^2), which reflects the percentage of the variation in a trait (e.g., brain volume) attributable to genetic factors. In contrast, "environmental" factors refer to trait variation not included in the heritabil-

TABLE I. Heritability of human brain phenotypes

Brain region	Sample size[a]	Heritability[b]
Intracranial volume	471 [254–1330]	0.87 [0.72–0.92] [Atwood et al., 2004; Baare et al., 2001; Hulshoff Pol et al., 2004; Posthuma et al., 2000, 2002]
Whole brain volume	194 [38–278]	0.78 [0.56–1.00] [Baare et al., 2001; Bartley et al., 1997; Geschwind et al., 2002; Hulshoff Pol et al., 2004; Narr et al., 2002; Posthuma et al., 2000; Wright et al., 2002]
Total gray matter volume	256 [256–258]	0.88 [0.82–1.00] [Baare et al., 2001; Hulshoff Pol et al., 2004; Posthuma et al., 2000]
Total white matter volume	256 [256–258]	0.85 [0.82–0.87] [Baare et al., 2001; Hulshoff Pol et al., 2004; Posthuma et al., 2000]
Frontal volume	278	0.65 [0.64–0.66] [Geschwind et al., 2002]
Temporal volume	278	0.58 [0.56–0.60] [Geschwind et al., 2002]
Parietal volume	278	0.52 [0.50–0.53] [Geschwind et al. 2002]
Occipital volume	278	0.33 [Geschwind et al., 2002]
Cerebellum volume	149 [40–258]	0.74 [0.66–0.87] [Posthuma et al., 2000; Wright et al., 2002]
Calosal volume	125 [80–170]	0.44–1.0 [Narr et al., 2002; Pfefferbaum et al., 2004]
Sulcus shape or length	58 [38–78]	0.22 [0.10–0.77] [Bartley et al., 1997; Eckert et al., 2002]
White matter hyperintensity	810 [290–1330]	0.76 [0.73–0.78] [Atwood et al., 2004; Carmelli et al., 1998]

[a] Mean n [range].
[b] Heritability = mean h^2 [range].

ity estimate, including nutrition, education and experience or experimental errors such as lack of reproducibility in the test. Studies in nonhuman primates have provided heritability estimates for brain weight ranging between 42% and 75% [Cheverud et al., 1990a,b; Mahaney et al., 1993]. Human magnetic resonance imaging studies have expanded upon these initial findings (see [Thompson et al., 2002] for a review), reporting high heritabilities for whole brain volumes, with somewhat lower heritabilities for lobar volumes (Table I). Reduced heritability estimates for lobar structures might be associated with the reliability of delineating lobar regions rather than an intrinsic reduction in the genetic influences of these regions. In contrast, ventricular volume seems to be mediated almost entirely by environmental factors [Baare et al., 2001; Wright et al., 2002] (see Styner et al. [2005] for contrary evidence). Estimated heritability for sulcal shape or length seems to vary considerably based on the sulcus in question, though these measurements traditionally suffer from poor reliability.

Bartley et al. [1997] reported 94% heritability for brain volume, based on structural equation modeling in 10 monozygotic (MZ) and nine dizygotic (DZ) twin pairs. In elderly twins, Sullivan et al. [2001] reported 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 et al. [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 [Baare et al., 2001]. 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.

