Genetic Influence on the Human Brain 13

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The current form of a species reflects advantageous behaviors ingrained and selected by the interaction of genes and environment. That the human mind is the apex of this process is a principle stated and restated by philosophers and scientists throughout history. Now more than ever science is on the cusp of directly linking genes to human brain function.

Imaging genetics—the combination of imaging and genetic information to map gene effects in the brain—enjoys an embarrassment of data riches and equally abundant unrealized discovery. In the late 1980s, the field of human genetics was revolutionized by the discovery of copious molecular markers, advances in fast and cost-effective genotyping methods, and the development of powerful statistical methods. The emergence of human brain mapping nearly paralleled this timeline. Functional magnetic resonance imaging (FMRI) in the 1990s, on the heels of discoveries spawned by positron emission tomography (PET) in the 1980s, pushed knowledge of the brain's inner workings to unprecedented levels. That these frontiers of scientific discovery could inform one another was demonstrated in 2001 (Thompson et al. 2001), just months after the completion of the first working drafts of the human genome sequence were published (Venter et al. 2001; Lander et al. 2001).

Today, we are in the midst of another chapter in the genomic revolution, driven by the development of massively parallel gene sequencing technology that is capable of rapidly genotyping

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hundreds of thousands of polymorphic markers per sample. As a result, the power of whole genome sequence data is outstripping biometric image-based discovery. Defining brain phenotypes that represent the action of genes is the challenge of our time. In particular, there is urgent need for programmatic criteria to extract meaningful phenotypes from neuroimages. Research to properly define traits from an endless possibility of image-based metrics has been shortsighted. This represents a fundamental dilemma that must be overcome. In turn, a systematic program for discovery will be established and our understanding of gene-brain interaction will embrace topics that we cannot yet envision. Indeed, the time is now and the potential for discovery is ripe!

13.1 Traits and Subjects

To date, an over-reliance on obsolete study designs has limited the progress of imaging-genetics and led to a minefield of inconsistent findings. As research of complex brain pathology progressed into the genomic age, investigators naturally gravitated toward methods that were successful for studying affected populations; notably, phenotype and subject criteria related to diagnostic status. Because the degree of impairment and presentation of symptoms in brain-related disorders vary widely among affected individuals (including subclinical impairment), diagnostic categorizations are problematic. This has motivated a more powerful alternative strategy, namely the use of quantitative traits as phenotypes (Blangero 2004; Gottesman and Gould 2003). To date, quantitative traits are applied in three general study design classes: Case-control, twin/sibling pair, and extended pedigree.

Studies utilizing large extended pedigrees have multiple benefits compared to twin designs, including increased power to detect heritable effects, less confounding of genetic effects with shared environmental effects because of the inclusion of multiple households within pedigrees, and greater mathematical power to localize and identify causal quantitative trait loci, and far more power to examine the effects of rare variation (Blangero 2004; for in depth discussion of the rare variation strategy, see Chap. 16 by Curran et al. this volume). However, these advantages are not without added burden. Familial studies typically require more participants than twin studies. Recruiting large families to participate in imaging-genetics studies requires that many family members live in close proximity. As is the case in all quantitative genetic studies, extremely reliable, nonlabile, phenotypes are required. An added benefit of focusing on randomly selected large extended pedigrees is that many different image-based phenotypes can be analyzed in a single study.

13.1.1 Normal Brain Variation

Early large-scale brain-imaging research focused on young, healthy, normal adult subjects (Mazziotta et al. 1995). In the past decade, normative studies of brain structure and function have been extended to the entire human lifespan, from childhood through senescence (Biswal et al. 2010; Glahn et al. 2010; Gogtay et al. 2004; Mazziotta et al. 2001; Sowell et al. 2003; Thompson et al. 2005). Going forward, these streams of research should be the foundation for image-based gene discovery instead of unfounded metrics in clinical populations. Additionally, it is highly likely that the genes involved in normal phenotypic variation are also involved in pathological variation. This further mandates research of genetic influence on normal brain structure and function, as truly understanding pathology may require a better understanding of normal variation.

In vivo MRI data is inherently quantitative and is capable of depicting an immense number of potential phenotypes. Image-based metrics can be drawn from any source of contrast including tissue type, anisotropy level, blood flow, and oxygenation level, among many others. Brain volume, total gray matter, and other global measurements were shown to be highly heritable (Bartley et al. 1997), lobar measurements followed (Geschwind et al. 2002), then measurements of Brodmann areas and specific gyri (Peper et al. 2007; Winkler et al. 2010), and most

recently voxelwise analysis of the whole image space (Stein et al. 2010). Unfortunately, the power to choose has been a double-edged sword.

