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Genetics of the Connectome

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Abstract

Connectome genetics attempts to discover how genetic factors affect brain connectivity. Here we review a variety of genetic analysis methods – such as genome-wide association studies (GWAS), linkage and candidate gene studies – that have been fruitfully adapted to imaging data to implicate specific variants in the genome for brain-related traits. We then review studies of that emphasized the genetic influences on brain connectivity. Some of these perform genetic analysis of brain integrity and connectivity using diffusion MRI, and others have mapped genetic effects on functional networks using resting state functional MRI. Connectome-wide genome-wide scans have also been conducted, and we review the multivariate methods required to handle the extremely high dimension of genomic and the network data. We also review some consortium efforts, such as ENIGMA, that offer the power to detect robust common genetic associations using phenotypic harmonization procedures and meta-analysis. Current work on connectome genetics is advancing on many fronts and promises to shed light on how disease risk genes affect the brain. It is already discovering new genetic loci and even entire genetic networks that affect brain organization and connectivity.

The term “connectome” refers to the totality of neural connections within a brain. It is currently not possible to assess all neuronal connections in a living organism, but using modern neuroimaging and specially designed analytic strategies, we can map the connectome at the macroscopic scale, in living individuals. Indeed, this is the topic of the other articles in this Special Issue of *NeuroImage*. Yet, even with precise and accurate delineation of a “macro-connectome”, the molecular factors that regulate the development

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and behavior of this system are largely unknown. The primary goal of imaging genetics is to identify and characterize genes that are associated with brain measures derived from images, including connectomic maps. Once a gene is shown to definitively influence 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 genes). Such biological insights offer a window into the developmental trajectories and, possibly, the adult physiological activities that control individual trait differences, including those that give rise to neurological or psychiatric illness. In this context, the analysis of brain connectivity using genetic methods, referred to here as connectome genetics, can provide new information on biological mechanisms that govern connectomic differences in healthy individuals and in disease.

In this review article, we summarize our current knowledge of genetic influences on the connectome. We first review the kinds of quantitative and molecular genetic approaches that can be used for analyzing complex traits in general. Then we review studies that reveal genetic influences on brain connectivity, either in terms of anatomy (diffusion-based measures) or function (resting state fMRI). Finally, we discuss some methodological challenges and innovations that arise in the genetic analysis of the connectome, and we describe future directions.

1 A Basic Introduction to Quantitative and Molecular Genetics Methodology

Heritability: How do we decide if a measure is genetically influenced?

In quantitative classical genetics techniques, all trait variance, such as a brain measure derived from an image, can be attributed to either genetic or environmental factors or their interactions. The proportion of trait variance within a population that is due to genetic factors is the conceptualized as the heritability of that trait. Broad-sense heritability reflects additive, dominant and epistatic (genetic interactions) genetic contributions to a heritability estimate and is defined as $h^2 = \sigma^2_g/\sigma^2_p$ where h^2 is heritability, σ^2_g is trait variance due to genetic factors and σ^2_p is the total phenotypic (measured) trait variance. This definition includes multiple sources of genetic variation, so broad-sense heritability is particularly important for selective animal breeding and for certain types of human behavioral genetic studies (such as twin studies). In contrast, narrow-sense heritability reflects only the contribution of additive (allelic) genetic effects to a heritability estimate and is defined as $h^2 = \sigma^2_a/\sigma^2_p$. This additive genetic effect is only a portion of the total genetic effect and it refers to the degree of the phenotypic variance predictable by the additive effect of allelic substitutions, such that the genetic contribution for a heterozygotic pair of alleles is halfway between that of the two homozygotic pairs. As molecular genetic experiments involve mapping allelic variation to trait variance, narrow-sense heritability is the focus of most modern genetic investigations, including imaging genetics studies.

Heritability estimates vary between 0, indicating no genetic influence at all on trait variance, and 1, indicating complete genetic determination. A heritability estimate of $h^2 = 0.5$ would imply that 50% of the phenotypic variation in a particular trait is due to genetic variation, in a particular population. A significant heritability estimate indicates that a trait is significantly influenced by genetic factors, making it an appropriate target for more specific molecular genetic analyses. Calculating heritability estimates is a valuable exercise for novel traits derived from complex image analyses (e.g., connectome maps), as little prior research has shown that such measures are under genetic control. In efforts to discover genetic variants affecting brain measures, preliminary studies of heritability can help to prioritize the more heritable measures for genetic analysis (Winkler et al., 2010, Glahn et al., 2012, Jahanshad et al., 2013a, Blokland et al., 2012).

Heritability is an important and compelling concept, but it is critical to understand its limitations. Indeed, heritability estimates have been misused or misunderstood in several ways in imaging genomics. First, a heritability estimate describes a property of the population being studied, rather than effects in individual members of the population. Furthermore, heritability estimates summarize the strength of genetic influences on trait variation in members of a specific population and may be population-specific, therefore not necessarily generalizable to other cohorts where environmental influences or ancestry may differ. Second, while a heritability estimate measures the proportion of the trait variance explained by variations across the entire genome, it does not tell us anything about which specific genes contribute to it, how many genes are involved, or the impact of any one gene on the trait. Multiple genes, each with a very small effect, can influence a highly heritable complex trait (e.g., normal human height (Yang et al., 2010)). Discerning the impact of any single gene/locus may be difficult. In contrast, a single gene could influence a trait with a much lower heritability (e.g., cis-regulated transcriptional measures) and the crucial locus may be far easier to localize. Some common hereditary diseases, hemochromatosis for example, are strongly influenced by a handful of genes (Jahanshad et al., 2013c), which together predict quite well whether or not someone will develop the disease. Most brain traits appear to be influenced by many common variants with relatively small effects and rare variants with larger effects. The next section discusses approaches for searching for genetic effects on specific traits.

Gene discovery methods

Gene discovery is a multi-stage process that requires an initial localization of a quantitative trait locus (QTL) harboring a genetic variant that is mechanistically related to a trait, followed by more focused analyses to identify a particular gene and study its biological effects. There are two main ways to localize chromosomal regions influencing a trait: *linkage* and *association*. Typically, association methods are utilized when one searches for relatively common variants that influence an illness or trait (e.g. common variant/common disease hypothesis). In contrast, linkage analyses are sensitive to both common and rare variation. As there is an increasing appreciation for the importance of rare variation in human illness, there is currently intense interest in developing methodologies for localizing rare variants.

Genetic linkage analysis tests for co-segregation of phenotype and genotype within families. Genes located in close physical proximity on a chromosome tend to be inherited together during meiosis. Linkage analysis exploits inheritance patterns and thus, is a function of physical connections among genes on chromosomes. The strength of linkage is typically reported as a LOD score (log of the odds ratio), which compares the likelihood of obtaining a linkage between two loci by chance. A LOD score of 3.0, which has a point-wise *p*-value of 1×10^{-4}, takes into account the multiple testing in a genome-wide linkage screen and is traditionally considered a significant effect. The LOD score can be used to compute the asymptotic p-value through the chi-squared distribution with one degree of freedom, for example in this case $p = ½ * P[X^2_{(dof=1)} > (2*\log10)*3] \sim 1\times10^{-4}$. Advantages of linkage analysis include that the power to find a QTL can be easily quantified, and that the approach is minimally influenced by allelic heterogeneity. Disadvantages of the approach include that it requires the study of related individuals and typically localizes relatively large genetic loci (e.g. 10-15 megabases). Such a large locus often harbors many genes and requires additional analytic methods to determine the gene of interest.