Most current reports of lobular or region specific heritability are based on region of interest analyses where specific brain areas are manually traced. Yet, this approach may be less sensitive to small variations in brain structure or tissue type distribution than more modern modeling methods [Good et al., 2002]. For example, Thompson et al. [2001] used an elastic deformation procedure to model the genetic influences on neuroanatomic variation between healthy mono- and dizygotic twin pairs at each voxel on the surface of the cortex. This analysis indicated that genetic factors significantly influenced cortical gray matter density in subregions of prefrontal and temporal lobes, particularly Broca's and Wernicke's language areas. However, other areas within these structures were less herit-
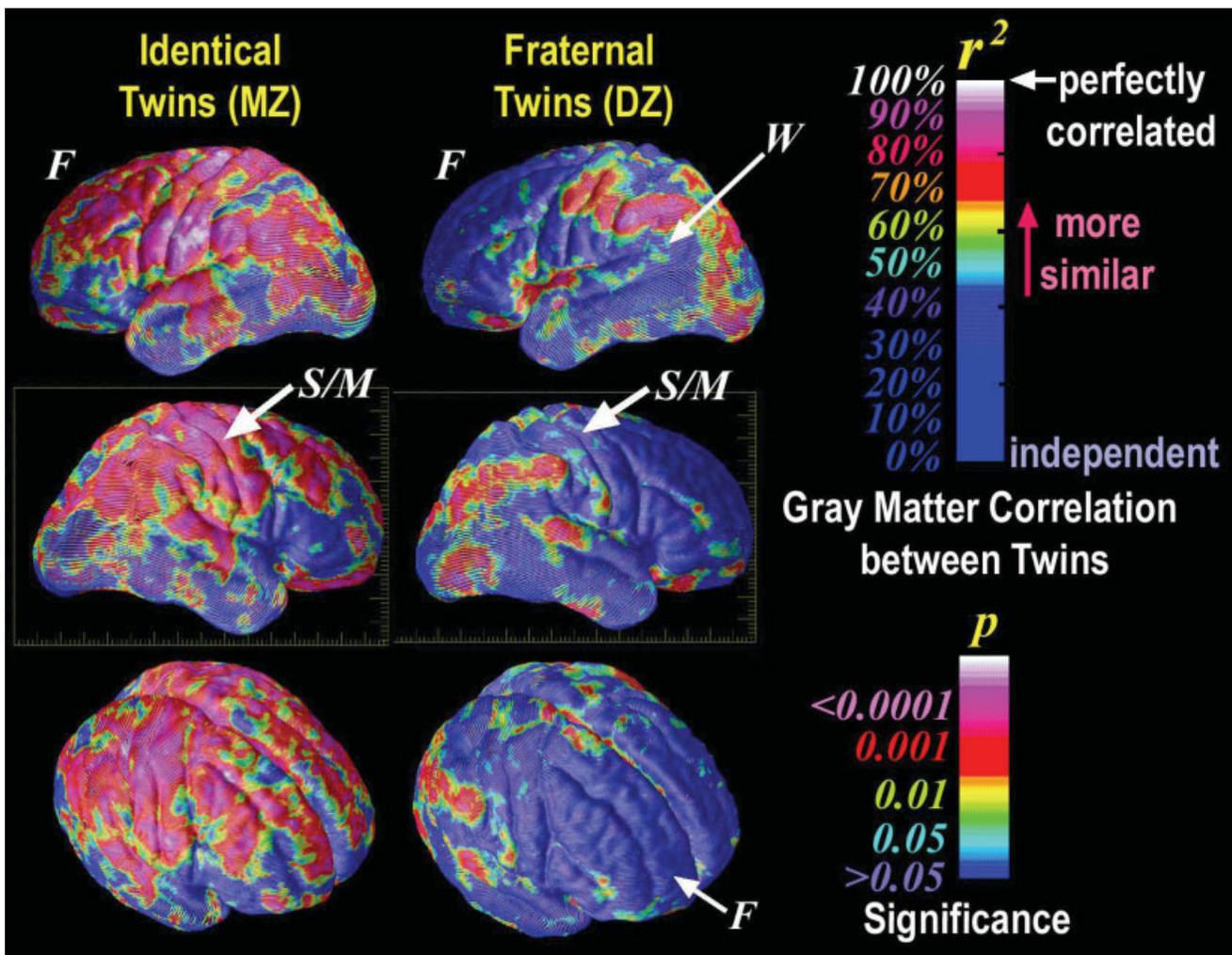
Figure 1.

Genetic influences on human neuroanatomy. Ten monozygotic twin pairs (*n* = 20 subjects) are almost perfectly correlated in their gray matter distribution, with near identity in frontal (F), sensorimotor (S/M), and perisylvian language cortices. In contrast, 10 dizygotic twin pairs (*n* = 20) are significantly less alike in frontal cortices, but are 90–100% correlated for gray matter in perisylvian language-related cortex, including supramarginal and angular territories and Wernicke's language area (*W*). The significance of these increased similarities, visualized in color, is related to the local intraclass correlation coeffcents (*r*) (From Thompson et al., Nat Neurosci, 2001, 4(12), 1253–1258, © Nature Publishing Group, reproduced by permission).

able, suggesting that heritability estimates based on gross lobular regions of interest blur more subtle local differences (Fig. 1; see Rogers et al., this issue, for similar work in nonhuman primates). A rather provocative implication of this study was that cognitive performance (specifically full-scale IQ) was correlated with brain structure volumes in the very regions where structure is under greatest genetic control [Thompson et al., 2001]. Although a wide body of work (reviewed in Gray and Thompson [2004]) supports the hypothesis that genetic variations contribute profoundly to IQ, and that gray matter volume is correlated with IQ, the high heritability of frontal gray matter

volume suggests that it may serve as a possible endophenotype for IQ. Taking this idea further, Posthuma et al. [2000] 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 IQ is highly genetic, in other words it is strongly mediated by common genetic differences [Posthuma et al., 2000]. Genetic factors may therefore contribute to structural differences in the brain that are linked with cognitive differences. 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 (see Gray and Thompson [2004] for an analysis of alternate explanations).