Phenotypes are often tested in abundance, as there is no established method for selecting phenotypes and data driven techniques provide un-biased perspective. Yet, mapping genes or sets of genes to structure–function relationships has remained elusive. An alternative approach is selecting, modeling, and evaluating potential phenotypes based on our ability to test neuroscience driven hypotheses. Though seemingly apparent, this notion is a drastic deviation from modern high-profile methods, such as testing every voxel in an image for genome-wide association. Not only does such a broad net increase type 1 error, but it also undermines decades of neuroscience-imaging research with a moot question: Do genetic variants influence voxels in MR images? Instead of addressing an arbitrary aspect of image processing (voxels), phenotypes used for gene identification analyses should reflect our understanding of the brain.

Herein, we share the results and conclusions drawn from testing and applying candidate phenotypic measurements in an extended pedigree MRI study. Subjects were randomly ascertained and phenotypes represent normal variation. Extended pedigree designs are more powerful than twin designs for localizing the effects of genes, but also require automated, quantitative, and robust metrics. Because the actions of genes are unknown, phenotypes should represent image-based neuroscientific truth, as we presume. We place focus on basic neuroanatomy. This will develop a foundation for understanding how genetic influence is reflected in the brain structure and function that we quantify using MRI.

While many genetic studies of mental disorders focus on the presence of a particular disease, this diagnostic endpoint is often distant from determinant etiology (Plomin et al. 2009). Conversely, quantitative phenotypes that are genetically correlated with disease liability can be measured in all individuals (both affected and unaffected) and provide greater power to detect disease-related genetic factors than affection status alone (Blangero 2004; Glahn et al. 2012; Gottesman and Gould 2003). Extended pedigrees provide an ideal framework to exploit these advantages, amongst others. Keeping with this strategy, MRI data was obtained from participants in the "Genetics of Brain Structure and Function" (GOBS) study. GOBS is a pseudorandom ascertainment of extended Mexican–American families in the San Antonio area. In 1991, initial investigations were designed to identify risk factors for diabetes, hypertension, and obesity. Since then, first, second, and third degree relatives of original probands and spouses have been recruited. The diversity of biological relationships and large number of informative pairs is indicative of the multigenerational depth and expanse of these large pedigrees (Table 13.1).

13.2 Background and Significance

13.2.1 Why Is Structural MRI Appropriate for Studying Genetic Underpinnings of the Brain?

Statistical genetics quantifies covariance between phenotypic and genetic variability. The statistical power of such analysis is strongly dependent on the precision of phenotypic measurements. Modern MRI technology is capable of providing phenotypic measurements with both high precision and reproducibility. The intersession, scan–rescan variability of MRI-based phenotypes such as global brain volume is less than 1 % (Lemieux et al. 1999). The intersession variability of more localized structural phenotypes such as hemispheric, lobar, and tissue volumes or gray matter thickness is estimated to be in the 3–10 % range (Agartz et al. 2001; Julin et al. 1997; Lerch and Evans 2005).

13.2.2 Is a Trait Influenced by Genetic Factors?

Quantitative genetic analysis partitions trait covariance among related individuals into genetic and environmental components. For the univariate case (a single trait, such as total brain volume),

the covariance matrix (Ω) in a family (pedigree) of n members can be modeled as $\Omega = 2\Phi\sigma_a^2 + I_n\sigma_e^2$, where Φ is the $n \times n$ kinship matrix for the pedigree (Table 13.1), σ_a^2 is the variance in the trait due to additive genetic effects, I_n is an $n \times n$ identity matrix, and σ_e^2 is the variance due to random environmental effects. The most fundamental genetic parameter is the heritability (h^2) of a trait $h^2 = \sigma_a^2/(\sigma_a^2 + \sigma_e^2)$. While this model is for the simplest case of only two variance components (additive genetic and environmental), it is readily extendable via the addition of variance terms in the denominator to allow for additional variance components such as those including dominance genetic variance, X-linked genetic variance, mitochondrial effects, and maternal effects (Almasy and Blangero 1998). Covariates such as sex, age, and their interaction (age × sex) are routinely included in these genetic models. Regression terms are estimated for each covariate, and the likelihood of a model in which the covariate effect is estimated is compared to the likelihood of a model in which the covariate effects are constrained to zero.