Genetic association analysis tests if variants at a single location on the genome occur more often than would be expected by chance, in one group relative to another (or in individuals with high versus low values for a measure), or with respect to a quantitative trait. We can

extend the notion of association to brain measures: a genetic variant is said to be associated with a brain measure if it helps to predict that measure (however weakly), using standard linear regression. However, genome-wide association studies (GWAS) are exclusively focused on a subset of common genetic variants, which do not represent the entirety of total genetic variation. As a result, GWAS rely on the linkage disequilibrium (statistical correlation) among nearby genetic variants, which arises naturally and depends to some extent on population ancestry. *Linkage disequilibrium* (LD) is the non-random association of alleles at two or more loci – the tendency for neighboring genetic variants to be inherited together. However, LD is unpredictable, varies across the genome, and across populations. Indeed, LD need not be present at all at a particular locus in a particular population, making it challenging to estimate statistical power for genetic association analysis, especially if the functional variant of interest is not correlated with anything actually genotyped. Population stratification is another potential source of bias in association studies. If a sample collected for genetic association analysis contains multiple populations that differ in the trait of interest, any locus whose allele frequencies differ between the populations could show an erroneous association (due to population stratification). A third major issue with genome-wide association is the need to correct for the hundreds of thousands (or even millions) of separate statistical tests conducted (requiring p-values $< 5.0 \times 10^{-8}$ to reject the null hypothesis of no genetic effect). When the genome is searched for predictive variants, so many loci are tested that heavy corrections must be made for the number of statistical tests. However, association analysis can be conducted on unrelated individuals, and statistical methods are fast and easy to apply making it a common and practical approach. Statistical corrections for population stratification and for multiple testing have been largely successful, and there are widely agreed methods available to perform these corrections. Furthermore, association analyses typically provide much smaller QTL localization intervals (∼500 kilobases) than linkage, reducing the search space for causal variation. It is critical to note that results from GWAS require follow-up analyses like those in linkage in order to identify the causal variants/gene. Indeed, the functionally relevant variant is likely not to be the allele identified through GWAS, and may not even be on the same genes.

Recently, whole genome sequence data has become far more cost effective to acquire. Whole genome sequence data provides unique information for each of the approximately 3 billion alleles in the genome, the totality of human genetic variation. However, to date, there are no examples of investigators using whole genome sequence data to explore the genetic underpinnings of image-derived traits. Whole genome sequencing has been acquired for several cohorts that have been studied extensively with neuroimaging methods (e.g. the “Genetics of Brain Structure and Function” study with over 1500 imaged individuals and over 1000 with whole genome sequence (Olvera et al., 2011) and the Alzheimer's Disease Neuroimaging Initiative, http://adni.loni.ucla.edu).

Testing candidate genes

The gene discovery methods described above involve genotyping markers spanning the genome and searching for loci that influence a particular trait. In contrast, candidate gene studies involve genotyped markers in genes hypothetically related to a particular trait. Thus, far fewer statistical tests are typically performed and, as genes are typically chosen *a priori*, it can be easier to interpret any findings. Candidate gene studies typically rely on association methods, so they are subject to the same potential biases (e.g., LD and population stratification). Most imaging and connectome related genetic studies have used a candidate gene approach, but others are beginning to perform genome-wide screens of connectome data.

Biological validation of potential gene findings

Regardless of the approach used to localize or identify a gene-phenotype relationship, once such a relationship is established, it must undergo biological validation. Such validation typically involves *in vitro* tests performed on cell lines or in populations of neurons, or the utilization of model organisms. One current limitation of imaging genomics in general, and connectome genetics in particular, is that imaging-derived measures are not readily translated into this type of biological experimentation, as there may not be comparable brain measures that can be studied in the wet lab.

One notable exception is a project that links neuroimaging to gene expression and maps of connectivity - the Allen Brain atlas. The Allen atlas (http://www.brain-map.org) is a growing database of gene expression patterns in the mouse and human brains, and also provides extensive information on mouse brain connectivity. In rodent studies, connectivity can be traced using tracers injected into brain regions such as the subcortical nuclei. The Allen atlas also allows users to browse online data from numerous types of transgenic mice - mice genetically engineered to have certain genetic alterations. This focus on transgenic mice reveals the anatomical consequences of manipulating specific genes, and also relates connection maps to gene expression patterns compiled from multiple sources.

Endophenotypes

Imaging genomics, and by extension connectome genomics, has two potential endpoints: (1) it can provide fundamental insights into basic neuroscience, particularly systems neuroscience; and (2) it can provide an understanding of the genetic underpinnings of brain-related illnesses. This second endpoint rests upon the observation that the genes that influence normal variation also influence pathological variation. For example, if a gene that influenced amygdala connectivity was identified, that gene would be an outstanding candidate for illnesses associated with disrupted amygdala connectivity (e.g. major depression or bipolar disorder (Anticevic et al., 2012)). In this context, the imaging trait can be considered an allied phenotype or endophenotype (Gottesman and Gould, 2003). An endophenotype is a heritable trait that is genetically correlated with an illness and has much greater power to localize genetic loci than affection status alone (Blangero, 2004, Glahn et al., 2012). Many neuroimaging traits, including some measures of connectivity, are disrupted in mental illness and are candidate endophenotypes for these illnesses. For example, individuals with schizophrenia and their unaffected relatives have aberrant default mode connectivity (Whitfield-Gabrieli et al., 2009), raising the possibility that default mode connectivity could be an endophenotype for schizophrenia.

In the next few sections, we review recent genetic analyses of brain measures related to connectivity. As standard anatomical MRI is so widely available, genetic studies of brain morphometry still far outnumber those focusing on connectivity. Indeed, a recent GWAS examining the effects of common variants on the hippocampus utilized a sample of over 20,000 subjects (Stein et al., 2012). Currently, similar GWAS experiments involving connectivity traits are limited to hundreds rather than thousands of subjects. Yet, as with other complex traits, our search for the genetic underpinnings of connectivity measures may benefit from a focus on rare variation observed in family studies, rather than common variants of small effects.

2 Genetic Studies of Diffusion-Based Measures of Connectivity

Diffusion indices, tracts, and networks

Diffusion imaging provides a number of measures that are amenable to genetic analysis. Diffusion tensor imaging (DTI) is sensitive to white matter integrity and its connections, so

it offers the potential to discover general principles that affect brain organization. As noted in other papers in this Special Issue, diffusion-weighted MRI and its more complex variants such as HARDI and DSI (Leow et al., 2011) are sensitive to the directional diffusion of water in the brain. By mapping the principal directions of diffusion from one part of the brain to another, neural pathways may be followed across the brain using tractography, and organized into bundles and fiber tracts (See e.g., Jin et al., 2011, Jin et al., 2013). By mapping fiber trajectories throughout the brain, it has become quite common to use an anatomical parcellation of the brain to group connections into pathways between all pairs of regions. Properties of these connections, particularly their density or fiber integrity, may be stored in connectivity matrices and compared or combined across subjects. The resulting connectivity matrices then become excellent targets for statistical analyses, and genetic analysis is no exception.

Genetic studies of structural brain connectivity, to date, fall into 3 broad categories, analyzing: (1) diffusion properties of the white matter, such as fractional anisotropy (FA) or mean diffusivity (MD); (2) 3D geometrical models of tracts or fiber paths extracted using tractography (including tract shapes (Jin et al., 2011)); and (3) networks of brain connections, represented as connectivity matrices or graphs. The genetics of some network properties, such as network efficiency, is also just beginning to be explored.

The first category of DTI analysis – mapping standard measures of white matter integrity, such as FA or MD – may be considered as not genuinely mapping connectivity. Even so, disruptions or failures of connectivity are often inferred when these white matter measures are altered, so we include them here in our review. A large number of genetic studies have focused on simple DTI measures. Some brain mapping studies of FA have been presented as if they are studies of connectivity, in that abnormal diffusion indices – in the corpus callosum, for example – are often signs of aberrant connectivity that are more conveniently measured than extracting tracts and networks. In addition, DTI indices have been the target of hundreds if not thousands of clinical neuroimaging studies (Thomason and Thompson, 2011), so genetic influences on these brain measures are important to identify.