Region of interest methods tends to focus on a relatively small number of brain areas and potentially miss important covariation between structures. Such covariation could suggest that different brain structures are being influenced by the same gene or sets of genes. In contrast, modern morphometric methods can simultaneously model even minor neuroanatomic variations throughout the brain [Ashburner et al., 2003], particularly given advances in MRI technology which provide exquisite soft-tissue contrast and very high resolution (e.g. less than 1 mm^3). Modern image analysis methods and high-resolution images should significantly improve estimates of the heritability of neuroanatomic regions and, more importantly, localize genes influencing brain structure. For example, Wright et al. [1999] parcellated 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 [Wright et al., 1999]. This identified shared genetic effects on the frontal-parietal cortices and bilateral temporal cortex and insula. As the size and scope of these studies increase, 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. Such a factor-analytic approach would be of interest to apply to voxel-based studies as well, given the interdependencies in structure volumes and the likely overlap in the sets of genes that influence the volumes of different substructures.

NEUROANATOMY OF BRAIN DISORDERS

Although neurological and psychiatric illnesses are typically identified through behavioral observation, these illnesses are closely associated with anomalous brain structure. Advances in neuroimaging have left little doubt that particular diseases preferentially disturb specific neuroanatomic structures. Furthermore, the distribution of structural anomalies seemingly reflects the underlying pathology, often dissociating illnesses; see Table II for a targeted summary of comparative findings. For example, early and disproportionate hippocampal atrophy in individuals with memory complaints typically points to a diagnosis of Alzheimer's disease. In contrast, focal atrophy of the temporal lobe, frontal lobe, or both, makes Alzheimer's disorder less probable and the potential for other dementias

TABLE II. Structural brain abnormalities in neurological and psychiatric illnesses

Complex genetic brain disorder	Illness heritability	Frontal lobe	Temporal lobe	Cerebellum	Hippocampus /limbic system	White-matter hyperintensity
Addictions	0.4–0.6 [Begleiter and Porjesz, 1999]	↓ [Lingford-Hughes et al., 2003]	↓ [Lingford-Hughes et al., 2003]	↓ [Lingford-Hughes et al., 2003]	↓ [Geuze et al., 2005]	↑ [Sullivan and Pfefferbaum, 2001]
Alzheimer's & dementia	0.5–0.7 [Bergem et al., 1997]	↓ [Scheltens et al., 2002]	↓ [Scheltens et al., 2002]	↓ [Karas et al., 2003]	↓ [Geuze et al., 2005]	↑ [Hanyu et al., 1999]
ADHD	0.60–0.90 [Rhee et al., 1999]	↓ [Castellanos et al., 1996, 2002; Mostofsky et al., 2002]	↓ [Castellanos et al., 2002]	↓ [Castellanos et al., 2002]	↓ [Castellanos et al., 2002; Geuze et al., 2005]	
Autism		↓ [Carper and Courchesne, 2005; McAlonan et al., 2005]	↓ [McAlonan et al., 2005]	↓ [McAlonan et al., 2005; Pierce and Courchesne, 2001]	↑ [Geuze et al., 2005; Rojas et al., 2004; Schumann et al., 2004]	
Epilepsy & seizure disorders	0.60–0.88 [Berkovic et al., 1998]				↓ [Geuze et al., 2005]	
Mood disorders	0.37–0.59 [Merikangas et al., 2002]	↓ [Monkul et al., 2005]	↓ [Monkul et al., 2005]	↓ [Mills et al., 2005]	↓ [Geuze et al., 2005; Monkul et al., 2005]	↑ [Monkul et al., 2005]
PTSD & anxiety disorders	0.20–0.66 [Stein et al., 2002]	↓ [Fennema-Notestine et al., 2002]			↓ [Geuze et al., 2005; Hull, 2002; Wignall et al., 2004]	↑ [Canive et al., 1997]
Schizophrenia	0.70–0.83 [Cannon et al., 1998]	↓ [Wright et al., 2000]	↓ [Wright et al., 2000]	↓ [Wright et al., 2000]	↓ [Geuze et al., 2005; Wright et al., 2000]	↔ [Brown et al., 1992]

Decrease (↓), increase (↑), or evidence for no change (↔) in overall or gray matter volume.

such as Pick's disease more likely [Scheltens et al., 2002]. Similar, though less robust, dissociations have been reported for psychiatric illnesses. For instance, reduced hippocampal volumes are consistently reported in both major depression [Videbech and Ravnkilde, 2004] and schizophrenia [Honea et al., 2005; Wright et al., 2000]. However, gray-matter reductions observed in affective disorders appear to be limited to the limbic system [McDonald et al., 2004b]. In contrast, schizophrenia is associated with widespread volumetric diminution [Cannon et al., 2002; Wright et al., 2000].