Table 13.1 A sample of the pair–wise relationships within Mexican–American pedigrees of participants in the GOBS study

Number of relative pairs	Familial relationship	Coefficient of relationship
2	Monozygotic twins	1
1,004	Parent-offspring	1/2
1,192	Siblings	1/2
352	Grandparent-grandchild	1/4
2,407	Avuncular	1/4
175	Half-siblings	1/4
7	Great grandparent-grandchild	1/8
675	Grand-avuncular	1/8
361	Half-avuncular	1/8
2,783	1st cousins	1/8
34	Great grand-avuncular	1/16
19	Half grand-avuncular	1/16
2,797	1st cousins, once removed	1/16
402	Half 1st cousins	1/32
343	1st cousins, twice removed	1/32
10	Half 1st cousins, once removed	1/32
955	2nd cousins	1/32
321	2nd cousins, once removed	1/64

13.2.3 Are Two Traits Influenced by the Same Genes?

Using the information contained in the kinship matrix and maximum likelihood variance decomposition techniques, the phenotypic correlation between any two traits can be partitioned into additive genetic and random environmental components. This is often referred to as multivariate genetic analysis. The phenotypic correlation (ρ_p) between two traits (x and y), the additive genetic (ρ_a) and random environmental correlations (ρ_e) between the two traits, and their heritabilities (denoted as h_x^2 and h_y^2) are related as follows:

$$\rho_p(x,y) = \left[h_x^2 h_y^2\right]^{1/2} \rho_a(x,y) + \left[\left(1-h_x^2\right)\left(1-h_y^2\right)\right]^{1/2} \rho_e(x,y) \quad (13.1)$$

The additive genetic correlation ranges from −1 to 1 and is a measure of the shared genetic basis of the two traits. An absolute additive genetic correlation of 1.0 indicates complete pleiotropy, where the same genes or sets of genes affect both traits (Almasy et al. 1997). Alternatively, a genetic correlation between 1 and 0 indicates incomplete pleiotropy, meaning that the two traits are influenced to some extent by the same genes, but each trait also has a unique genetic basis. A genetic correlation between −1 and 0 indicates a slightly more complicated circumstance where the two phenotypes are divergent. Similarly, the random environmental correlation is estimated and serves as a measure

of the strength of the correlated response of the traits to nongenetic factors. In the maximum likelihood framework, the likelihoods of models that constrain the genetic correlation (or environmental correlation) between the traits to zero are compared to the likelihood of models that allow the genetic correlation (or environmental correlation) between the traits to be estimated.

This method of genetic correlation analysis allows the determination of (prior to gene mapping or QTL studies) whether two or more brain-related phenotypes are: (1) Influenced by the same sets of genes, (2) by partly overlapping sets of genes, or (3) have no genetic effects in common. These analyses can be used to test a wide variety of hypotheses concerning the genetic architecture of brain-related phenotypes. For example, a series of tests can evaluate whether genes that influence brain structure also influence brain function (as measured by neurocognitive testing).

13.3 Genetic Analysis of Brain-Based Phenotypes

13.3.1 Heritability of the Human and Nonhuman Primate Brain

The size, shape, and internal structure of the primate brain vary considerably between individuals within a species and a significant portion of this intrasubject variability is influenced by genetic factors. While very early stages of primate brain development are predominately mediated by genetic programs (Rubenstein et al. 1999; Rubenstein and Rakic 1999), later stages of development, organization, and brain maturation result from a complex interaction of genetic and environmental influences (Rakic 1988). Studies in nonhuman primates have provided heritability estimates for brain weight ranging between 0.42 and 0.75 (Cheverud et al. 1990a, b; Rogers et al. 2007). Human imaging studies have expanded upon these initial findings. Phenotypes based on lobar measurements are less heritable than global phenotypes and have been shown to vary by lobe (Geschwind et al. 2002). Brodmann areas or specific gyri, though widely variable, are slightly less heritable than lobar phenotypes (Winkler et al. 2010; Wright et al. 2002). Together, these reports demonstrate an indirect relationship between estimated genetic influence and phenotype spatial resolution. Reduced heritability estimates for smaller structures might be associated with the reliability of image analyses rather than an intrinsic reduction in the genetic influences of these regions. However, it is more likely that whole brain phenotypes reflect the action of many genes and are more readily transmitted. Therefore, high heritability values do not convey gene-finding feasibility.