Heritability of structural connectivity

Some early genetic studies with DTI simply aimed to show that DTI measures are heritable at all, and therefore worthy targets for more in-depth genetic analysis. Using a twin design, Chiang and colleagues (Chiang et al., 2009) assessed white matter integrity using DTI at high magnetic field (4 Tesla), in 92 identical and fraternal twins. By fitting structural equation models to a variety of DTI-derived indices, they were able to show that white matter integrity (FA) was under strong genetic control and was highly heritable in bilateral frontal ($a^2 = 0.55$, $p = 0.04$, left; $a^2 = 0.74$, $p = 0.006$, right), bilateral parietal ($a^2 = 0.85$, $p < 0.001$, left; $a^2 = 0.84$, $p < 0.001$, right) and left occipital ($a^2 = 0.76$, $p = 0.003$) lobes. These measures of white matter integrity were also correlated with full-scale IQ (FIQ) and performance IQ (PIQ) in the cingulum, optic radiations, superior fronto-occipital fasciculus, internal capsule, callosal isthmus, and the corona radiata ($p = 0.04$ for FIQ and $p = 0.01$ for PIQ, corrected for multiple comparisons). They also used a modeling approach called a “cross-twin cross-trait” design, to demonstrate “genetic correlations” between DTI and IQ measures, in the sense that the DTI measure in one twin is correlated with the IQ of the other twin and this correlation is significantly higher in monozygotic twins than dizygotic twins. This type of design can reveal pleiotropy – overlapping genetic influences on IQ and DTI measures, or common underlying genes that affect them both. In other words, if some genetic variants could be found that are associated with DTI measures, they may also be good candidates for affecting cognition. Ultimately, this is the premise of the endophenotype

approach, whereby genetic analysis of images is intended to eventually shed light on the genetics of cognition, or risk for disease.

The heritability of DTI measures was confirmed in a much larger, family based study. Kochunov and colleagues (Kochunov et al., 2010) performed heritability, genetic correlation and quantitative linkage analyses for DTI measures derived from the whole-brain and from 10 major cerebral white-matter tracts. The sample included 467 healthy individuals from large extended pedigrees (182 males/285 females; average age 47.9+/−13.5 years; age range: 19-85 years) from the “Genetics of Brain Structure and Function” study. Average measurements for fractional anisotropy (FA), radial and axial diffusivities served as quantitative traits. Significant heritability was observed for FA ($h^2 = 0.52+/-0.11$; $p = 10^{-7}$) and radial diffusivity ($h^2 = 0.37+/-0.14$; $p = 0.001$), while axial diffusivity was not significantly heritable ($h^2 = 0.09+/-0.12$; $p = 0.20$). Genetic correlation analysis indicated that the FA and radial diffusivity shared 46% of the genetic variance. Tract-wise analysis revealed a regionally diverse pattern of genetic control, which was unrelated to ontogenic factors, such as tract-wise age-of-peak FA values and rates of age-related change in FA. Linkage analysis indicated linkages for whole-brain average FA (LOD=2.36) at the marker D15S816 on chromosome 15q25, and for radial diffusivity (LOD=2.24) near the marker D3S1754 on the chromosome 3q27. These sites have been reported to have significant co-inheritance with two psychiatric disorders (major depression and obsessive-compulsive disorder) in which patients show characteristic alterations in cerebral white matter. These findings suggest that the microstructure of cerebral white matter is under a strong genetic control and further studies in healthy as well as patients with brain-related illnesses are imperative to identify the genes that may influence white matter connectivity.

Ranking the heritability of DTI measures

Among various imaging measures, metrics from DTI have been shown to be especially promising phenotypes for genetic analyses (Blokland et al., 2012). The search for specific genes or SNPs that affect DTI measures can clearly be empowered by pooling large amounts of DTI data, from cohorts worldwide where genetic data is available. The ENIGMA Consortium DTI Working Group is leading one such effort as they have created a common DTI template from 4 large cohorts of subjects, and subdivided it into regions of interest for assessing genetic influences of the diffusion imaging indices (Kochunov et al., 2012, Jahanshad et al., 2013a). Both voxel-wise tract-based spatial statistics (TBSS; Smith et al. 2006) and regional average measures were evaluated. By ranking the ROI measures in order of their heritability, brain regions could be prioritized in order of their promise for future genetic analysis. Measures from some regions, such as the cortico-spinal tract, showed poor (i.e., low) heritability, and it was challenging to measure them consistently across a cohort. Most regional measures were highly heritable (with around half of the observed variance attributable to genetic factors) across two different cohorts –cohorts of different ethnicities scanned using different scanners and protocols on different continents. As mentioned previously, a highly heritable trait does not necessarily mean that a GWAS will produce significant results. Even so, this large-scale genetic analysis of DTI lends confidence to the notion that the DTI measures show consistent and reliable heritability measures across populations and imaging sequences. Meta-analytic GWAS may therefore be feasible for DTI, without being seriously limited by differences among cohorts and scanning protocols. A meta analytic approach is extremely important as some single site GWAS of DTI measures have already been conducted (Sprooten et al., 2012, Lopez et al., 2012), yet while results are extremely promising, these studies were not able to find statistically significant variants associated with the DTI measures.

Searching for anatomic connectivity genes

Kochunov and colleagues (Kochunov et al., 2011) combined cortical thickness and track based DTI measures to search for genes influencing anatomic connectivity. The thickness of the brain's cortical gray matter and the fractional anisotropy of the cerebral white matter are positively correlated and may be modulated by common biological mechanisms. Whole-brain and regional gray matter thickness and FA values were measured from high-resolution anatomical and diffusion tensor MR images collected from 712 participants of the “Genetics of Brain Structure and Function” study (438 females, age range: 47.9+/−13.2 years). Significant genetic correlation was observed among gray matter thickness and FA values, suggesting that the same genetic factors influenced these traits. Linkage analysis implicated a region of chromosome 15q22-23, with the strongest LOD of 4.51 observed for a bivariate linkage between superior parietal thickness and FA values in the corpus callosum. These data strongly suggest that a gene in this area influences anatomic connectivity.

Candidate genes

Several studies have attempted to find associations between single nucleotide polymorphisms (SNPs) and DTI-derived measures, such as FA. To some degree, FA may reflect axonal packing, coherence and even the extent of myelination, so there is a host of candidate biological pathways and genes already implicated in axonal guidance and neural migration that may also affect DTI measures. As such, it seems logical to test whether SNPs in these candidate genes might affect white matter integrity on DTI.

One class of studies of FA has focused on brain growth factors, or neurotrophins, which influence brain growth and the guidance and migration of axons during development. Many commonly carried variants in growth factor genes have been implicated in neuropsychiatric disorders, albeit not entirely consistently. Among them, the brain-derived neurotrophic factor (*BDNF*) gene is critically involved in learning and memory – it modulates hippocampal neurogenesis, synaptic transmission, and activity-induced long-term potentiation and depression (Poo, 2001). In a landmark study, Egan and colleagues (Egan et al., 2003) showed that a common variant in the *BDNF* gene, a methionine (Met) for valine (Val) substitution at codon 66 in the 5′-proregion of the BDNF protein (Val66Met; dbSNP number rs6265), led to poorer episodic memory and hippocampal activation in a cohort of 641 cognitively intact adults aged 25-45.

Chiang et al. (Chiang et al., 2011) genotyped 455 healthy adult twins and their non-twin siblings and scanned them with high angular resolution DTI, and found that the *BDNF* Val66Met polymorphism appears to affect white matter microstructure. By applying genetic association analysis at every 3D point in the brain images, they found that the *Val-BDNF* genetic variant was associated with lower white matter integrity in the splenium of the corpus callosum, left optic radiation, inferior fronto-occipital fasciculus, and superior *corona radiata.* Recently, plasma levels of *BDNF* have also been associated with differences in brain microstructure (Dalby et al., 2013).

Braskie et al. (Braskie et al., 2012) also found associations between white matter integrity (FA) and common variants in the *NTRK1* gene (also known as *TRKA*), which encodes a high affinity receptor for *NGF*, a neurotrophin involved in nervous system development and myelination.

Jahanshad et al. (Jahanshad et al., 2012a) used a twin study design to show that white matter integrity (measured by FA) is genetically correlated to serum transferrin levels in the blood; searching all variants in two genes known to associate with transferrin, they found that FA also relates to whether a person carries the H63D polymorphism in the *HFE* gene. This

gene, involved in iron metabolism, is one of the main genetic contributors to the most common hereditary disorder in the world – hemochromatosis. This disorder affects up to 1% of the population in some countries (e.g., Ireland). As iron is an essential component in neural development and has also been linked to neurodegeneration, the authors first determined the association between an iron measure proxy, transferrin, and brain volumetric measures in healthy adults; finding significant associations, they then determined whether genes associated with iron regulation correlated with healthy brain structural variations. This general inductive approach uses genetic effects on biomarkers (iron) as a way to discover genetic effects on the brain.