The neuroanatomic anomalies seen in individuals affected with neurological or psychiatric illnesses often predate overt symptom expression [Fleisher et al., 2005; Harris et al., 2004; Moffat et al., 2000], though typically in a less severe form. In addition, many of the neuroanatomic variations associated with illness have been observed in individuals at risk for these same disorders. For example, women with mild cognitive impairment (MCI) and the apolipoprotein E epsilon4 (ApoE4) genotype have smaller hippocampal volumes and are more likely to develop Alzheimer's disease than MCI women without the ApoE4 variant [Fleisher et al., 2005]. Similar, though less significant trends were observed in males [Fleisher et al., 2005]. Adolescents and young adults from families with more than one individual who abuses alcohol have significantly smaller amygdala volumes than comparison subjects without ancestral history for alcoholism [Hill et al., 2001]. Unaffected family members of individuals with schizophrenia or individuals with bipolar disorder have discrete gray matter volume deficits but comparable white matter anomalies, suggesting both distinct and common abnormalities associated with genetic liability for these major psychiatric illnesses [McDonald et al., 2004a]. While unaffected cotwins of patients with schizophrenia have widespread gray matter reductions, healthy monozygotic cotwins have significantly lower gray matter volumes in polar and dorsolateral prefrontal cortex than healthy dizygotic cotwins, suggesting that these regions are sensitive to genetic liability for schizophrenia [Cannon et al., 2002]. Taken together, findings of anomalous neuroanatomy in individuals affected by neurological and psychiatric illnesses and those at increased genetic risk for these disorders suggest that at least a portion of these indices may be appropriate endophenotypic markers [McDonald et al., 2004a].

HERITABILITY OF FUNCTIONAL NEUROIMAGING

Functional neuroimaging involves the assessment of physiologic or metabolic states in a living organism. Most human functional neuroimaging experiments use radioactive ligands (e.g., SPECT or PET) or less invasive magnetic resonance procedures (e.g., fMRI). Functional neuroimaging experiments may be grouped into those that include a cognitive or psychological challenge and those that index resting metabolic state. Those experiments that include a challenge typically focus on an a priori brain region or a system putatively linked to the behavioral, cognitive, or physiological demands placed upon the subject (e.g., prefrontal activity during a working memory task). Since PET [Ragland et al., 1997] and fMRI [Callicott et al., 1999] signals are impacted by cognitive or behavioral performance, neuroactivation studies should consider performance level when examining individual differences or familial variability. Given these concerns, the complexity of functional neuroimaging analyses and the relatively high cost of collecting these data, few studies have examined genetic influences on functional neuroimaging signals. Indeed, to our knowledge, there are no published heritability estimates for functional neuroimaging measures. However, there is a good deal of circumstantial evidence supporting the hypothesis that functional neuroimaging measures are influenced by genetics. First, conceptually similar electrophysiological measures (e.g. ERP, EEG) have repeatedly been shown to be highly heritable (van Beijsterveldt and van Baal, 2002; van Beijsterveldt et al., 1996] and have even been successfully applied in large-scale linkage analysis [Edenberg et al., 2004]. Second, a number of recent manuscripts have reported associations between specific genes and functional activation patterns [Hariri et al., 2002,2003; Meyer-Lindenberg et al., 2005; Pezawas et al., 2004], suggesting genetic underpinnings for functional neuroimaging markers. Third, several investigators have demonstrated that healthy siblings or cotwins of individuals with psychiatric disorders have activation patterns similar to their affected family member [Hirvonen et al., 2005; Karlsgodt et al., 2007; Macdonald et al., 2006], suggesting that at least a portion of the aberrant signal detected in the proband may be genetically mediated. Finally, many of the cognitive and behavioral challenges applied in neuroimaging experiments have high levels of heritability [Bouchard and McGue, 1981; Glahn et al., 2007], implying that the activation pattern associated with this challenge may also be heritable. Thus, while there is currently little published data on the heritability of functional neuroimaging measures, much of brain function is genetically mediated, so that, assuming adequate reliability of the measurements, functional neuroimaging data is likely heritable.