13.3.2 Genetic Influence on Gray Matter

Gray matter primarily consists of neuronal cell bodies. Gray matter is distributed across the surface of the cerebral hemispheres (cerebral cortex) and of the cerebellum (cerebellar cortex). Large collections of gray matter are also present in the thalamic nuclei and basal ganglia and cerebellar nuclei.

The most thorough demonstration of genetic influence on gray matter was provided independently by Panizzon et al. (2009) and Winkler et al. (2010). Specifically, these efforts sought the fundamental actions of genes by investigating the relationship between gray matter volume, surface area and thickness in brain regions similar to Brodmann Areas. Using different samples and designs, both studies concluded that variability of both cortical surface area and thickness were influenced by independent genetic factors, indicating that measurements of gray matter volume confound these effects. Furthermore, focusing on cortical surface area or thickness rather than volume places the investigator closer to the theoretical action of genes.

Since these studies, investigators have increased the resolution of genetic investigations of gray matter by moving from Brodmann Areas to pointwise cortical reconstructions (Figs. 13.1

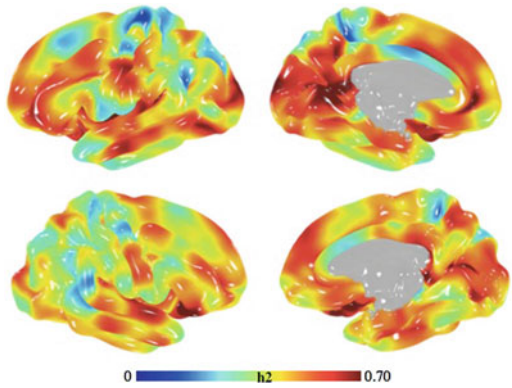

Fig. 13.1 Heritability of pointwise cortical surface area. Phenotypes were defined by parceling each hemisphere into 40,962 vertices using the Freesurfer image analysis suite, which is documented and freely available (Dale et al. 1999; Fischl et al. 1999, http://surfer.nmr.mgh.harvard.edu/). Genetic analyses were performed using the SOLAR software package, which is also freely available (Almasy and Blangero 1998, http://www.txbiomed.org/departments/genetics/genetics-detail?p=37)

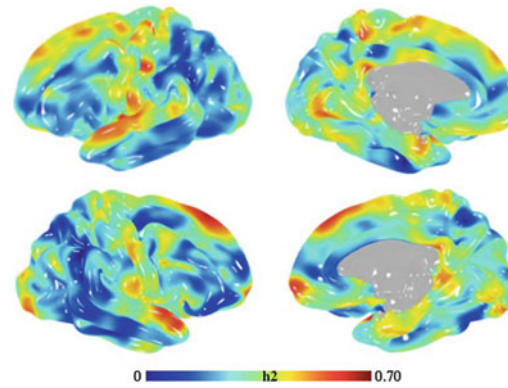

Fig. 13.2 Heritability of pointwise cortical thickness. Image and genetic analyses were performed analogously to those of Fig. 13.1

and 13.2, Winkler et al. 2012). Doing so, alleviates any undue influence of assuming the genetic underpinnings of the cortex correspond to Brodmann Areas.

The conscientious student may draw similarities between this pointwise approach and the voxelwise genome-wide association approach that was criticized in Sect. 13.1. It is important to note that the goal of the analytic techniques used to create Figs. 13.1 and 13.2 is not to identify genes, but to identify heritable traits (i.e. brain regions) that cluster genetically and will therefore have more power for subsequent gene discovery. Such a pointwise approach contributed to the search for genetic roots of the brain by providing phenotypes for the first cortical atlas constructed entirely from genetic information (Chen et al. 2012). In this extremely elegant work, Chen and colleagues used a fuzzy clustering technique in 406 twins to parcel cortical surface area into genetic subdivisions. Boundaries of the cortical map corresponded to meaningful structural and functional organization. Therefore, the Chen subdivisions represent traits that will have greater statistical power for gene identification studies than phenotypes that are nothing more than products of image processing (e.g., individual voxels or vertices).

13.3.3 Genetic Influence on White Matter

Cerebral white matter tracts, or fasciculi, consist primarily of glial cells, myelin, and axons that transmit signals from one region of the cerebrum to another and between the cerebrum and lower brain centers.

