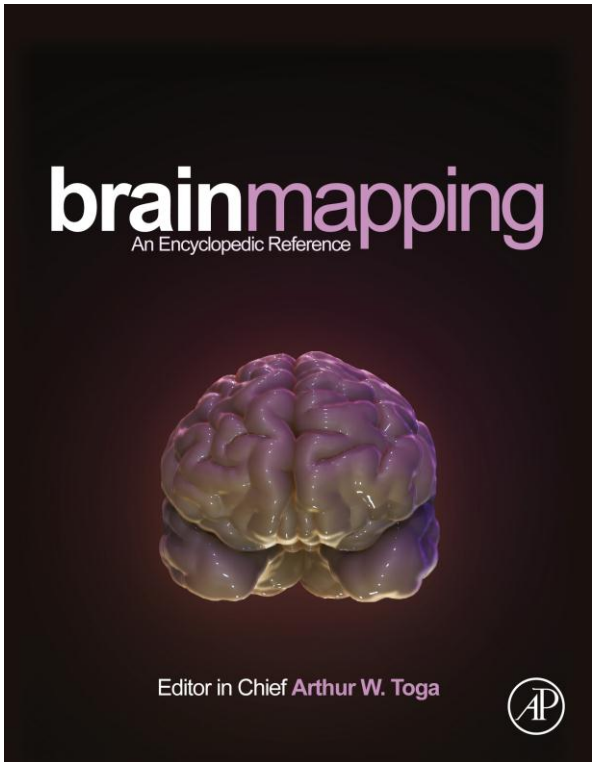

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Imaging Genetics

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Glossary

Genetic linkage A genetic analysis that tests for co-segregation of phenotype and genotype within families and the physical size of the QTL it identifies varies depending on the recombination rate (in centimorgans).
Genome-wide association A genetic analysis that tests for deviations of phenotype-genotype combinations from that predicted by their separate frequencies (genotype and phenotypes).
Heritability That fraction of total trait variance that is explained by genetic factors.
Imaging genetics A sub-field of genetics and imaging research where anatomical or physiological imaging methods are used to create phenotypes for genetic analyses.
Linkage disequilibrium (LD) The non-random association of alleles at two or more loci that is created by population history.
Pleiotropy When one gene or genetic locus influences multiple, seemingly unrelated traits.
Quantitative trait locus (QTL) A chromosomal region that influences a quantitative trait.

The primary goals of imaging genetics are to identify and to characterize genes associated with phenotypes derived from images, particularly indices of brain structure or function. Gene identification involves searching the genome for simple genetic variants, like single-nucleotide polymorphisms, or more complex mutations, like copy number variants, that influence image-derived phenotypes. In contrast, gene characterization involves investigating the impact and mechanism of a known gene or variant on imaging phenotypes. Once a gene is shown to be associated with or linked to an imaging trait, that trait can be anchored to a set of biological processes, such as the protein expressed by the gene, or an entire network of interacting proteins. Such biological insights offer a window into the developmental trajectories and, possibly, the adult physiological processes that control individual trait differences, including those that give rise to neurological or psychiatric illness. In this context, imaging genetics can provide new information on biological mechanisms that govern neuroanatomical and neuropsychological differences in healthy individuals and in disease.

Imaging genomics, like any area of complex genetics, involves numerous different types of analyses, each with different assumptions and challenges to inference. Rather than attempting to describe all of these potential avenues of academic pursuit, this article focuses on four areas of current research, namely, heritability, genetic correlation, candidate gene studies, and gene discovery. Thus, this article is designed to provide an understanding of the scope of imaging genomics and the current evidence in support of using imaging measures in genetics, rather than a complete recapitulation of the field.