FUNCTIONAL NEUROIMAGING OF BRAIN DISORDERS

Functional neuroimaging methods provide information on the integration and interaction of brain regions in large-scale spatially distinct neural networks during cognitive or behavioral challenges or in response to physiological stimuli. Such data are critical for understanding the neuropsychological response to information processing demands at the systems level and, thus, may be particularly sensitive to neuropathologic changes found in individuals with

brain-related disorders [Gothelf et al., 2005; Hirvonen et al., 2006; Liguori et al., 2006; Seidman et al., 2006]. Furthermore, there is growing evidence that functional neuroimaging methods can distinguish between behaviorally asymptomatic individuals at high and low genetic risk for a neurological or psychiatric illness [Small, 2006; Whalley et al., 2006] For example, Bookheimer et al. [2000] studied 30 neurologically healthy individuals who performed a declarative memory task during a functional MRI experiment. Sixteen of these subjects had at least one copy of the apolipoprotein (APOE) ε4 allele, a gene strongly linked to Alzheimer's dementia [Corder et al., 1993; Saunders et al., 1993]. Although the mean age and level of education were similar in the two groups, those individuals with an ε4 allele had significantly stronger imaging responses in regions affected by Alzheimer's disease, including the left hippocampal, parietal, and prefrontal regions, than persons who were ε3 homozygous [Bookheimer et al., 2000]. In addition, the degree of baseline brain activation correlated with the degree of decline in memory 2 years after the scan, suggesting that patterns of brain activation are sensitive to genetic risk of Alzheimer's disease and predicted subsequent memory impairment. More recently, a number of studies have demonstrated that functional neuroimaging methods are sensitive to polymorphisms in genes associated with neurotransmitter systems [Egan et al., 2001; Mattay et al., 2003; Pezawas et al., 2005; Smolka et al., 2005] or neurodevelopment [Hariri et al., 2003]. Together, these data suggest that markers of brain function may be more sensitive to subtle genetic variations than overt behavior [Hariri and Weinberger, 2003]. This claim is supported by Hariri et al. [2002], who found that a functional polymorphism in the promoter region of the human serotonin transporter gene (SLC6A4) predicted amygdala response to fearful or angry faces, while behavioral measures of normal fear or pathological anxiety did not statistically differ between groups. However, questions remain about the generalizability or reproducibility of genetic association studies employing functional neuroimaging markers and the utility of this approach for genes lacking a clear functional link to brain processing. Nonetheless, the application of functional neuroimaging methods to genetic association studies represents a significant proof of concept for the integration of imaging and genetic approaches to understanding neurological and psychiatric illnesses.

DETECTION, LOCALIZATION AND IDENTIFICATION OF DISEASE-RELATED QUANTITATIVE TRAIT LOCI

In this postgenomic era, one approach to understanding the genetic architecture of a complex phenotype follows a specific route often described as positional cloning. Initially, an underlying QTL is localized by a genomic scan to a potentially large chromosomal region. This localization is usually accomplished by linkage analysis using data on the cosegregation of phenotypes and genetic markers in families. Whole genome scanning using an association approach in unrelated samples is an alternative design, although it is still in its infancy as huge numbers of single nucleotide polymorphisms (SNP) are typically required to adequately cover the genome and there is a lack of statistical methods or power to adequately control Type I and II error. After a QTL is localized, its chromosomal location should be refined through fine mapping methods, typically including the saturation of the positional candidate region with additional genetic markers. It is possible to simultaneously exploit information on both linkage and linkage disequilibrium (whose effective signal spans a much smaller region than a linkage signal does).

The genetic analysis of brain structure is one of the most critically important areas of biomedical science. However, the genetic architecture of the brain is complex, involving multiple genetic and environmental components and their interactions. The specific QTLs that are involved in the developmental pathways producing adult brain structure, and their individual effects on the general population, are still largely unknown. Recent studies have pointed to specific genes that may have significant influence on variation in human brain structure [Evans et al., 2005; Mekel-Bobrov et al., 2005] but the significance of these genes has not yet been quantified, and there are certainly many other genes that affect variation in brain morphology. The complexity of the genotype–phenotype relationships relevant to such complex phenotypes requires that statistical inference play a prominent role in the dissection of the underlying genetic architecture. Statistical genetic methods suitable for this immense task are still in their early development.

In recent years, substantial advances have been made in the techniques for finding QTLs influencing disease-related traits. High-throughput genotyping methods have revolutionized the search for complex disease loci and the resulting emphasis on linkage studies utilizing total genome scans represents the current state-of-the-science. Additional molecular advances in high-throughput resequencing and SNP typing are also of considerable value for identifying the functional variants in positional candidate loci identified by linkage-based genome scans. Given an adequate sampling design, it will be possible to localize important genes involved in both normal and pathological variation using a genomic scan strategy coupled with follow-up fine mapping using linkage disequilibrium/association-based methods. It is now clear, with the advent of high throughput resequencing, that the next phase of genetic research requires new methods to identify functionally relevant polymorphisms in positional candidate genes.