Kochunov et al. (2010) demonstrated a significant genetic influence on cerebral white matter in 467 subjects from extended pedigrees. White matter heritability for fractional anisotropy [FA, a measure of white matter integrity (Beaulieu 2002)] averaged across the whole brain was 0.53, $p = 2 \times 10^{-7}$. Figure 13.3 depicts voxel-level heritability estimates projected onto the white matter skeleton. Evidence for genetic control was relatively higher in the inferior fronto-occipital fasciculus ($h^2 = 0.74$), the anterior corona radiate ($h^2 = 0.84$), genu ($h^2 = 0.73$), and the superior longitudinal fasciculus ($h^2 = 0.81$). Heritability estimates were consistently higher for left hemisphere regions than their contralateral area, inline with observations that left hemisphere FA-values are less variable than those on the right (Hua et al. 2009).

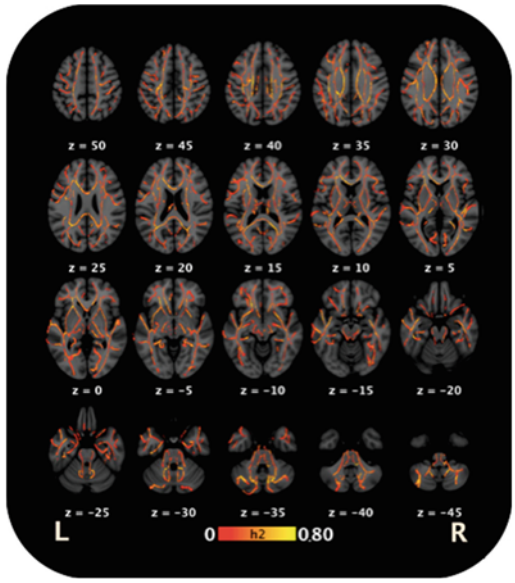

Fig. 13.3 Voxel-level heritability estimates of white matter tract microstructure are presented in standard brain space. Heritability estimates varied from 0 to 0.80 and indicate genetic control of FA-values throughout cortex

Genetic correlations for analogous tracts in left and right hemispheres were high, indicating that common genes influence contralateral tracts. Genetic correlations between the corpus callosum and the other white matter tracts were significant, with the exception of the internal capsule and the cingulum. However, the internal capsule and the cingulum were genetically correlated with each other and other tracts, providing evidence for pleiotropy between different tracts.

This data suggests that voxel-level FA-values are influenced by genetic factors, the microstructure of the major white matter tracts is heritable and that partially overlapping, but not completely common, genetic factors control axonal anatomy of these tracts. These findings are consistent with the notion that a relatively large set of genes influence white matter microstructure and that these genes are not common to all observed white matter tracts. Rather, some tracts are influenced by relatively unique genetic factors. These findings imply that diffusion-based genetic studies of brain-related illnesses should focus on the tract or tracts implicated in disorders, rather than genes that may influence white matter more generally.

13.3.4 Genetic Influence on Functional Connectivity in the Default-Mode Network

When the brain is not engaged in specific tasks, spontaneous fluctuations in neuronal activity give rise to coherent and structured connectivity networks (Biswal et al. 1995; Fox and Raichle 2007, Beckmann et al. 2005), as identified through connectivity analyses with functional MRI and PET. One network, termed the default mode (Raichle et al. 2001), is believed to support self-referential or nondirected cognitive processing (Gusnard et al. 2001) and thought to characterize basal neural activity. Aberrant default-mode connectivity has been reported in individuals with a host of neurological and psychiatric illnesses, suggesting that this intrinsic network is sensitive to pathophysiologic alterations in brain function and structure (Broyd et al. 2009).

Glahn et al. (2010) demonstrated significant genetic influence ($h^2 = 0.42$, $p = 4.6 \times 10^{-3}$) over default-mode functional connectivity independent of genetic influence on regional gray matter density in 333 subjects from extended pedigrees (Glahn et al. 2010). Establishing the heritability of default-mode functional connectivity authorizes the use of resting-state networks as phenotypes in the search for the genetic roots of illnesses that have been associated with altered default-mode connectivity. Furthermore, identification of the genes that influence the intrinsic functional architecture of the human brain would represent a significant advance for basic neuroscience, independent of the ramifications for brain disorders.