Combining SNPs in DTI

As the effects on the brain of any one SNP are likely to be small, some studies have boosted the predictive power by using a set of SNPs, along with regression methods that favor sparsity or efficiency in the resulting predictive model (Kohannim et al., 2012b). Kohannim et al. (Kohannim et al., 2012c) investigated the aggregate effects of commonly carried variants in 6 well-studied candidate genes, on white matter structure in 395 healthy adult twins and siblings (aged 20-30 years). When combined using mixed-effects linear regression, a joint model based on five candidate SNPs (*COMT*, *NTRK1*, *ErbB4*, *CLU*, and *HFE*) explained ∼6% of the variance in the average FA of the corpus callosum. Clearly, such a predictive model requires replication, but the known function of these genes suggests a number of mechanisms whereby these pathways might affect white matter integrity.

Genetics of brain networks

Only a handful of papers have studied genetic effects on brain networks computed from DTI. Several studies use whole-brain tractography to compile a network of connections between all pairs of regions in the brain, resulting in an N × N matrix, or “connectome” for each person in the study. These N × N matrices may be treated as 2D images, and analyzed statistically across subjects, using voxel-wise methods, or any multivariate method used to analyze images (we note of course that there is not necessarily smoothness in an matrix of connectivity as adjacent matrix elements may not index adjacent tracts, so the data in the matrix is not a discrete representation of an underlying spatially continuous function. Adjacent elements in the connectivity matrix do not always correspond to neighboring regions of the brain, but there is a covariance structure that can still be estimated and exploited).

Similar to DTI, candidate gene studies on these N×N networks and topological network measures (see **Methodological Issues**) are also growing in popularity. Dennis et al. (Dennis et al., 2011b) examined a known autism risk gene, *CNTNAP2*; carriers of a common variant in this gene had shown altered brain connectivity on functional MRI (Scott-Van Zeeland et al., 2010). Dennis et al. (Dennis et al., 2011b) found that subjects homozygous for the risk allele (CC) had lower characteristic path length, greater small-worldness and global efficiency in anatomical network analyses, and greater eccentricity (maximum path length) in most nodes of the anatomical network. These results were not reducible to differences in more commonly studied traits such as fiber density or FA. This was one of the first studies to link graph theory measures of brain connectivity to a common genetic variant.

In another study, Jahanshad et al. (Jahanshad et al., 2013b) fitted a structural equation model to every element of the anatomical connectivity matrices from twins, to find connections with significant heritability. After discarding connections with low heritability and those not found reliably across the cohort, they performed a GWAS on each of the remaining connections. A commonly carried variant in one gene, *SPON1*, survived the extremely stringent correction for multiple comparisons, involved in searching across both the genome

and the network. This kind of study will no doubt become more popular, as more population studies of the connectome are published.

These connectome-wide methods are in a sense, an extension of the voxel-wise genome-wide association methods (known as "vGWAS") that are now are under rapid development. Early work on vGWAS (Stein et al., 2010a) showed that it is computationally feasible to search the entire image and genome in a large cohort of subjects, but suffered from lack of power, due to the heavy correction for multiple testing. Later works using dimension reduction or sparse modeling has allowed more efficient and much more highly powered searches of the genome and the image (Vounou et al., 2010, Hibar et al., 2011, Ge et al., 2012, Chi et al., 2013). See the **Methodological Issues** section below for more detail on these methods.

The genetic analysis of brain networks may involve evaluating topological summary measures of network properties to describe network organization – for example, integration, interconnectedness, or segregation of nodal measures rather than strictly examining nodes or edges of the network. As in other connectomics studies, summaries of network topology – such as efficiency, small-worldness, and clustering – may also be computed and analyzed. The Brain Connectivity Toolbox (Rubinov and Sporns, 2010), for example, is one of many toolkits now used to derive a range of summary measures of local and global network properties in connectivity studies. See **Methodological Issues** section for more details.

Clearly, there is an enormous potential for "fishing" – screening measures until some show promising associations. To address this in a principled way, Duarte-Carvajalino et al. (Duarte-Carvajalino et al., 2012) suggested a hierarchical hypothesis testing approach, specialized for analyzing network measures. They advocate efficient hypothesis testing while not unduly inflating the false positive rate with the vast numbers of possible tests. Such methods are important, as connectomics is still in its infancy, and it is not always clear in advance which network measures will be the most promising targets of analysis. As in all areas of genetics, studies are sorely needed that gauge the reproducibility of genetic associations. This is especially the case in neuroimaging. Small samples are the rule, partly because of the expensive of collecting images relative to other types of phenotypic data (e.g., clinical diagnosis). Only a handful of studies have examined how connectomic measures, such as network properties, depend on the algorithms used to compute them (e.g. Zhan et al., 2013a, Bassett et al., 2011).

3 Genetic Studies of Functional Connectivity using Resting State fMRI

As discussed in several articles in this Special Issue, intrinsic brain activity, assessed while an organism is at rest, provides a sensitive measure of default mode connectivity (Fox and Raichle, 2007). It can also assess connectivity in networks that support information processing (Smith et al., 2009). In this section, we examine evidence that resting state networks are, to some extent, under genetic control and provide some clues about the genes that may influence functional connectivity. Task based functional MRI measures have been used as quantitative phenotypes for GWAS (Potkin et al., 2009b, Ousdal et al., 2012). To date, however, no gene discovery experiments (e.g., linkage or GWAS) have been reported using resting state functional MRI or PET derived traits. Thus, our review focuses on evidence for heritability of these traits, and a selection of candidate gene studies.

Heritability of functional connectivity

Functional connectivity has been assessed with EEG (Smit et al., 2008) as well as resting state fMRI. Our focus in this review is on the latter. Assessing functional connectivity in resting state functional MRI data typically involves placing seed regions in the brain (often

followed by graph theory to analyze temporal correlations with signals in the seed regions) or using multivariate decomposition methods (typically ICA). While these analytic approaches have very different underlying assumptions and interpretive utility, it is assumed that the functional connectivity measures index the same neurophysiological processes. However, this assumption has not been directly biologically validated. At one level, heritability estimates provide an external biological validator for imaging measures. To date, heritability estimates generated using either ICA (Glahn et al., 2010) or graph theory (Fornito et al., 2011, van den Heuvel et al., 2012), indices of functional connectivity have been strikingly similar, suggesting that the analytic approach to define resting state connectivity may index similar biological processes. Heritability measures vary between 0.42 and 0.60. So while functional connectivity is heritable, it is probably less influenced by genetic factors than anatomical connectivity measures (see above). Or, it may be that resting state measures are simply noisier or less reproducible than DTI measures of connectivity.

Glahn and colleagues (Glahn et al., 2010) were the first to publish heritability estimates for measures of default mode connectivity. They used an ICA approach in 333 individuals from 29 randomly selected large extended pedigrees. Heritability for default mode connectivity was estimated to be 0.424 ± 0.17 ($p = 0.0046$). While an index of anatomic variability (gray matter density) within this brain network was also heritable ($h^2 = 0.327+/-0.17$, $p = 0.020$), the genetic correlation between functional connectivity and anatomic variance was non-significant ($\rho_g = 0.077+/-0.38$, $p = 0.836$), suggesting that different genes may influence structure and function within the default mode, or that there is a lack of power to detect genetic overlap at this point.

By balancing different graph theory based parameters to maximize “communication efficiency” while minimizing “connection cost”, Fornito et al. (Fornito et al., 2011) developed optimized cost-efficiency network from resting state functional MRI data in 58 healthy twins (16 monozygotic pairs and 13 dizygotic pairs). While there was little evidence for genetic control of BOLD signal fluctuations in the 0.02-0.04 Hz, 0.04-0.09 Hz, or 0.18-0.35 Hz ranges, the heritability estimate for network connectivity in the 0.09-0.18 Hz range was $h^2 = 0.60$ (95% confidence interval 0.17-0.83), suggesting substantial heritability. Decomposing this global network effect in the 0.09-0.18 Hz range indicated that genetic influences were not distributed homogeneously throughout the cortex, and regional heritability estimates ranged from < 0.10 to 0.81 (0.51 median).