Evidence is accumulating rapidly that it is feasible to identify the underlying genes influencing quantitative variation by combining molecular and statistical approaches. A number of specific functional genes that influence complex phenotypes in humans have been successfully identified, including genes underlying QTLs for taste sensitivity

to PTC [Kim et al., 2003], asthma [Zhang et al., 2003], IgE serum levels [Zhang et al., 2003], stroke [Gretarsdottir et al., 2003], and osteoporosis [Styrkarsdottir et al., 2003]. Each of these genes was found through linkage-based localization of QTLs. Similar methods will eventually identify genes influencing brain structure.

MAPPING GENES INFLUENCING QUANTITATIVE RISK FACTORS

Much of the recent success in the initial localization of QTLs influencing quantitative disease risk factors in extended human pedigrees is attributable to the development of the variance component method of linkage analysis. Variance component linkage/disequilibrium methods have several advantages over classical penetrance-model-based quantitative trait linkage methods. The simpler parameterization of variance component models leads to a more parsimonious and better-estimated set of focal parameters. In variance component-based linkage analysis, the focal parameter is the QTL-specific additive genetic variance or QTL-specific heritability. For a simple one-locus model with a diallelic QTL, the QTL-specific additive genetic variance can be written as $\sigma_q^2 = 2p_q(1 - p_q)\alpha^2$, where p_q is the allele frequency of the QTL polymorphic variant and α is half the displacement between the two homozygous genotypes. Thus, at minimum, a penetrance-based linkage analysis would need to specify or estimate p_q and α, while in variance component-based linkage analysis, these two parameters are absorbed into σ_q^2. We have recently shown that little power is gained over the simpler variance component parameterization even when the penetrance model can be specified [Goring et al., 2001]. Moreover, the power for variance component-based linkage analysis can greatly exceed that of penetrance-model based analysis when the penetrance model is misspecified, as is always the case when there are multiple QTLs or many functional variants at a QTL. The variance component approach can accommodate pedigrees of any size and complexity, while penetrance-based models rapidly become computationally intractable as pedigree size/complexity increases. Since it is now clear that large complex pedigrees have substantially more power per sampled individual than do smaller families [Blangero et al., 2000a,b, 2001, 2003], the advantage of using variance component methods for localizing QTLs is considerable. Hence, the optimal design for identifying genes that influence neuroanatomic variation is large extended pedigrees.

DETECTING GENETIC ASSOCIATION

In addition to linkage-based approaches to QTL localization and identification, it is possible to examine the potential effect of known polymorphic variation on a given trait using an association-based paradigm. Association studies either involve family-based sampling or involve a sampling strategy including unrelated individuals. Genetic association tests are dependent on the sequence variant in question having a true functional effect on the phenotype, or possibly being in linkage disequilibrium with a functional variant. Linkage disequilibrium simply represents the statistical correlation between two sequence variations due to a shared history and, thus, is a purely stochastic phenomenon. The extent of linkage disequilibrium is highly circumscribed (usually less than 200–300 kb) and thus can be exploited to limit the continued search for the responsible gene(s) to a much smaller genomic region than is possible with linkage (linkage signals can span more than 20 Mb). However, linkage represents a much more predictable force than disequilibrium, since it is ruled by a biophysical phenomenon with a well-known and precise mathematical form.

Association studies of quantitative endophenotypes, like neuroimaging measures, usually involve simple tests for differences in means between marker genotypes, typically a single nucleotide polymorphism or SNP. The total relative signal of a genetic marker is given by the marker-specific genetic variance [$\sigma_m^2 = 2p_m(1 - p_m)\alpha^2$] or heritability [$h_m^2 = \sigma_m^2/(1 + \sigma_m^2)$]. In the simple case of a single variant underlying a QTL, the marker-specific heritability is related to the QTL-specific heritability by the equation $\sigma_m^2 = \rho^2\sigma_q^2$, where ρ is the correlation between the marker variant and the true functional variant [Blangero et al., 2005]. Thus, ρ is a direct measure of linkage disequilibrium and the higher ρ values reflect greater relative signal due to the marker. If ρ is 1, then the marker is itself the functional variant or is in such strong statistical correlation with the true variant that the two could not be separated using statistical inference.