Because the default-mode reflects a "baseline" system, it is plausible that the genes that influence default-mode connectivity also contribute to general regulation of brain metabolism, cerebral blood flow, or other aspects of basic neuronal activity. Identification of these genes will provide an important vantage point for understanding the brain's intrinsic architecture and the influence

that those systems have on a host of neurological and psychiatric illnesses. Future studies mapping and identifying the actual quantitative trait loci will provide insight into the genes that influence default-mode functional connectivity.

13.3.5 Cognitive Ability: Genetic Influence on Intelligence

Evidence in favor of pleiotropic effects on various anatomic phenotypes and neurocognitive function has been reported, however, there is little work examining pleiotropic influences on brain morphology, network activity, and neurocognitive variation in triad. Thompson et al. (2001) provided preliminary evidence that prefrontal gray matter density and general cognitive ability covary in healthy twins. These findings were extended by Posthuma et al. (2002) who applied a formal bivariate correlational analysis, concluding that gray and white volume matter and intelligence are mediated by a common set of genes. Since, this same group reported that a single underlying genetic factor mediates working memory ability and global gray and white matter volumes. In contrast processing speed was genetically related only to white matter volume (Posthuma et al. 2003). More recently, performance on a spatial delayed response task and integrity of the superior longitudinal fasciculus were found to share common genetic factors (Karlsgodt et al. 2010). Together, these reports provide strong evidence for overlap between neurocognitive and neuroanatomic phenotypes.

13.4 Initial Conclusions

A decade after the decade of the brain and a decade after the sequencing of the human genome, many thought more would have been discovered. The most glaring nonevent, given the emphasis and allocation of resources, is the general lack of early diagnosis, treatment or prevention of complex disorders. Indeed, the density and combinatorial nature of the two fields has proven immense. Yet and still, many efforts are underway to define measurements from cortex, subcortical nuclei, white matter, and functional connectivity for use as phenotypes in imaging-genetics studies. In time, a systematic program for discovery will yield genetic roots of neuroanatomy and basic brain function.

The remainder of the chapter includes our prospective on the directions that imaging genomics should move in the next decade, pointing out several pitfalls and limitations of the current field.

13.4.1 Over-Reliance on Association and Dysfunction

Human brain mapping relied solely on association of lesion location and neurological deficit for a century after Broca (and others) first made clear associations between structure and function in the 1860s. Investigators observed behavioral deficits, formed hypotheses, and awaited a postmortem autopsy to hunt for lesions in the brain. Due to over-reliance on this method, brain mapping lapsed into a scientific backwater, lasting well into the 1900s. Swapping the brain of that era with the genome of the 2000s, the fields of brain mapping and imaging-genetics employed similar strategies: associations were drawn between dichotomous behavioral traits and a poorly understood entity. Often, a genome wide association study from thousands of case-control subjects was used to nominate candidate genes. Thereafter, functional imaging was used to associate brain traits with a specific variant of those candidate genes. Such a “double association” approach has failed to establish a foundation for further discovery and frequently caused more muddle than clarity in attempted replication studies.

13.4.2 Under-Reliance on Quantitative Traits and Function

Priority and focus must sway from categories of illness toward indices of normal variation. Understanding the genetic influences that

determine variation in neuroanatomic structure and connectivity among normal healthy subjects are likely to elucidate how those processes are disrupted in brain illnesses. Because brain measures vary within the normal population, it is possible to localize influential genes in samples of healthy individuals. Such samples could significantly improve our ability to find genes associated with neuroanatomic variability. Identifying such genes would constitute a significant step forward in understanding the biological mechanisms that govern brain anatomy, providing prospective a priori hypotheses for testing in clinical populations. With properly defined quantitative traits, this will lead to superior gene discovery efforts.

13.4.3 Relation to Gene Discovery

Most of the studies discussed herein do not provide information concerning the identity of causal genes. However, they do provide substantial evidence that there are genes involved in the variability of brain structure and function, and that image-based biometrics are sensitive to genetic mediation. Identification of the underlying genes will provide an important vantage point for understanding the brain's intrinsic structural architecture and the influence that it has on other domains of neuroscience, including clinical impairment.