Heritability

Are imaging measures influenced by genetic factors and if so, what is the strength of that genetic influence? Heritability is defined as the fraction of phenotypic variance (total trait variance) that is explained by genetic factors. More formally, narrow-sense heritability is the proportion of phenotypic variance in a trait attributable to the additive effects of genetic variants or $h^2 = \sigma^2_a/\sigma^2_p$. Typically, heritability is estimated in twin or extended pedigree studies where the kinship between individuals is known. Heritability estimates vary between 0 and 1, where 0 suggests that genetic factors do not influence trait variance and 1 indicates that trait variance is completely under genetic control. For example, if $h^2 = 0.50$, then 50% of phenotypic variation is due to genetic variation. It is important to note that this does not mean that the trait in 50% of the observed cases is caused by genetics. There are at least three common misconceptions about heritability that should be noted. First, heritability is a population parameter, summarizing the strength of genetic influences on variation in a trait among members of the population from which the study's participants are recruited. Heritability estimates may vary between populations, and these estimates are uninformative at the single subject level. Second, heritability is an aggregate of the effects of multiple genes and is not informative about how many genes influence a phenotype. Finally, a high heritability estimate does not necessarily mean that the phenotype is more powerful for gene identification than a phenotype with lower heritability estimate, if the higher estimate is driven by a larger number of genes, for example, in the case of human height (Lango Allen et al., 2010).

There is substantial evidence for heritability for many brain imaging measures. Specifically, neuroanatomical measures of cortical thickness, surface area, and gray matter volume are consistently reported to be heritable (Kremen et al., 2010; Thompson et al., 2001; Winkler et al., 2010). Similarly, diffusion tensor measures of white matter integrity are typically heritable (Hulshoff Pol et al., 2006; Jahanshad, Kochunov, et al., 2013; Kochunov, Glahn, Lancaster, Winkler, Smith, et al., 2010). Measures of task-based brain activation derived from blood oxygen level-dependent (BOLD) imaging are also heritable (Blokland et al., 2011; Koten et al., 2009; Matthews et al., 2007), though

typically less so than anatomical measures. Furthermore, resting-state connectivity measures derived through multivariate data reduction (Glahn et al., 2010) or graph theoretical approaches (Fornito et al., 2011) appear to be as heritable as task activation measures. Likewise, white matter hyperintensities, small regions of high intensity observed on T_2-weighted MRI scans, which are associated with aging and a number of neurological diseases, are heritable (Carmelli et al., 1998; Kochunov et al., 2009). Together, these data support the notion that brain anatomy and physiology are under genetic control.

Pleiotropy

Since many brain imaging phenotypes are found to be under genetic control, the question arises to what extent the genetic variants that influence them are the same. This is a question concerning pleiotropy, which occurs when one gene influences multiple traits. Unless a specific gene is the focus of a study, pleiotropy is typically assessed in pedigree or twin studies via genetic correlation (ρ_g), which reflects the genetic, as opposed to the environmental (ρ_e), component of a phenotypic correlation (ρ_p). Conceptually, the genetic correlation is a measure of the overlap in genetic effects between traits and varies between -1 and 1, where -1 and 1 reflect complete pleiotropy and 0 implies no pleiotropy.

While fewer genetic correlation studies have been performed with imaging data than heritability studies, evidence for pleiotropy may be more informative. For example, there is almost no genetic correlation between measures of cortical thickness and surface area (Schmitt et al., 2008; Winkler et al., 2009), suggesting that different genetic sources influence these common neuroanatomical measures. Evidence for genetic correlation between neuroanatomical traits and neurocognitive tests bolster claims that genetic factors influencing brain structure also influence function (Brans et al., 2010; Carmelli, Reed, & DeCarli, 2002; Karlsgodt et al., 2010). Similarly, evidence for pleiotropy between neuroanatomical variation and mental illnesses like schizophrenia (Hulshoff Pol et al., 2012) and major depression (Glahn et al., 2012) has been provided through genetic correlation.