LEVELS OF INFERENCE IN GENETIC ASSOCIATION

Association studies can have different levels of focus. In the extreme case, it is possible to scan the whole genome for association using chip-based genotyping. In such cases, more than 500,000 SNPs may be analyzed [Lawrence et al., 2005]. At the other extreme, a study may be interested in testing a point hypothesis about a specific genetic marker in a known candidate gene. This latter situation should only be undertaken in the presence of extremely strong prior evidence for a marker. Testing a single marker may be appropriate in replication studies or in studies done subsequent to the definitive identification of the molecular functionality of a variant. All other studies of candidate genes should generally focus on exhaustive (or nearly exhaustive) examination of the sequence variation within the gene. A HapMap-based approach that employs common marker variants chosen to cover major blocks of linkage disequilibrium within a gene may or may not prove useful. If rare variants are important in quantitative variation, such disequilibrium-based approaches will not work, since

rare variants will not be in high correlation with common marker variants. Given the increasing evidence for the importance of rare variation, the future of human genetic analysis is certain to lay in the area of large-scale comprehensive resequencing in which all variants are identified and tested for statistical association [Blangero, 2004]. Such an approach requires new statistical techniques for the prioritization of the most likely function.

There are several critical issues in the design of a valid association study, including the overall power of a study to detect a true association is a function of both the sample size and the number of variants to be tested. The multiple testing problem can be potentially enormous and dramatically limit the power of association studies. Figure 2 shows the power function for a hypothetical study involving the analysis of a single quantitative endophenotype studied in 1,000 unrelated subjects. The three lines represent the level of variant examination being undertaken running the gamut from the analysis of a single SNP (blue line) to the comprehensive analysis of a single gene (red line, 50 total sequence variants) to the genome-wide analysis of 5,000,000 markers (black line). Each power function is based on an experiment-wide significance level of 0.05 as calculated by a standard Bonferroni correction. As is clearly shown in Figure 2, the reduction in power that is observed in multiple testing can be appreciable. If we are studying only a single SNP, we have 80% power to detect an association that accounts for as little as 0.8% of the total phenotypic variance of the endophenotype. For a study in which a gene is comprehensively analyzed with 50 variants, we have 80% power to detect an association that accounts for as little as 1.7% of the total variation, while for a genome-wide association study, we require a large genetic signal that accounts for at least 3.7% of the total phenotypic variation before we achieve 80% power of detection. This latter marker-specific heritability would be on the high side for a single functional variant. The Bonferroni correction is conservative but the overall pattern of these results is retained for other potentially more powerful multiple test correction methods such as utilization of a false discovery rate [Benjamini and Hochberg, 1995].

This simple example also suggests the great importance of providing accurate experiment-wide *P*-values for results when publishing. A nominal significance level of 0.05 has little place in modern complex disease genetics, since the likelihood of a study typing only a single variant is very small. Thus, the nominal *P*-values published so widely in the incipient brain endophenotype association literature have little validity for inference in the presence of multiple testing.

Another important consideration in the design of a valid association study is the avoidance of genetic stratification in which individuals from diverse genetic backgrounds are mixed within a single study. It is well known that such hidden stratification leads to excessive Type 1 error due to the confounding of population-level genetic variation with phenotypic variation. A number of methods have been
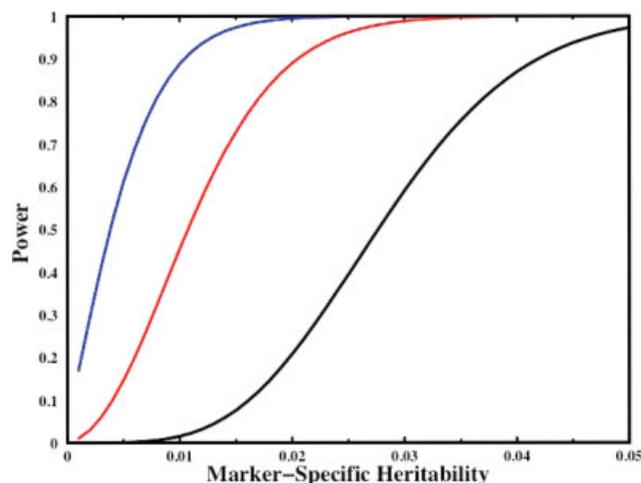