A third recent manuscript found evidence for resting state connectivity in normally developing children (age=12). Using 21 monozygotic and 22 dizygotic healthy twin-pairs, van den Heuvel et al. (van den Heuvel et al., 2012) found significant heritability ($h^2 = 0.42$, $p < 0.05$, CI = 0.05-0.73) for a global network measure, lambda (the normalized characteristic path length) derived from resting state connectivity graphs, while gamma, the normalized mean clustering coefficient, of the network was not. The authors therefore suggest that even in childhood, the global efficiency of communication in the network is heritable

Candidate genes

There have been numerous candidate gene studies of resting state functional connectivity. However, most include only a single polymorphism in relatively small samples and have not been replicated by other groups. Where possible we focus here on candidate genes studied in at least two separate samples or with relatively large samples, using resting state functional MRI.

The apolipoprotein E (*APOE*) gene is the most well-verified susceptibility gene for the most common form of (sporadic late-onset) Alzheimer's disease (Farrer et al., 1997, Coon et al.,

2007). The odds ratio for individuals homozygous for the ε4 risk allele is 14.9, while the ε2 allele is moderately protective (OR=0.6) (Farrer et al., 1997). In an early study, Filippini et al. (Filippini et al., 2009b) reported increased default mode connectivity, particularly in hippocampal and surrounding regions, in 18 healthy ε4 carriers (age 20-35 years) relative to 18 demographically matched non-carriers. This finding was replicated in a larger sample (N = 95) of healthy individuals between 50 and 80 years of age (Westlye et al., 2011). Recently, Trachtenberg et al. (Trachtenberg et al., 2012) extended these results by examining 77 healthy participants aged 32 to 55 with different *APOE* genotypes in a number of resting state networks. Relative to ε3 homozygotes, ε2 and ε4 carriers showed similar connectivity patterns. Indeed, carriers of the risk and the protective alleles were almost identical across a number of resting state networks. Thus, while it is clear from these studies that *APOE* influences functional connectivity, the effects of the gene do manifest in a manner reflective of the link between *APOE* and Alzheimer's risk.

The *COMT* gene encodes for the catechol-O-methyltransferase enzyme that is involved in the extra-neuronal degradation of dopamine, particularly in the prefrontal and temporal cortex (Matsumoto et al., 2003, Tunbridge et al., 2006). The Val158Met allele of *COMT* is a functional polymorphism that results in a substitution of valine (Val) by methionine (Met) at amino acid 158 of the membrane-bound form of *COMT* (Lachman et al., 1996). Val homozygotes have a fourfold increase of *COMT* activity relative to Met homozygotes (Chen et al., 2004). Liu et al. (Liu et al., 2010) examined the impact of the Val158Met polymorphism on prefrontal functional connectivity in 57 healthy subjects. Compared with heterozygotes, Val homozygous has decreased prefrontal-related connectivities, suggesting that *COMT*'s effects on prefrontal dopamine levels modulate prefrontal default network connectivity.

Table 1 summarizes a list of recent studies focusing on genetics of the connectome. These include heritability analyses, candidate gene associations, validation of new connectome metric methodologies, and genome-wide connectome-wide association scans.

4 Methodological Issues

Imaging genetic methods are evolving, particularly those involving the connectome. Some connectome-related association studies used functional data (resting state reviewed above), while others used networks from diffusion imaging. In this section, we review some common methodological approaches for imaging genetic studies, and also present some of the more novel, uniquely network based analyses and methods that can provide for promising endophenotypes for future genetic studies.

Almost all methods developed to date for general voxel-, surface-based, or ROI-derived imaging data, may also be applied to the rich phenotypes computable from connectome data. Here we review some key methods used for genetic analysis of images, even though not all of them have yet been applied to connectome phenotypes. As these methodologies have proven extremely successful in other works, the application to connectome phenotypes holds great promise for the future.

The field of imaging genetics started with candidate gene and candidate phenotype studies, as it was uncommon, and costly, to genotype subjects at more than a handful of genetic loci. Prior biological knowledge was typically used to select specific, well-studied genetic variations or a single characteristic measure of brain anatomy, function, or connectivity. This allowed people to test biologically plausible hypotheses and assess genetic effects on the brain in a range of neurological and psychiatric disorders. Genetic association studies using images may be broadly categorized into one of the 3 classes: (1) candidate-phenotype

candidate-SNP/gene association (e.g., Joyner et al., 2009); (2) candidate-phenotype genome-wide association (e.g., Potkin et al., 2009a, Stein et al., 2010b), which is a traditional GWAS; and (3) brain-wide candidate-SNP/gene association (e.g., Filippini et al., 2009b, Braskie et al., 2011, Roussotte et al., 2013, Rajagopalan et al., 2012), which is a traditional imaging analysis – performing association tests at each single voxel to form statistical maps. Eventually, the trend in imaging genetics may be to embrace the brain-wide, genome-wide association paradigm, where both the entire genome and entire brain are searched for non-random associations (Hibar et al., 2011, Stein et al., 2010a, Jahanshad et al., 2013b). This brings unprecedented opportunities to identify novel genetic determinants of imaging measures and generate 3D maps of their effects in the brain. Figure 1 summarizes some of the imaging genetics association studies in the literature.

Univariate-imaging univariate-genetic association

The first completely unbiased whole-brain whole-genome search was a voxel-wise genome-wide association study (vGWAS) (Stein et al., 2010a) (See Figure 2A). Independent association tests were performed for each pair of SNPs and voxels in maps of local brain volume differences calculated by tensor-based morphometry (TBM) (Leow et al., 2005). This typical massive univariate approach resulted in a total of more than 10^{10} statistical tests. Only the minimum *p*-value across the genome was recorded at each voxel to accommodate the huge number of statistical tests performed. The *p*-value distribution for the most associated SNP was modeled as a Beta distribution, Beta(1, N_{eff}), where N_{eff} is an estimate of the effective number of independent tests performed, accounting for the genetic correlation along the genome. The minimum *p*-value at each voxel was then adjusted by the fitted theoretical distribution, and corrected over the brain using the false discovery rate method (FDR) (Benjamini and Hochberg, 1995). This work is pioneering, as it showed that a full scan of the genome with brain imaging phenotypes is feasible. However, the drawbacks of this approach are also clear. Univariate-imaging univariate-genetic association tests completely ignore the spatial correlation in 3D imaging data and therefore typically have poor reproducibility and low power. Also, with millions of billions of statistical tests performed, the computational burden is extremely heavy, and the colossal multiple comparisons correction often leaves no significant associations (Stein et al., 2010a). Clearly, more sophisticated multivariate methods are needed to account for the spatial structure in both the imaging and genetic data.

Univariate-imaging multivariate-genetic association

Multivariate methods can be used to model the interaction between SNPs or the joint effect of multiple SNPs on imaging traits. SNP sets can be formed by SNPs located in or near a gene, SNPs located within a gene pathway, SNPs within evolutionary conserved regions, or other *a priori* biological information. Alternatively, the grouping may be based on a sliding window or the haplotype blocks to cover the entire genome (Wu et al., 2010). Grouping SNPs and performing set-based association tests can alleviate the stringent multiple comparison correction compared to individual-SNP tests. Set-based SNP tests also offer the possibility to accommodate genetic interaction, model joint effects of SNPs, and test cumulative effects of rare variants. Importantly, multivariate methods often have improved reproducibility and increased power relative to univariate methods, especially when individual SNPs have similar but modest effects.

Early work on set-based tests combined test statistics or *p*-values from standard individual-SNP tests, so they suffered from many of the same problems as univariate tests (Hoh et al., 2001, Purcell et al., 2007). The simplest and classical way to test the overall effect of multiple SNPs is to use a multiple linear regression. However, the high LD between co-segregated SNPs in haplotype blocks often produces collinearity between the SNP

regressors and can substantially overestimate the available degrees of freedom in the model. If it is reasonable to assume that the effects of all SNPs are in the same direction and most of the SNPs are causative, one can collapse all SNPs into a single regressor and perform a so-called burden test (Morgenthaler and Thilly, 2007, Li and Leal, 2008, Madsen and Browning, 2009, Morris and Zeggini, 2010).

Alternatively, penalized and sparse regression techniques (Yuan et al., 2012, Wang et al., 2013) may be used, including ridge regression (Hoerl, 1985, Kohannim et al., 2011), the least absolute shrinkage and selection operator (LASSO; Tibshirani, 1996, Kohannim et al., 2012b), and elastic net (Zou and Hastie, 2005, Kohannim et al., 2012a). (See Figure 2B.)