Showing significant heritability provides critical information necessary before these methods can be appropriately used in studies designed to identify or functionally characterize genes. The identification of one or more genes that influence gross anatomy should provide a causal point in the biological chain that governs variation in anatomical features across individuals. The discovery of such genes could dramatically improve our understanding of how molecular processes influence structure–function relationships throughout the brain. This, in turn, should provide important leads for how these processes are disrupted in illnesses associated with aberrant anatomical traits. The characterization of normal genetic influence in phenotypes relevant to fundamental neuroscience is the initial step toward this vast discovery process (Glahn et al. 2007).

13.5 Implications for the Immediate Future

13.5.1 Lessons Learnt

Some parallels between the fields of brain mapping and imaging-genetics are unavoidable. Others, particularly those that have proven detrimental for brain mapping, should be avoided at all costs by imaging-genetics researchers. Already discussed was an over-reliance on dysfunction, and the lesion method in particular; unfortunately, it is too late to avoid this wave of influence. Another parallel is over-localization of function. Neuroscientists, to some degree, still suffer from the "Grandmother cell" dogma where the sole function of a hypothetical neuron was theorized to identify one's grandmother (Konorski 1967). More fashionably, recent reports have adopted the term "Jennifer Aniston neuron" (Quiroga 2012). From this unfounded line of thought, imaging-geneticists must take caution in implicating single genes or SNPs for highly complex (and conceptualized) function. Rather, the field should take note of the breakthrough that has taken place in many fields and embrace the network-of-genes concept over the single-gene concept.

13.5.2 FMRI

FMRI is slowly becoming a one-stop-shop in brain mapping research. Limitations for use in imaging-genetics research must be considered. As our goal is to characterize phenotypes that will eventually lead to the discovery of causal gene sets, the extraction of highly stable traits is a prime directive. Paradigm-based FMRI is intrinsically state-dependent and less stable than

structural and resting-state MRI. Typically, functional imaging data is averaged across subjects to improve signal to noise ratio because individual subject data can be sporadic. Furthermore, each block of FMRI data is only indicative of a single paradigm, meaning separate scans would have to be acquired in every subject for every task of interest. To guide gene discovery with task-based FMRI, it will become obligatory to model results from published activation studies to identify the most stable and consistent paradigm-induced activation patterns.

13.5.3 Meta-Analysis

Meta-analytic uses of functional imaging data are more reliable. Recently, the BrainMap database (www.brainmap.org) was used to guide a study seeking genetic influence of general cognitive ability. Specifically, regions corresponding to activations induced by working memory tasks were defined meta-analytically. The boundaries of these regions were then exported to a separate cohort for subsequent analyses (Karlsgodt et al. 2010). This work provides proof-of-concept that the spatial extent of paradigm task activations predicted by models of published results can be used to lessen the search space in studies conducted in independent populations. However, it remains to be seen whether the results of Karlsgodt and colleagues would have been improved had FMRI data been acquired on a per subject basis.

Recently, independent component analysis on the entire BrainMap database was used to extract functional connectivity networks (FCNs). The same FCNs were then shown to closely correspond to resting-state networks extracted from thirty subjects, entirely independent of BrainMap (Smith et al. 2009). This groundbreaking finding provides compelling evidence for the coherence of FCNs extracted from resting state data and networks activated by behavioral and cognitive challenges. Because meta-analytic results pool information from many studies, they can be used to guide genetic analysis of structural MRI perhaps with more stability and power than traditional functional MRI. Furthermore, using resting state data in conjunction with meta-analytic results to investigate genetic influence of networks that correspond to task activations is a powerful, cutting edge construct.

13.6 Implications for the Distant Future

13.6.1 Epigenetics

Neuroplasticity is partially modulated by genetic factors and partially modulated by epigenetics, which are dynamic changes that influence the expression of genes without changing the DNA sequence. Epigenetic processes are of particular clinical interest because their external triggers (e.g., diet, drug abuse, and stress) can affect a person's vulnerability to many diseases, including psychiatric disorders. This fledgling field is a natural progression of genetic and environment influence that will gain momentum as our knowledge of gene function improves.

13.6.2 Social Science

The human brain is particularly sensitive to social stimuli. Some feel this has accelerated the rate of human brain evolution in that humans have complex neuronal circuitry for processing interactive social information (i.e. predicting others' reactions and emotions and responding appropriately). Research has revealed that parenting style and early-life stress can epigenetically modify the expression of genes that influence brain morphology and function (Weaver et al. 2004). Such findings may seem farfetched, considering we do not fully understand the function(s) of genes whose expression levels are reportedly influenced. However, we should not expect the diversity of implications to have bounds.

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