Figure 2.
Power to detect genetic association. A power function for a hypothetical study involving the analysis of a single quantitative endophenotype studied in 1,000 unrelated subjects. The three lines represent the level of variant examination being undertaken running the gamut from the analysis of a single SNP (blue line) to the comprehensive analysis of a single gene (red line, 50 sequence variants) to the genome-wide analysis of 5,000,000 markers (black line). Each power function is based on an experiment-wide significance level of 0.05 as calculated by a standard Bonferroni correction. For a single SNP, we have 80% power to detect an association that accounts for as little as 0.8% of the total phenotypic variance of the endophenotype. For a gene with 50 variants, we have 80% power to detect an association that accounts for 1.7% of total variation, while for a genome-wide association study, we require a large genetic signal that accounts for at least 3.7% of the total phenotypic variation before we achieve 80% power of detection.

proposed for detecting and correcting for such hidden heterogeneity. However, the best study design actively avoids such stratification by focusing on more homogenous samples or by the utilization of family-based data, which is not influenced by this issue. In fact, family-based studies are probably the most justifiable design for the genetic analysis of quantitative brain structure and function, since both linkage and linkage disequilibrium information can be jointly exploited to localize and identify underlying QTLs.

CONCLUSIONS

Genetically complex brain-related disorders cost the United States as much as $1.2 trillion annually [Uhl and Grow, 2004], in addition to the enormous personal cost to patients and their caregivers. Any novel insights into biological mechanisms that predispose individuals to these

illnesses hold the promise of potential new therapies and significant reduction of this considerable burden and improve the lives of individuals affected by these illnesses. The use of neuroimaging measures as endophenotypes for neurological and psychiatric illnesses could lead to new gene discoveries, and a better understanding of the biological mechanisms in these disorders. Thus the application of imaging measures in molecular genetics investigations (and vice versa) could significantly improve our understanding of brain function and structure. In this manuscript, we reviewed evidence that many neurological and psychiatric illnesses are associated with identifiable neuroanatomic and neurophysiologic changes and that many of these measures are heritable. Additional information may be needed when studying a specific illness, but nonetheless, we strongly advocate the use of neuroimaging measures in genetic studies.

Despite our enthusiasm for integrating genetic and neuroimaging investigations, we must discuss several caveats. First, both imaging and genetic data are complex. Each has millions of possible variables and the potential for spurious findings is tremendous. To minimize the computational requirements and to limit the number of potential statistical tests, many groups reduce the imaging data to a small number of scalar values per subject (e.g., prefrontal gray matter density or amygdala activation). Alternately, one could use only a small subset of the available genetic information by focusing on a single SNP or haplotype. These data reduction procedures are currently necessary because the mathematical procedures needed to control Type I error are not yet available. However, by significantly reducing one or both data types, important relationships will be missed. Thus, the development of high-dimensional procedures to allow whole genome—full brain analyses is necessary to fully explore these rich sources of data.

Independent of the complexity of these two data types, one should be concerned with measurement reliability. Large-scale genetic studies routinely apply methods to determine the reliability and validity of each sample being processed (e.g., SNP consistency, gender matching, relationship within pedigree) and procedures to minimize potential genotyping error. Similar methods are not ubiquitously applied in neuroimaging studies, though quality assurance procedures typically reduce error related to data acquisition. Most neuroimaging studies require significant postprocessing to render raw data into behaviorally/genetically meaningful information (e.g., statistical activation maps for fMRI studies or hippocampal demarcation for neuroanatomic studies). However, the reliability of these measures for specific experiments is often not provided. Although many neuroimaging measurements are quite reliable [Specht et al., 2003], the relative reliability across individuals or over time of specific dependent measures (e.g. the exact locus of activation vs. the mean activation vs. the maximum statistical value in a region for a functional neuroimaging experiment) should be considered when choosing measures to apply in genetic analyses.

Another caveat is related to sample size. Genetic studies typically require large sample sizes (between 1,000 and 3,000) to be powered to detect medium to small gene effects. In contrast, most functional neuroimaging studies include 10–20 subjects. Such small studies require strong prior hypotheses (which are generally lacking in complex disease genetics) and extreme ascertainment strategies to have any chance of detecting a true relationship. This disparity in typical sample sizes is a potential point of friction between the traditional geneticist and those originally trained as neuroimagers. Hariri and Weinberger [2003] recently proposed that functional neuroimaging data might represent a final common pathway for neuronal activity before it is transformed into a myriad of possible behaviors. As such, functional neuroimaging data could be significantly more sensitive to gene action than overt behavior and thus far smaller sample sizes may be needed to detect activity using neuroimaging data than behavioral data. To date, this hypothesis has not been formally tested and the number of subjects needed for imaging genomics studies is an open debate.

Despite possible limitations, we believe that the integration of neuroimaging and genetics information will significantly advance our understanding of systems-level neuroscience and provide novel insights into brain-related disorders.

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