Hibar et al. (Hibar et al., 2011) used a method known as principal components regression (PCReg) to approach the collinearity problem. They first performed PCA on the set of SNPs to extract mutually orthogonal predictors that explain the majority of the total genetic variance, and then built a partial-F regression model. By grouping SNPs based on gene membership, a voxel-wise gene-wide association study (vGeneWAS) was carried out, using the same imaging and genetic data as in vGWAS (Stein et al., 2010a, Hibar et al., 2011) showed increased power of their methods although no gene survived multiple testing correction, perhaps due to the over-simplification of the empirical and linear method, and the massive univariate nature of the method on the images.

Recently, Ge et al. (Ge et al., 2012) presented a suite of methods to address the limitations of the existing whole-brain genome-wide association studies. They introduced to imaging genetics a kernel machine-based multi-locus model (Liu et al., 2007, Wu et al., 2011) that provides a biologically-informed way to capture the interactions between SNPs and model their joint effect on imaging traits. This method models non-SNP covariates and offers a flexible framework to model epistatic effects between genetic variants based on the choice of kernels, whose elements are measures of genetic similarity between pairs of subjects. By using a connection to linear mixed models, the semi-parametric model can be fitted efficiently at each voxel, and a standard variance component test can be used to make inference (Lin, 1997), yielding an approximate chi-squared statistical map whose degrees of freedom can adapt to the correlation structure of the sets of SNPs (Liu et al., 2007). A fast implementation of voxel- and cluster-wise inferences based on random field theory (RFT) (Worsley et al., 1996, Friston et al., 2006, Ge et al., 2012) was then applied to the statistical map, which makes use of the 3D spatial information in the imaging data and performs multiple testing correction over the brain by implicitly accounting for the search volume and smoothness of the statistic image. A head-to-head comparison to vGWAS (Stein et al., 2010a) and vGeneWAS (Hibar et al., 2011) using the same data set shows boosted statistical power when combining these methods. Several genes were identified with whole-brain whole-genome significance for the first time.

Joint multivariate association

In order to respect the multivariate nature of both imaging and genetic data, joint consideration of the imaging and genetic data appears to be promising. One candidate for joint multivariate modeling is a regularized version of the two-block method, e.g., the canonical correlation analysis (CCA) (Hotelling, 1936) and the partial least squares (PLS) regression (Wold et al., 1983) with an additional l^1 or l^2 regularization to handle high dimensional data and perform variable selection. Both methods hypothesize that imaging and genetic data are linked through two unobserved latent variables, and seek linear combinations of the two data blocks – as an approximation to the latent variable – that have the maximum correlation with each other. (See Figure 2C.) Recently, Le Floch et al. (Le Floch et al., 2012) applied the sparse PLS method in the context of imaging genetics. Liu et al. (Liu et al., 2009) proposed another two-block method known as parallel independent

component analysis (paraICA or PICA), which discovers independent components of the imaging and genetic data respectively, and at the same time determines and maximizes the correlation between the components of the two modalities. One challenge of this approach is that it may be hard to recover the contributing SNPs and locate the spatial effect in the brain from large genetic and imaging components, making the results harder to interpret. A slightly different but related perspective on joint multivariate modeling is to consider a multivariate multiple regression, i.e., regressing the entire imaging data block on the genetic data, and impose different structures or regularizations on the regression coefficient matrix. Recent work in this category include group-sparse multi-task regression (Wang et al., 2012a) and sparse multi-modal multi-task regression (Wang et al., 2012b), which used a group-sparse or group-lasso penalty to incorporate the grouping of SNPs and to enforce a sparse structure across different SNP groups and imaging modalities. Vounou et al. (Vounou et al., 2010) introduced a sparse reduced-rank regression (sRRR) method. They reduced the rank of the regression coefficient matrix to a number much smaller than the number of imaging traits and the number of SNPs, and then factorized the coefficient matrix into the product of two small full-rank matrices, which are constrained to be sparse. (See Figure 2D.) The method was applied to a whole-brain whole-genome data set in a subsequent publication (Vounou et al., 2012).

Joint multivariate methods better capture the multivariate nature of the data and significantly reduce the number of statistical tests, alleviating the multiple testing correction problem. Therefore, they may provide increased power relative to massive univariate methods. A common drawback of these methods is the over fitting issue, especially when handling very high dimensional data. Currently, in most applications, data reduction is needed before these methods can be applied. Moreover, these complex multivariate methods normally use iterative optimization procedures, so computational demand is high, especially when one needs to tune some regularization parameters and to validate the results through cross-validation or permutation schemes.

Data reduction methods

Due to the ultra-high dimensionality of both the imaging and genetic data, comprehensive modeling of whole-brain voxel-wise and genome-wide data remains challenging and may cause a number of statistical and computational problems. Therefore, a balance is often needed between pure discovery methods and those that invoke data reduction. *A priori* biological information may be used to restrict the analysis to some particular brain regions or a wide list of possibly associated SNPs and genes. Alternatively, various softwares and templates may be used to split the brain into a number of cortical and subcortical regions of interest (ROI), and extract a summarized measure from each ROI to get a coarse coverage of the entire brain. Such parcellation is easy to perform and consistent across subjects, but has the risk of missing patterns of effects that lie only partially within the chosen ROIs. Data-driven feature extraction approaches such as principal component analysis (PCA) and independent component analysis (ICA) may be used to avoid these problems. Recently, Chiang et al. (Chiang et al., 2012) proposed a novel approach to data reduction on voxel-wise data. Specifically, they selected highly genetically influenced voxels and then clustered these voxels into ROIs based on their genetic correlation within images. This approach can potentially be applied to any imaging modalities that show pleiotropy. As for the dimension reduction of the whole-genome data, a preliminary univariate filtering is commonly applied. Multivariate methods may also be used iteratively, removing the lowest ranked variables at each iteration (Guyon et al., 2002). Iterative sure independence screening (Fan and Lv, 2008, Fan and Song, 2010) iterates a univariate screening procedure, conditional on the previously selected features to capture important features that are marginally uncorrelated

with response. This may be a promising method for data reduction and has been applied to genome-wide association studies (He and Lin, 2011).

Connectome methodologies

The human brain connectome can be represented as a matrix, or a graph, containing regions of interest as nodes and connections or correlations between them as edges. Based on this matrix or graph, many topological graph theory measures can be evaluated on the connectome. These more abstract measures provide complementary information to the more traditional imaging features, including details regarding the more global organization of structural and functional connections in the brain. The genetic influences on these organizational properties may reflect gene effects that are involved in a host of biological pathways having global effects on the brain, rather than just those with an effect at the cellular level or an effect on the integrity of brain tissues. Combining information on anatomical and functional integrity with measures of network organization will allow a more comprehensive understanding of genetic effects on the brain. As mentioned previously, one of several publically available toolboxes for calculating these measures is the Brain Connectivity Toolbox (Rubinov and Sporns, 2010). While genetic analyses on more standard and readily available measures such as path length, efficiency, clustering coefficient, and small-worldness have been described previously, other measures to analyze and more robustly understand the network are being continually developed and proposed.

Evaluation of measures on the structural “backbone”, or core, of the matrix by thresholding out low density connections can yield higher signal-to-noise and hence more stable results than including small noisy connections in the topological measures (Hagmann et al., 2008). This network core at a range of thresholds can also be used to describe a ‘rich-club’ network, defining the set of high-degree nodes that are more densely interconnected among themselves than nodes of a lower degree (van den Heuvel and Sporns, 2011, Daianu et al., 2013); once genetic analyses are performed at these levels, this increased signal-to-noise could then facilitate more robust analyses and the opportunity for successful replication studies. On another hand, other methods are being adapted to the connectome to devise a multi-scale framework to model the connectome at all the possible thresholds using filtration methods (Lee et al., 2012). These works improving and expanding connectome-specific analyses methods are potential targets for the variety of genetic analyses described above.