Potentially, the most exciting work to date examining pleiotropy with imaging measures involves using genetic correlations to delineate the genetic control over cortical organization. In a set of influential studies, Chen and colleagues used genetic correlation to propose a hierarchical organization of cortical surface area and thickness based on common genetic influences that are readably comparable to those observed in other species (Chen et al., 2013, 2012, 2011). To date, few studies have examined the genetic correlations between different functional neuroimaging traits (e.g., Glahn et al., 2010) or between functional neuroimaging measures and cognitive or pathological traits.

Candidate Gene Studies

The goal of a candidate gene study is to test the hypothesis that a specific gene influences a particular trait. The basic model assumes that genetic variants within or around a gene affect the function of that gene that has subsequent (direct) consequences on individual phenotypic variation. Typically, a candidate gene is chosen because its function is thought to be of theoretical importance to the trait or because it was previously associated with the same trait (replication) or with closely related phenotypes. The most convincing candidate genes are those that demonstrate an effect on the trait at multiple biological levels and where the genetic variant (typically a single-nucleotide polymorphism or SNP) is known to have a clear effect on the structure or abundance of its protein product. Unfortunately, many of candidate gene studies do not meet these requirements, and even when they do, most findings do not replicate (Munafo & Flint, 2004). Despite the rather dubious nature of candidate gene studies, the vast majority of imaging genetics studies conducted to date involve this approach. We review a select few of these findings in the succeeding text.

One of the first and most impactful candidate gene-imaging studies examined the association of the *APOe4* genotype, previously associated with Alzheimer's disease (Corder et al., 1993), and fMRI activation within the hippocampus during a memory task (Bookheimer et al., 2000). Another study examined the association between a nonsynonymous (protein-altering) polymorphism in the *COMT* gene and prefrontal cortex activation in a small group of healthy subjects performing a working memory task (Egan et al., 2001). A series of high-profile studies followed quickly, demonstrating surprisingly strong associations of functional polymorphisms in genes of interest in psychiatry in relatively small samples of healthy subjects studied with fMRI activation protocols (Egan et al., 2003; Hariri et al., 2002). Unfortunately, many of these findings did not replicate over the following decade, which is a common problem in candidate gene studies (Munafo & Flint, 2004). Recent candidate gene studies often had much larger sample sizes, examining multiple variants within the same gene (e.g., Bralten et al., 2011), and/or include additional biological information to characterize gene-imaging associations (e.g., Carless et al., 2011), thereby gaining reliability and reducing SNP selection biases.

Searching the Genome

Similar to most behavioral phenotypes, imaging traits are genetically highly complex and polygenic in nature. Thus, a handful of candidate genes, even if reliably established, will not completely capture the heritable portion of phenotypic variation. It is thus necessary to search the entire genome to discover the multitude of novel genetic variants influencing any particular imaging trait. In general, gene discovery experiments include two phases: localization and identification. Localization involves the identification of a quantitative trait locus (QTL), often a relatively large portion of a chromosome containing many potential genes that likely harbor a gene of interest. In contrast, gene identification involves establishing which gene in the QTL region is driving the association or linkage effect and often includes an understanding of the biological pathways involved.

There are two common methods for QTL localization: association and linkage. Genetic association analyses test for

deviations of phenotype–genotype combinations from that predicted by their separate frequencies (genotype and phenotypes). A genome-wide association analysis for a quantitative trait typically involves an additive effects test using linear regression with the minor allele as a predictor. Any polymorphism identified through association reflects the (joint) contributions of any nearby SNP in linkage disequilibrium (LD) with that variant. LD is the nonrandom association of alleles at two or more loci that are created by population history. Given that LD levels vary throughout the genome, it is possible that SNPs identified through association analyses are representative of a QTL spanning hundreds of thousands of base pairs. Association analyses succeed when the genotyped marker is a functional polymorphism or the genotyped marker is in close LD with a functional polymorphism. In contrast, linkage analysis tests for cosegregation of phenotype and genotype within families, and the physical size of the QTL it identifies varies depending on the recombination rate (in centimorgans) but is typically much wider than in association studies. While association studies can be conducted on unrelated individuals and are only sensitive to common variants (for complex traits typically a frequency >1% in the population studied), linkage analysis requires a family-based design and is sensitive to the effects of both common and rare variants, as long as multiple individuals in the sample are carriers.