5 Replication and Future Directions

As can already be seen, the connectome offers a rich and promising target for genetic analysis. Some analyses have already screened connectomes from hundreds of twins and others for hundreds of family members. They discovered genes that may affect our risk for Alzheimer's disease (Jahanshad et al., 2013b). Others have found that functional networks are heritable, with several promising candidate gene findings. Even so, most genetic analyses consider a single trait – such as a diagnosis of Alzheimer's disease or schizophrenia. Clearly, in the case of imaging – and connectomics in particular – we need to adapt genetic methods to cope with networks, graphs, connectivity matrices, and other unusual data types (such as path lengths in networks (Jahanshad et al., 2012d)). In this review we have summarized some of the efforts to cope with the high dimension of genomic and imaging data at the same time, which will be vital in connectomics, as connectivity is essentially an $N \times N$ signal storing information on connections between all pairs of brain regions.

Failures to reproduce findings

Early work by Potkin and others emphasized the sample sizes needed to detect and replicate a genetic effect of a SNP on a brain measure, or any other quantitative trait. Gene effects tend to be orders of magnitude smaller than many other statistical effects on brain images – such as the effect of a cognitive or behavioral task on brain activity in functional MRI, or the effect of a neurological disease such as Alzheimer's disease or epilepsy on brain measures such as hippocampal volumes. In clinical studies, a degenerative disease may reduce the mean volume of a structure (such as the hippocampus) by 10-15% on average, but large-scale genetic studies (such as those by the ENIGMA and CHARGE consortia) suggest that it is rare for a SNP to affect hippocampal volume by more than about 1% per allele. Even the most credible and highly replicated findings from ENIGMA influenced brain phenotypes by around one percent. Although a one percent difference in volume may be highly significant to an individual (equivalent to 3-4 years of aging), it stands to reason that most studies finding a much larger SNP effect than that, in samples of a few hundred subjects or fewer are somewhat suspicious, as power considerations suggest that studies can pick up only moderate to large effects.

If a study reports a high effect size in a small sample, some skepticism is warranted, because small effect sizes are much more common. Although some published findings may be false positives or errors (Ioannidis, 2005), other more subtle phenomena such as the “winner's curse” are well known in quantitative genetics, where the effect size of a finding is often not as strong in a replication sample as it is in the initial discovery sample. With the development of large neuroimaging genetics consortia combining data from many cohorts worldwide, the risk of spurious findings should be progressively lowered, and the chance of a false positive effect remaining credible for a long time is greatly reduced. The same meta-analysis approach may be able to resolve some of the controversies regarding very small but subtle effects on brain measures in psychiatry (Hibar et al., 2013b, Turner et al., 2013).

Replication and meta-analysis

One of the early disappointments in psychiatric genetics was that genes discovered to affect risk for schizophrenia and depression, were often not replicated in future studies, leaving the literature full of un-replicated findings whose reliability and credibility is now unclear (Flint et al., 2010). In psychiatry, the issue of non-replication was addressed by forming very large consortia to pool data from many cohorts, often involving discovery and replication samples in the tens of thousands (Sullivan, 2010). In addition, there has been a good deal of debate as to exactly what constitutes replication and what needs to be replicated. For GWAS studies of common variants, the gold standard has been replication of the exact variant in the exact direction in a separate sample. As the field moves to examining rare variants, what constitutes replication is changing, as it is often not possible to replicate a specific rare variant. Indeed, for findings based on rare-variants, gene-level replication, based on a burden test, is considered acceptable. Ultimately, the goal of replication is to show that one's findings are not spurious or unique to a single sample. In this context, the requirement for biological validation of linkage/GWAS/sequence results provides additional support for a finding.

In 2009, the ENIGMA Consortium (http://enigma.loni.ucla.edu) was founded to help pool data from imaging genetics studies worldwide, and perform studies with enough power to find single common variants in that affect the brain. One such effort pooled data on hippocampal volume, and intracranial volume, from 21,151 individuals scanned at 125 institutions worldwide, and discovered several common genetic variants affecting these brain measures (Stein et al., 2012). A follow-up effort screening the genome for effects on all subcortical structures is underway (Hibar et al., 2013a) and working groups studying

brain connectivity and integrity are harmonizing phenotypes to allow data pooling (Kochunov et al., 2012, Jahanshad et al., 2013a). For these efforts to succeed, there needs to be a common effort to agree on brain measures that can be consistently computed from brain images worldwide. Promising targets for genetic analysis must be heritable, and reproducible to measure. Zhan et al. (Zhan et al., 2013b) and Dennis et al. (Dennis et al, 2012) studied the stability of connectomic measures at different field strengths and their repeatability over time; Jahanshad et al. (Jahanshad et al, 2012b) studied diffusion imaging protocol effects on genome-wide scanning results.

While efforts to identify common variants influencing brain connectivity are progressing, far fewer studies have attempted to examine the impact of functional rare variation on these traits. Yet, there is growing recognition that rare variation is important for human disease and normal variation. Given that rare variants are uncommon in the general population, family studies offer an advantage over studies of unrelated individuals, as related individuals are more likely to share rare variants. To our knowledge, there are currently no efforts designed to develop imaging genetics consortium dedicated to the study of rare variants.

An alternative line of work is exploring how disease risk genes affect the brain, and how they affect measures derived from neuroimaging, including connectivity measures. As noted earlier, brain connectivity appears to differ in people who carry some common Alzheimer's disease risk genes (*CLU*; Braskie et al., 2011) or risk genes for schizophrenia (*NTRK1*; Braskie et al., 2012) or autism (*CNTNAP2*; Dennis et al., 2011b). Carriers of disease risk genes and people with the disease may also have common network abnormalities (Engel et al., 2013, Toga and Thompson, 2013). Some of the larger psychiatric genetic efforts are unearthing SNPs that appear to confer disease risk in schizophrenia and autism, and efforts are underway to screen connectomic and other neuroimaging data to see what these variants do to the brain. To ease the search, informatics tools can make it easier to look up risk genes or common variants and see how they affect brain phenotypes in various cohorts worldwide (e.g., ENIGMA-Vis; Novak et al., 2012). A major line of discovery will be possible once connectomic data can be searched and meta-analyzed with genome-wide, connectomic-wide screens. Such an effort will combine many of the methods discussed in our review, as well as others not yet conceived or imagined.

Freely available datasets

One recent benefit to the imaging genetics community is the availability of some freely available datasets with MRI, DTI, GWAS, and other biomarker data. ADNI, for example (adni.loni.ucla.edu), freely provides both GWAS and MRI data to any interested and qualified researcher. There is no doubt that freely available datasets can lead to many more published findings – if many analysis groups study the same dataset, they also greatly increase the scrutiny of the data for errors, which is helpful for data quality control and curation and promotes scientific integrity. As not all neuroimaging data is made freely available, it is also important to consider solutions for datasets that are restricted to users at one site. Sometimes, restrictions on the dissemination of personal genetic data may be imposed at the outset of a study, in a human subjects consent form, for example. Intermediate solutions may involve the sending of software and analysis protocols to many remote sites, and the reporting of statistical summaries or aggregates to a working group. Rather than the sending of all imaging data to a centralized repository, this distributed processing approach has been adopted by consortia such as ENIGMA; it is also computationally efficient as it draws on the computational and personal resources of many sites in parallel, while respecting constraints on the wider dissemination of scans or personal genetic information.

6 Conclusion

To summarize, connectome genetics is still a nascent field. Yet even in its infancy, the connectome is proving to offer highly favorable phenotypes as genetic associations made or even discovered in the connectome have already been replicated. In several cases, genetic variants associated with brain connectivity have been shown to affect other brain measures, or risk for disease. Clearly, future studies using meta-analytic methods may be required to make stronger statements about genetic associations that are robust across multiple cohorts. Statistical approaches are rudimentary compared to imaging-only or genetic-only methods. The field is moving towards a complete discovery science, seeking new and credible associations between whole-connectome genome-wide data without any *a priori* assumptions. Computationally efficient, biologically plausible, and statistically powerful methods are urgently needed to tackle the ultra-high dimensional imaging and genetic data with complex covariance and noise structures.

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Highlights

Connectome genetics attempts to discover how genetic factors affect brain connectivity. Here we review a variety of genetic analysis methods and studies of brain connectivity, particularly DTI and resting state fMRI methods that used a genetic design. Current work on connectome genetics is advancing on many fronts, and promises to shed light on how disease risk genes affect the brain. It is already discovering new genetic loci and even entire genetic networks that affect brain organization and connectivity.

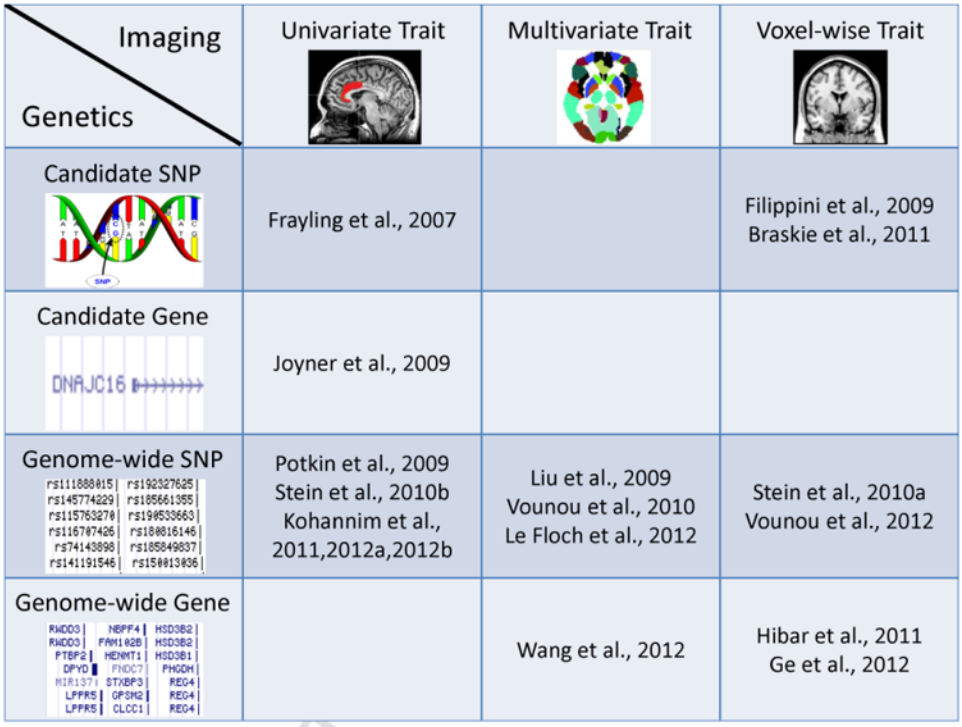

Figure 1.
A menu summarizing some of the imaging genetics association studies in the literature. (Originally created by Dr. Andrew J. Saykin).

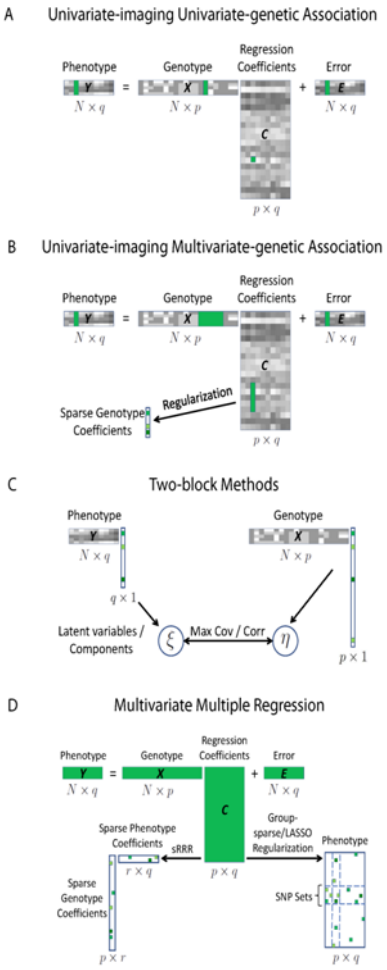

Figure 2.
A cartoon figure summarizing univariate and multivariate association methods.

Table 1

Table of recent genetic studies of brain connectivity, categorized by analysis type and imaging modality

	Study	Modality	Type of Genetic Analysis	Connectomic Methodology	Finding
1	(Glahn et al., 2010)	Resting state fMRI	Heritability	Independent components analysis	Default-mode network was heritable
2	(Braskie et al., 2012)	Structural connectivity (HARDI)	Candidate Gene – *NTRK1*	Element-wise analysis on cortical connections	*NTRK1* associated with differences in the density of fiber connections
3	(Brown et al., 2011)	Structural connectivity (DTI)	Candidate Gene – ApoE4	Nodal and global network measures	*APOE*-4 by age interaction associated with network measures
4	(Chiang et al., 2012)	Structural connectivity (DTI)	Heritability and GWAS	Voxel-wise genetic network of integrity	Variance in white matter hubs were influenced by genetic variants also associating with IQ
5	(Dennis et al., 2011a)	Structural connectivity (HARDI)	Candidate Gene -*CNTNAP2*	Regional and global network measures	*CNTNAP2* associated with global and regional network measures
6	(Duarte-Carvajalino et al., 2012)	Structural connectivity (HARDI)	Kinship prediction	Hierarchical element-wise, regional and global measures	Network measures can be used to predict relatedness among individuals
7	(Fornito et al., 2011)	fMRI network measures	Heritability	Regional and global network measures	Global cost efficiency is heritable; the connectivity of some cortical regions is more heritable than others
8	(Jahanshad et al., 2012e)	Structural connectivity (HARDI)	Candidate Gene -ApoE4	Element-wise analysis, nodal efficiency and strength	ApoE4 associated with FA based nodal strength
9	(Jahanshad et al., 2012d)	Structural connectivity (HARDI)	Heritability and Candidate Gene -*CLU*	Path length distance	Path length distance was heritable and associated with *CLU* variant
10	(Jahanshad et al., 2012c)	Structural connectivity (DTI)	Candidate Gene -ApoE4	Element-wise analysis; multivariate analysis	ApoE4 boosted network association to cognitive scores
11	(Jahanshad et al., 2013b)	Structural connectivity (HARDI)	Heritability + GWAS	Element-wise, nodal, and global	Variant in *SPON1* found to associate with the density of specific connections
12	(Smit et al., 2008)	Resting EEG	Heritability	Global network measures	Clustering coefficient and characteristic path length of the EEG network are heritable
13	(van den Heuvel et al., 2013)	Resting state fMRI	Heritability	Global network measures	Global efficiency is heritable in brain networks of children
14	(Scott-Van Zeeland et al., 2010)	fMRI -Reward guiding learning task	Candidate Gene -*CNTNAP2*	Frontal lobe connectivity	*CNTNAP2* associates to frontal lobe task based connectivity
15	(Rudie et al., 2012)	Resting state fMRI and DTI	Candidate Gene -*MET*	Default mode network connectivity seeded in the PCC and MPFC; TBSS	*MET* associates with functional and structural connectivity in temporo-parietal regions
16	(Tunbridge et al., 2013)	Resting state fMRI	Candidate Gene – *COMT*	Independent components analysis	*COMT* affects resting state prefrontal cortex

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	Study	Modality	Type of Genetic Analysis	Connectomic Methodology	Finding
17	(Filippini et al., 2009a)	Resting state and memory task fMRI	Candidate Gene – *APOE*	Independent components analysis	Increased resting state default mode co-activation in e4 carriers
18	(Liu et al., 2010)	Resting state fMRI	Candidate Gene – *COMT*	Default mode network connectivity in ROIs	*COMT* affects resting state prefrontal cortex
19	(Schmitt et al., 2008)	Structural MRI	Heritability	Global connectivity measures, small worldness	Small worldness is implicated using networks based on genetically correlated cortical regions
20	(Canuet et al., 2012)	Resting state EEG	Candidate Gene – *APOE*	Lagged phase synchronization	ApoE4 associated with differences in interhemispheric “alpha” connectivity
21	(Esslinger et al., 2011)	Resting state and emotional task fMRI	Candidate Gene – *ZNF804A*	Right dorsolateral prefrontal cortex connectivity	*ZNF804A* associated with reduced interhemispheric prefrontal connectivity
22	(Trachtenberg et al., 2012)	Resting state fMRI	Candidate Gene – *APOE*	Independent components analysis	Several resting state networks differ by genotype group (e2/e3,e3/e3,e3/4,e4/e4)