A number of whole-genome association studies have been carried out with imaging phenotypes. For example, the ENIGMA consortium used a combined sample of over 21 000 individuals to examine common variants influencing hippocampal volume and intracranial volume (Stein et al., 2012). These investigators localized a genome-wide significant QTL influencing hippocampal volume at an intergenic variant (rs7294919) on chromosome 12q24.22. Additionally, a variant of chromosome 12q14.3 (rs10784502) located within *HMGA2* was associated with intracranial volume. Using data from the CHARGE consortium ($n=9232$), Bis et al. (2012) localized two different loci on chromosomes 12q14 and 12q24 that influenced hippocampal volume, one of which appears to be in LD with a variant identified in the ENIGMA analysis.

Recently, probabilistic tracts derived from diffusion tensor imaging were used to localize a genome-wide significant QTL at variant rs2618516 on chromosome 11p15.2 in *SPON1* gene (Jahanshad, Rajagopalan, et al., 2013). This variant appears to be associated with increased anatomical connectivity, and older carriers of the variant had significantly milder clinical dementia scores and lower risk of Alzheimer's disease.

Several large-scale imaging genomics studies have been conducted in families, and genome-wide linkages have been identified for white matter hyperintensities (Kochunov, Glahn, Lancaster, Winkler, Kent, et al., 2010; Kochunov et al., 2009) and, in a bivariate linkage analysis, between supramarginal gyrus surface area and body mass index (Curran et al., 2013).

While several QTLs have been identified, some of which have also been replicated, to date, no imaging genomics study has definitively identified a gene, though a number of investigators are exploring the use of whole-genome sequence data in conjunction with imaging data for this purpose. In addition, molecular experiments are pivotal in the establishment of causal gene identification and gene characterization; however, these are time-consuming and costly.

Conclusion

Imaging genomics involves imaging-derived traits, primarily neuroanatomical or neurophysiological measures, in conjunction with genetic information in order to gain biological insights into the genetic architecture of brain structure and function. Substantial progress has been made demonstrating the heritability of and genetic correlation (pleiotropy) between imaging traits. Numerous candidate gene studies helped to characterize the impact of theoretically selected genes on brain structure and function. Several large-scale genome-wide association and linkage studies have generated a number of novel loci for neuroanatomical and connectivity traits, and the field is poised for gene identification.

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See also: **INTRODUCTION TO ANATOMY AND PHYSIOLOGY**: Evolution of the Cerebral Cortex; Fetal and Postnatal Development of the Cortex: MRI and Genetics; Genoarchitectonic Brain Maps; **INTRODUCTION TO CLINICAL BRAIN MAPPING**: Depression; Emotion and Stress; Frontotemporal Dementias; Huntington's Disease for Brain Mapping: An Encyclopedic Reference; Hypomania; Imaging Genetics of Neuropsychiatric Disease; Imaging Studies of Anxiety Disorders; Insights into Gilles de la Tourette Syndrome from the Neuroimaging Perspective; Mapping Neurobiological Alterations in Obsessive-Compulsive Disorder; Neuroimaging Approaches to Understanding Youth Antisocial Behavior; Neuropsychiatry; Organic Amnesia; Schizophrenia; Structural Abnormalities in Autism Spectrum Disorder; Temporal Lobe Epilepsy; The Anatomy of Parkinsonian Disorders; **INTRODUCTION TO METHODS AND MODELING**: Integrative Computational Neurogenetic Modeling; **INTRODUCTION TO SOCIAL COGNITIVE NEUROSCIENCE**: Genetic Neuroimaging of Social Perception.

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